Gaceta Médica de México

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Official scientific journal of the *Academia Nacional de Medicina de México, A.C.*

CONTEMPORARY MEDICINE

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- National Cancer Institute scientific production scientometric analysis
- Cardiovascular risk factors in Mexico and the United States: a comparative cross-sectional study between the HABLE and MHAS participants
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EDITORIAL

Training of the specialist in critical medicine

La formación del especialista en medicina crítica

Jorge A. Castañón-González, Luis A. Gorordo-Delsol, Jessica Garduño-López, Marcos A. Amezcua-Gutiérrez and María de los A. Espino-Ángeles*

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The vertiginous expansion of knowledge in all areas (technology, organization, education, research, administration, health services' financing, etc.) affects health professionals education and training,[1] which has resulted in medical specialties and subspecialties no longer being only classified according to the traditional form by organs and systems (neurology, nephrology, etc.), but also by the attention they pay to age (pediatrics, geriatrics) and gender groups (gynecology & obstetrics), to the type of conditions (infectology, oncology), the setting (anesthesiology, emergency medicine), type of procedure (colon and rectum surgery, neurophysiology, neurological surgery), level of care (primary or secondary care), or according to their horizontal (critical medicine, family medicine) or vertical structure, such as core specialties (internal medicine, general surgery)[2] (Figs. 1, 2 and 3).

Currently, hospital medical care is provided in the form of multidisciplinary collaboration, where intervention of the specialist or subspecialist is occasional, selective and generally for short and intermittent periods; participation of other health professionals who have different but complementary training is required. To deal with the shortage of specialists (for which a short-term solution is not envisioned), some specialties, particularly critical medicine, compensate it in two forms:

– Acquisition of technical skills that were exclusive to other specialties, such as ultrasound to guide procedures, to perform neurological, hemodynamic and respiratory evaluation; bronchoscopies, renal replacement therapy, etc.
– Generation of mixed postgraduate training programs such as trauma-surgery and intensive care, trauma-anesthesia and intensive care, intensive coronary care, pulmonology-critical medicine.

Both solutions have gained ground and proven effective in other countries, the former particularly in Europe and the latter in the United States, where sufficient economic and technical resources are available for each specialty to carry out its own procedures.

In Mexico, most critical medicine schools, including those the authors graduated from, have leaned toward the first solution,[3-7] due to economic difficulties to finance the number of places required for postgraduate mixed courses and difficulties to reach agreements with the 47 medical specialty boards grouped in the Medical Specialty Boards National Regulatory Committee (Conacem – *Comité Normativo Nacional de Consejos de Especialidades Médicas*); of note, in the United States there are only 24 boards.

Acquiring and sharing technical skills that are exclusive to other specialties can be an alternative to compensate and complement the number of specialist physician positions in the mid-term without increasing the number of specialty boards, unless this is strictly necessary. This approach has been so successful that many core specialization programs such as emergency medicine, internal medicine, general surgery, anesthesiology and now also obstetrics & gynecology, cardiology, neurology and pulmonology, among others, perform clinical rotations or training in intensive care units.

Given that the intensive care unit is the place in modern hospitals where the largest number of surgical procedures

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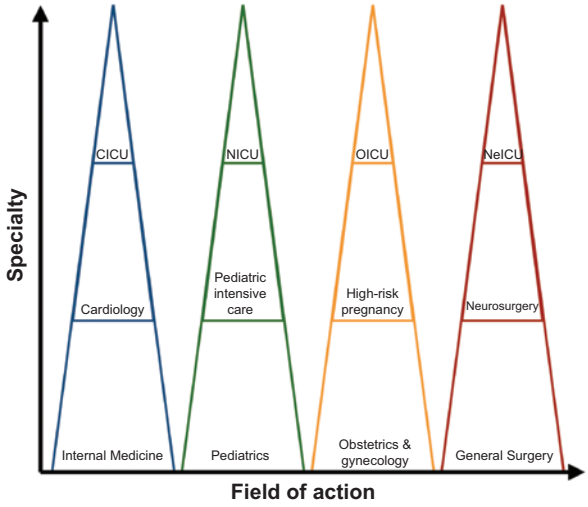

Figure 1. *Vertical (traditional) arrangement of specialties and subspecialties in medicine. CICU = Cardiovascular Intensive Care Unit, NICU = Neonatal Intensive Care Unit, OICU = Obstetric Intensive Care Unit, NeICU = Neurointensive Care Unit.*

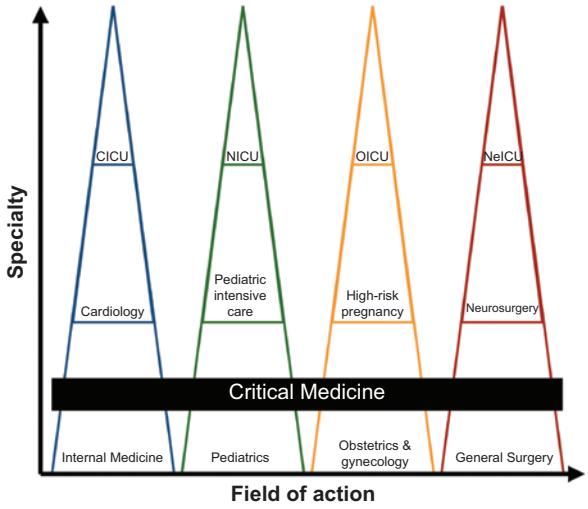

Figure 2. *Horizontal arrangement of the critical medicine specialty in a general hospital.*

are carried out after the operating room, the benefits of these approaches in terms of skill acquisition have not been slow in coming, since critical medicine has brought diagnostic modalities such as ultrasound to patient bedside, which has added a "fifth" element to classical physical examination: insonation is added to inspection, palpation, percussion and auscultation.[8,9] Furthermore, bronchoscopy is currently considered essential for difficult tracheal intubations, aspiration of secretions, resolution of atelectasis and bronchoalveolar lavage sampling for microbiological analysis in lower respiratory infections.

The evolution of critical medicine has allowed the comprehensive care of the seriously and critically ill patient in an expedited and continuous manner 24 hours

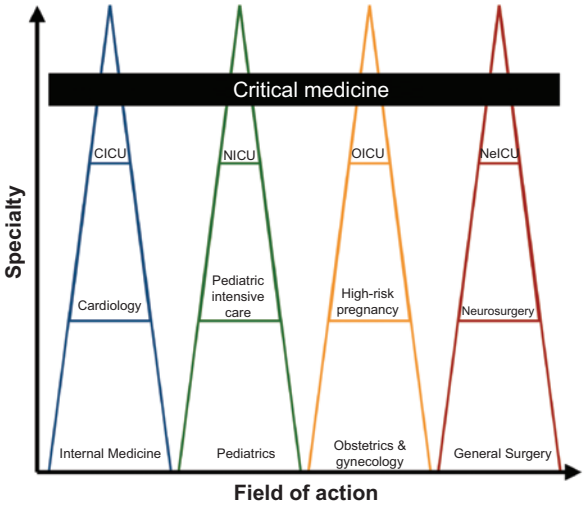

Figure 3. *Horizontal arrangement of the critical medicine specialty in a specialty hospital.*

a day and seven days a week; moreover, it has helped to establish diagnoses, to hierarchically organize and prioritize relevant consultations and for treatment to be provided in an early and efficient form and at lower cost by decreasing intensive care unit length of stay.

Mexico is a developing country where cutting-edge technology lacks a homogeneous distribution across the national territory, which makes for it not to be within reach for everyone. In addition, Mexico is a country where the intensive care unit bed-day cost is exorbitant due to the country's dependence on foreign technology: in 2018 it was established at $ 35,400 Mexican pesos, which is the most expensive unit concept in the tabulator after surgery.[10] Fortunately, Mexico is also a nation where pressures exerted by society and its official bodies curb the increasing cost of medical care, still largely regulated by our profession, and it is thus the responsibility of critical medicine specialists to make a deep and careful reflection on the cost-benefit of our practice in order to optimize resources, which are limited in the face of a demand for services that is exponentially increasing.

It is important to explain resident physicians that clinical observations based on adequate propedeutics, semiology and clinical context recognition are fundamental and will be complemented by imaging studies, but it is the doctor who must confer them their clinical value for their application. The principle of William of Ockam, a 13th century scholastic philosopher ("*Entia non sunt multiplicanda praeter necessitatem*"), says that entities should not be multiplied beyond necessity or, in other words, that it is futile to do with more what can be done with fewer.

It is important to reiterate this principle of logical and common sense analysis to resident physicians, since it is often lost in the educational process and is likely to be deliberately destroyed in the political process. We believe that, even in ideal working conditions, the critical medicine specialist should be austere at his/her clinical practice by conviction in and not by necessity or institutional fashion, and always base his/her decisions on solid clinical propedeutics, broad knowledge on the subject and supported by the most up-to-date scientific evidence.[11]

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ORIGINAL ARTICLE

National Cancer Institute scientific production scientometric analysis

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Abstract

Introduction: *Scientometrics allows analyzing scientific publications productivity and impact through bibliometric and computational techniques.* **Objective:** *To propose a multidimensional methodology in order to obtain the scientometric profile of the National Cancer Institute (INCan), Mexico, and rank it with regard to other national health institutions.* **Method:** *Using the LabSOM software and the ViBlioSOM methodology based on artificial neural networks, the INCan scientific production indexed in the Web of Science from 2007 to 2017 was analyzed. The multidimensional scientometric profile of the Institute was obtained and compared with that of other national health institutions.* **Results:** *In terms of productivity, INCan ranks fourth among the 10 Mexican public health institutions indexed in the Web of Science; in the normalized impact ranking, it ranks sixth. Although out of 1323 articles 683 (51.62 %) did not receive citations, 11 articles classified as excellent (0.83 %) obtained 24 % of 11,932 citations and, consequently, INCan normalized impact rate showed a mean productivity higher than the world mean.* **Conclusion:** *Multidimensional analysis with the proposed neural network enables obtaining a more reliable and comprehensive absolute and relative institutional scientiometric profile than that derived from measuring isolated variables.*

KEY WORDS: *Research in public health systems. Outcome measure. Mexico.*

Análisis cienciométrico de la producción científica del Instituto Nacional de Cancerología

Resumen

Introducción: *La cienciometría permite analizar la productividad e impacto de las publicaciones científicas mediante técnicas bibliométricas y computacionales.* **Objetivo:** *Proponer una metodología multidimensional para obtener el perfil cienciométrico del Instituto Nacional de Cancerología (INCan), México, y compararlo respecto a otras instituciones nacionales de salud.* **Método:** *Con el programa LabSOM y la metodología ViBlioSOM, basada en redes neuronales artificiales, se analizó la producción científica del INCan indexada en la Web of Science entre 2007 y 2017. Se obtuvo el perfil cienciométrico multidimensional del Instituto y se comparó con el de otras instituciones nacionales de salud.* **Resultados:** *En productividad, el INCan ocupa el cuarto lugar de las 10 instituciones mexicanas de salud pública indexadas en la Web of Science.; en el ranking de impacto normalizado, el sexto lugar. Aun cuando de 1323 artículos, 683 (51.62 %) no recibieron citas, 11 artículos de excelencia (0.83 %) lograron 24 % de 11 932 citas y, consecuentemente, el impacto normalizado del INCan evidenció una productividad media por arriba de la media mundial.* **Conclusión:** *El análisis multidimensional con la red neuronal propuesta permite obtener un perfil cienciométrico institucional absoluto y relativo más fidedigno e integral que el derivado de conteos de variables aisladas.*

PALABRAS CLAVE: *Investigación en sistemas de salud pública. Medición de resultados. México.*

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Introduction

Article three of the National Cancer Institute (INCan – *Instituto Nacional de Cancerología*), Mexico, Organic Statute states that, for the fulfillment of its purpose, it shall:

> Conduct clinical, epidemiological, experimental, technological development and basic studies and research in the biomedical and socio-medical areas in the specialty of neoplasms, for the understanding, prevention, diagnosis and treatment of diseases, and rehabilitation of those affected, as well as promote health measures. It shall also publish the results of the research and work that is carried out, as well as to disseminate technical and scientific information on the advances it achieves in matters of health.[1]

The research that is carried out at INCan is basic and clinical. Its integration is sought through translational research. In addition, clinicians are involved in research by evaluating medications and monitoring new protocols. From 2003 to 2013, an average of 186 research protocols were developed annually.[2] How to know whether said research has the level of "excellence" dictated by the INCan mission?

One resource is scientometrics, which addresses the problem by analyzing scientific publications through bibliometric and computational techniques, incorporating algorithmic methods such as machine learning and data mining to generate indicators of productivity and impact of scientific production,[3] such as cancer research.[4-7] In Mexico, researchers are increasingly deciding what to investigate and where to publish based on scientometric criteria, given that their performance is assessed with that same methodology. Moreover, scientometric indicators are the main support for the allocation of resources for research. Especially when resources are limited and the costs of care are so high, as in the case of cancer,[8,9] rigorous evaluation of scientific activity is essential. Therefore, we consider that scientometric analysis of INCan scientific production is, on one hand, an element for diagnosis of health research current situation in Mexico and, on the other, a contribution to future decision making. The methodology we propose can be transferred in order to obtain the scientometric profile of other national health institutions where research is part of their regular activities.

Method

With the LabSOM software, developed by the Laboratory of Nonlinear Dynamics of the Faculty of Sciences of the National Autonomous University of Mexico, a scientiometric diagnosis of INCan scientific productivity was carried out through the analysis of the articles indexed in the Web of Science (WoS) during the 2007-2017 period.

The scientometric indicators obtained were the following:

- Total documents (Ndoc).
- Total cited documents (CD).
- Percentage of cited documents (CD %).
- Total accumulated citations (TC).
- Average citations received by each article (CI).
- Hirsch index (H).
- Impact relative to world (IRW).
- Category normalized citation impact (CNCI).
- Type of document and year.
- Total documents in national inter-institutional collaboration (NC).
- Total documents in international inter-institutional collaboration (IC).
- NC and IC percentages of Ndoc (IC %)
- Percentage within 1 % of the most cited articles worldwide (EXC %).
- Percentage within 10 % of the most cited articles worldwide (HP %).
- Total hot papers (HP) or articles within 0.1 % of the most cited in the previous two months.
- Total highly cited (HC) papers or articles within 1 % of the most cited in the year.

In addition, subject categories and scientific journals where INCan researchers have the highest number of publications and citations were identified.

To put these results in context, a comparison was made with the results obtained for other institutions. Initially, total scientific production of Mexico indexed in WoS during the 2007-2017 period was identified by institution, selecting through InCites those articles where at least one of the authors was a staff member of a Mexican institution. Subsequently, a second screening was made in order to focus on scientific production in the biomedical area. To this end, the production was screened based on eight research areas: Clinical Medicine, Biology & Biochemistry, Immunology, Microbiology, Molecular Biology & Genetics, Neuroscience & Behavior, Pharmacology & Toxicology and Psychiatry/Psychology, of the 22 areas defined by the European Scientific Institute classification system. The selection includes only scientific articles in journals (original articles and review articles), and excludes letters to the editor, revisions, abstracts and retracted articles.

Table 1. Scientometric indicators of INCan WoS-indexed annual production for the 2007-2017 period

Year	Ndoc	CD	CD %	TC	CI	H	IRW	CNCI	IC	IC %
2007	67	45	62.69	1212	18.09	17	0.897	0.82	13	19.4
2008	78	55	69.23	1803	23.12	21	1.234	1.12	24	30.77
2009	89	54	57.3	977	10.98	16	0.635	1.23	19	21.35
2010	88	54	61.36	920	10.45	17	0.659	0.5	19	21.59
2011	105	61	53.33	1144	10.9	19	0.785	0.87	21	20
2012	125	73	57.6	1003	8.02	17	0.67	0.72	38	30.4
2013	133	79	58.65	944	7.1	17	0.714	0.52	43	32.33
2014	124	80	61.29	1320	10.65	14	1.35	1.25	52	41.94
2015	142	73	50	2086	14.69	14	2.611	2.56	57	40.14
2016	176	92	52.27	432	2.45	10	0.776	2.39	67	38.07
2017	196	46	22.45	91	0.46	4	0.455	0.65	81	41.33

Source: Own creation with WoS data. Ndoc = number of documents, CD = cited documents, CD % = cited documents percentage, TC = total citations, CI = citation index, H = Hirsch index, IRW = impact relative to world, CNCI = category normalized citation impact, IC = international collaborations, IC % = percentage of documents with international collaboration.

In this tool, the above-described indicators were chosen, health institutions were selected and two variables were added: number of researchers members of the National System of Researchers (SNI – *Sistema Nacional de Investigadores*) and institutional scientific production (SP), which was calculated by dividing the total number of documents by the number of researchers who are members of the SNI: Ndoc/SNI.[10]

Finally, a multi-parametric computational analysis was carried out using the ViBlioSOM methodology, which is based on the family of SOM (Self-organizing Maps) artificial neural network algorithms. This methodology, based on artificial intelligence, allowed to detect the scientometric profiles of the institutions and represent them through topographic clusters, according to their similarities. Briefly, the process carried out by ViBlioSOM consists of five steps: WoS data collection, data selection, cleaning and integration thereof, generation of the mathematical model and its processing through neural networks. The last step of the methodology is implemented in the LabSOM computational tool, which is freely distributed at: http://www.dynamics.unam.edu/DinamicaNoLineal3/labsom.htm.

Results

During the 2007-2017 period, 87 Mexican institutions published 146,933 articles indexed in WoS. Taking into account only the total number of articles, INCan ranked 33 with 1,405 documents. Out of these, 49,008 articles belonged to biomedical areas. In this ranking, INCan was 11th with 1,323 articles.

Table 1 summarizes the information related to INCan. A steady, gradual growth can be observed in the number of documents, number of citations and number of international collaborations; except for two years, where there was a slight regression, 2010 and 2014, and two in which there was an atypical growth. This is because, in 2008, four articles together accumulated a total of 705 citations, which accounts for 39.1 % of all citations for the 78 articles published that year. The other year is 2015, when the most cited article throughout the period was published: “Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer”, published in 2015 in the New England Journal of Medicine, a journal located in quartile 1, as a result of a broad international contribution. This article concentrated 1,460 citations (69.9 %) of the 2,086 obtained by 142 articles published that year (Table 1).

Contrary to what it might be expected, the aforementioned article was a “highly cited paper”, not a hot paper. No hot papers were found throughout the period. The 11 highly cited papers describe and discuss comparative results between treatments in cancer patients and are the result of international inter-institutional collaborations. During the period, 926 collaborations were recorded, involving 609 different institutions, as shown in Figure 1.

Naturally, oncology is the WoS subject category where INCan researchers published more (589) and more citations received (6004). Within this category, the most outstanding sub-subjects for the period were oncology, respiratory system, dentistry, surgery and obstetrics and gynecology.

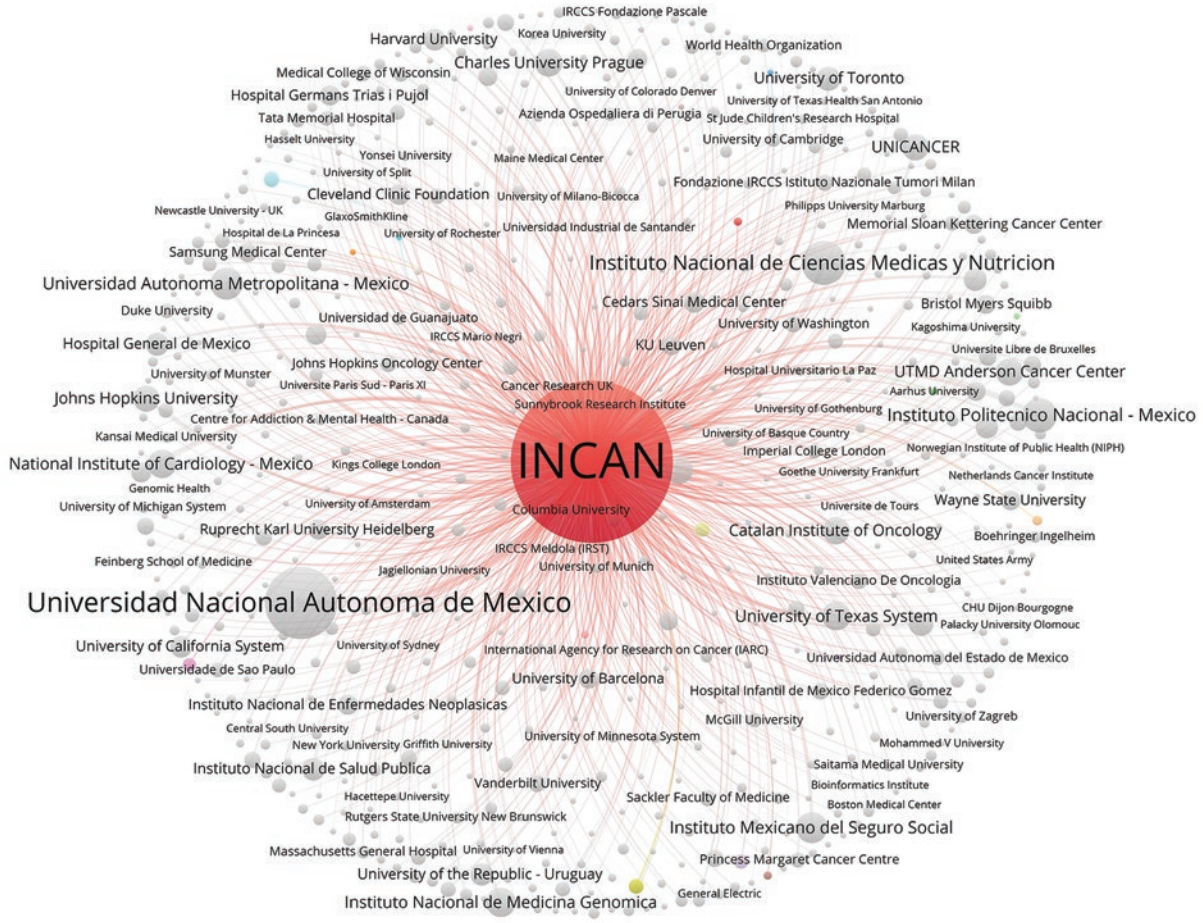

Figure 1. *National Cancer Institute (INCan) collaboration links during the 2007-2017 period. Source: Own creation with WoS information using the free VOSviewer software tool (http://www.vosviewer.com).*

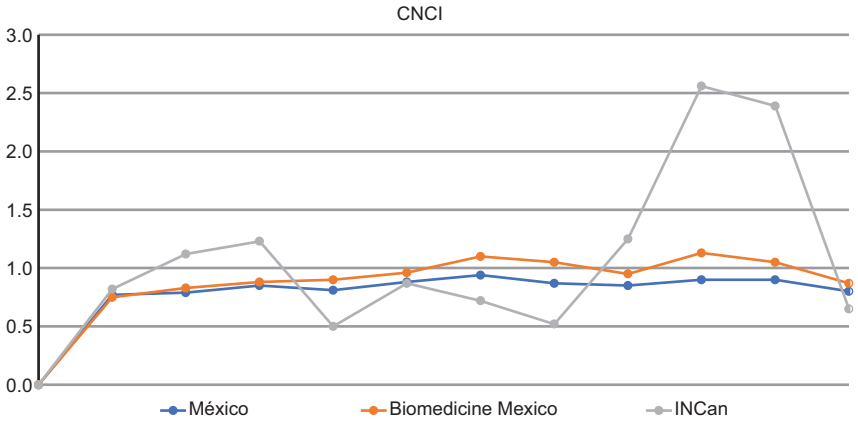

Figure 2. *Subject category normalized citation impact. Source: Own creation with WoS data.*

The category normalized citation impact (CNCI) global ranking is an indicator that allows impact comparisons between different areas, since it normalizes citation styles. Through it, it is feasible to compare institutions with production in different areas, such as mathematics and biology. Figure 2 shows that biomedical production has consistently obtained more citations than the national mean. In addition, in 2012, 2013, 2015 and 2016, the CNCI indicator for biomedicine is higher than 1, indicating

Table 2. Scientometric indicators of health institutions with WoS-indexed production (2007-2017) in the biomedical area

Rank	Name	Ndoc	CD %	CI	H	IRW	CNCI	IC %	EXC %	HP %	SNI	SP
3	Mexican Institute of Social Security	4121	62.12	8.35	68	0.5	0.76	26.13	0.73	5.44	324	12.7
5	National Institute of Medical Sciences and Nutrition "Salvador Zubirán"	2764	59.59	11.01	68	0.66	1.14	34.52	1.59	8.21	189	14.6
9	National Institute of Public Health	1601	64.77	22.05	73	1.33	2.77	60.46	4.68	14.55	185	8.6
10	National Institute of Cardiology	1328	65.81	13.65	56	0.82	1.06	31.1	1.2	10.17	107	12.4
11	National Cancer Institute	1323	52.15	9.02	47	0.54	1.22	32.8	0.83	7.11	92	14.3
12	Children's Hospital of Mexico "Federico Gómez"	1165	50.64	5.96	35	0.36	0.85	37.17	1.03	6.27	77	15.1
14	National Institute of Psychiatry "Ramón de la Fuente Muñiz"	907	71.33	34.33	59	2.07	3.24	40.35	5.29	13.56	92	9.8
17	General Hospital of Mexico	789	61.22	12.72	44	0.76	1.57	37.26	3.42	10.65	45	17.5
20	National Institute of Genomic Medicine	527	67.17	19.94	37	1.20	1.63	31.31	2.28	9.11	48	10.9
31	Central Hospital "Dr. Ignacio Morones Prieto"	267	55.81	18.98	23	1.14	2.27	23.97	3.37	8.24	0	NA

Source: Created by the authors with WoS and Conacyt Beneficiaries' Registry data. Ndoc = number of documents, CD % = cited documents percentage, CI = citation index, H = Hirsch index, IRW = impact relative to world, CNCI = category normalized citation impact, IC % = percentage of documents with international collaboration, EXC % = production of excellence (percentage of articles within most-cited 1 %), HP % = high performance production (percentage of articles within most-cited 10 %), SNI = Members of the National System of Researchers 2017, SP = institutional scientific production (Ndoc/SNI).

that it exceeded world average. As for INCan, although from 2010 to 2013 its works had a low impact, in six of the 11 years of the period its impact exceeded the national mean and the international mean in five (Figure 2).

In order to better understand the results obtained for INCan, they were located in the national context of scientometric performance in the biomedical area. Table 2 shows the results obtained for the 10 Mexican health institutions indexed in WoS during the 2007-2017 period. In this ranking, INCan is located at place five out of 10.

The data in Table 2 were processed by means of the ViBlioSOM methodology to practice a multidimensional analysis in order to find the different scientometric performance profiles of the institutions and represent them in topographic clusters according to their similarities. Five indicators were chosen to represent each institution: SP, HP %, EXC %, CNCI and IC %. Consequently, for the neural network, each institution is a five-dimensional mathematical object (vector). During the training, the network simultaneously considers the five dimensions to organize the institutions on the map, placing the most similar institutions in a close position.

The artificial neural network automatically generates the maps shown in Figure 3. On map A, INCan is grouped with the National Institute of Medical Sciences and Nutrition "Salvador Zubirán" (INCMNSZ – *Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán"*), which means that during the study period these institutions exhibited a similar scientometric profile. Conversely, the behavior of the other institutions differs enough to be positioned in different clusters. Maps B to F correspond to one of the five indicators. The green color corresponds to the lowest value, the yellow color to the mean and the red color to the highest value (Figure 3).

The orange color for INCan on map B indicates that it is in the group of the second most productive institutions, i.e. those with the largest number of articles per SNI member, after General Hospital of Mexico, Children's Hospital of Mexico "Federico Gómez" and INCMNSZ. As for impact, map E places INCan in the mean, together with the National Cancer Institute and INCMNSZ. The CNCI indicator indicates that INCan exceeds the global mean in terms of impact. The indicators on maps C and D are quality indicators and, in both, INCan has low values. During the studied period, it produced scarce research of excellence (EXC %) and high performance research (HP %). Map F shows that INCan's behavior regarding international collaboration is low, as in the other institutions.

Discussion

The fact that INCan is located among the most scientifically productive Mexican institutions is an irrefutable positive indicator. The first place in the ranking is for the Mexican Institute of Social Security, an

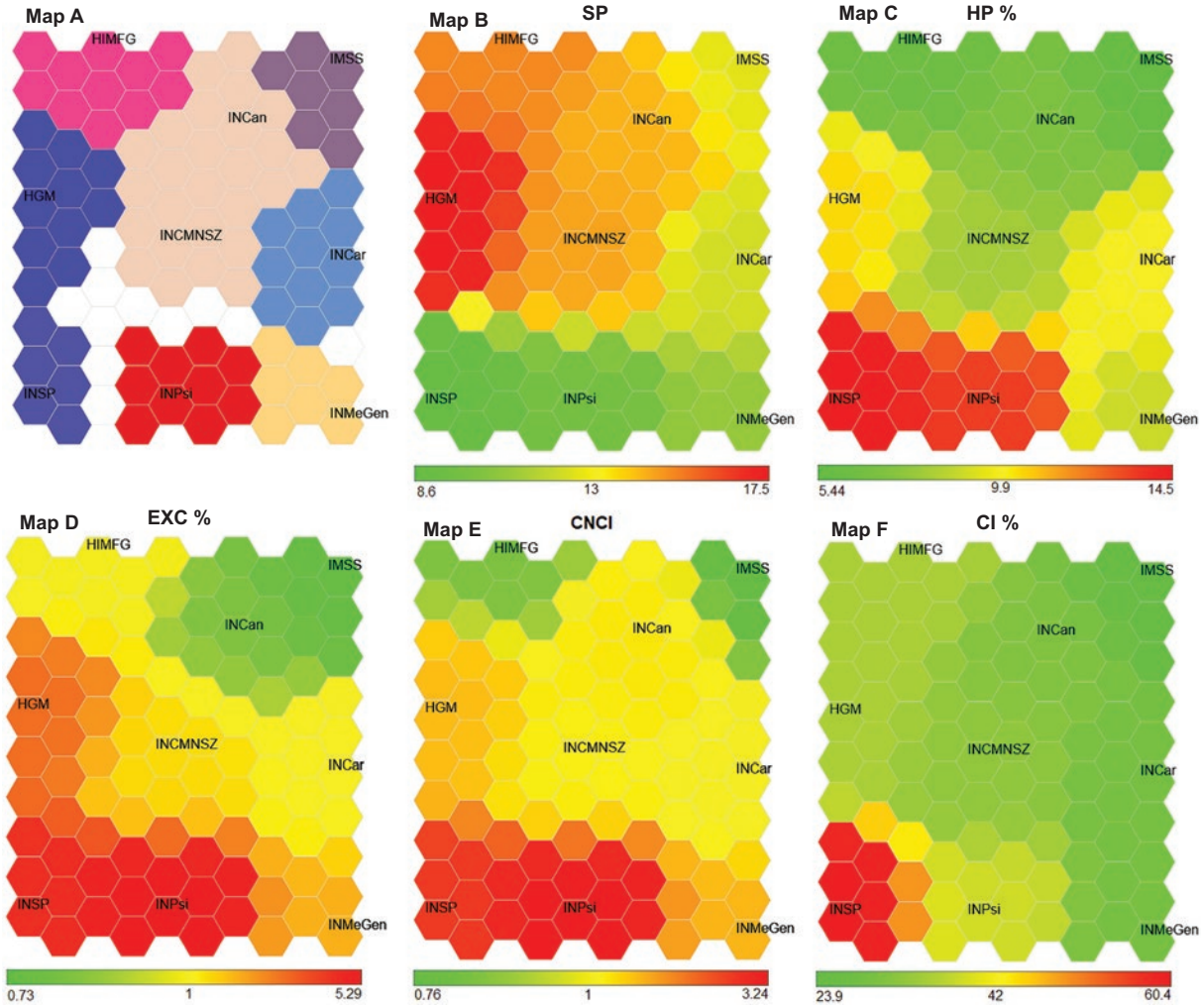

Figure 3. *Topographic maps resulting from the multi-parametric analysis with ViBlioSOM. HIMFG: Children's Hospital of Mexico "Federico Gómez", IMSS: Mexican Institute of Social Security, INCan: National Cancer Institute, HGM: General Hospital of Mexico, INCMNSZ: National Institute of Medical Sciences and Nutrition "Salvador Zubirán", INCar: National Institute of Cardiology, INSP: National Institute of Public Health, INPsi: National Institute of Psychiatry, INMeGen: National Institute of Genetic Medicine. Source: Own creation with WoS data using the LabSOM tool.*

institution that was assigned 49.1 % of the net budget for the Health Sector. In 2017, the Mexican Institute of Social Security allocated 727.1 million Mexican pesos to research and had 324 researchers who were SNI members; therefore, it is not surprising that it published the largest number of documents. With that being said, the relationship between annual budget and total number of published documents is not linear: the National Institute of Public Health (INSP – *Instituto Nacional de Salud Pública*), INCMNSZ and the National Institute of Cardiology had assigned a lower budget than INCan and published more.

The number of researchers who are members of the SNI is more directly correlated with the number of publications than the budget. The ranking of institutions that is generated by the number of SNI members is almost equal to the number of published documents. This correlation has the advantage of being a resource for comparing the institutions taking into account only the resources allocated to research. For example, although total absolute number of documents published by the Mexican Institute of Social Security is much higher than that of INSP, INSP institutional scientific productivity and citation index are higher. In the institutional scientific productivity ranking, INCan is at fourth place.

The maps in Figure 3 reveal the discrepancy between quantitative and qualitative productivity. The areas of the map that correspond to quality (red areas in maps C, D and E) do not match those of productivity. If the institutions are listed by their citation index, INCan appears in number 8 out of 10. When

delving into the analysis of INCan's exclusive production, we find that of the 1,323 documents published in the period, 633 did not have a single citation. That is, 52.15 percent of the published documents generated the 12,243 accumulated citations.

In fact, the 11 highly cited papers (0.78 %) generated 26.9 % of all citations. The scientometric behavior of the article "Nivolumab versus docetaxel in advanced non-squamous, non-small-cell lung cancer" is even more atypical. Its impact has been such, that the year of its publication is the only one where the average number of citations per INCan article (11.01) almost doubled the world average (5.94), whereas in all other years it was below. This article is an outlet that modifies the dynamics of the system. Without it, INCan would be ranked last in the list by citation index.

Of the 583 institutions INCan collaborated with, 223 appear on the list only once. The most intense collaboration in terms of number of articles and permanence in time, was with the most scientifically productive Mexican institutions, which is also a good indicator of INCan researchers' level. Among the international collaborations with higher durability and productivity, those established with US institutions are predominant.

The multi-parametric analysis indicates that the majority of Mexican public health institutions have achieved high productivity and impact with a low percentage of international collaborations, with the exception of INSP, which has a low productivity (low SP), but high quality (high CNCI) profile and the highest values in production of excellence (EXC %), high performance (HP %) and international collaboration (IC %).

The subjects and journals where INCan researchers publish the most and have the highest impact are those that link oncology to clinical research. The link between research and clinical care a national institute enables has been positively exploited by INCan researchers. In contrast, the publications clearly show a deficit in research on medical education, another one of INCan's primary activities, and that should help address the deficit of oncologists Mexico has.

Another neglected research subject is social medicine. Cancer in Mexican disadvantaged population evinces social inequalities and exacerbates them. Therefore, developing research that contributes to design and implement culturally appropriate programs that take into account social determinants and behavioral factors that increase the risk of suffering from cancer is a priority, through interventions that include gender, intercultural and community-based approaches.

Conclusions

Although peer review is irreplaceable and can conclusively establish the relevance of a scientific research, scientometry specialists have strived to design new standardized and size-independent indicators that allow measuring and fairly comparing the activity of different scientific communities. On the other hand, scientific activity cannot be evaluated considering one or two variables, given that, like any social activity, it is a complex multidimensional phenomenon. Scientometric profiles resulting from the multi-parametric analysis with SOM allow an institutional, comprehensive diagnosis of scientific performance, considering several dimensions simultaneously. Globally, INCan exhibits a scientometric profile with a high mean productivity and normalized impact above the world mean. Its areas of opportunity are found in the production of excellence (EXC %) and high performance (HP %) dimensions.

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ORIGINAL ARTICLE

Occult renal failure and associated factors in patients with chronic conditions

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Abstract

Introduction: *Timely diagnosis and early therapeutic intervention reduce premature mortality associated with chronic renal failure.* **Objective:** *To identify the prevalence and factors associated with occult renal failure in patients with chronic diseases.* **Method:** *Cross-sectional study of 1268 patients with type 2 diabetes mellitus and systemic arterial hypertension. A measuring instrument with questions about associated factors such as osteoarthritis, treatment of chronic conditions, smoking, analgesic consumption, alcoholism, body mass index, physical activity and serum glucose, cholesterol and triglyceride levels was used.* **Results:** *The prevalence of occult renal failure was 13.2 % (167/1,268), 13.4 % in diabetic patients (117/876) and 14.9 % in hypertensive patients (150/1,010). In the multivariate analysis, the factors associated with occult renal failure were being older than 60 years (aOR = 1.96, 95 % CI = 1.22-2.49), belonging to the female gender (aOR = 2.17, 95 % CI = 1.30-2.82), suffering from systemic arterial hypertension (aOR = 1.96, 95 % CI = 1.22-2.50) and not having overweight/obesity (aOR = 0.49, 95 % CI = 0.41-0.8).* **Conclusions:** *The prevalence of occult renal failure was 13 %. Female patients older than 60 years with overweight/obesity and systemic arterial hypertension should be examined in detail by the family doctor for occult renal failure early detection.*

KEY WORDS: *Occult renal failure. Diabetes mellitus. Systemic arterial hypertension.*

Insuficiencia renal oculta y factores asociados en pacientes con enfermedades crónicas

Resumen

Introducción: *El diagnóstico oportuno y la intervención terapéutica temprana disminuyen la mortalidad prematura asociada con insuficiencia renal crónica.* **Objetivo:** *Identificar la prevalencia y factores asociados con insuficiencia renal oculta en pacientes con enfermedades crónicas.* **Método:** *Estudio transversal de 1268 pacientes con diabetes mellitus tipo 2 e hipertensión arterial sistémica. Se usó un instrumento de medición con preguntas sobre factores asociados como artrosis, tratamiento de padecimiento crónico, tabaquismo, ingesta de analgésicos, alcoholismo, índice de masa corporal, actividad física y niveles séricos de glucosa, colesterol y triglicéridos.* **Resultados:** *La prevalencia de insuficiencia renal oculta fue de 13.2 % (167/1268), 13.4 % en pacientes diabéticos (117/876) y 14.9 % en hipertensos (150/1010). En el analisis multivariado, los factores asociados con insuficiencia renal oculta fueron edad > 60 años (RMa = 1.96, IC 95 % = 1.22-2.49), sexo femenino (RMa = 2.17, IC 95 % = 1.30-2.82), padecer hipertensión arterial sistémica (RMa = 1.96, IC 95 % = 1.22-2.50) y no tener sobrepeso u obesidad (RMa = 0.49, IC 95 % = 0.41-0.8).* **Conclusiones:** *La prevalencia de insuficiencia renal oculta fue de 13 %. Los pacientes mayores de 60 años, con sobrepeso u obesidad e hipertensión arterial sistémica deben ser examinados detalladamente por el médico familiar para la detección temprana de insuficiencia renal oculta.*

PALABRAS CLAVE: *Insuficiencia renal oculta. Diabetes mellitus. Hipertensión arterial sistémica.*

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Introduction

In 1990, chronic kidney disease ranked 27th in the list of global mortality causes, with an annualized age-standardized rate of 9.6 per 100,000 population, which was increased to 11.1 per 100,000 population by 2010.[1] Globally, the prevalence of chronic kidney disease is estimated to be 10 %,[2] and it is a disease that together with other chronic comorbidities increases the risk of early death.[3,4] In Mexico, premature death due to chronic kidney disease increased by almost 400 % from 1990 to 2010.[5] Despite the above, the frequency of this condition is unknown; one study in subjects older than 18 years found a prevalence of 8 %.[6]

In Mexico, the 2012 National Health and Nutrition Survey identified 22.4 million adults with systemic arterial hypertension (SAH) and 6.4 million adults with type 2 diabetes mellitus (DM2). The figures are relevant because only half the people with hypertension are aware of it and only one quarter of diabetics have their disease under control.[7] The combination of chronic conditions, with the resulting negative impact on individual health and high social cost, turns chronic renal failure into a catastrophic event.[8-10]

Renal function initial failure is the result of complex interactions, mainly of chronic and degenerative conditions. Progression factors that worsen and accelerate kidney damage are persistent proteinuria,[11] SAH,[12] poorly-controlled DM2,[13] smoking,[14] dyslipidemia,[15] anemia,[16] associated vascular disease and obesity.[11] There is a higher frequency of occult renal failure in women[17,18] and in people older than 50 years.[19] Body mass index > 25 has been associated with occult renal failure.[20] Some dietary restrictions modify the consumption of protein, sodium and phosphorus and stop renal damage,[21] with higher benefit if they are established in a timely manner. The purpose of this study was to estimate the prevalence of occult renal failure and associated factors in patients with SAH or DM2 under the care of the Family Medicine Unit 29 of the Mexican Institute of Social Security in Acapulco, Guerrero, Mexico.

Method

Cross-sectional study conducted in users of the Family Medicine Unit 29 of the Mexican Institute of Social Security, from November 1, 2014 to January 31, 2015. The following criteria were used for patient selection:

- *Inclusion*: patients with clinical diagnosis of SAH (systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg) or DM2 (blood glucose > 126 mg/dL), and with no recorded diagnosis of chronic kidney disease.
- *Exclusion*: patients without recent laboratory tests (blood glucose, cholesterol, triglycerides and creatinine levels) or who had a single kidney, any type of cancer or systemic lupus erythematosus.

The sample size was calculated considering a prevalence of occult renal failure of 7.6 %,[22] a 95 % confidence level (alpha error), study power of 0.20 (beta error) and an odds ratio (OR) of 1.9 between SAH and occult renal failure. The resulting sample size was 1268 patients; five were excluded.

To measure the potential factors associated with occult renal failure, a 28-item questionnaire was used to directly collect data from the patients. The questionnaire was previously validated by a panel of experts:[23] one family doctor, one nephrology specialist and two epidemiologists. With the questionnaire, patient general data were confirmed: gender, age, ethnicity and chief complaint. Time of evolution and current treatment of the condition were verified, and patients were asked about the use of non-steroidal analgesics, tobacco and alcohol consumption, osteoarthritis and periodicity of physical activity (physical exercise for at least 30 minutes daily, including household chores). After the interview, body weight, height and blood pressure were measured in each patient. The body mass index was estimated with body weight and height.

Data on cholesterol and triglyceride plasma concentration levels were taken from the electronic medical record. With patient age, gender and ethnicity, as well as with the most recent serum creatinine level result, the glomerular filtration rate was calculated using the formula proposed by the Chronic Kidney Disease Epidemiology Collaboration group.[24]

Occult renal failure operative definition was the following: a patient with glomerular filtration rate < 60 mL/minute for more than three months and who was unaware of having chronic kidney disease. With the glomerular filtration rate, the severity of chronic kidney disease was classified in the six stages proposed by the Kidney Disease Outcomes Quality Initiative guideline.[24]

Data analysis was carried out with the statistical program CIETmap.[25] The association between study-included variables and occult renal failure was estimated with the Mantel-Haenszel procedure using the odds ratio (OR), both in the bivariate and multivariate analyses.[26] The 95 % confidence interval (CI) of the OR was estimated with Miettinen's proposal.[27]

Table 1. Glomerular filtration rate staging, according to the Kidney Disease Outcomes Quality Initiative guidelines

Stage and definition	Glomerular filtration rate (mL/minute)	n = 1268	%
No kidney damage	> 91	677	53.4
1 Evidence of kidney damage and normal GFR	≥ 90	17	1.3
2 Evidence of kidney damage and slightly decreased GFR	60-89	407	32.1
3 Moderate GFR decrease	30-59	161	12.7
4 Severe GFR decrease	15-29	5	0.4
5 End-stage renal failure	< 15	1	0.1

GFR = Glomerular filtration rate.

Table 2. Bivariate analysis of factors associated with occult renal failure

Factor	Occult renal failure (%)		naOR*	95 % CI**
	n	%		
Gender Females Males	 120/794 47/474	 15.1 9.9	**1.62**	**1.13-2.31**
Age (years) > 60 < 60	 118/624 49/644	 18.1 7.6	**2.83**	**2.01-3.99**
Type 2 diabetes mellitus With Without	 117/876 50/392	 13.4 12.8	1.05	0.74-1.50
Systemic arterial hypertension With Without	 150/1 010 17/258	 14.9 6.6	**2.47**	**1.49-4.10**
Glycemic control Controlled Uncontrolled	 63/424 67/558	 14.9 12	1.28	0.88-1.85
Systemic blood pressure control Controlled Uncontrolled	 146/1 096 21/172	 13.3 12.2	1.11	0.68-1.80
Dyslipidemia With Without	 38/285 119/926	 13.3 12.9	1.04	0.70-1.54
Smoking Yes No	 13/102 154/1 166	 12.7 13.2	0.96	0.52-1.76
Osteoarthritis With Without	 23/173 144/1 094	 13.8 13.2	1.01	0.63-1.63
Body mass index < 25 ≥ 25	 117/1 000 50/268	 11.7 18.7	**0.58**	**0.83-0.40**

*Non-adjusted odds ratio. **95 % confidence intervals.

All patients signed the informed consent. The information provided by the patients was confidential but not anonymous. The study was approved by the Local Research Committee 1101 of the Mexican Institute of Social Security, with authorization number R-2014-1101-15.

Results

A total of 1268 patients with a clinical diagnosis of DM2 or SAH and without a diagnosis of chronic kidney disease participated in the study; 31 % (392) had been

Table 3. Final model of the multivariate analysis of factors associated with occult renal failure

Factor	naOR*	aOR**	a95 % IC&	het$\chi^{2\#}$	p
Female gender	1.62	1.78	1.24-2.56	9.8	0.53
Age older than 60 years	2.83	2.63	1.84-3.76	28.4	0.57
Systemic arterial hypertension	2.47	2.03	1.18-3.47	6.6	0.67
Body mass index > 25	0.58	0.60	0.88-0.41	7.0	0.60

*Non-adjusted odds ratio. **Adjusted odds ratio. &Adjusted odds ratio 95% confidence intervals. #Chi-square test for heterogeneity.

diagnosed with SAH, 20 % (258) had been diagnosed with DM2 and 49 % (618) had been diagnosed with both conditions; 63 % (794) were females, and average age was 60.1 ± 11.1 years, with a range of 22 to 91 years.

Forty-one (3 %) patients reported practicing daily physical exercise, 8 % (107) had a smoking history, 0.3 % (4) referred alcohol consumption and 14 % (173) reported suffering from some type of osteoarthritis. According to the level of blood lipids, the patients had the following distribution: normal 40 % (507), hypertriglyceridemia 26 % (325), hypercholesterolemia 12 % (151) and dyslipidemia 23 % (285).

One-hundred and sixty-seven patients (13.2 %) had occult renal failure; 53 % (677) had a glomerular filtration rate > 91 mL/minute. Patient glomerular filtration rate distribution is shown in Table 1. In those patients only with DM2, the occurrence of occult renal failure was 45 % (117/258), in those who only had SAH, it was 38 % (150/392) and in patients with both conditions, 16.2 % (100/618).

In the bivariate analysis, four factors were found to be significantly associated with occult renal failure: female gender, age older than 60 years, suffering from SAH and body mass index < 25. Table 2 shows the strength of association and the 95 % confidence intervals of the factors included in the bivariate analysis.

The multivariate analysis showed an independent effect of the four factors identified in the bivariate analysis. Age > 60 years had the highest strength of association (aOR = 2.63, a95 % CI = 1.84-3.76) and, in decreasing order, it was followed by suffering from HAS and being a female. Body mass index < 25 was shown to be a protective factor (aOR = 0.60, a95% CI = 0.88-0.41) against occult renal failure; Table 3 shows the multivariate analysis final model.

Discussion

In this study, a prevalence of occult renal failure of 13.2 % was found in patients with SAH or DM2. There was also evidence of four factors associated with occult renal failure: female gender, age > 60 years, presence of SAH and body mass index < 25.

In our study, we used the equation proposed by the Chronic Kidney Disease-Epidemiology Collaboration because it provides more advantages and greater accuracy in comparison with the formula proposed by the Modification of Diet in Renal Disease, in addition to improving the predictive power of glomerular filtration and being useful in the prediction of overall and cardiovascular mortality and of the risk for developing end-stage chronic kidney disease.[28]

We found that 13.2 % of patients with DM2 or SAH had occult renal failure, a figure close to the 13.5 % reported by Peralta in the United States.[8] Since prevalence in our study was estimated in patients with DM2 or HAS, the occurrence must have been overestimated, given that the entire population had risk factors for occult renal failure.

In our research, the female gender was the factor with the highest strength of association with occult renal failure, a finding that is not new.[17,19] Various theories suggest that it is more common in women due to anatomical differences with regard to man's kidney size,[29] to a differentiated response to angiotensin,[30] to differences in lifestyles according to gender[31] and hormonal changes in women.[32] Being a woman and being older than 60 years are risk factors for developing occult renal failure.[33] We also found that age > 60 years was associated with occult renal failure. Other studies have found similar results.[12,18]

SHA associated with occult renal failure has been reported by multiple observational studies that have identified it as a modifiable risk factor, both for the development of chronic kidney disease and for its progression.[34-37]

Our study revealed that a body mass index < 25 was a protective factor against occult renal failure. The same result was reported by Kalyesubula.[17] Otero found a similar mean body mass index (< 27) to be a protective factor.[15] Da Silva suggests that the relationship between obesity and kidney damage is due to an accumulation of adipose tissue, mainly in viscera, which causes kidney compression, with a consequent increase in intrarenal pressure. Obesity also increases inflammatory and adipocyte production processes.[38]

Timing is one of the main limitations of cross-sectional studies. In our study, it is necessary to discern whether low body mass index is the result of the presence of DM2, SAH or occult renal failure, since in the context of these patients, following a diet and practicing physical exercise as part of the treatment and control of the disease lead to body weight reduction. We consider that high body mass index precedes occult renal failure. Our result is similar to that reported by other studies that also found a protective effect of a normal body mass index.[15,17]

It is necessary to train and update health professionals as part of the improvements to the health system, so that primary care doctors have the ability to identify patients at kidney disease early stages.[39] Occult renal failure early detection implementation in patients with chronic diseases is feasible at primary care.

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ORIGINAL ARTICLE

Cardiovascular risk factors in Mexico and the United States: A comparative cross-sectional study between the HABLE and MHAS participants

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Abstract

Introduction: *In the United States, information on the Mexican-American population is available through the Health and Aging Brain among Latino Elders (HABLE) study; in Mexico, the results of the Mexican Health and Aging Study (MHAS) are available.* **Objective:** *To compare the prevalence of cardiovascular risk factors between men and women of the HABLE and MHAS studies.* **Method:** *The prevalence of hypertension, diabetes, hypercholesterolemia and abdominal obesity was transversely analyzed in 559 HABLE participants and compared with data from 13,663 MHAS participants. The comparison was made using Student's t-test and the chi-square test, according to the type of variable.* **Results:** *The analysis showed that the prevalence of hypertension (50 %, 95 % CI = 41.8-51.8), diabetes (35.5 %, 95 % CI = 27.6-43.8) and abdominal obesity (59.3 %, 95 % CI = 50.5-68.1) were significantly higher in HABLE males, whereas females had a higher prevalence of diabetes (36.8 %, 95 % CI = 32.2-41.5) and abdominal obesity (89.6 %, 95 % CI = 86.6-92.5). Hypercholesterolemia had a higher prevalence in MHAS females (53.3 %, 95 % CI = 50.3-56.2).* **Conclusion:** *The prevalence of cardiovascular risk factors was higher in Mexican-American HABLE participants, than in Mexican MHAS participants.*

KEY WORDS: *Cardiovascular disease. Risk factors. Mexico. Mexican-Americans.*

Factores de riesgo cardiovascular en Estados Unidos y México: comparación de los estudios HABLE y ENASEM

Resumen

Introducción: *En Estados Unidos se dispone de información acerca de la población mexicoamericana por el Estudio de Salud y Envejecimiento del Cerebro en Latinos Mayores (HABLE); en México se dispone de los resultados del Estudio Nacional de Salud y Envejecimiento en México (ENASEM).* **Objetivo:** *Comparar la prevalencia de factores de riesgo cardiovascular entre hombres y mujeres de HABLE y ENASEM.* **Método:** *Se analizó transversalmente la prevalencia de hipertensión, diabetes, hipercolesterolemia y obesidad abdominal en 559 participantes de HABLE y se comparó con datos de 13 663 participantes del ENASEM. La comparación se realizó mediante t de Student y chi cuadrada, según el tipo de variable.* **Resultados:** *El análisis demostró que la prevalencia de hipertensión (50 %, IC 95 % = 41.8-51.8), diabetes (35.5 %, IC 95 % = 27.6-43.8) y obesidad abdominal (59.3 %, IC 95 % = 50.5-68.1) fueron significativamente mayores en hombres del HABLE, mientras que las mujeres presentaron una prevalencia más elevada de diabetes (36.8 %, IC 95 % = 32.2-41.5) y obesidad abdominal (89.6 %, IC 95 % = 86.6-92.5). La hipercolesterolemia tuvo una prevalencia más elevada en mujeres del ENASEM (53.3 %, IC 95 % = 50.3-56.2).* **Conclusión:** *La prevalencia de factores de riesgo cardiovascular fue mayor en mexicoamericanos participantes del HABLE, que en mexicanos participantes del ENASEM.*

PALABRAS CLAVE: *Enfermedad cardiovascular. Factores de riesgo. México. Mexicoamericanos.*

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Introduction

In the United States, the main causes of death are heart conditions, cancer and unintentional injuries.[1] In Mexican-Americans, which constitute 63.4 % of Latinos in that country,[2] cancer is the leading cause, followed by heart conditions and unintentional injuries.[3] Data from the National Institute of Statistics and Geography of Mexico (INEGI – *Instituto Nacional de Estadística y Geografía*) show that heart conditions, diabetes and cancer are the top three causes of death in Mexico.[4] Since several years ago, the World Health Organization has determined that approximately 31 % of all recorded deaths are due to cardiovascular diseases, which constitute the leading cause of death worldwide.[5]

Due to the increase in life expectancy at birth, a larger percentage of people age and develop cardiovascular diseases,[6] but there are several risk factors such as systemic arterial hypertension, diabetes mellitus, dyslipidemias and obesity, which can be measured, modified or controlled.[7] Studies conducted in Mexican-Americans (subjects born in Mexico living in the United States and subjects of Mexican ancestry born in the United States), such as the San Antonio Heart Study or the Hispanic Community Health Study/Study of Latinos, have demonstrated that the prevalence of cardiovascular risk factors (CVRF) is higher in Mexican-Americans than in non-Hispanic whites.[8,9]

In Mexico, the 2012 National Health and Nutrition Survey reported an elevated prevalence of CVRF in the general population,[10] which is consistent with the results of the CARMELA trial[11] and of the study carried out by Orozco González et al. in a sample of health workers in two hospitals of the Mexican Institute of Social Security.[12]

Several researchers have suggested that the years of residence in the United States, the language spoken at home and other behavioral changes negatively impact Mexican-Americans lifestyle, and place this population at higher risk of developing CVRF.[13,14] However, due to methodological limitations and inconsistency in the methods used to quantify these variables, data are contradictory.

In the present analysis, we compare the prevalence of CVRF in a sample of Mexican-Americans residing in the United States, part of the Health and Aging Brain among Elderly Latinos (HABLE) study, with a sample of the Mexican Health and Aging Study (MHAS). The hypothesis was that Mexican-Americans have a higher prevalence of cardiovascular risk factors than their Mexican counterparts. Understanding the similarities and differences in the distribution of these risk factors on both sides of the border is important in order to develop and implement effective prevention measures.

Method

Epidemiological, descriptive, cross-sectional study of two populations taken from two longitudinal studies: HABLE in the United States and MHAS in Mexico. HABLE analyzes the relationship of different biological factors and diseases such as diabetes, hypertension, depression, etc., with changes in memory, knowledge and aging in Mexican-Americans and non-Hispanic whites. HABLE has been ongoing since 2012 at the Health Science Center of the University of North Texas, in Fort Worth, Texas; it recruits subjects older than 50 years directly from the community, through community recruiters, presentations, press releases, announcements and word of mouth information. The participants undergo a detailed interview on demographic and health information, neuropsychological assessment tests, fasting blood clinical tests, anthropometric measurements and a medical evaluation.

In turn, MHAS is a national longitudinal study in Mexico that has been ongoing since 2001. The interview and data collection are carried out in people older than 50, from urban and rural areas of the 32 states of the country. This study is a collaboration between the University of Texas Medical Branch in Galveston, Texas, the National Institute of Statistics and Geography and the National Institute of Public Health of Mexico. MHAS is investigating diseases and disability associated with aging and assessing the effects of individual behavior, migration, socioeconomic status and community health characteristics.[15] The MHAS questionnaire includes information on demographic data, general health status, chronic conditions, socioeconomic status, migration, family structure and housing condition. Anthropomorphic measurements, blood tests and neuropsychological tests were carried out in a subsample of participants.[16]

Both investigations adhered to the relevant ethical conditions for research in human beings and were approved by the corresponding ethics committee. All participants signed an informed consent form.

Between May 2012 and June 2015, 771 participants were admitted to the HABLE study, out of

Table 1. Demographic characteristics according to gender

	Men				Women			
	HABLE (n = 138)		MHAS (n = 5786)		HABLE (n = 421)		MHAS (n = 7877)	
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	
Age (years)	63.9 ± 8.3		68.2 ± 15.5		60.4 ± 8.2		67.0 ± 17.8	
Education (years)	7.7 ± 4.8		6.1 ± 5.8		7.7 ± 4.2		5.2 ± 5.1	
Marital status married	n	%	n	%	n	%	n	%
Yes	103	74.6	4580	87.8	202	48.2	4323	72.6
No	33	25.4	636	12.2	217	51.8	1630	27.4

HABLE = Health & Aging Brain among Latino Elders, MHAS = Mexican Health and Aging Study.

Table 2. Prevalence of cardiovascular risk factors for the male gender

	HABLE			MHAS			p*
	n	%	95 % CI	n	%	95 % CI	
Hypertension	138	50.0	41.8-51.8	5786	41.2	39.9-42.4	0.03
Diabetes	138	35.5	27.6-43.8	5786	22.4	21.2-23.4	0.0003
Hypercholesterolemia	138	34.8	26.7-42.8	770	40.6	37.1-44.1	0.2
Abdominal obesity	138	59.3	50.5-68.1	767	37.9	34.5-41.3	< 0.0001

*Chi-square test. HABLE = Health & Aging Brain among Latino Elders, MHAS = Mexican Health and Aging Study.

Table 3. Prevalence of cardiovascular risk factors for the female gender

	HABLE			MHAS			p*
	n	%	95 % CI	n	%	95 % CI	
Hypertension	421	50.6	45.9-55.5	7877	54.3	53.2-55.4	0.1
Diabetes	421	36.8	32.2-41.5	7877	27.5	26.5-28.4	< 0.0001
Hypercholesterolemia	421	45.8	41.0-50.6	1083	53.3	50.3-56.2	0.009
Abdominal obesity	421	89.6	86.6-92.5	1112	77.0	74.5-79.4	< 0.0001

*Chi-square test. HABLE = Health & Aging Brain among Latino Elders, MHAS = Mexican Health and Aging Study.

which 559 were of Mexican origin (138 men and 421 women), residents of the Dallas-Fort Worth, Texas area; their data were used for the analysis. The age range was 50 to 85 years. For the analysis of the Mexican population, the free database of the third MHAS 2012 round was accessed.[17] During this round, 18,465 interviews were conducted. Final analysis on diabetes and hypertension was carried out in 13,663 participants (5,786 men and 7,877 women) and total cholesterol and abdominal obesity analysis was conducted in a subsample of 1,882 participants (1,112 women). The age range was 50 to 110 years.

The diagnosis of hypertension and diabetes mellitus was imputed based on previous medical diagnosis self-report or on the use of medications for these two pathologies. According to established standards, high cholesterol levels were considered at values > 200 mg/dL and abdominal obesity as a waist circumference > 40 inches in men and > 35 inches in women.

Statistical analysis

A descriptive analysis of all study variables was carried out. Demographic characteristics are presented as the mean ± standard deviation for continuous variables and as frequency and percentage for categorical variables. The prevalence of CVRF was established. Prevalence is reported in percentages with a 95 % confidence interval. The comparison between groups was made using Student's t-test for continuous variables and the chi-square test for categorical variables.

The analysis was divided by gender. A p-value ≤ 0.05 was considered significant. The SPSS statistical program for Windows, version 23 (SPSSW Inc., Chicago, IL), was used for the analysis.

Results

MHAS men and women had a higher mean age than the participants of the HABLE study (68.2 and 67.0, respectively) (Table 1). HABLE participants had a higher level of education, with a mean of 7.7 years both in men and women. Eighty-eight and 75 % of men in MHAS and HABLE reported being married; in women, the difference was larger: 73 % *versus* 48 %, in MHAS and HABLE, respectively. It should be noted that all differences between the samples were statistically significant (p ≤ 0.05).

The prevalence of CVRF in men is shown in Table 2. The prevalence of hypertension was 50 % (95 % CI = 41.8-51.8), of diabetes 35.5 % (95 % CI = 27.6-43.8) and of abdominal obesity 59.3 % (95 % CI = 50.5-68.1), with the analysis showing that the prevalence of these conditions in HABLE men was significantly higher than in MHAS males. As for hypercholesterolemia, the difference between men in both studies was not statistically significant (p = 0.2).

The prevalence of diabetes and abdominal obesity was also significantly higher in HABLE women, with 36.8 % (95 % CI = 32.2-41.5) and 89.6 % (95 % CI = 86.6-92.5), respectively, in comparison with their MHAS counterpart (Table 3). As for hypercholesterolemia, the prevalence was significantly higher in MHAS women, with 53.3 % (95 % CI = 50.3-56.2). The difference in the prevalence of hypertension between women in both studies was not statistically significant (p = 0.1).

Discussion

The results of our study suggest that MHAS participants have a lower prevalence of CVRF than HABLE participants. HABLE men had a higher prevalence of hypertension, diabetes and abdominal obesity than MHAS men. Among women, the percentage with diabetes and abdominal obesity was also higher in HABLE in comparison with the MHAS participants. The results were not modified when level of education and marital status were included in the models.

Not all risk factors were higher in women in the United States study. The percentage of women with high cholesterol levels was higher in MHAS women; the explanation for this could lie in the type of diet or in the level of physical activity. This is consistent with studies that suggest that Latinos with low levels of acculturation in the United States are at higher risk for poorly controlled hypercholesterolemia,[18] and it has even been suggested that the only CVRF that improves with high degrees of acculturation is dyslipidemia.[19] In any case, more detailed research is required in order to elucidate these findings.

The results of our study are consistent with those of other authors, who suggest that Mexicans residing in Mexico are at lower risk for developing CVRF than those living in the United States and their descendants.[20,21] Although the findings of several analyses have been contradictory, in general, attempts have been made to relate them to the degree of acculturation. Acculturation is defined as the process whereby immigrants adopt the culture, beliefs and practices of the place they reside in.[22] It has been suggested that the higher the degree of acculturation, the higher the risk for developing CVRF. The explanation might be that these subjects adopt less healthy behaviors,[23] as well as the high levels of psychological stress associated with immigration.[24] It has even been observed that Mexicans living near the US border have a higher risk of mortality associated with cardiovascular problems when compared with inhabitants of other regions of Mexico,[25] possibly due to the proximity and influence of the culture on the other side of the border.

There are several limitations in this study: due to its cross-sectional design, it is not possible to assess the effect that diet, physical activity, and stress exert on the prevalence of CVRF; the diagnosis of diabetes and hypertension relied on participants' self-report, which could have caused an underestimation of the prevalence of these factors; in addition, the analyses were not controlled for other confounding variables such as socioeconomic status, access to health services or use of medications, which might have an important effect on the prevalence of CVRF. Some of the strengths of this study include the similarity between both samples: both included community-dwelling subjects who were randomly selected.

Conclusions

Our study contributes to the scarce literature on the prevalence of cardiovascular risk factors on both sides of the border. Our analysis suggests that the prevalence of CVRF was higher in Mexican-Americans enrolled in the HABLE study, than in Mexicans participating in the MHAS study. New studies are needed in order to investigate cardiovascular

problems in Mexicans from both countries, using representative samples and with similar demographic and socioeconomic characteristics. A better insight on these cardiovascular risk factors should lead to the design of interventions aimed at preventing and counteracting the effect these factors have on the health of Mexicans and Mexican-Americans.

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Conflict of interests

The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Agreement analysis of three mandibular third molar retention classifications

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Abstract

Introduction: *Pell & Gregory and Winter classifications are basic in third molar categorization; Sánchez-Torres classification is used in Mexico, but it has not been previously evaluated.* **Objective:** *To assess the degree of agreement in the radiographic evaluation of impacted mandibular third molar with the use of three classifications: Pell & Gregory, Winter and Sánchez-Torres.* **Method:** *Observational, descriptive, inter-observer degree of agreement study that included 10 oral and maxillofacial surgeons and 10 training residents, who recorded the radiographic categorization of third mandibular molars (left and right) according to Pell & Gregory, Sánchez-Torres and Winter classifications. Inter-observer degree of agreement was assessed with Fleiss' kappa.* **Results:** *Pell & Gregory classification had the lowest degree of agreement (kappa = 0.05 and 0.185), followed by Sánchez-Torres classification (kappa = 0.125 and 0.326); the best value was obtained by the Winter classification, with kappa = 0.28 and 0.636 for oral and maxillofacial surgeons and training residents, respectively.* **Conclusion:** *The Winter classification showed an acceptable (moderate) degree of agreement to classify mandibular third molars by training residents.*

KEY WORDS: *Third molar. Exeresis of retained teeth. Pell & Gregory classification. Winter classification. Sánchez-Torres classification.*

Análisis de concordancia de tres clasificaciones de terceros molares mandibulares retenidos

Resumen

Introducción: *Las clasificaciones de Pell y Gregory y de Winter son básicas en la categorización de terceros molares; la clasificación de Sánchez Torres es usada en México, pero no había sido evaluada previamente.* **Objetivo:** *Evaluar el grado de acuerdo en la valoración radiográfica de terceros molares mandibulares impactados, con el empleo de tres clasificaciones: Pell y Gregory, Winter y Sánchez Torres.* **Método:** *Estudio observacional, descriptivo, de concordancia interobservador, que incluyó a 10 cirujanos orales y maxilofaciales y 10 residentes en formación, quienes registraron la categorización radiográfica de terceros molares mandibulares (izquierdos y derechos) de acuerdo con las clasificaciones de Pell y Gregory, Sánchez Torres y Winter. Se evaluó el grado de acuerdo entre observadores mediante la prueba de kappa de Fleiss.* **Resultados:** *La clasificación de Pell y Gregory obtuvo el menor grado de acuerdo (kappa = 0.05 y 0.185), seguida de la clasificación de Sánchez Torres (kappa = 0.125 y 0.326); el mejor valor lo obtuvo la clasificación de Winter, con kappa = 0.28 y 0.636 para cirujanos orales y maxilofaciales y residentes en formación, respectivamente.* **Conclusión:** *La clasificación de Winter mostró un grado de acuerdo aceptable (moderado) para categorizar terceros molares mandibulares en los residentes en formación.*

PALABRAS CLAVE: *Tercer molar. Exéresis dental. Clasificación de Pell y Gregory. Clasificación de Winter. Clasificación de Sánchez-Torres.*

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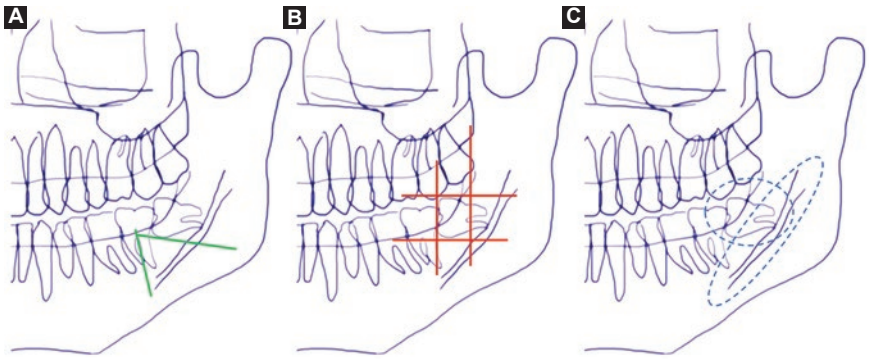

Figure 1. *Schematic representation of the most common mandibular third molar classifications.* **A:** *Winter classification, based on the position of the third molar in relation to the longitudinal axis of the second molar.* **B:** *Pell & Gregory's classification, based on depth in relation to the occlusal plane of the second lower molar and the mesiodistal diameter of the impacted tooth, according to the distance between the second inferior molar and the anterior part of the mandibular ramus.* **C:** *Sánchez-Torres classification, based on three fundamental factors: depth and direction of the third molar, and number, direction and shape of the roots, as well as on two complementary factors: relationship with the inferior dental canal and relationship with the second molar.*

Introduction

Exeresis of retained dental pieces is one of the most recurrent practices in oral and maxillofacial surgery,[1] especially of mandibular third molars, which are of the dental pieces with the highest rate of impaction.[2] The indications for dental extraction are varied and are related to the position, shape and pathologies associated with each dental piece.[3] Third molar anatomical features include multi-cusp, conical or square crowns, among others. In addition, root fusions, multiple roots, supernumerary roots and root dwarfism or gigantism are sometimes observed.[4]

Mandibular third molars anatomical disposition is practically unpredictable,[5] and a correct diagnosis is therefore necessary for surgical management, prevention of complications and postoperative management. Radiographic study is essential, since identifying the point of least resistance is necessary in order to overcome the root anchoring in the alveolar bone with surgical maneuvers.[6]

Third molars have been radiographically classified according to their position with regard to the second molar and the mandibular branch. According to Pell & Gregory, third molars can be categorized as level A, B or C according to their depth with regard to the occlusal plane, and as class I, II or III according to the available space (with regard to the ascending mandibular branch and the adjacent second molar).[7] The position in space has been classified according to Winter in four inclination categories with regard to third molar longitudinal axis.[8] Finally, Sánchez-Torres developed a classification based on third molar depth and direction, number, direction and shape of the roots and on complementary considerations such as the relationship with the inferior dental canal and the relationship with the second molar. This classification, which is less known than the previous ones and has not been previously assessed,[9] considers a larger number of elements.

Table 1. **Interpretation of the kappa values**

Kappa value	Strength of agreement
< 0.000	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Perfect

In the clinical, medical-legal and research fields, it is important for the same perception of a problem to be established for different observers. In the process of third molar categorization, Pell & Gregory and Winter classifications are basic; the one by Sánchez Torres is a method that is used in Mexico.[10] The purpose of this study was to assess the degree of agreement in the assessment of third molars according to these three classifications (Fig. 1), between a group of certified oral and maxillofacial surgeons and training residents.

Method

The study was conducted at the Oral Surgery Clinic of the Faculty of Stomatology of the Autonomous University of San Luis Potosí, in Mexico. Panoramic digital

Table 2. Kappa values per group

Group	Classification	Fleiss' Kappa	p
MFS	Sánchez-Torres	0.125*	0.000**
MFS	Sánchez-Torres (radicular component)	0.105*	< 0.001**
MFC	Pell & Gregory	0.05*	0.0017**
MFC	Winter	0.28*	0.000**
Residents	Sánchez-Torres	0.326*	0.000**
Residents	Sánchez-Torres (radicular component)	0.338*	< 0.001**
Residents	Pell & Gregory	0.185*	0.0017**
Residents	Winter	0.636*	0**

*Kappa value. **Significance value. MFC = maxillofacial surgeons.

radiographs of patients who attended the clinic were used; the study was submitted for approval by the Institutional Ethics Committee (CEI-FE-012018232072). The radiographs were only identified by age and gender of the patient they belonged to. The raters were 10 oral and maxillofacial surgeons and 10 residents of that specialty at the Ignacio Morones Prieto Central Hospital of San Luis Potosí, Mexico.

The 20 observers recorded the classification of the left and right mandibular molars according to Pell & Gregory, Winter and Sánchez-Torres classifications. Each observer assessed 20 radiographs (10 left and 10 right third molars). Prior to the assessment, all of them were provided with a manual with the characteristics to be considered for each classification, in order for criteria to be standardized. The radiographs were randomly shown in digital images with sufficient sharpness and contrast. Data were recorded on collection sheets.

Statistical analysis was carried out with the R program, version 3.4, using the "irr" package. An agreement analysis was performed using Fleiss' kappa for multiple raters. The significance of the test was determined at $p < 0.05$; interpretation of the kappa values (Table 1) was based on the table reported by Posner.[11]

Results

The results on the degrees of agreement can be observed in Table 2, which shows that the classification with the lowest degree of agreement was that of Pell & Gregory, while Sánchez-Torres instrument had a slight degree of agreement for maxillofacial surgeons and a fair degree of agreement for residents. Sánchez-Torres classification had a similar degree of agreement in its coronal and spatial, as well as in the radicular anatomical components, which demonstrates that both maxillofacial surgeons and residents have a sound command of this instrument. Finally, the Winter classification showed the highest degree of agreement in both groups of observers.

Discussion

There is a reasonable justification for the need to group "objects" with similar characteristics in order to distinguish complex from simple entities. In medicine, diagnosis is an important classification process.[12] A classification determines the response or reaction to an object or group of objects whose boundaries are clearly defined.[12] There are multiple classifications for third molars, and the preference for using one or another lies with the surgeon's criteria and not with numerical parameters of its usefulness; there is no national or international standard, and most classifications have not been validated.

Routine dental procedures, such as fillings, endodontics or oral surgery, among others, are selected based on the severity, risks, anatomical characteristics and conditions of the patient. In these clinical scenarios, it is essential to correctly classify the pathological entity in order to reduce or prevent possible complications, as well as to select the most appropriate therapeutic approach for each patient. If the classification method lacks the capability to allow common agreement between observers, clinical procedures become difficult and hard to accomplish.

In addition to the usual clinical settings, a correct classification is vital for clinical research. Historically, Winter and Pell & Gregory classifications have been used for different research designs around third molar surgery. Currently, they continue to be used to define selection criteria;[13] however, other studies have focused on classifying patients only based on the degree of impaction of the third molar,[14] which is related to the degree of bone resorption, especially in studies that have used the dental impaction pain model.[15]

Lack of agreement can lead to legal controversies; for example, injury to the inferior alveolar nerve is one of the complications most commonly associated with discomfort and legal actions by the patient.[16] For this reason, it is relevant for the degree of agreement on the interpretation of the classifications that are most commonly used by oral and maxillofacial surgeons to be determined.

Another aspect in the development of new scales and evaluation and classification instruments is that they

require an adequate validation and reliability evaluation process. The validity of a diagnostic test is determined by the sensitivity, specificity and positive and negative predictive value of the test, which should ideally have values higher than or equal to 80 % and that have the disadvantage of requiring a gold standard, which in third molar classifications does not exist.[17] In turn, reliability refers to the degree at which similar results would be obtained after applying the measurement process more than once.[18]

With regard to dental retention, current classification systems are based on clinical and radiographic parameters[16,19,20] to assess third molar position; however, they have been accepted without prior validation.[21] Several studies have been found in the literature that estimate the degree of agreement of the Winter and Pell & Gregory classifications; in the present work, it is interesting to observe the poor level agreement with the Pell & Gregory classification (Table 2), which is accepted as standard in the classification of mandibular third molars. These results are consistent with those obtained by García et al.[17] and Lima et al.,[22] who demonstrate that there is no reliability and validity in the classification criteria, since there are countless combinations between positions and classes, which makes categorization difficult.

Since 2000, García et al.[17] reported that Pell & Gregory classification is not useful for predicting the degree of surgical difficulty; in addition, it has been pointed out that it implies vast knowledge on the surgical technique[23] and that its poor degree of agreement between observers is driven by its large number of categories;[22] in addition, much of its variability is due to the subjective interpretation by the observer to determine which criterion to apply for each case.[21]

On the other hand, the results in the Winter classification show a substantially higher degree of agreement between training residents (kappa = 0.636) than between maxillofacial surgeons (kappa = 0.28), which are similar findings to those reported in 2012 by Lima et al.,[22] who indicated a degree of agreement higher than 78 %. It could be assumed that such degree of agreement is mainly due to the fact that only one anatomical characteristic of third molars is taken into account (direction of the piece), in comparison with the other variables used in the studied classifications, which is a fact that was confirmed by Almendros Marqués et al.[21]

To the best of our knowledge, the degree of agreement of the Sánchez-Torres classification has not been reported. This classification is thoroughgoing and at the same time complex, since it considers a large number of conditions. Nevertheless, unlike Pell & Gregory's classification, it obtained a higher score (kappa = 0.12 and 0.32 in maxillofacial surgeons and in residents Table 2). This result might be due to the fact that Sánchez-Torres' classification is more commonly used in Mexico, particularly in the training center where the study was carried out, although this does not clarify its relevance as a possible classification method.

This research had the following limitations: only one group of experts trained in the same surgical school was included; the kappa value showed a gradual and considerable decrease with the growing number of classification categories,[24] which was reflected in low levels of agreement. In addition, in this type of study, observers may be concordantly wrong, even if it is at low levels.

The conduction of future research in order to validate these classifications is suggested and, to the extent possible, new methods should be defined, such as the one proposed by Juodzbalys and Daugela,[25] based on parameters related to the surgical setting and that follow a validation process[26] to confirm their usefulness, or based on data obtained from systematic reviews and meta-analyses, to ensure that they are efficient and relevant both in theory and in the clinical practice of one of the most common procedures in maxillofacial surgery.

Conclusion

Pell & Gregory's classification had the lowest degree of agreement, followed by Sánchez-Torres' instrument; the Winter classification was shown to have higher capability for agreement between oral and maxillofacial surgeons, as well as between training residents.

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ORIGINAL ARTICLE

Intense craving for appetizing foods: validation and standardization of the Food Cravings Questionnaire-Trait in Mexico

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Abstract

Introduction: *Food craving is a motivational and physiological response for eating specific foods, mainly with high caloric content. To assess food craving, the Food Cravings Questionnaire-Trait, which is a multi-dimensionally structured instrument that has been validated in several countries and has been shown to be sensitive and adaptable to contextual-cultural changes, is used among others.* **Objectives:** *To validate and standardize the Food Cravings Questionnaire-Trait in adults of Mexico City.* **Method:** *Non-experimental, cross-sectional, randomized study of 1059 subjects of both genders, between 18 and 84 years of age; 71.86 % of the female gender. Psychometric properties were examined with exploratory and confirmatory factor analyses.* **Results:** *The domains of the questionnaire were reduced and the items were reorganized differently with regard to the original version. The confirmatory factor analysis showed an adequate fit and acceptable standardization of factors. High internal consistency was found for the global questionnaire (α = 0.973 and rho = 0.975) for each one of the domains.* **Conclusion:** *This study determines the viability of the Food Cravings Questionnaire for the population of Mexico City.*

KEY WORDS: *Food Craving. Alimentary behavior. Food Cravings Questionnaire-Trait.*

Deseo intenso por alimentos apetecibles: validación y estandarización del Food Craving Questionnaire-Trait en México

Resumen

Introducción: *El food craving o "ansia por comer" es una respuesta motivacional y fisiológica por comer alimentos específicos, principalmente con alto contenido calórico. Para evaluarlo se usa, entre otros, el Food Craving Questionnaire Trait, estructurado multidimensionalmente y validado en diversos países, el cual ha mostrado ser sensible y adaptable a los cambios contextuales-culturales.* **Objetivos:** *Validar y estandarizar el Food Craving Questionnaire-Trait en adultos de la Ciudad de México.* **Método:** *Estudio no experimental, transversal y aleatorizado de 1059 sujetos de uno y otro sexo, entre 18 y 84 años; 71.86 % del sexo femenino. Se examinaron propiedades psicométricas con análisis factoriales exploratorios y confirmatorios.* **Resultados:** *Se redujeron los factores del cuestionario y los ítems se reorganizaron de forma diferente al original. El análisis factorial confirmatorio mostró ajuste adecuado y estandarización aceptable de los factores. Se encontró alta consistencia interna para el cuestionario global (α = 0.973 y rho = 0.975) para cada uno de los factores.* **Conclusión:** *Este estudio determina la viabilidad del Food Craving Questionnaire para población de la Ciudad de México.*

PALABRAS CLAVE: *Ansia por comer. Conducta alimentaria. Food Craving Questionnaire-Trait.*

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Introduction

The presence of food, the environment,[1] culture and learning are related to the decision on what a subject will eat;[2-4] desire, choice, quantity and frequency are related to the inability to inhibit ingestive behavior. It has been hypothesized that it is related to over-ingestion of foods with high caloric content, a behavior similar to that of addicted subjects.[5]

Food craving (FC) is a physiological and behavioral response[6] that triggers intense desire, very difficult to resist,[7] for eating specific foods,[8] particularly those with high caloric content. Due to its proximity to addiction, FC is described as a comorbid factor of eating disorders, overweight and obesity.[6,9,10]

Cepeda Benito, Gleaves, Williams and Erath[11] developed the Food Cravings Questionnaire-Trait (FCQ-T), a multifactorial questionnaire that encompasses behavioral, cognitive, emotional and physiological components, with α = 0.97, composed of nine factors:

- An intention and planning to consume food.
- Anticipation of positive reinforcement that may result from eating.
- Anticipation of relief from negative states and feelings as a result of eating.
- Possible lack of control over eating if food is eaten.
- Thoughts or preoccupation with food.
- Craving as a physiological state.
- Emotions that may be experienced before or during food cravings or eating.
- Environmental cues that may trigger food cravings.
- Guilt that may be experienced as a result of cravings and/or giving into them.

It consists of 37 items, where the frequency the "craving" occurs with is shown, as determined with a Likert scale: never (1), rarely (2), sometimes (3), often (4), almost always (5) and always (6).

Avitia et al.[12] used the original versions of the FCQ-T and Food Cravings-State to measure it in the Mexican population; however, they were not validated, in addition to not explaining the application procedure. Therefore, the results of that research are questionable.

Due to the combined prevalence of overweight and obesity in Mexico and given that FC is an important component of addiction to sugary and fatty foods, it is imperative to assess it in the Mexican population. The purpose of this work was to validate and standardize the FCQ-T in Mexico City adult subjects.

Method

Non-experimental, cross-sectional and randomized study of 1059 adults attending the jurisdictions of the Ministry of Health of Mexico City, who were between 18 and 83 years of age and who read and signed the informed consent. The FCQ-T was used in the Spanish version, and the R Statistical Software, version 3.4.4, was used for statistical analysis.

A pilot test was conducted at the Lázaro Cárdenas Unit of the National Polytechnic Institute, with a convenience sample of 50 subjects, who were asked to comment on the wording. Reliability analysis was performed, the wording was adapted to Mexican regionalisms and another group was asked to answer the revised questionnaire. Subsequently, the Miguel Hidalgo, Azcapotzalco, Cuauhtémoc and Álvaro Obregón jurisdictions of the Ministry of Health of Mexico City were randomized and the questionnaire was applied to 1059 adults of either gender, who attended medical appointments; they were asked to voluntarily participate and to sign the informed consent.

Statistical analyses were carried out with R Statistical Software, version 3.4.4 (R psych1[3] and lavaan packages),[14] looking for significance at $p < 0.05$.

FCQ-T validity was verified by exploratory and confirmatory factor analyses. Item normality was considered acceptable for asymmetric values between -0.5 and 0.5, and kurtosis between -2 and 2. We used the Kaiser-Meyer-Olkin value and Bartlett's test of sphericity for adequacy of data for the factor analysis; Kaiser-Meyer-Olkin values < 0.6 indicated inadequate sampling.[15] Exploratory factor analysis with Promax oblique rotation was applied. To create an FCQ-T property, items were extracted for each factor if they were loaded at $\geq$ 0.35 in a particular factor, but $\geq$ 0.35 in the others.

Subsequently, in the confirmatory factor analysis model, the robust maximum likelihood estimator was used, which provides standard errors/robust adjustment indices in the nature of the Likert scale items and non-normality.

To assess that the model would fit, the comparative fit index (CFI), the Tucker-Lewis index (TLI), the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA) were used.

Table 1. **Exploratory and confirmatory factor analysis**

Factors and items	EFA				CFA	
	ARE	PR	LC	PE	SFL	95% CI
Factor 1. Anticipation and reinforcement for eating						
17. *Cuando como algo que deseo con intensidad me siento culpable* (When I eat what I am craving I feel guilty about myself)	0.454	0.176	0.004	0.217	0.694	0.642-0.747
20. *Siento deseos de comer cuando estoy aburrido (a), enfadado (a), o triste* (I crave foods when I feel bored, angry, or sad)	0.587	0.054	0.116	0.077	0.725	0.681-0.768
21. *Después de comer no tengo tanta ansiedad* (I feel less anxious after I eat)	0.573	-0.126	0.176	0.204	0.687	0.640-0.735
25. *No tengo la fuerza de voluntad de resistir mis deseos de comer lo que se me antoja* (I have no will power to resist my food crave)	0.544	0.174	0.278	-0.207	0.718	0.817-0.876
26. *Una vez que me pongo a comer algo tengo problemas para dejar de hacerlo* (Once I start eating, I have trouble stopping)	0.767	0.168	-0.025	-0.027	0.847	0.817-0.876
27. *Por mucho que lo intento, no puedo parar de pensar en comer* (I can't stop thinking about eating no matter how hard I try)	0.883	0.042	-0.143	0.088	0.859	0.831-0.887
28. *Gasto demasiado tiempo pensando en lo próximo que voy a comer* (I spend a lot of time thinking about whatever it is I will eat next)	0.860	0.015	-0.194	0.151	0.815	0.755-0.854
29. *Si me dejo llevar por la tentación de comer, pierdo todo el control* (If I give in to a food craving, all control is lost)	0.937	0.065	-0.175	0.022	0.869	0.840-0.897
30. *A veces me doy cuenta de que estoy soñando despierto y estoy fantaseando con comer* (I daydream about food)	0.865	-0.008	-0.180	0.154	0.813	0.774-0.853
31. *Cada vez que se antoja una comida sigo pensando en comer hasta que como lo que se me antojó* (Whenever I have a food craving, I keep on thinking about eating until I actually eat the food)	0.794	-0.012	0.056	0.027	0.827	0.792-0.862
32. *Cuando tengo muchas ganas de comer algo estoy obsesionado con comer lo que deseo* (If I am craving something, thoughts of eating it consume me)	0.799	-0.008	0.024	0.037	0.820	0.783-0.858
33. *A menudo deseo comer cuando siento emociones fuertes* (My emotions often make me want to eat)	0.828	-0.011	-0.037	0.059	0.812	0.775-0.848
34. *Cada vez que voy a un banquete termino comiendo más de lo que necesito* (Whenever I go to a buffet, I end up eating more than what I needed)	0.626	0.060	0.303	-0.192	0.745	0.706-0.784
35. *Para mí es difícil resistir la tentación de tomar comidas apetecibles que están a mi alcance* (It is hard for me to resist the temptation to eat appetizing foods that are in my reach)	0.621	0.138	0.283	-0.205	0.779	0.743-0.815
36. *Cuando estoy con alguien que se excede comiendo, yo también me excedo* (When I am with someone who is overeating, I usually overeat too)	0.747	0.090	0.108	-0.103	0.809	0.773-0.844
Factor 2. Loss of control						
1. *Cuando estoy con alguien que está comiendo me da hambre* (Being with someone who is eating often makes me hungry)	-0.099	0.622	0.277	-0.046	0.649	0.600-0.697
2. *Cuando tengo deseos intensos de comer, una vez que lo hago no puedo parar* (When I crave something, I know I won't be able to stop eating once I start)	0.151	0.758	-0.029	-0.071	0.782	0.764-0.834
3. *A veces, cuando como lo que se me antoja, pierdo el control y como demasiado* (If I eat what I am craving, I often lose control and eat too much)	0.109	0.726	0.093	-0.073	0.799	0.764-0.834
4. *Detesto no poder resistir la tentación de comer* (I hate it when I give into cravings)	0.127	0.747	0.035	-0.066	0.798	0.761-0.835
5. *Sin duda alguna, las ganas de comer me hacen pensar en cómo voy a conseguir lo que quiero comer* (Food cravings invariably make me think of ways to get what I want to eat)	0.028	0.736	0.001	0.102	0.778	0.739-0.817

(Continued)

Table 1. **Exploratory and confirmatory factor analysis *(Continued)***

Factors and items	EFA				CFA	
	ARE	PR	LC	PE	SFL	95% CI
Factor 2. Loss of control						
6. *No hago más que pensar en la comida* (I feel like I have food on my mind all the time)	-0.045	0.675	0.138	0.112	0.753	0.712-0.794
7. *A menudo me siento culpable cuando deseo ciertas comidas* (I often feel guilty for craving certain foods)	0.110	0.710	-0.074	0.101	0.765	0.721-0.808
8. *A veces me encuentro pensativo preocupado con comida* (I find myself preoccupied with food)	0.283	0.620	-0.208	0.205	0.802	0.761-0.842
Factor 3. Physiological response						
11. *Se me hace agua la boca cuando pienso en mis comidas favoritas* (Thinking about my favorite food makes my mouth water)	-0.226	0.322	0.635	0.085	0.621	0.578-0.665
12. *Siento deseos intensos de comer cuando mi estómago está vacío* (I crave foods when my stomach is empty)	-0.179	0.102	0.826	0.030	0.671	0.632-0.710
13. *Siento que mi cuerpo me pidiera ciertas comidas* (I feel as if my body asks me for certain food)	0.119	0.159	0.497	0.088	0.724	0.680-0.768
14. *Me da tanta hambre que mi estómago se siente como un pozo sin fondo* (I get so hungry that my stomach seems like a bottomless pit)	0.202	0.219	0.366	0.080	0.711	0.667-0.754
15. *Cuando como lo que deseo, me siento mejor* (Eating what I crave makes me feel better)	-0.224	-0.050	0.748	0.365	0.695	0.657-0.733
18. *Cada vez que deseo comer algo en particular, me pongo a hacer planes para comer* (Whenever I have cravings, I find myself making plans to eat)	0.301	0.059	0.353	0.174	0.734	0.695-0.773
19. *El comer me tranquiliza* (Eating calms me down)	0.208	-0.216	0.357	0.578	0.734	0.695-0.772
22. *Si tengo la comida que deseo, no puedo resistir la tentación de comerla* (If I get what I am craving I cannot stop myself from eating it)	0.310	-0.001	0.626	-0.081	0.770	0.736-0.803
23. *Cuando se me antoja una comida, normalmente intento comerla tan pronto como pueda* (When I crave certain foods, I usually try to eat them as soon as I can)	0.399	-0.048	0.554	-0.030	0.786	0.755-0.817
24. *Comer lo que me apetece mucho me sienta estupendamente* (When I eat what I crave I feel great)	0.099	-0.170	0.719	0.192	0.740	0.706-0.774
Factor 4. Positive emotions						
9. *Como para sentirme mejor* (I eat to feel better)	0.014	0.365	-0.073	0.657	0.779	0.733-0.824
10. *Algunas veces, mi vida parece perfecta cuando como lo que me apetece* (Sometimes, eating make things seem just perfect)	-0.197	0.365	0.218	0.596	0.718	0.673-0.764
16. *Cuando como lo que deseo me siento menos deprimido* (When I satisfy a craving, I feel less depressed)	0.343	0.029	0.133	0.460	0.802	0.768-0.836
37. *Comer me alivia* (When I eat food, I feel comforted)	0.228	-0.192	0.207	0.638	0.716	0.672-0.761

EFA=exploratory factor analysis, CFA=confirmatory factor analysis, ARE=anticipation and reinforcement for eating, LC=loss of control, PR=physiological response, PE=positive emotions, SFL=standardized factor loading, CI=confidence interval.

Values between 0.90 and 0.95 are considered adequate for CFI and TLI and between 0.06-0.08 for RMSEA and SRMR, while values > 0.95 were considered excellent for CFI and TLI, as values < 0.06 were for RMSEA and SRMR.

Finally, the regression method was used to extract factor scores and score descriptive statistics and reliability indices (Cronbach's α and Dillon-Goldstein's rho coefficients) from each factor that makes up the instrument. A coefficient value > 0.80 indicates a high level of internal consistency. The relationship between

Table 2. **Estimated goodness of fitness model statistics**

χ^2	df	p	CFI	TLI	RMSEA	SRMR
2588.959	623	0.0001	0.889	0.882	0.055	0.051

χ^2=chi-square test for exact fit. EFA=exploratory factor analysis, CFA=confirmatory factor analysis, df=degrees of freedom, CFI=comparative fit index, TLI=Tucker-Lewis index, RMSEA=root mean square error of approximation, SRMR=standardized root mean square residual.

Table 3. Descriptive statistics, internal consistency and correlations between factors

Factors	Descriptive statistics		Internal consistency		Correlations			
	Mean	SD	Cronbach's α	Dillon- Goldstein's rho	ARE	LC	PR	PE
Anticipation and reinforcement for eating	0.000	1.155	0.960	0.965		0.859*	0.854*	0.865*
Loss of control	0.000	1.115	0.920	0.935	0.842-0.874**		0.819*	0.852*
Physiological response	0.000	1.201	0.913	0.929	0.837-0.870**	0.798-0.838**		0.936*
Positive emotions	0.000	1.169	0.838	0.894	0.849-0.879**	0.835-0.868**	0.928-0.943**	

SD=standard deviation; ARE=anticipation and reinforcement for eating; LC=loss of control; PR=physiological response; PE=positive emotions. *Pearson's correlation. **95 % confidence interval.

domains was assessed with Pearson's correlations; if higher than 0.81, it was considered excellent, between 0.61 and 0.80 very good, and between 0.41 and 0.60, good. Of the 1059 participants, 71.86 % (761) were females; mean age was 39.90 ± 14.97 years.

Results

In the factor analysis, a simple adequacy of 0.977 was obtained, and with Bartlett's test of sphericity, χ^2 = 31143.93 and df = 666, with p < 0.0001, which indicates items adequacy for structure detection.

With the Promax analysis, all items obtained weight factors higher than 0.35 and were reorganized differently with regard to the Spanish version, and had therefore the name changed and were redefined as follows (Table 1):

- Factor 1, *anticipation and reinforcement for eating*: thinking frequently about the food that is craved makes remembering and anticipating the pleasant emotions that are generated after eating, which will reinforce the search for food and its consumption.
- Factor 2, *loss of control*: the intense desire to consume the food that generates craving will trigger overeating and cause guilt for giving in to it.
- Factor 3, *physiological response*: craving arises as a physiological response to physical stimuli or evocation of memories related to appetizing food and its consumption.
- Factor 4, *positive emotions*: the consumption of appetizing food is associated with hedonic states that will magnify the feeling of relief and well-being.

The FCQ-T was observed to explain 52.91 % of variance.

The confirmatory factor analysis was performed using the robust maximum likelihood estimator. The goodness of fit statistics and the information criteria of the estimated model are presented in Table 2. The chi-square test was significant and the robust fit indicators were analyzed: RMSEA and SRMR showed excellent goodness of fit in the structural equation model, whereas a poor value was obtained for CFI and TLI.

The confirmatory factor analysis revealed an adequate standardized factor loading (anticipation and reinforcement for eating = 0.687-0.869, loss of control = 0.649-0.802, physiological response = 0.621-0.786, positive emotions = 0.716-0.802) and all standardized factor loading confidence intervals were significant (Table 1).

Table 3 shows the mean and standard deviation of the scores obtained from the factors. A Cronbach's α = 0.973 and Dillon-Goldstein's rho = 0.975 were obtained, indicating that it is reliable, while the values obtained by factors are higher than 0.80. With the confirmatory factor analysis, correlations between all factors were excellent and positive; all correlation coefficient confidence intervals were statistically significant.

Discussion

FCQ-T's reliability was found to be consistent with research conducted in America and Europe (α ≥ 0.90). Regarding the factorial structure, differences were found in the number of total dimensions, as it has occurred in various validations.[16-18]

Structurally, factor reduction and item regrouping were performed: all 37 items that originally made up the Spanish version were preserved,[19] but were regrouped in four factors that were consistent with those subtracted in other studies.[16-18] Item interpretation is influenced by emotional, behavioral, cognitive and contextual-cultural variables, which might explain the rotation of factors.[17]

Interestingly, factor disposition in this study was similar to that of the Cuban validation:[18] in both, the elements that refer to positive reinforcements generated by ingestion are observed in factor 1.

The data obtained in this research show that there are thoughts related to food that cause pleasant emotions, which motivates overeating. The difference lies in certain items: items 17 ("when I eat what I am craving intensely I feel guilty about myself"), 20 ("I crave foods when I feel bored, angry, or sad"), 21 ("I feel less anxious after I eat") and 22 ("if I get what I am craving I cannot stop myself from eating it") are grouped differently in the Cuban version,[18] and in this version they have been included in the first factor, which explains that consumption triggers guilt, boredom, anger or sadness for not being able to resist temptation.

Factor 2 was named loss of control, consistent with the Dutch[16] and the Cuban versions.[18] In the former, items 2 ("when I crave something, I know I won't be able to stop eating once I start") and 3 ("if I eat what I am craving, I often lose control and eat too much") coincided,[16] whereas in the in Cuban version, items 2, 3 and 1 ("being with someone who is eating often makes me hungry")[18] coincide. The other items integrated into this factor explain the intensity of the desire to eat certain type of foods that cause overeating and feelings of guilt. Unlike Rodríguez Martín and Molerio Pérez observations,[18] loss of control is not due to environmental cues but to intrinsic characteristics of the subject that drive him/her to impulsively consume.[19]

Factor 3 was named "physiological response", based on the conditioned response to hunger, such as salivation when remembering food, feeling of "non-satiety", "being dissatisfied" and a feeling of pleasure when eating. Items 11 ("thinking about my favorite food makes my mouth water"), 13 ("I feel as if my body asks me for certain food") and 14 ("I get so hungry that my stomach seems like a bottomless pit") coincide with factor 5 (craving as a physiological state) of the original,[11] the Spanish[20] and the Brazilian versions[21] and in factor 6 (renamed "hunger") of the German version.[17]

The last factor (factor 4) was named "positive emotions", unlike Rodríguez Martín and Molerio Pérez proposal,[18] who explain this factor as "eating to regulate emotions or emotional ingestion". However, both factors only coincide in items 19 ("eating calms me down") and 37 ("When I eat food, I feel comforted"). In the present investigation, the referred items were added and other were regrouped (Table 1). Consumption is associated with positive emotions, and the sense of reward is thus magnified.

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ORIGINAL ARTICLE

Renal transplantation recipient patients survival

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Abstract

Introduction: *The Bajío High Specialty Regional Hospital started operating in 2007 to tackle the health demands of 5.8 million inhabitants. It has 184 beds and a transplant unit with 26 beds. In 2008, the renal transplant program launched activities.* **Objective:** *To describe the survival of kidney transplant receptor patients and of the grafted kidney at the Bajío High Specialty Regional Hospital.* **Method:** *Retrospective cohort study, where consecutive transplants carried out between 2008 and 2016 were included. Statistical analysis was performed using the Kaplan-Meier method.* **Results:** *A total of 837 transplants were analyzed. Graft survival censored for death, with a functional graft at one and five years, was 94.6 % and 78.9 %. Patient survival at one and five years was 95.4 % and 88.1 %.* **Conclusions:** *The renal transplant program is one of the best programs established in Mexico, both for the number of deceased-donor kidney transplants performed and for the patient and graft survival achieved. These data indicate that the renal transplant program has had a sustained development.*

KEY WORDS: *Renal transplant. Patient survival. Graft survival.*

Supervivencia de los pacientes receptores de trasplante renal

Resumen

Introducción: *El Hospital Regional de Alta Especialidad del Bajío inició sus funciones en 2007 para atender la demanda de salud de 5.8 millones de habitantes, cuenta con 184 camas y una unidad de trasplantes con 26 camas. En 2008 inició actividades el programa de trasplante renal.* **Objetivo:** *Presentar la supervivencia de los pacientes receptores de trasplante renal y del riñón injertado en el Hospital Regional de Alta Especialidad del Bajío, Guanajuato, México.* **Método:** *Estudio de cohorte retrospectivo en el que se incluyeron los trasplantes consecutivos realizados entre 2008 y 2016. El análisis estadístico se efectuó con el método de Kaplan-Meier.* **Resultados:** *Se analizaron 837 trasplantes. La supervivencia del injerto censurada para muerte con injerto funcional a uno y cinco años fue de 94.6 y 78.9 %. La supervivencia del paciente a uno y cinco años fue de 95.4 y 88.1 %.* **Conclusiones:** *El programa de trasplante renal constituye uno de los mejor establecidos en México, tanto por el número de trasplantes renales de donante fallecido realizados como por la supervivencia obtenida de paciente einjerto. Los datos indican que el programa de trasplante renal ha tenido un desarrollo sostenido.*

PALABRAS CLAVE: *Trasplante Renal. Supervivencia paciente. Supervivencia injerto.*

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Introduction

Renal transplantation is the best treatment alternative for chronic end-stage renal disease.[1] The first successful renal transplant in humans was carried out in 1954 (Boston, United States). In Mexico, the first renal transplant was performed on October 22, 1963 at the General Hospital of the National Medical Center of the Mexican Institute of Social Security.[2] Currently, in Mexico there are 248 hospitals authorized to carry out kidney transplants; however, only 142 have this type of activity.[3] In 2017, the Bajío Regional High Specialty Hospital (HRAEB – *Hospital Regional de Alta Especialidad del Bajío*) ranked fourth among the establishments with the largest number of transplants, with 129 procedures during that year, and ranked first in deceased-donor transplants.[4] The national donation rate in 2016 was 32.2 per million population, with the rate of deceased-donor transplants being 15.5 per million population and the rate of brain-dead donor transplants 4.1 per million population.[5] Over the last five years, an average of 2901 renal transplants were performed annually in Mexico, and there are 12477 patients waiting for a kidney.[3]

The HRAEB is a public institution and receives federal resources. It started operating in 2007 to address the health demands of approximately 5.8 million inhabitants of the states of Guanajuato, Jalisco, Michoacán, Aguascalientes and Zacatecas. It is a tertiary care hospital located in León, Guanajuato, in Central-Western Mexico, which has 184 beds, including 16 in the intensive care department, 15 in the emergency department and 26 in the transplant unit. In 2008, it started the kidney transplant program and, since 2014, it has a medical residency to train specialists in kidney transplantation surgery.[6]

This document analyses the survival of kidney transplant recipients and that of the grafted kidney, as well as relevant epidemiological information related to kidney transplant recipients at the HRAEB.

Method

Retrospective cohort study of 837 kidney transplants carried out from January 26, 2008 to December 31, 2016. The following variables were analyzed: age, gender, donor type, kidney disease etiology, immunosuppression, affiliation status, state of origin, mortality and graft loss. Measures of central tendency and dispersion (mean and standard deviation) were obtained for quantitative variables and proportions for qualitative variables. Survival analysis was carried out with the Kaplan-Meier method. Patient and graft survival censored for death with a functional graft is shown. To establish the differences in survival according to the type of donor, the log-rank test was used; the level of significance was established at $p < 0.05$. All information came from the HRAEB Transplant Unit database and from each patient's electronic medical record and physical file.

Table 1. Characteristics of 837 patients who underwent kidney transplantation at the Bajío High Specialty Regional Hospital

Variable	Mean ± SD	
Recipient age (years)	26.2 ± 12.1	
	n	%
Male recipient	575	68.6
Deceased donor	409	48.8
Related living donor	385	45.9
Unrelated living donor	43	5.1
Renal disease etiology		
Unknown	631	75.3
Secondary glomerulopathy	106	12.6
Primary glomerulopathy	57	6.8
Nephropathy due to urinary tract malformation	20	2.3
Polycystic disease	20	2.3
Congenital glomerulopathy	3	0.3
Immunosuppression		
Induction with basiliximab	492	58.7
Induction with thymoglobulin	92	10.9
Induction with daclizumab	5	0.5
No induction	248	29.6
Cyclosporine-mycophenolate mofetil-prednisone	542	64.7
Tacrolimus-mycophenolate mofetil-prednisone	290	34.6
No immunosuppression due to patient death	5	0.5
Affiliation status		
No social security	511	61
Mexican Institute of Social Security	315	37.6
Institute of Social Security and Services for State Workers	10	1.1
National Ministry of Defense	1	0.1
State of origin		
Guanajuato	789	94.2
Jalisco	21	2.5
Zacatecas	15	1.7
Michoacán	7	0.8
San Luis Potosí	2	0.2
Querétaro	2	0.2
Distrito Federal	1	0.1

Results

Data from the first nine years of the HRAEB kidney transplant program were analyzed, i.e., 837 renal

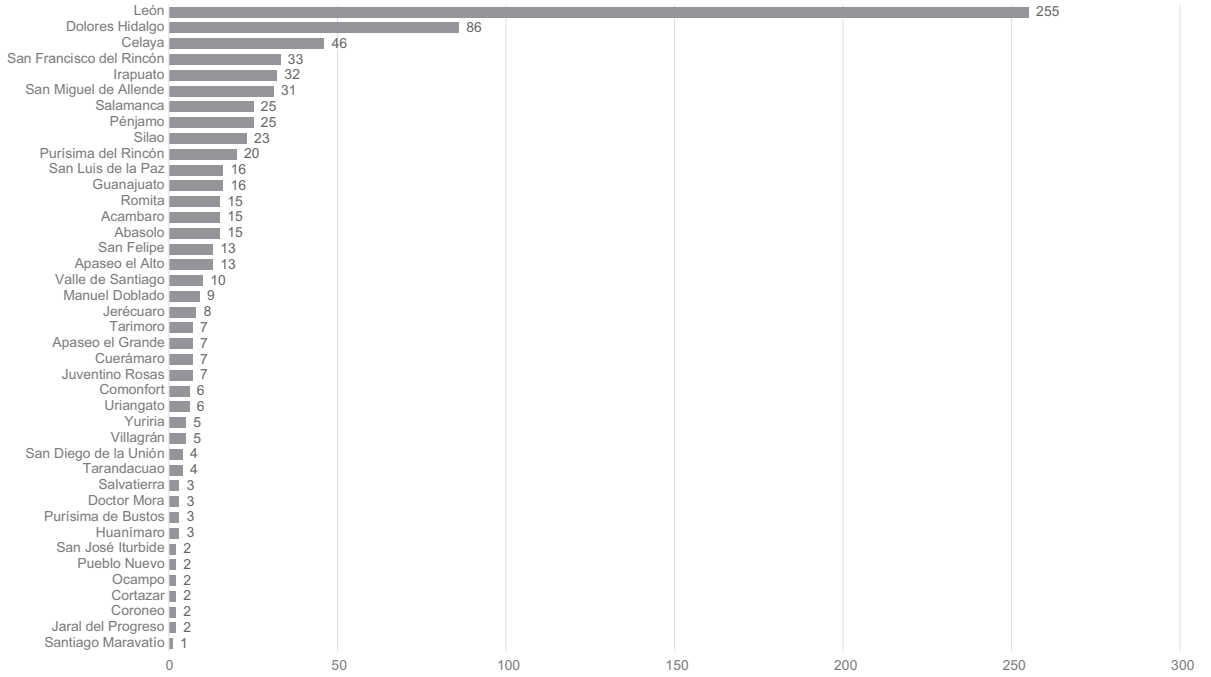

Figure 1. *Guanajuato State municipality of origin of patients undergoing kidney transplantation at the Bajío Regional High Specialty Hospital (n = 789).*

Table 2. Causes of death in 69 patients with kidney transplantation

Cause	n	%
End-stage renal disease (graft failure)	26	37.6
Acute graft rejection	14	20.2
Graft-related chronic kidney disease	6	8.6
Unknown	3	4.3
Infection and subsequent graft removal	2	2.9
Graft primary dysfunction	1	1.4
Infectious	26	37.6
Neoplasms	7	10.1
Non-infectious lung disease	2	2.8
Acute myocardial infarction	2	2.8
Hemorrhage	2	2.8
Suicide	2	2.8
Diabetes mellitus complications	1	1.4
Homicide	1	1.4

transplantations carried out between January 26, 2008 and December 31, 2016. Of the kidney transplant recipient patients, only four received a second renal graft. Four-hundred and nine (48.8 %) deceased donor and 428 (51.1 %) living donor transplants were performed. Renal transplant recipients mean age ± standard deviation was 26.2 ± 12.1 years, with a range of 3 to 69.

As for deceased donors, mean age was 28.6 ± 15 years, with a range of 0 to 65. Regarding living donors, 385 were related and 43 unrelated, and their mean age was 36.4 ± 10.3 years, with a range of 18 to 54. When donor ages were compared, a significant difference ($p < 0.001$) was found between the deceased and the living donors.

Renal failure etiology was unknown in 631 recipients (75.3 %). Immunosuppression induction was used in 589 patients 70.4 %. The most commonly used immunosuppression scheme was that of cyclosporine. Among the kidney transplant recipients, 511 (61 %) had no social security (Table 1) and 94.2 % were natives to the state of Guanajuato; the municipality of origin is indicated in Figure 1.

A mortality rate of 8.2 % was recorded (69 deaths among 837 transplanted subjects); the causes of death are described in Table 2. One-hundred and eleven grafts were lost (13.2 % of those transplanted).

Graft survival censored for death with a functional graft at one, three, five and eight years was 94.6, 88.6, 78.9 and 69.4 %. Figure 2 shows the Kaplan-Meier curves for graft survival censored for death with a functional graft according to the type of donor. The log-rank test was used to compare both groups for graft survival according to the type of donor at nine

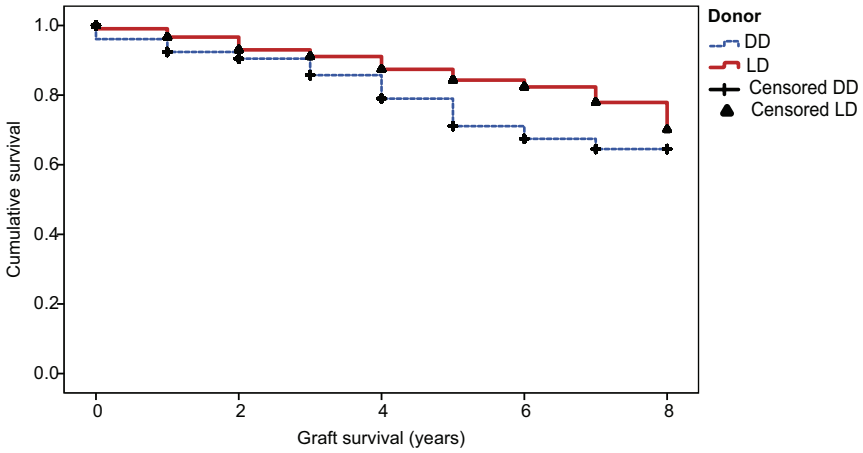

Figure 2. *Kaplan-Meier curves for the survival of kidney grafts transplanted at the Bajío Regional High Specialty Hospital. LD = living donor, DD = deceased donor.*

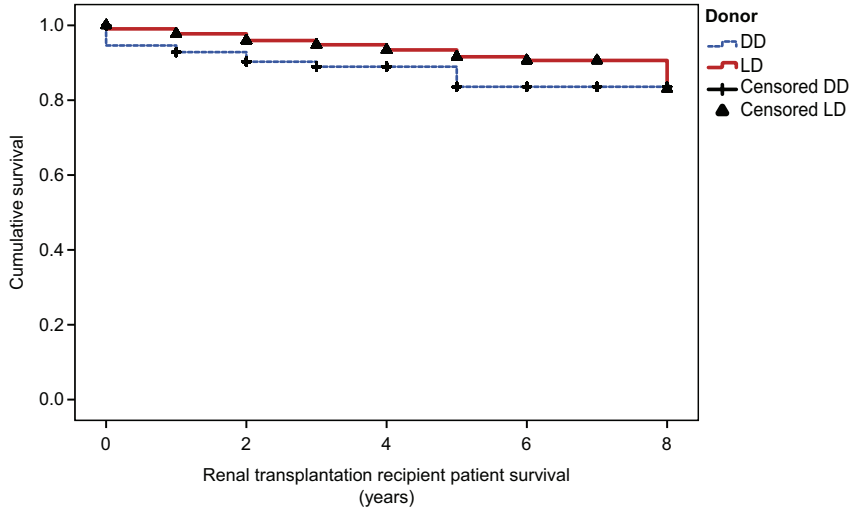

Figure 3. *Kaplan-Meier curves for the survival of patients receiving a kidney transplant at the Bajío Regional High Specialty Hospital. LD = living donor, DD = deceased donor.*

years, with a statistically significant difference being found (p = 0.002).

Kidney transplant recipient patients censored survival at one, three, five and eight years was 95.4, 92, 88.1 and 84.4 %, respectively. Figure 3 shows the Kaplan-Meier curves for renal transplant recipient patients' survival according to the type of donor. The log-rank test was used to compare nine-year recipient survival in both groups according to the type of donor, whereby a statistically significant difference was found (p = 0.003).

Discussion

The results of the first nine years of the HRAEB kidney transplant program are presented. In 2016, 3.2 % of renal transplants performed in Mexico (98 out of 2970 procedures) and 6.7 % of deceased donor kidney transplants (57 out of 844 performed in the country) were carried out at the HRAEB, whereby it was ranked first in Mexico among the establishments with higher deceased-donor renal transplantation activity.[5]

The number of kidney transplants carried out in similar hospitals in Mexico, such as the National Institute of Medical Sciences and Nutrition "Salvador Zubirán", which in 44 years (1967-2011) performed 1000 kidney transplants,[7] and the Veracruz Regional High Specialty Hospital, which in a period of 10 years (2006-2016) carried out 95 kidney transplantations,[8] is in contrast with the 837 procedures practiced in nine years (2008-2016) at HRAEB, which makes it one

of the most important hospitals in Mexico with regard to this procedure.

The HRAEB is a regional hospital, i.e., it has to cover the demands of the Guanajuato, Jalisco, Michoacán, Aguascalientes and Zacatecas populations. However, 94.2 % of patients who receive kidney transplants are from Guanajuato and 30.4 %, i.e., 255 of the recipients from the Guanajuato state belong to the municipality of León, which is explained by the location of this hospital in León.

Patients from 41 of the 46 municipalities of the state of Guanajuato have been included in the HRAEB transplant program, but there are no patients from Atarjea, Tierra Blanca, Xichú, Santa Catarina and Victoria, which are municipalities located northeast of the Guanajuato state, far away from the HRAEB, which may be one of the reasons why patients of these municipalities are not referred, do not attend the HRAEB, and are treated in other hospitals such as the "Dr. Ignacio Morones Prieto" Central Hospital, in San Luis Potosí (if they are affiliated to the Mexican Institute of Social Security) or the Querétaro Regional Hospital 1.

Patients receiving renal transplantation at HRAEB were young adults with an average age of 26.2 years, similar to that reported at the National Institute of Medical Sciences and Nutrition "Salvador Zubirán" (31.7 ± 11.3 years),[7] at Veracruz Regional High Specialty Hospital (31.4 ± 12.8 years),[8] at National Cardiology Institute "Ignacio Chávez" (29.9 ± 11.6 years),[9] at "Bernardo Sepúlveda" Specialty Hospital of the National Medical Center *Siglo XXI* (31.4 ± 10.5 years),[1] at Hospital Miguel Hidalgo in Aguascalientes (29.3 ± 15 years),[10] at "Dr. Ignacio Morones Prieto" Central Hospital (26.8 ± 16.6 years)[11] and at the Mexican Institute of Transplants (31 ± 10 years).[12]

The etiology of end-stage renal disease was unknown in 75.3 % of cases, since HRAEB is a reference hospital and the majority of transplanted patients were at late stages of the disease, and renal biopsy for diagnostic purposes was therefore no longer an option. To avoid this, it is necessary for early detection programs to be implemented at primary care hospitals and health centers.

During the reported period, only two immunosuppression schemes were used at HRAEB: cyclosporine-mycophenolate mofetil-prednisone and tacrolimus-mycophenolate mofetil-prednisone.

Comparisons with data reported in the literature regarding kidney transplant recipients and graft survival in Mexico are limited due to the variability in the methodology of analysis and data handling, as well as for the fact that cohorts with different periods were analyzed;[1,7-12] however, we can point out that there are differences ($p > 0.05$) regarding the survival of patients with renal transplantation reported in Spain: 91, 81 and 57 % at one, two and three years respectively,[13] in contrast to the survival rates found in this study: 95.4, 93.2 and 92 %, for the same periods.

In this study, survival of the living-donor kidney transplantation recipient, both of the patient and the graft, was higher in comparison with that of the deceased-donor renal transplant recipient, as noted in other investigations.[1,7-12] According to different analyses, there are several factors that might contribute to explain the better survival and glomerular filtration of living-donor transplants,[14-16] such as blood group typing and histocompatibility tests that are routinely practiced at HRAEB:

- Donor and recipient HLA typing through molecular biology with sequence-specific primer (SSP)-type polymerase chain reaction for classes I and II (A, B, DRB1 and DQB1).
- Anti-HLA alloantibodies through the antibody reactive panel with the ELISA methodology (solid phase).
- Lymphocyte crossmatch assay for complement-mediated cytotoxicity, with the use of total lymphocytes and dithiothreitol.

Regarding living donors, we did not have the HLA compatibility data of 5.1 % (22/428) of donor-recipient dyads, 64.5 % (276/428) did match in one donor-recipient haplotype and 9.1 % (39/428) did match in two donor-recipient haplotypes; therefore HLA identity (matching of one and two haplotypes) contributed for 73.6 % (297/428) of living-donor kidney transplant recipients to have a better survival than deceased-donor kidney transplant recipients.

Conclusions

The HRAEB renal transplant program is one of the more robust programs in Mexico, both for the number of deceased-donor kidney transplants performed and for the patient and graft survival obtained. Despite being a relatively recent program (nine years) in a hospital with barely 10 years of existence, recipient and graft survival is better than in other hospitals with more experience in the procedure. Our data also indicate that the renal transplant program has had a sustained development.

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ORIGINAL ARTICLE

Academic and sociodemographic predictors of anxiety and psychological well-being in Mexican medical students. A cross-sectional study

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Abstract

Introduction: *Medical students report higher levels of anxiety than students from other majors. Knowledge about their psychological well-being is scarce.* **Objective:** *To identify sociodemographic and academic factors that predict the level of anxiety and psychological well-being in Mexican medical students.* **Method:** *Cross-sectional study of Mexican medical students of first (n = 59), third (n = 43) and fifth semester (n = 59), who answered a sociodemographic questionnaire, Beck Anxiety Inventory, the Psychological Well-being Scale for adults and the Family Adaptability and Cohesion Evaluation Scale.* **Results:** *Females showed higher levels of anxiety (p < 0.01). Anxiety in males was similar in the different semesters (p > 0.05); women of third and fifth semesters were more anxious than those at first semester (p < 0.01). Anxiety and psychological well-being were negatively correlated (p <0.001). The "Less anxiety, higher level of well-being" and "More anxiety, lower well-being" subgroups were characterized, and a logistic regression identified that being a woman (OR = 4.70) and not practicing any religion (OR = 2.49) are predictive factors of higher levels of anxiety.* **Conclusions:** *Female medical students constitute a population at risk for higher levels of anxiety and less psychological well-being, which compromises their learning, quality of life and future professional practice.*

KEY WORDS: *Mental health. Gender differences. Predictive factors. Medical students.*

Predictores académicos y sociodemográficos de ansiedad y bienestar psicológico en estudiantes mexicanos de medicina. Estudio transversal

Resumen

Introducción: *Estudiantes de medicina reportan mayor ansiedad que estudiantes de otras carreras. El conocimiento sobre su bienestar psicológico es escaso.* **Objetivo:** *Identificar factores sociodemográficos y académicos predictores del nivel de ansiedad y bienestar psicológico en estudiantes mexicanos de medicina.* **Método:** *Estudio transversal de estudiantes mexicanos de medicina de primer (n = 59), tercer (n = 43) y quinto semestre (n = 59), que contestaron un cuestionario sociodemográfico, la Escala de Ansiedad de Beck, la Escala de Bienestar Psicológico para Adultos y la Escala de Evaluación de la Cohesión y la Adaptabilidad Familiar.* **Resultados:** *Las mujeres presentaron mayor ansiedad (p < 0.01). La ansiedad en hombres fue similar en los distintos semestres (p > 0.05); las mujeres de tercer y quinto semestre fueron más ansiosas que las del primero (p < 0.01). Ansiedad y bienestar psicológico correlacionaron negativamente (p < 0.001). Se identificaron los*

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subgrupos "Menor ansiedad, mayor bienestar" y "Mayor ansiedad, menor bienestar", y una regresión logística identificó que ser mujer (OR = 4.70) y no profesar alguna religión (OR = 2.49) son factores predictores de mayor ansiedad. **Conclusiones:** *Las estudiantes de medicina constituyen una población de riesgo para mayor ansiedad y menor bienestar psicológico, lo que compromete su aprendizaje, calidad de vida y futuro ejercicio profesional.*

PALABRAS CLAVE: *Salud mental. Diferencias entre sexos. Factores predictores. Estudiantes de medicina.*

Introduction

Medical students show higher levels of stress and a prevalence of more severe psychopathologies in comparison with students of other majors and the general population.[1-3] Stress can cause anxiety disorders[4] and comorbidity with different psychopathologies, including other anxiety disorders.[5] Anxiety is a warning system that alerts the body about real or supposed threats.[6] Its prevalence in medical students varies between countries,[1,7-11] although some conditions are constant: the level of anxiety increases depending on the curricular development,[2] it is higher in females,[1] and its main sources include academic, psychosocial and economic issues.[12]

Stress in medical students negatively impacts their psychological well-being and potentiates the risk of psychopathologies.[13] Psychological well-being is a positive affective state that favors optimal functioning in personal and social life, and allows individuals to perceive control of their life and surroundings.[14-16] It is considered a critical aspect of medical training,[11] although its decrease has been reported over the course of studies in the medical area.[17]

More research has focused on the study of anxiety in medical students than on psychological well-being.[18] This study identified sociodemographic and academic factors that predict the level of anxiety and psychological well-being in Mexican medical students.

Method

Cross-sectional study. Through convenience non-probabilistic sampling, medical students enrolled in first, third and fifth semester were recruited. The inclusion criteria were: attending an academic evaluation in November 2018, voluntarily participating in the study and completing four questionnaires. Out of 186 invited students, 10 refused to participate.

The sociodemographic and academic variables questionnaire, Beck Anxiety Inventory (BAI),[19] the Psychological Well-being Scale for Adults (PWBS-A)[16] and the Family Adaptability and Cohesion Evaluation Scale (FACES-III),[20] all validated in the Mexican population, were applied.[21-23]

The BAI comprises 21 items organized in four factors: subjective anxiety, neurophysiological anxiety, autonomic anxiety and panic, which explain 56 % of the variance (α = 0.93). The level of anxiety was considered according to the score: minimum, 0 to 5 points; mild, 6 to 15; moderate, 16 to 30; and severe, 31 to 63.[21] The presence of anxiety was established with a score $\geq$ 6.7.

The PWBS-A scale comprises 12 items organized in four factors: autonomy, projects, links and acceptance/control, which explain 60 % of the variance (α = 0.79). The level of psychological well-being was considered average when total score was less than or equal to the 50th percentile, low if it was inferior to this value or high if it was higher than or equal to the 95th percentile.[24]

The FACES-III scale comprises 20 items organized in two factors: cohesion and adaptability (α = 0.70). Its interpretation according to the cohesion score indicated a disengaged (10 to 34 points), separated (34 to 40), connected (41 to 45) or enmeshed family (46 to 50). For adaptability, it indicated a rigid (10 to 19 points), structured (20 to 24), flexible (25 to 28) or chaotic family (29 to 50).

One researcher asked the students for their voluntary collaboration in the study, explained its objectives and clarified all doubts. Those who agreed to participate were given an informed consent form and the printed questionnaires.

Gender and semester differences regarding anxiety and psychological well-being were analyzed using one-factor, two-factor ANOVA and Tukey's post hoc test. To assess the association between variables, Pearson's product-moment correlation coefficient and chi-square test of independence were calculated. For the latter, with a significant result, Pearson's standardized residues were calculated as a post hoc test and Cramer's V as an indicator of the effect size. The strength of association between variables was interpreted as trivial with absolute values < 0.10, as low

Table 1. **Total prevalence, by gender, semester and level, of anxiety and psychological well-being in medical students**

	n	%	n	%	n	%	χ^2	p	V
Anxiety									
	Total sample		**Females**		**Males**				
Minimal	47	29.2	21	18	26	59.1	28.81	0.001*	0.43
Mild	52	32.3	41	35	11	25			
Moderate	40	24.8	38	32.5	2	4.5			
Severe	22	13.7	17	14.5	5	11.4			
	Semester 1		**Semester 3**		**Semester 5**				
Minimal	25	42.4	11	25.6	11	18.6	11.26	0.04**	0.18
Mild	16	27.1	14	32.6	22	37.3			
Moderate	12	20.3	9	20.9	19	32.2			
Severe	6	10.2	9	20.9	7	11.9			
Well-being									
	Total sample		**Females**		**Males**				
Low	68	42.2	49	41.9	19	43.2	0.98	0.61*	0.07
Medium	70	43.5	53	45.3	17	38.6			
High	23	14.3	15	12.8	8	18.2			
	Semester 1		**Semester 3**		**Semester 5**				
Low	26	44.1	17	39.5	25	42.4	0.30	0.98**	0.04
Medium	25	42.4	20	46.5	25	42.4			
High	8	13.5	6	14	9	15.2			

*Comparison between genders. **Comparison between semesters.

Table 2. **Anxiety and psychological well-being scores obtained by gender and by semester in the total sample, in males and in females**

	Mean ± SD	Mean ± SD	Mean ± SD		F	p
	Total sample	**Females**	**Males**			
Anxiety	15.10 ± 13.49	17.25 ± 13.07	9.36 ± 13.04		15.08*	0.001
Well-being	32.69 ± 2.65	32.66 ± 2.65	32.77 ± 2.70		0.28*	0.86
		Semester 1	**Semester 3**	**Semester 5**		
Anxiety	Total sample	11.71 ± 11.54	17.51 ± 16.18	16.74 ± 12.68	1.52**	0.22
	Females	12.26 ± 10.68	23.81 ± 16.14	18.47 ± 11.35	7.75**	0.001
	Males	9.76 ± 14.51	6.87 ± 9.47	11.66 ± 15.27	0.51**	0.59
Well-being	Total sample	32.74 ± 2.66	32.90 ± 2.30	32.49 ± 2.90	0.40**	0.66
	Females	32.86 ± 2.49	32.62 ± 2.40	32.47 ± 2.97	0.24**	0.78
	Males	32.30 ± 3.25	33.37 ± 2.12	32.53 ± 2.79	0.63**	0.53

SD = standard deviation. *Comparisons between genders. **Comparisons between semesters.

with 0.11 to 0.29, as medium with 0.30 to 0.49 and as high with ≥ 0.50.[25]

After the elimination of atypical multivariate values, a cluster analysis was carried out to create mutually exclusive subgroups with the anxiety and psychological well-being data. A hierarchical technique with Euclidean squared distance and Ward's grouping method were used. The solution was validated by confirmatory cluster analysis[26] and the gamma, tau-b, tau-c, and Somers' d coefficients.[27] The

resulting subgroups were validated using a single-tailed t-test for independent groups, with Cohen's d as the effect size index (small, medium and large effect: d ≥ 0.20, 0.50, and 0.80, respectively).[28]

A logistic regression model considered belonging to the "More anxiety, lower level of well-being" subgroup as a response variable and sociodemographic and academic data as predictive variables. The model was validated by assessing the null hypothesis (omnibus test) and its goodness of fit (Hosmer-Lemeshow). The correct percentage of case classification was calculated, as well as Nagelkerke's R.[2] Version 20 of the SPSS program was used.

This study was submitted to the Research Committee of the National Medical Arbitration Commission for approval.

Table 3. Student characteristics and sociodemographic, academic and familiar predictors according to their levels of anxiety and psychological well-being

	< A > B		> A < B		p*	d	OR	CI	p**
	Mean ± SD		Mean ± SD						
Total BAI	7.94 ± 5.55		33.15 ± 9.68		0.001	3.26			
Subjective anxiety	4.22 ± 3.31		14.20 ± 4.74		0.001	2.38			
Neurophysiological anxiety	2.16 ± 2.47		10.90 ± 4.86		0.001	2.38			
Autonomic anxiety	0.66 ± 1.02		4.29 ± 2.38		0.001	2.14			
Panic	0.89 ± 1.16		3.75 ± 2.07		0.001	1.75			
Total PWBS-A	33.09 ± 2.31		31.88 ± 2.85		0.007	0.43			
Autonomy	10.24 ± 1.59		9.68 ± 1.73		0.05	0.30			
Projects	11.54 ± 0.86		11.40 ± 0.89		0.38	0.13			
Links	5.69 ± 0.56		5.31 ± 0.95		0.002	0.49			
Acceptance/control	5.61 ± 0.75		5.47 ± 0.84		0.33	0.15			
Age	19.48 ± 1.12		19.79 ± 1.15		0.12	0.24	1.16	0.66-2.04	0.59
Grade-point average	89.93 ± 3.86		87.68 ± 3.61		0.001	0.53	0.86	0.76-0.97	0.01
Failed courses	0.05 ± 0.25		0.22 ± 0.60		0.01	0.40	1.36	0.40-4.53	0.61
	n	%	n	%	p**	V	OR	CI	p**
Gender									
Female	78	67.2	38	86.4	0.01	0.19	4.70	1.55-14.19	0.006
Male (R)	38	32.8	6	13.6					
Marital status									
Single	116	100	44	100	NA	NA			
Practices religion									
Yes (R)	76	65.5	21	47.7	0.04	0.16	2.49	1.05-5.88	0.03
No	40	34.5	23	52.3					
Works									
Yes (R)	5	4.3	3	6.8	0.51	0.05			
No	111	95.7	41	93.2			1.20	0.19-7.56	0.84
Maternal level of education									
Basic education or no data (R)	5	4.3	1	2.3	0.64	0.07			
High school education	25	21.6	12	27.3			1.72	0.11-25.22	0.69
Higher education	86	74.1	31	70.5			1.50	0.11-19.44	0.75

(Continued)

Table 3. Student characteristics and sociodemographic, academic and familiar predictors according to their levels of anxiety and psychological well-being (*Continued*)

	n	%	n	%	p**	V	OR	CI	p**
Paternal level of education									
Basic education or no data (R)	11	9.5	1	2.3	0.22	0.13			
High school education	10	8.6	6	13.6			11.32	0.71-178.35	0.08
Higher education	95	81.9	37	84.1			6.62	0.57-75.99	0.12
Medicine as option 1									
Yes (R)	107	92.2	41	93.2	0.84	0.01			
No	9	7.8	3	6.8			0.42	0.08-2.22	0.30
Semester									
First (R)	47	40.5	12	27.3	0.29	0.12			
Third	29	25	14	31.8			1.17	0.33-4.18	0.80
Fifth	40	34.5	18	40.9			0.65	0.10-4.11	0.65
Shift									
Morning	71	61.2	20	45.5	0.17	0.14	0.45	0.13-1.53	0.20
Evening	25	21.6	12	27.3			0.80	0.18-3.54	0.77
Mixed (R)	20	17.2	12	27.3					
Cohesion									
Disengaged (R)	18	15.5	7	15.9	0.28	0.15			
Separated	21	18.1	14	31.8			2.15	0.53-8.60	0.27
Connected	39	33.6	12	27.3			1.13	0.28-4.44	0.85
Enmeshed	38	32.8	11	25			0.91	0.22-3.75	0.90
Adaptability									
Rigid (R)	6	5.2	2	4.5	0.97	0.03			
Structured	16	13.8	7	15.9			0.72	0.06-8.75	0.79
Flexible	24	20.7	8	18.2			0.34	0.02-4.38	0.40
Chaotic	70	60.3	27	61.4			0.54	0.04-6.17	0.62

< A > B = less anxiety, higher level of psychological well-being; > A < B = more anxiety, lower level of psychological well-being; SD = standard deviation, NA = does not apply, R = reference variable. *t-test. **χ^2. ***Logistic regression.

Results

One-hundred and seventy-six medical students participated, but the data of 15 were eliminated for having answered the instruments only partially. The 161 retained students had an average age ± standard deviation of 19.57 ± 1.13 years, 117 (72.7 %) were females and 44 (27.3 %) were males; 59 were at first semester (36.6 %), 43 at third (26.7 %) and 59 at fifth semester (36.6 %); 91 were in the morning shift (56.5 %), 38 in the evening shift (23.6 %) and 32 had mixed hours (19.6 %). Grade-point average at current semester ranged from 78 to 98/100 (89.29 ± 3.91) and 12 participants (7.4 %) had between one and three failed courses (0.09 ± 0.39). Medicine major was the first option for 148 students (91.9 %); all were single, 97 (60.2 %) practiced any religion and eight (5 %) reported having a job.

Anxiety of some level, from mild to severe, was experienced by 70.8 % of students, 82 % of females and 40.9 % of males. A high proportion of males did not exhibit anxiety (lowest level), while a considerably high proportion of females experienced it at a moderate level (Table 1). Regardless of gender, most first semester students did not show anxiety (lowest level) (Table 1). Average BAI score in males was lower than in females (Table 2), who also had higher scores at third and fifth semesters with regard to the first (Table 2). Low or

average level of psychological well-being was independent of gender or current semester (Table 1). There were no differences between genders or semesters in PWBS-A average score (Table 2). BAI and PWBS-A total scores showed a medium-intensity negative correlation (r = -0.32, p < 0.001).

Prior to the cluster analysis, one participant's data were eliminated because they were shown to be multivariate outliers. The hierarchical cluster analysis suggested a two-subgroup solution, which was validated by confirmatory analysis, by coefficients gamma = 1, tau-b = 0.95, tau-c = 0.74 and Somers' d coefficient = 0.95, and by t-tests. Table 3 shows the characteristics of the "less anxiety, higher level of well-being" (n = 116) and "more anxiety, lower level of well-being" subgroups (n = 44).

The logistic regression model identified belonging to the "more anxiety, lower level of well-being" subgroup, being a woman and not practicing any religion as risk factors. Grade-point average was a protective factor (Table 3). The model was significant (χ^2 = 34.95, p = 0.02), had an adequate fit (χ^2 = 9.35, p = 0.31), explained 28.4 % of the variance and correctly classified 74.4 % of cases.

Discussion

The main result of this study was that being a woman and not practicing a religion are predictors of higher levels of anxiety and lower levels of psychological well-being, with grade-point average being a protective factor.

The prevalence of anxiety is similar to that of other studies: 57, 73 and 79.7 %,[13,29,30] and it contrasts with national data that were obtained using the same instrument (BAI), but reported only 24.8 % of medical students with anxiety.[8] This might be due to differences in the diagnostic criteria that were used. Consistently with other studies, females had a higher level of anxiety with regard to males.[1,2,10,31-33] This asymmetry may be due to cultural, neurophysiological and evolutionary factors that make women more susceptible to anxiety.[34] A novel finding is that anxiety in males did not differ between semesters, while females in advanced semesters were more anxious. The slower recovery of hormonal response to stress in women[35] and the larger amount of academic stressors at advanced semesters may explain this result.

Gender equivalence in psychological well-being is consistent with data referred to in the literature.[15] In males, maintaining the same level of psychological well-being and anxiety between semesters indicates some independence between these variables.[36] In females, the anxiety increase did not decrease their psychological well-being. These data may suggest a protective role of anxiety that prevents psychological well-being decrease. In this regard, there are data indicating that anxiety promotes risk-aversion behavior,[37] which in the context of medical education might prevent impulsive decisions in health care that might compromise psychological well-being in female physicians. It is possible that, with higher levels of anxiety, female medical students better plan the behaviors and decisions to be adopted regarding the care of their patients' health, which would help to maintain their psychological well-being stable.

Consistent with the above, the reported strength of association between anxiety and psychological well-being indicates a certain degree of independence between these variables. This suggests that intervening in one of them will not necessarily intensely affect the other.

An important contribution of the study was the description of the profile of medical students with "less anxiety, higher levels of well-being" and "more anxiety, lower levels of well-being". The former included mostly males who practice a religion, with a higher grade-point average and fewer failed courses; the latter included mostly females who do not practice a religion, with lower grade point average and a larger number of failed courses. However, the logistic regression did not retain the number of failed courses as a predictor for belonging to the second profile. Practicing a religion can have a protective function against anxiety, which raises quality of life and academic performance and, consequently, the grade-point average. A similar association was previously suggested.[38]

The difference between profiles lies mainly in the level of anxiety, the discrepancy of which in total and per BAI factor score showed a large effect size. Regarding the PWBS-A scale score, the equivalence in the "projects and acceptance/control" factors indicates that, in general, the assessed students have defined their goals and give meaning to their lives, while accepting themselves for who they are and perceiving control over their circumstances.[16] However, the second profile showed less general well-being, less ability to independently make decisions (autonomy), and to establish empathic social relationships (links). The latter is important because, in the future, these students will have to establish empathic relationships with their patients, which has

been shown to favor the quality of health care.[39] In addition, there are data that demonstrate the protective effect of social support on the risk for developing anxiety disorders in females.[40]

One limitation of this study was that the data were collected during a semi-annual evaluation. This may have introduced some bias in the levels of anxiety. However, the data obtained are consistent with the literature, which implies minimal influence of this event. Conducting cross-sectional and longitudinal studies to assess anxiety and psychological well-being at different times of the semester in order to verify their stability or trend is recommended.

Conclusions

Female medical students show more anxiety and lower levels of psychological well-being, which compromises their quality of life, their learning process and their future professional practice. Strategies for support and resilience are required for medical students in general and for female medical students in particular.[41]

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ORIGINAL ARTICLE

Validity and consistency of an outpatient department user satisfaction rapid scale

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Abstract

Background: *User satisfaction is key to define and assess the quality of care; however, there is no patient satisfaction rapid scale in Mexico. Our objective was to determine the validity and consistency of an outpatient department user satisfaction rapid scale (ERSaPaCE).* **Method:** *Comparative, observational, cross-sectional, prolective study. In phase 1, a rapid scale model was developed, which was submitted to experts in medical care for assessment; the instrument was pilot-tested in 10-patient groups, using as many rounds as required until it obtained 20 approvals. In phase 2, the resulting questionnaire and the Outpatient Service User Satisfaction (SUCE) scale were applied to outpatient department users. ERSaPaCE was reapplied by telephone 10 days later. Descriptive statistics, Cronbach's α, Spearmans correlation and intra-class correlation coefficient (ICC) were used.* **Results:** *Two-hundred patients were recruited, out of which 53 % were aged 31-60 years; 51.5 % were women and 48.5 % men, all of them users of outpatient services from 13 specialties. Cronbach's α for ERSaPaCE was 0.608, whereas ICC was 0.98 (p = 0.000). Convergent validity was 0.681 (p = 0.000) using Spearmans rho.* **Conclusion:** *ERSaPaCE was a valid and consistent instrument for the assessment of outpatient department user satisfaction.*

KEY WORDS: *Validity. Consistency. Quality of care. Patient satisfaction. SUCE. ERSaPaCE.*

Validez y consistencia de una escala rápida de satisfacción del paciente de consulta externa

Resumen

Antecedentes: *La satisfacción del usuario es clave para definir y valorar la calidad de la atención, sin embargo, no existe una escala rápida de satisfacción del paciente en México. El objetivo fue determinar la validez y consistencia de la Escala Rápida de Satisfacción del Paciente de Consulta Externa (ERSaPaCE).* **Método:** *Estudio comparativo, observacional, transversal, prolectivo. En la fase 1 se elaboró un modelo de escala rápida, que se sometió a la valoración de expertos en atención médica; se realizaron pruebas piloto con 10 pacientes por ronda, tantas veces como fuera necesario hasta lograr 20 aprobaciones. En la fase 2 se aplicó el cuestionario resultante y la escala de Satisfacción del Usuario de Consultas Externas (SUCE) a usuarios de consulta externa; la ERSaPaCE se reaplicó telefónicamente siete a 10 días después. Se utilizó estadística descriptiva, α de Cronbach, Spearman y coeficiente de correlación intraclase (CCI).* **Resultados:** *Se reclutaron 200 pacientes, 53 % con edad de 31 a 60 años, 51.5 % mujeres y 48.5 % hombres de la consulta externa de 13 especialidades; α de Cronbach de ERSaPaCE = 0.608, CCI = 0.98 (p = 0.000) y validez convergente = 0.681 (p = 0.000) por rho de Spearman.* **Conclusión:** *ERSaPaCE fue un instrumento válido y consistente para evaluar la satisfacción del usuario de consulta externa.*

PALABRAS CLAVE: *Validez. Consistencia. Calidad de la atención. Satisfacción del paciente. SUCE. ERSaPaCE.*

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Introduction

Quality of medical care has become an essential requirement in health services. Although scientific-technological advances have had a great impact on the improvement of the quantity and quality of life for many patients, it has also generated numerous problems with negative consequences, which affect health care in one way or another.[1] On the other hand, the convergence of administrators and professionals in the field of health, the increase in the costs and use of services by the population, as well as patient demands, forces to look for standards to meet patients' expectations to the maximum.[2]

In Mexico there are various backgrounds, since the 1962 edition of *Auditoría Médica* (Medical Audit), launched by the Mexican Institute of Social Security, and its updates in 1972 and 1973, with an emphasis on the medical record. In 1981, Donabedian initiated the evaluation of the quality of medical care itself based on the systems theory. Finally, since 1999, the Ministry of Health has designed a hospital certification model to improve health care in Mexico.[3-7]

The quality of medical care can be defined as "granting the patient medical attention in a timely manner, with professional competence, safety and respect for ethical principles, with the purpose to meet his/her health needs and expectations".[7,8]

Outpatient department user satisfaction expresses an individual and subjective value judgment that is key in the definition and assessment of the quality of care, and it is therefore an indicator to assess the quality of care in health services.[5,6] This construct includes treating the patient with kindness, availability of equipment, material, supplies and required medications, sufficient and qualified personnel, continuity in the process of care, comfort in the service areas and reasonable costs.[8,9]

Thus, outpatient department user satisfaction surveys require psychometric properties that ensure their reliability and validity and, therefore, it is necessary to have validated and readily applicable surveys available in order to measure the level of satisfaction and identify the main causes of outpatient health service users dissatisfaction, which allow implementing actions for improvement.[8-10] On the other hand, given that satisfaction is a subjective construct, it is preferable using self-report scales, which are considered the standard criterion for this type of variables.[11,12]

Although there are several reports on user satisfaction,[13-15] in Mexico there is no rapid scale available to assess user satisfaction in secondary care facilities. For this reason, we believe it is necessary to develop an instrument that helps to subject the institution or health service to an improvement program and thus offer quality care that meets the expectations of patients and their families.

The instrument that is intended to be designed must be a rapid, functional, self-report (if possible) scale, in order for the patient not having to invest much time or effort on answering it, and at the same time prove that the instrument is valid and consistent. The purpose of this study was to design a new secondary care outpatient department user satisfaction rapid scale and determine its validity and consistency.

Method

Comparative, longitudinal, prolective, homodemic observational study in patients cared for at outpatient services of Regional General Hospital 20 of the Mexican Institute of Social Security in Puebla, upon leaving the department. The study was approved by the Local Research and Ethics on Health Research Committee 2102 of the Mexican Institute of Social Security (registration number R-2013-2102-20). Patients of both genders, regardless of their age, who agreed to answer the survey were included. Subjects who did not complete the questionnaire were eliminated.

Phase 1. Development of the scale

A fast-scale model was developed (by a committee of experts: a quality consultant psychologist, a pediatrician expert in quality and clinimetrics and an expert in outpatient services), and subsequently was submitted for assessment by different experts in the area (a master in hospital administration, the director of the unit and two hospital quality of care supervisors). The scale was subjected to a pilot study with users in order for wording clarity, ease of response and rapidness and practicality to be determined; modifications were made in these aspects without affecting the expert opinion. The pilot study was repeated as many times (10 patients per round) as necessary until total approval of 20 patients was achieved.

Phase 2. Validity and consistency phase

In a six-month period, all outpatient service users were applied the questionnaire resulting from phase 1, the Outpatient Department User Satisfaction Rapid

Escala Rápida de Satisfacción de Consulta Externa (ERSaPaCE)

Name (optional): _____ Telephone (optional): _____

Attended outpatient department: _____

APPRECIATED AFFILIATE: with the purpose to rate the quality of care, we respectfully ask you to answer the following survey. We appreciate your understanding and sincerity. Your answers will be confidential.

INSTRUCTIONS: Mark with an "x" the answer you choose	PARAMETERS				
	1	2	3	4	5
How do you rate …	Very dissatisfied	Dissatisfied	Little satisfied	Satisfied	Very satisfied
1. Cleanness and order in the Medical Unit?					
2. Personal treatment by the Medical Assistant?					
3. Treatment, respect, attention and availability by the Nursing staff?					
4. Treatment, respect, attention and availability by the GP or Treating Physician?					
5. Information by the Doctor about the patient health status?					
6. Assistance at the Medical Records Department window when requesting your record?					
7. Assistance at the Pharmacy to fill your prescription?					
8. Doctor, Nurse and Medical Assistant institutional image?					
9. Time in the waiting room for your medical appointment?					
a. Please write down the waiting time in minutes: _____					

10. According to your answers above, the medical unit should:

a. Be congratulated for its valuable and effective performance	
b. Receive suggestions to improve the medical service	
c. Receive complaints to express your dissatisfaction with the medical service	

Please write down your congratulations, suggestions or complaints:

Figure 1. *Outpatient department user satisfaction rapid scale.*

Scale (ERSaPaCE – *Escala Rápida de Satisfacción del Paciente de Consulta Externa*), as well as the Outpatient Service User Satisfaction (SUCE – *Satisfacción del Usuario de Consultas Externas*) scale.[10] In each case, ERSaPaCE was reapplied by telephone between seven and 10 days later.

Written informed consent was requested to the outpatient department users; any intervention that could involve any harm to the patient was avoided, and confidentiality of data was kept to avoid possible negative consequences with regard to medical care at the unit.

Table 1. Characteristics of SUCE and ERSaPaCE scales respondents and their distribution in outpatient services by medical specialty

Gender Male Female			48.5 % 51.5 %		
Age (years) 17-30 31-45 46-60 ≥ 61			16.5 % 24 % 29 % 30.5 %		
Outpatient services specialties					
Surgery	20 %	Urology	6.5 %	Pulmonology	4 %
Internal Medicine	19.5 %	Cardiology	6.5 %	Otorhinolaryngology	4 %
Angiology	9 %	Gastroenterology	6 %	Ophthalmology	3 %
Pediatrics	7.5 %	Neurology	5.5 %	Pediatric surgery	1.5 %
Nephrology	7 %				

SUCE (*escala de Satisfacción del Usuario de Consultas Externas*) = Outpatient Service User Satisfaction scale.
ERSaPaCE (*Escala Rápida de Satisfacción del Paciente de Consulta Externa*) = Outpatient Department User Satisfaction Rapid Scale.

Descriptive statistics were used. For internal consistency evaluation, Cronbach's α was used; for convergent validity of the scales, Spearman's rho; and for test-retest of the rapid scale, the intraclass correlation coefficient (ICC) was resorted to.[16]

Results

Phase 1

The scale that was designed and approved by the experts required three pilot rounds until the wording of the questions was accepted by the users. To improve items applicability and reinforce their understanding, the decision was made to add, to each value of the responses, the drawings of faces used in a facial pain scale,[11] whose construct validity was widely demonstrated. This phase ended with the conclusion of the scale, as shown in Figure 1.

Phase 2

Two-hundred patients who were users of the outpatient services from different specialties were surveyed; their characteristics are detailed in Table 1. There were no patients eliminated from the study. In the case of minors, SUCE and ERSaPaCE were applied to the parents or accompanying adults.

The result when Cronbach's α was applied to ERSaPaCE was 0.608, whereas the ICC result for test-retest agreement was 0.98 (p = 0.000). The correlation of both scales using Spearman's coefficient was 0.681 (p = 0.000). The results for both scales are shown in Table 2.

ERSaPaCE included a section for congratulations, suggestions and complaints; textually, the most common were the following:

- Improve the service in the medical records department, please.
- More frequent cleaning in bathrooms; there are no disposable towels or paper.
- The treating physician should change his attitude.
- The doctor does not explain my condition, is arrogant and yelled at me.
- Please, supply medications to the pharmacy.
- The guards are arrogant and rude.
- Congratulations (to three different treating physicians).

Discussion

Given that patient satisfaction is useful, although indirectly, to determine the quality of care, various efforts to assess it from different angles and with varying depths are recorded.[6,8-10,13-15]

This study presents a hospital outpatient service user satisfaction scale that can be applied at any medical unit or ambulatory care area of any level of care, in addition to complying with the characteristics of brevity, rapidness, practicality for being answered; with this instrument, it is possible for different services or moments of outpatient care to be assessed.

The phase 1 procedure of the study, which involved the participation of up to 10 different experts in the

Table 2. Comparison of SUCE and ERSaPaCE results

SUCE scale		ERSaPaCE	
Waiting room comfortability		**Cleanness and order of the medical unit**	
1 point	0.5 %	Very dissatisfied	2 %
4 points	1 %	Dissatisfied	4 %
5 points	3.5 %	Little satisfied	17 %
6 points	2.5 %	Satisfied	50 %
7 points	7 %	Very satisfied	27 %
8 points	16 %		
9 points	30 %		
10 points	39.5 %		
Treatment by the nursing staff		**Treatment, respect, attention and availability by the nursing staff**	
3 points	0.5 %	Very dissatisfied	0.5 %
5 points	1 %	Dissatisfied	6 %
6 points	2.5 %	Little satisfied	13 %
7 points	4 %	Satisfied	44.5 %
8 points	17.5 %	Very satisfied	36 %
9 points	27.5 %		
10 points	47 %		
Treatment by the medical staff		**Treatment, respect, attention and availability by the medical staff**	
1 point	1 %	Very dissatisfied	0 %
3 points	2 %	Dissatisfied	7.5 %
4 points	0.5 %	Little satisfied	13.5 %
5 points	1 %	Satisfied	34 %
6 points	2.5 %	Very satisfied	45 %
7 points	6 %		
8 points	12 %		
9 points	29.5 %		
10 points	45.5 %		
Information received about your health problem		**Information by the doctor about your health status**	
3 points	0.5 %	Very dissatisfied	0.5 %
4 points	1 %	Dissatisfied	6 %
5 points	4 %	Little satisfied	13 %
6 points	1.5 %	Satisfied	37.5 %
7 points	9 %	Very satisfied	43 %
8 points	12.5 %		
9 points	31.5 %		
10 points	40 %		
Paperwork that had to be done at the admission office		**Response at the medical records department window when requesting your record**	
1 point	1 %	Very dissatisfied	2.5 %
3 points	2 %	Dissatisfied	9.5 %
4 points	0.5 %	Little satisfied	12.5 %
5 points	1.5 %	Satisfied	40 %
6 points	2 %	Very satisfied	35.5 %
7 points	7 %		
8 points	23 %		
9 points	31.5 %		
10 points	31.5 %		

(Continued)

Table 2. Comparison of SUCE and ERSaPaCE results *(Continued)*

SUCE scale		ERSaPaCE	
		Waiting time in minutes	
		10-15 minutes	21 %
		16-30 minutes	25.5 %
		31-60 minutes	35 %
		61-120 minutes	16 %
		121-180 minutes	2 %
		More than 180 minutes	0.5 %

SUCE (*escala de Satisfacción del Usuario de Consultas Externas*) = Outpatient Service User Satisfaction scale.
ERSaPaCE (*Escala Rápida de Satisfacción del Paciente de Consulta Externa*) = Outpatient Department User Satisfaction Rapid Scale.

design and evaluation, confers face value and criterion validity to ERSaPaCE. This way, the scale allows an evaluation of different aspects of outpatient care, including those inherent to the medical unit, as well as those involving the medical-paramedical and administrative staff (medical records department), similar to other scales.[6,10,13-20] In addition, it introduces waiting time (an important indicator of the quality of the service) and the opportunity for the patient to express any positive or negative opinion (congratulations, suggestions or complaints), bringing the patient closer to the service provider. The latter two innovative aspects make for the scale to provide highly useful information for health services administrators.

Full completion of the questionnaire is favored by its short extension: it consists only of 10 items that are rapidly and easily answered and a written opinion (optional), which is a great advantage in relation to other more extensive, more elaborate scales or instruments to be answered before and after the visit (appointments). All our patients completed the survey, and thus no one was eliminated. In addition, the faces designed by García Galicia et al., which have demonstrated great consistency and construct validity for subjective global scales,[12] were added as an equivalent to the values for each item.

The participation of different quality assessment experts who serve both in operational and directive areas, and who kept within the purposes of rapidness and practicality, gave the questionnaire a high value in terms of soundness and face value (construct validity).

When assessing patient satisfaction, the surveyed population was distributed in a gender-balanced manner, which avoided the bias that might exist for this reason. Regarding the age of the respondents, a wide

range of ages was obtained that included young, mature and older adults.

The specialties and departments involved were diverse (13 different specialties) and, sometimes, more than one doctor of some specialty was involved, which demonstrates the applicability of the scales.

ERSaPaCE registered an internal consistency of 0.608 by Cronbach's α, perhaps because it consists of few items (only 10) and because the aspects of the outpatient care process that were assessed were also quite varied and, presumably, of an independent behavior (assistants, nursing staff, doctors, medical records department, pharmacy, etc.). However, it showed acceptable convergent validity with SUCE, which in its validation recorded 0.8 by the same test.[10]

Given the characteristics and temporality of our study, exploration of the sensitivity to change remains outstanding, perhaps with the comparison of patient satisfaction before and after some maneuver intended to modify the outpatient care process, and thus improve the quality of care in this modality.

The findings of this work allow us claiming that ERSaPaCE is valid and consistent and that it constitutes a useful alternative to assess the quality of care in medical units.

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REVIEW ARTICLE

Considerations on genetic engineering: regarding the birth of twins subjected to gene edition

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Abstract

In this essay, the bioethical implications of the recent genetic manipulation in human embryos with CRISPR-Cas9 to eliminate the CCR5 gene and the birth of a pair of discordant twin girls are analyzed. The experiment was disseminated via social media. The main bioethical flaws identified include the justification of the model, the informed consent process and the lack of disclosure of evident conflicts of interest. The consequences of the experiment on the life of the twins that were born were not properly evaluated, such as the impact on their autonomy, the alleged benefits to be received and the future risks of harm during their lifetime. Having manipulated the germ cell line, the effects on their future offspring were not considered. This type of actions negatively affects the way society conceives science. Genetic engineering should be reserved to the basic experimental context or as clinical research for the correction of known serious diseases of genetic origin under strict regulatory and bioethical supervision and using a gradualist approach in accordance with the advances of gene editing techniques.

KEY WORDS: *Gene editing. CRISPR-Cas9. Bioethics.*

Reflexiones sobre la ingeniería genética: a propósito del nacimiento de gemelas sometidas a edición génica

Resumen

En este ensayo se analizan las implicaciones bioéticas de la reciente manipulación genética en embriones humanos con CRISPR-Cas9 para eliminar el gen CCR5 y el nacimiento de dos gemelas discordantes. El experimento se divulgó en medios sociales. Los principales problemas bioéticos identificados son la justificación del modelo, el proceso de consentimiento informado y la falta de declaración de evidentes conflictos de interés. No se evaluaron apropiadamente las consecuencias del experimento sobre la vida de las gemelas nacidas como la afectación a su autonomía, los supuestos beneficios por recibir y los riesgos futuros de daño durante su vida. Habiendo manipulado la línea celular germinal, no se consideraron los efectos sobre su descendencia futura. Este tipo de acciones tiene un impacto negativo en la forma como la sociedad concibe la

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ciencia. La ingeniería genética debe reservarse al contexto experimental básico o bien como investigación cínica para la corrección de enfermedades conocidas graves de origen genético, bajo estricta supervisión regulatoria y bioética y de manera gradualista de acuerdo con el progreso de las técnicas de edición genética.

PALABRAS CLAVE: *Edición genética. CRISPR-Cas9. Bioética.*

Introduction

By the end of November 2018, a story was released stating that a pair of twin girls that had been born a few weeks prior had undergone genetic engineering (genetic surgery, according to the promoter) by applying the CRISPR-Cas9 technique, when they were at embryonic stage, allegedly to protect them against the human immunodeficiency virus (HIV), which was carried by their father.

In Mexico, at the College of Bioethics we have established a reflective and analytical discussion about the particular case and, more broadly, about genetic engineering in the biomedical field. In this manuscript, we present the main arguments and reflections resulting from said discussion.

Human beings have learned to manipulate the genetic characteristics of living beings since thousands of years ago, even without knowing how and why such changes occur. Agriculture and domestication of some species of non-human animals are clear examples (*teocintle* is little recognizable as the plant that originated current corn). Scientific knowledge has allowed understanding the mechanisms whereby these evolutionary phenomena occur.

Genetic engineering brings together various tools and techniques that serve to make, very precisely, additions, deletions and alterations to the DNA; one of its purposes is to modify specific genes that are responsible for functional alterations in living beings, including humans. Although these techniques are practiced in any living cell (plant or animal), this document discusses exclusively genomic editing in human cells.

Currently, it is feasible to modify some genes responsible for alterations that result in diseases, which is known as gene therapy. However, it is recognized that the feasibility of something must always be subjected to a reflexive review that allows to justify the "why", "what for" and "when" of something about which we only know the "how" (and only halfway).[1] Being able to do something does not necessarily imply it should be done.

International and national documents relating the human genome

More than 20 years ago, the Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention, April 4, 1997) and the Universal Declaration on the Human Genome and Human Rights of the United Nations Educational, Scientific and Cultural Organization (UNESCO, November 11, 1997) were established. Both documents establish that respect for human dignity is above the applications that could be generated in this regard and restrict human genome modification exclusively for diagnostic or therapeutic reasons "... and only when it is not intended to introduce a modification in the offspring genome" (Article 13 of the Convention).

The General Statute of Health of Mexico considers that the study, research and development of the human genome is a matter of general public health and the Ministry of Health will be in charge of establishing the cases where control is required on this matter, making sure not to limit research freedom (title fifth bis). On the other hand, the Penal Code for the Federal District establishes sanctions for those who, for purposes other than elimination or reduction of serious diseases or defects, manipulate human genes in ways that may alter the genotype (Article 154).

Classification of the use of genetic engineering

Currently, the potential use of these genetic engineering techniques occurs in four contexts that deserve differentiated ethical-regulatory considerations.[2]

1. *Basic research:* use of genome editing to clarify the mechanism of biological processes in human disease and its treatment. There are established ethical and regulatory provisions to monitor human genome editing through laboratory in vitro models (e.g., registration of research protocols, evaluation and approval of the research process by ad hoc committees, monitoring of results, data presentation to peers, publication of final reports, etc.).

2. *Clinical application in somatic cells:* use of genome modification with the purpose to treat or prevent diseases or disability (e.g., to "correct" cells of different human tissues, except for germ cells). In addition to the provisions mentioned in the previous point, the use in somatic cells should be carried out in the context of clinical trials restricted to the treatment and prevention of disease or disability, with continuous safety and efficacy evaluation, within a context of expected risks/benefits assessment and within a framework of transparency.
3. *Clinical application in germ cells:* this use generates greater concern due to the fact that it is modifying the genome of cells whose changes can be inherited, i.e., human genome-integrated modifications induction and distribution in the population without properly knowing the effects they may have. Greater caution is required in terms of safety and unanticipated effects, since it can importantly impact on human beings from an individual point of view, but also as a species. From the bioethical point of view, germ cells genome modification can affect principles such as autonomy (insofar as the heirs of the modification do not decide on such inclusion in their genome), beneficence/non-maleficence (weighing of the potential benefits against the harm or risks it represents) and, finally, fairness (uneven distribution of benefits, risks and harm among the population, thus unequally affecting or benefiting parts of society). In this sense, international consensus recommends its use exclusively in situations whose only purpose is the treatment or prevention of a serious disease or disability (especially in situations where no other alternative is known), under strict supervision and following very specific criteria.
4. *Human enhancement:* it refers to the use of these technologies to cause cell changes in situations where there is no disease and functional capabilities of the individual are normal, through "human enhancement" (e.g., increased muscle mass to have more strength, increased cognition abilities, esthetic modifications). The use of these technologies outside the context of treatment of diseases or disabilities is currently considered improper, as long as no further information on the risks and potential side effects is available and the impact on the principles of autonomy, beneficence/non-maleficence and fairness cannot be assessed.

The CRISPR-CAS9 system

An important advance in genetic engineering techniques is derived from the description of DNA sequences with "clustered regularly interspaced short palindromic repeats" (CRISPR) originally found in bacteria.[3] The RNA produced with these sequences, in conjunction with an enzyme named Cas (cellular apoptosis susceptibility), such as Cas-9,[4] act as "scissors" to cut DNA at specifically determined sites and constitute that which is known as the CRISPR-Cas9 system, which is more efficient, cheaper and easier to use than other gene editing strategies.

On the other hand, the CRISPR-Cas9 technique has been widely used in the modification of genes in unicellular organisms, plants, non-human animals, somatic human cells and even in human embryos (with no reproductive purposes). The interest aroused by CRISPR-Cas9 in human medicine derives from the possibility to modify immune cells to attack cancer cells and developing treatments to cure genetic diseases such as sickle cell anemia, Huntington's disease, muscular dystrophy, cystic fibrosis, congenital hypertrophic cardiomyopathy, among others, as well as to create cells that are more resistant to different infections (e.g., infection triggered by the human immunodeficiency virus, HIV).

The Chinese experiment and its scientific-ethical flaws

On November 25, 2018, a video was launched in social networks where researcher He Jiankui (Southern University of Science and Technology in Shenzhen, China) announced the birth "a few weeks prior" of two twin girls who in the embryonic stage underwent gene editing using the CRISPR-Cas9 technology to inactivate the *CCR5* gene.[5]

This *CCR5* gene encodes the CCR5 membrane protein, which is necessary for HIV to enter the CD4 lymphocyte and infect it. The father of the twins is HIV-positive, while the mother is not and both wanted to procreate but feared the possibility of HIV transmission to their offspring. For this reason, they looked for help to assess the possibility of using the in vitro fertilization (IVF) technique with intracytoplasmic sperm injection (ICSI) using washed sperm, to generate an embryo and later transfer it to the mother's uterus for its gestation.

Dr. He, however, instead of following the recommended procedures for obtaining virus-free embryos,

manipulated them via CRISPR-Cas9 to achieve the modification of the *CCR5* gene. None of the procedures used by He are technically novel. Of course, assisted reproduction techniques such as IVF with ICSI have been clinically used throughout the world for years; furthermore, the sperm washing procedure is widely used to separate and obtain HIV virus-free mobile sperm. There is experience with the CRISPR-Cas9 technique in embryos of various species, even in human embryos. These techniques have barely been evaluated for their potential repercussions and risks in the short and long term, and bioethical discussion therefore revolves around intrauterine transfer of genetically modified embryos. The main identifiable bioethical issues in the "experiment" described by He are the following:

a) *Unsound experimental design*. One of the problems is that Dr. He experimented in humans (since their embryonic stage), i.e., he transferred human embryos manipulated with the CRISPR-Cas9 technique to the uterus of women for gestation. Technically, this experiment is already within the category of clinical application for reproductive purposes in embryonic cells and contravenes the consensus recommendations published since 2015 by a group of experts in gene editing.[6] Dr. He reported other gestations, but the data are unknown. The twin girls should be considered as an experiment by themselves and not only as the product of an experiment. The effects of the genetic manipulation they were subjected to must still pass the test of time in terms of the alleged beneficial effects expected for the babies and their future offspring, which only follow-up throughout time will be able to identify. The theoretical benefits (e.g., protection against HIV infection) can only be confirmed by unprotected exposure to HIV infection, which in turn would be bioethically unacceptable.

b) *That which was offered was not done.* He's experiment has the problem that it did not correct a genetic defect, but deleted a gene; the twin girls turned out being discordant (one without the two alleles of the gene [complete knockout] and the other with an allele [partial knockout]). People with *CCR5* gene mutations are known to naturally exist in the population and to be resistant to HIV infection, which was the rationale for the manipulation performed by He. However, these mutations may predispose to other infections or increase their severity (e.g., West Nile[7] or influenza virus[8]). In addition, in the twin girls experiment, it is unknown if the "gene edition" (or genetic surgery as the involved researchers euphemistically called it) was achieved in all cells of the embryo or only in a certain number (mosaicism) and if the CRISPR-Cas9 effect on these cells occurred only in the position of the *CCR5* gene or if there were other DNA sites subjected to the same effect (off-target effect, which can only be determined by sequencing the entire genome of the babies, which was not done).

c) *Invalid medical justification*. There is no medical justification about the reasons for conducting the experiment. The reason presented to the parents was "to make their daughters immune to HIV infection", which is misleading, since the blockage or absence of CCR5 does not provide immunity, but makes the host not susceptible to infection (the virus cannot enter the cells). In addition, the parents did not require what they were offered, since there are established and highly effective recommendations for generating HIV-free children of infected parents (sperm washing, pre-exposure prophylaxis [highly active antiretroviral therapy]).[9]

d) *Presentation of the facts in the form of publicity.* Scientific knowledge acquires a progressive value when the data supporting research are subjected to scrutiny by peers, when they are tested and the results are replicated. This is usually made through short communications in conferences and scientific meetings or through publication in scientific journals, after peer review and approval. In this case, the specific experimental data are unknown and no scientific communication has been generated in this regard. He preferred the use of electronic social media (YouTube[5]) in a sensationalist and misleading format.

e) *Inappropriate informed consent process.* The informed consent process is essential for the participation of human subjects in experimental projects and is based on respect for the autonomy and dignity of people. The consent process would appear to be biased towards the interests of the researcher and be misleading, as it offers the parents something beyond its proven possibilities and hides information about the risks and uncertainty of potential benefits. It is not known if the parents were clearly explained that they were actually making a proxy decision for their

daughters, if they realized that this decision was for life and that it includes their potential offspring. In other words, the future interests of the babies were transgressed without a really informed consent of their parents, who allegedly agreed to the experiment.

f) *Serious ethical-regulatory offenses.* The protocol registration process appears to have been extremely soft, with little information about what the experiment was really intended for (gestating genetically manipulated embryos) and using a triumphalist language (as they wrote in the protocol approval application: "This is going to be a great science and medicine achievement ever since the IVF technology, which was awarded the Nobel Prize in 2010").[10] The hospital where the embryo transfer and implantation clinical procedure was carried out and where the babies were finally supposed to have been born, published a statement denying their participation and claiming that "the signatures approving the protocol by its Medical Ethics Committee were forged". All of the above contravenes the principles of transparency, openness and peer review a scientific process is currently committed to, and generates the perception in society that the scientific process is not serious and even fraudulent due to laxity in regulations and to the fact that only economic or media profits are sought.

g) *Serious non-disclosed conflicts of interest.* Finally, the researcher He has serious conflicts of interest he did not declare, since he is shareholder of seven high-tech genetics companies and legal representative in six more, possibly involved in the experiment.

Impact of the "HE case" on genetic engineering and genome editing technologies

Genome editing using CRISPR-Cas9 and similar techniques is a highly promising tool with high potential to eliminate, control or mitigate various diseases. Being able to cure monogenetic diseases such as Huntington's disease, Tay-Sachs disease or cystic fibrosis is not only permissible but also desirable. Clinical trials using this technology for the deactivation of the PD-1 protein gene to treat patients with lung, prostate, bladder and kidney cancer have already been carried out.[11,12] *ApoE* gene edition to control Alzheimer's disease is being explored, and manipulating the same CCR5 gene to improve HIV control is being attempted (in somatic cells of patients with HIV, not in embryonic cells). Recently, it was published that this *CCR5* gene is a therapeutic target for nerve regeneration and functional recovery after stroke and traumatic brain injury.[13]

Conclusions

Demonizing scientific research (basic and clinical) due to cases such as the referred one is a negative effect that should be avoided. The analysis of these flaws coincides with others that have been published[14] and is a call of attention for the scientific community to recognize the importance of bioethical aspects in the execution of projects of this nature. Based on the above, and considering that this is a relevant issue that affects science in Mexico, the following final considerations are proposed:

1. Genome editing should be gradually applied, in such a way that it answers to the state of existing scientific evidence. Its use in basic research and its therapeutic use in somatic cells should be allowed and stimulated following existing ethical guidelines, transparently and under the supervision of established and duly registered review structures (research committees, research ethics committees, National Bioethics Commission, etc.).
2. The use in germ cells should only be allowed in the context of the resolution of diseases or serious disability, under special registration and supervision, as well as with a broadly informed consent of the parents, as long as potential risks and short- and long-term side effects and those with transgenerational reach (inheritable genomic modification) are not determined by other means (similar position to others that have been published[15-18]).
3. Application of these technologies to human medicine should be carried out in academic institutions with proven capacity (human resources and equipment), with clear lines of research and beyond possible conflicts of interest. The use of gene editing should respond to genuine scientific and medical interest and the researchers involved should be free of potential conflicts of interest, either economic, industrial, political or media notoriety-related.
4. The scientific community has an ethical obligation to be transparent before society and to diffuse the facts and data it confirms, as well as to

explain the methodologies it uses in order to lift scientific culture and make society in general, and decision makers in particular, see the difference that said scientific knowledge has with regard to other knowledge deriving from dogmas, superstitions, traditions and customs.

5. Introduction of public policies and regulatory norms that inhibit or are contrary to scientific and medical activity in the field of genome editing in humans should be avoided, following the above-set forth guidelines.

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REVIEW ARTICLE

Fragile X syndrome: clinical presentation, pathology and treatment

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Abstract

Fragile X syndrome is the monogenetic condition that produces more cases of autism and intellectual disability. The repetition of CGG triplets (> 200) and their methylation entail the silencing of the FMR1 gene. The FMRP protein (product of the FMR1 gene) interacts with ribosomes by controlling the translation of specific messengers, and its loss causes alterations in synaptic connectivity. Screening for fragile X syndrome is performed by polymerase chain reaction. Current recommendation of the American Academy of Pediatrics is to test individuals with intellectual disability, global developmental retardation or with a family history of presence of the mutation or pre-mutation. Hispanic countries such as Colombia, Chile and Spain report high prevalence of fragile X syndrome and have created fragile X national associations or corporations that seek to bring patients closer to available diagnostic and treatment networks.

KEY WORDS: *Fragile X syndrome. FMR1 gene. FMRP protein.*

Síndrome X frágil: presentación clínica, patología y tratamiento

Resumen

El síndrome X frágil es la condición monogenética que produce más casos de autismo y de discapacidad intelectual. La repetición de tripletes CGG (> 200) y su metilación conllevan el silenciamiento del gen FMR1. La proteína FMRP (producto del gen FMR1) interacciona con los ribosomas, controlando la traducción de mensajeros específicos y su pérdida produce alteraciones de la conectividad sináptica. El tamizaje de síndrome X frágil se realiza por reacción en cadena de la polimerasa. La recomendación actual de la Academia Americana de Pediatría es realizar pruebas a quienes presenten discapacidad intelectual, retraso global del desarrollo o antecedentes familiares de afección por la mutación o premutación. Países hispanos como Colombia, Chile y España reportan altas prevalencias de síndrome X frágil y han creado asociaciones o corporaciones nacionales de X frágil que buscan acercar a los pacientes a redes disponibles de diagnóstico y tratamiento.

PALABRAS CLAVE: *Síndrome X frágil. Gen FMR1. Proteína FMRP.*

Introduction

Fragile X syndrome (FXS) is a non-Mendelian nucleotide repeat disorder. FXS is due to the loss of function of the fragile x mental retardation 1 (*FMR1*) gene. The *FMR1* gene is found in chromosome Xq27.3 and encodes the FMRP protein, whose function is to control the translation of specific messengers. The repetition of CGG triplets (> 200 repeats) and methylation of the promoter entail silencing of the gene. However, the biological mechanism responsible for

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the presence of FXS is not fully elucidated. Approximately 30 % of girls and 90 % of boys affected with the full mutation have intellectual disability and 60 % of boys are diagnosed with autism spectrum disorders (ASD). Anxiety disorders occur in between 70 and 80 % of individuals with FXS.

FXS most accepted prevalence is approximately one in 5000 males and one in 4000 to 8000 females. However, there is still no global consensus due to the complexity of molecular diagnosis and the variety of clinical presentations in those who are not severely affected.[1] Much higher prevalence rates have been reported in Spain[2] and Colombia, where a genetic conglomerate with the highest prevalence of the syndrome so far was recently reported,[3] whereas an almost non-existent prevalence is reported in China, where the lack of research and clinical specialization in neurodevelopmental areas are speculated to be the main causes of the diagnostic sparsity of the syndrome.

Fragile X syndrome biological bases

The exact biological mechanism responsible for the occurrence of FXS is not known; however, it is known to lie in the ability of the FMRP protein to bind to RNA and proteins. Specifically, FMRP binds to ribosomes and is present in synaptic compartments, where it controls the translation of specific messengers. The loss of FMRP causes synaptic connectivity alterations in neurons, which result in FXS specific symptoms. These synaptic connectivity alterations are clearly observed in the brain as a decrease in the amount of dendrites and spines in the neurons of patients with FXS.

The lack of FMRP in neurons leads to glutamate receptors, both metabotropic ($mGluR_5$) and ionotropic (AMPA and NMDA), exacerbated expression.[4] γ-aminobutyric acid (GABA) and GABA receptors synthesis, degradation and transport proteins are also reduced.[5] The mechanisms whereby these changes in neurotransmitter systems affect the morphology of dendrites and spines in neurons is not exactly known, but they are suspected to be related. The role of the FMRP protein in glial cells is less known, but in FXS, the FMRP protein is known to regulate the translation of $mGluR_5$ in astrocytes[6] and the production of myelin in oligodendrocytes.[7] During prenatal development, radial glial cells contain FMRP, which intervenes in messenger RNA active transport along the glial fiber.[8] A change in any of these mechanisms can contribute to the development of cognitive disorders in patients with FXS.

FMRP has been associated with ion channel regulation. FMRP binds to the C-terminus of potassium-activated Slack channels. Slack channels' activation contributes to the activation patterns of a wide variety of neurons, suggesting that the alterations observed in FXS may be generated by altered activity patterns.[9] In turn, FMRP can also regulate the release of neurotransmitters through modulation of the action potential via large-conductance calcium-activated potassium channels (BK channels).[10]

The presence of a small fraction of FMRP in the cell nucleus indicates that said protein may have previously unrecognized functions. In fact, several studies have unveiled functions related to DNA expression and genomic function, such as DNA stabilization, DNA epigenetic regulation, nuclear RNA regulation and response to DNA damage.[11]

The amyloid β precursor protein (APP) has also been associated with FXS, through an $mGluR_5$ receptor-dependent mechanism. APP is processed by secretases that produce amyloid β (Aβ), a peptide that is predominant in senile plaques in Alzheimer's disease.[12]

Clinical presentation

Individuals affected with the *FMR1* gene full mutation have special phenotypic features that include an elongated face, large and prominent ears, joint hypermobility and macroorchidism.[13] More than 90 % of affected children have developmental delay and approximately 50-60 % are diagnosed with ASD.[14] During the course of their lives, both males and females show behavioral alterations commonly associated with the syndrome, usually of onset during childhood: anxiety and attention deficit and hyperactivity disorder (ADHD) are the most prevalent, although compulsive disorders such as hyperphagia and aggressiveness are also common (Table 1). In addition to behavioral alterations and learning and social adaptation problems, 15 to 20 % of patients with FXS have seizures, which are more prevalent in those with autism; more than 30 % have obesity problems, sleep disturbances and some gastrointestinal dysfunction, including gastroesophageal reflux. Strabismus and recurrent otitis media are common problems during early childhood.

The phenotype has some variants. Males are most commonly affected with the mutation; females have a phenotype that is attenuated by the activation index of the second unaffected X chromosome. More than 70 % of affected females have a low IQ, although this is considered average in comparison with the general

Table 1. Clinical characteristics

	Clinical characteristics	Prevalence
Physical	Long and narrow face Macrocephaly Prominent ears Prominent jaw Flat feet Macroorchidism Joint hypermobility	83 % more common in adults 50-81 % 75 % 80 % in adults 29-69 % 95 % since adolescence 50-70 % more common in boys
Psychological/psychiatric	ADHD ASD Anxiety Aggressiveness	80 % boys and 40 % girls 50-60 % boys and 20 % girls 58-86 % 40 % boys and 10-15 % girls
Developmental	Intellectual disability Language deficit	85 % boys and 25-30 % girls 100 % boys and 60-75 % girls
Other	Strabismus Otitis Gastrointestinal problems Obesity Seizures	8-30 % 50-75 % in childhood 30 % 30-60 % 15-20 %

Adapted from reference 14. ADHD = attention deficit and hyperactivity disorder, ASD = autism spectrum disorder.

population and in a lower proportion in comparison with males who have language problems.[13] The second variant are mosaics, which have some cell lines with the full mutation and others within the premutation range, which exposes them to the risk of suffering from the problems inherent to premutation such as tremor/ataxia syndrome (FXTAS);[15,16] or some cell lines with methylation and, therefore, with the silenced gene, and others without methylation, and in this case those affected also have a lower degree of cognitive compromise.[17]

In addition to the commonly recognized phenotypic characteristics, affected individuals have connective tissue anomalies of variable presentation, which are attributed to the fact that FMRP regulates essential components of the extracellular matrix. In addition to the most common musculoskeletal alterations, such as hyperextension of the metacarpophalangeal joints, flat feet and scoliosis, alterations in the cardiovascular and genitourinary systems have been described.[18]

Magnetic resonance imaging (MRI) of the brain of patients with FXS show that the brain is usually larger than normal and with an increase in the size of the lateral ventricles. The cerebellar vermis exhibits hypoplasia, one of the most representative features, which can be accompanied by a reduction of the entire cerebellum and alterations of the cerebellar peduncles. In addition, the caudate nucleus, especially the head, is larger, mainly in males. The hippocampus is also enlarged in young patients. In contrast, the insula and the amygdala are smaller. In addition, the uncinate fasciculus also exhibits white matter alterations.[13]

Interaction between FXS, autism and attention deficit and hyperactivity disorder

There is a close relationship between the presence of FXS, ASD and ADHD. Approximately 2 % of all cases diagnosed with autism spectrum disorders (ASD) are attributable to FXS, whereas more than 60 % of children with FXS are diagnosed with ADHD, ASD or both. FXS is the main genetic known cause of ASD; however, only 20 % of autism cases are recognized as the result of monogenic mutations, and only 2 to 6 % are due to *FMR1* gene mutation. Individuals affected by both morbidities, as it occurs in 50 to 60 % of boys and 20 % of girls with FXS, have more severe involvement of both cognitive and language deficits and behavioral problems.[19] Controlled clinical trials have demonstrated that, although FXS and ASD share psychiatric symptoms, affected individuals do not respond with the same efficacy to specific treatments,[20,21] which suggests that the same symptoms are originated by different mechanisms.

Diagnosis

Approximate age at FXS diagnosis is 36 months,[22] despite the fact that most parents report identifying some type of neurodevelopmental delay during the first year of life. Screening of high-risk populations can be carried out with polymerase chain reaction (PCR), a test of relatively low cost that requires a single drop of blood. The method uses a chimeric primer that

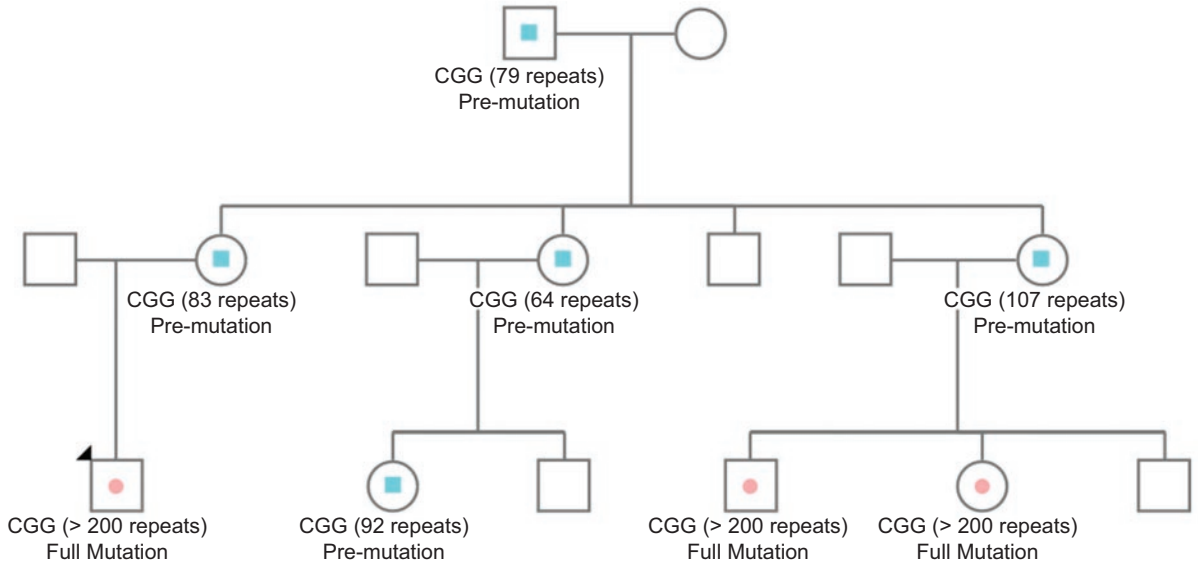

Figure 1. *Family tree. When establishing the molecular diagnosis, diagnostic cascade testing of all members of the immediate family is suggested. The male carrying the first-generation pre-mutation passes the pre-mutation to 100 % of his daughters, while his sons will not be carriers of the pre-mutation or the full mutation. The sons and daughters of women in the second generation have a 50 % likelihood of having the pre-mutation or the full mutation. Only females with the pre-mutation have the capability to expand the full mutation to both their male and female children and they have the capability to develop FXS, as well as those affected in third generation.*

Table 2. Fragile X syndrome clinical checklist

Characteristic	Score	
	1	2
Skin soft and velvety on the palms with redundancy of skin on the dorsum of hand		X
Flat feet		X
Large and prominent ears		X
Plantar crease	X	
Macroorchidism*	X	
Family history of intellectual disability	X	
Autistic behavior	X	
Total	4	6

*Males after puberty. The highest score is 10 points for males after puberty and nine for males prior to puberty or females. In patients with a score higher than 5, FXS molecular diagnosis should be considered. Adapted from reference 27.

randomly targets within the CGG enlarged region in the *FMR1* gene.[23] This method has been successfully used in several population-based studies.[2,3] The confirmatory diagnostic test is Southern Blot. Tejada made a thorough evaluation of the advantages and controversies of FXS prevention using prenatal diagnosis.[24] In 2017, Riley and Wheeler described the problems for postnatal screening to be established in the United States.[25] The American Academy of Pediatrics current recommendation is to carry out genetic testing in children with intellectual disabilities or global developmental delay.[26] If a new FXS case is found, diagnostic cascade testing should be performed in all members of the immediate family, in order to identify carriers of the premutation that have the potential to expand the full mutation to their offspring (Figure 1). Recently, Lubala et al. carried out a meta-analysis where 10 screening studies were included and a clinical score was proposed for the seven most specific features of FXS; this list takes into consideration the differences, especially the facial ones, which can be found in different ethnic groups. This clinical tool is of utmost importance in areas where not all individuals affected with intellectual disability or ASD can undergo genetic testing due to limitations in available resources (Table 2).[27]

Diagnosis in Hispanic countries

Despite the recommendation to carry out genetic tests in children with intellectual disabilities or global developmental delay and in those whose families are affected, these tests are not practiced in numerous Hispanic countries. Genetic diagnostic tests are available and several countries in Latin America have reported studies on the prevalence of FXS; however, determining the true prevalence of genetic disorders is difficult because in numerous Hispanic nations there is no official national registry. Countries such as Chile, Brazil, Colombia, Argentina, Peru and Spain have raised awareness on the

Table 3. Medications with efficacy in the treatment of fragile X syndrome

Medication	Maximum dose/day	Common adverse effects
Metformin	1000 mg < 50 kg 2000 mg > 50 kg	Nausea, diarrhea, headache, weight loss
Sertraline	2.5 to 5.0 mg children from 2 to 6 years 10 to 100 mg children older than 6 years and adolescents	Diarrhea, appetite loss, hyperhidrosis, tremor
Minocycline	25 mg < 25 kg 50 mg 25-45 kg 100 mg > 45 kg	Nausea, diarrhea, headache, dizziness, appetite loss, tooth and oral cavity discoloration, rash
Lovastatin	40 mg	Weakness, gastrointestinal symptoms, muscle pain/ tenderness/weakness, dizziness, headache, irritability
Acamprosate	1332 mg < 50 kg 1998 mg > 50 kg	Irritability, depressive symptoms, increased repetitive behavior, gastrointestinal symptoms including diarrhea and constipation

Adapted from references[21,29,33,38].

need for better screening and diagnostic processes for prevalent genetic diseases, including FXS, to be implemented. In addition, there are economic, political and social barriers the neurogenetic field has to face, mainly in developing countries.[2,3] Currently, FXS diagnosis is mainly based on phenotypic findings, with the possibility of genetic testing upon recommendation of the specialist. In many cases, tests are not performed due to their high cost, because they are not covered by health insurances and, in other cases, due to the limited availability of certified laboratories to perform DNA analyses in blood samples.

Treatment

There is no cure for FXS, and treatment is therefore limited to the control of associated symptoms. Currently, the research lines focus on developing effective treatments for the different psychiatric and cognitive problems suffered by those affected (Table 3). In 2017, Gantois et al. investigated the efficacy of metformin as a modulator of the mGluR/mTORC1-ERK cascade in animal models of FXS, and reported an improvement in social and cognitive behavior, as well as in morphological (dendritic spine dysgenesis and macroorchidism) and electrophysiological abnormalities (long-term depression).[28] These findings motivated the initiation of metformin treatment research in clinical practice. The first report showed benefit mainly in problematic behaviors such as irritability, aggressiveness and social evasion in adult patients with FXS, in addition to benefits in appetite and weight control in subjects with the Prader-Willi phenotype.[29] For this reason, current controlled studies both in the United States and Canada seek to determine the efficacy of metformin in the treatment for this syndrome.

Sertraline is a first-line medication for the management of depression and anxiety. It was studied for its potential benefit on language; however, it showed better results in motor and visual perceptual skills and social participation in FXS.[21]

Minocycline is also considered a beneficial treatment in FXS. It has been shown to reduce the levels of matrix metallopeptidase 9 (MMP-9),[30] a zinc-dependent endopeptidase responsible for regulating synaptic activity, which is critical for central nervous system development and plasticity.[31] Its inhibition is caused by its binding to FMRP, a protein that is absent in FXS. MMP-9 regulation problems are considered part of the pathophysiology not only of learning problems, but also of abnormalities found in the connective tissue.[18]

Acamprosate, an mGluR5 receptor antagonist, modified anxious behavior and locomotor tests in an FXS animal model[32] and demonstrated improvement in areas of social behavior and hyperactivity in pediatric patients with ASD and FXS.[33] It should be considered a beneficial medication for the management of patients with FXS and alcohol addiction problems.[34]

Studies of lovastatin treatment in FXS animal models postulate this medication as prophylactic treatment for epileptogenesis and suggest that it might improve sensory and cognitive functions.[35] Non-controlled clinical trials demonstrated good tolerance to the treatment, with few adverse effects, and reported benefits in both behavior and adaptive skills.[36] At the molecular level, changes in extracellular signal-regulated kinase (ERK) phosphorylation were shown to be related to clinical response to lovastatin.[37]

There are other medications that can improve neurobiological systems in FXS and that are not considered specific treatments for the syndrome, but that

help to control the most common psychiatric characteristics. These include stimulants (methylphenidate and amphetamines) and atomoxetine, which can improve symptoms of attention disorder and hyperactivity syndrome, usually in children older than five years; alpha adrenergic agonists (guanfacine or clonidine) can also be used in children younger than five years of age to calm hyperactivity. Clonidine is especially effective in improving sleep disorders, should there not be a good response to melatonin treatment. For the management of aggressiveness or mood disorders, antipsychotics (risperidone or aripiprazole) are adequate, but they can cause weight gain.

Conclusion

Individuals affected with FXS have intellectual disability, ASD and ADHD. Although there are many medications for the management of common comorbidities, there are no specific treatments. The goal of early treatment is to improve intellectual disability and communication and social interaction difficulties, which are characteristic of FXS. In addition, despite the recommendation to perform genetic testing in children with intellectual disabilities or global developmental delay, this is not carried out in many of the Latin American countries. It is of utmost importance for FXS analysis to be implemented in all Hispanic countries.

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Conflicts of interest

Randi J. Hagerman has received funds from Roche, Novartis, Neuren, Marinus and Alcobra to carry out therapeutic studies in patients with FXS. He has also consulted with Fulcrum and Zynerba about therapeutic studies in individuals with FXS. The other authors declare that they have no conflicts of interest.

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REVIEW ARTICLE

Acquired hemophilia

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Abstract

Acquired hemophilia (AH) is an autoimmune hemostatic disorder mediated by autoantibodies directed against factor FVIII:C. In 52 % of cases, the cause is unknown or is not associated with other pathological entities; in the rest, there are concomitant factors: lupus, rheumatoid arthritis, cancer, pregnancy, and medications. In Mexico, there is not a registry of AH, and awareness of the disease among health personnel is low. The groups with the highest incidence are women of childbearing age and individuals older than 70 years. It is characterized by severe bleeding, especially after trauma and normal childbirth or cesarean delivery, and large ecchymoses in the trunk and extremities. The suspicion is simple, it just takes for sudden, severe hemorrhage and a prolonged aPTT that is not corrected with plasma to concur in an individual. Treatment involves achieving hemostasis and eradicating the antibody. The former is achieved with recombinant activated factor VII or activated prothrombin complex concentrate. Cyclophosphamide, prednisone or rituximab are used to eradicate the antibody. Most cases of AH are not diagnosed, which translates into a high mortality rate. Given that awareness about the disease among physicians is low, it is not suspected, neither diagnosed, and nor is it treated. This document reviews the most recent data on AH and expands on its diagnosis and treatment.

KEY WORDS: *Hemophilia. Acquired hemophilia. Factor VIII. Autoimmunity. Autoantibodies*

Hemofilia adquirida

Resumen

La hemofilia adquirida (HA) es un trastorno hemostático autoinmune ocasionado por autoanticuerpos dirigidos contra el factor VIII:C. En 52 % de los casos, la causa se desconoce o no se asocia con otra entidad patológica; en el resto, existen factores concomitantes: lupus, artritis reumatoide, cáncer, embarazo y medicamentos. En México no existe registro ni conciencia de la enfermedad entre el personal de salud. Los grupos de mayor incidencia son las mujeres en edad reproductiva y los indiv duos mayores de 70 años. Se caracteriza por hemorragia grave, sobre todo posterior a traumatismos y parto o cesárea, y equimosis grandes en tronco y extremidades. La sospecha es simple, basta que concurran hemorragia súbita, grave y un TTPa prolongado que no se corrige con plasma. El tratamiento consiste en lograr la hemostasia y erradicar el anticuerpo; lo primero se logra con el factor VII activado recombinante o concentrado del complejo de protrombínico activado. La ciclofosfamida, prednisona o rituximab sirven para erradicar el anticuerpo. La mayoría de los casos no son diagnosticados y la mortalidad es alta. Ya que los médicos desconocen el problema, no se sospecha, no se diagnostica y no se trata. Este documento revisa los datos más recientes de la HA y abunda en el diagnóstico y tratamiento.

PALABRAS CLAVE: *Hemofilia. Hemofilia adquirida. Factor VIII. Autoinmunidad. Autoanticuerpos.*

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Introduction

Acquired hemophilia (AH) is a hemostatic disorder resulting from the development of autoantibodies (auto-Ab) mainly directed against factor FVIII:C (FVIII coagulant activity). These antibodies cause hemorrhages with a high risk of morbidity and mortality. In this review, most concepts refer to AH caused by anti-FVIII auto-Abs, although there are cases involving other factors: V, VII, IX, X, XII and XIII.[1]

AH is an autoimmune condition. Most usually, it appears as a result of uncontrolled production, with no apparent cause, of IgG-type auto-Abs capable of neutralizing the effect of FVIII; therefore, these auto-Abs are also called "inhibitors". Unlike congenital hemophilia A, where the inhibitor is an anti-FVIII alloantibody (allo-Ab) induced by the applied factor, in AH, auto-Abs appear without exposure to FVIII[2] (Table 1).

In 52 % of AH cases there are no concomitant diseases; however, in the rest, it coexists with other pathologies:

- Autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, pemphigus, chronic inflammatory bowel disease, asthma or severe allergic reactions.
- Lymphoproliferative conditions and solid tumors (lymphoma, leukemia, macroglobulinemia, prostate and lung cancer).
- In primiparous women within the first three months of postpartum[3] (Figure 1).

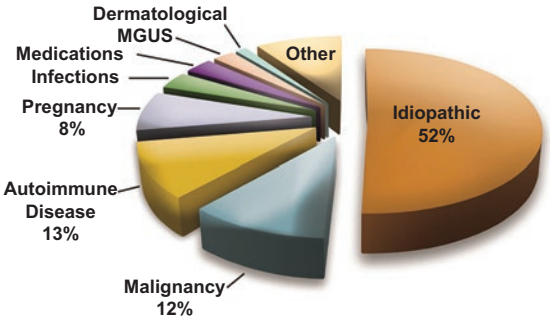

Figure 1. *Human FVIII domains.*

Epidemiology

The incidence of AH is very low. The literature is limited to case series, records and single-center experiences. It is estimated at 1.3 to 1.5 cases/million people/year,[4] which is why it is considered an "orphan" disease, although probably there are many undiagnosed cases.[3] In Mexico there is no registry, but we can make inferences based on experience from La Raza National Medical Center of the Mexican Institute of Social Security, whose area of influence is three million population and only 13 cases have been recorded in 30 years (estimated incidence of 0.43 patients/year). However, this is a reference center and underdiagnosis of the disease seems therefore evident. The incidence graph shows a bimodal pattern. The first peak corresponds to fertile women aged between 19 and 40 years; the second occurs in older adults (median age: 73.9 years, range 64 to 78), with a predominance in males (1.4:1)[4,5] (Figure 2).

Immunological aspects

AH occurs as a result of the production of polyclonal IgG1 and IgG4, with kappa light chains, directed against hot spots of FVIII A1, A2 and C2 domains. Although auto-Abs can be generated against any hemostatic factor, FVIII characteristics make it a preponderant target. It is not clear why tolerance to FVIII is lost, but genetic and environmental factors are argued.[2] Genetic predisposition (immune response

Table 1. Main differences between acquired and congenital hemophilia

Acquired hemophilia	Congenital hemophilia
Mainly older adults	Usually during childhood
Has no hereditary pattern	X chromosome-linked inheritance pattern
Male:female ratio is 1:1	Most are males
Hemarthrosis is rare	Hemarthrosis is common
Auto-Ab with type 2 kinetics	Allo-Ab with type 1 kinetics
No correlation between FVIII:C concentration and hemorrhage severity	Correlation between FVIII:C concentration and hemorrhage severity
Elevated mortality	No immediate impact on mortality

Taken from Webert KE. Acquired hemophilia A. Semin Thromb Hemost 2012;38:735-741.

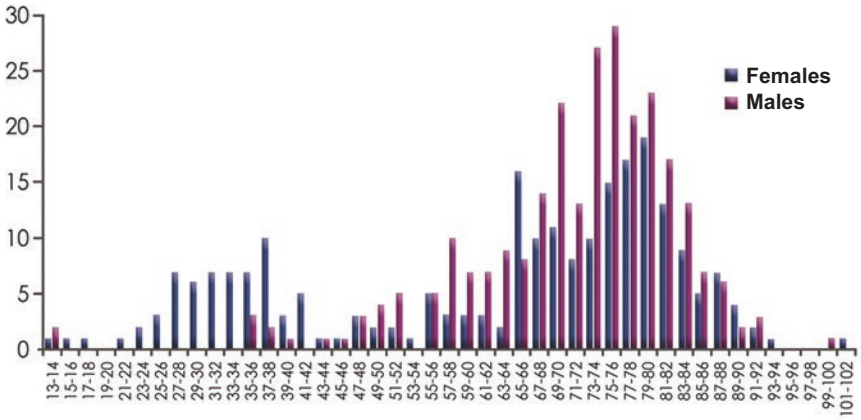

Figure 2. *Distribution of acquired hemophilia cases from the European registry EACH2.*[3]

Figure 3. *Acquired hemophilia distribution according to its primary or secondary nature (taken from reference 15).*

genes and HLA genotype) is suggested due the association between AH and cytotoxic T-lymphocyte antigen-4 polymorphisms (CTLA-4 + 49 G) and expression of HLA class II DRB1*16 and DQB1*050210 alleles.[2] There is an abnormal balance of TCD4 + Th1 and Th2 cells, which enables the production of the auto-Ab. The predominance of the IgG subclass induced by CD4-Th2 T-cells is associated with higher concentrations of auto-Ab and a poorer prognosis; when Th1 T-cells predominate, the response to immunosuppressive therapy increases.[6]

AH-associated auto-Abs inhibit FVIII function or increase its clearance, which induces a drop in the hemostatic effect. Figure 3 shows a diagram of this factor's molecule. By reacting against FVIII, auto-Abs inhibit its interaction with activated FIX (a) and with FX (A2-A3 domains). This inhibition alters thrombin and fibrin generation. The C2 domain is where FVIII binds to vWF and phospholipids, so that if this domain is intervened, FVIII stabilization provided by vWF is modified, which shortens the half-life of the latter.[7]

Clinical presentation and diagnoses

AH presentation is characterized by two elements. The first one is clinical, usually in the form of typical extensive ecchymoses, mucosal hemorrhage or even internal hemorrhage in patients without a bleeding history. Almost always, AH occurs abruptly, severely and aggressively in previously healthy patients. Less frequently, there is an underlying or primary pathology that is exacerbated by hemorrhage or anemic syndrome due to blood loss. The second element is paraclinical, characterized by isolated activated partial thromboplastin time (aPTT) prolongation that is not corrected when mixed with normal plasma. AH is suspected in patients without a hemorrhagic history, with or without apparent bleeding and who, without receiving anticoagulants, have isolated and unexplained prolonged aPTT. The suspicion increases if the patient has any risk factor: autoimmune disease, cancer, age older than 60 years and pregnancy or puerperium. Other hemostatic tests (platelets, prothrombin time, fibrinogen and thrombin time) are usually normal. AH should be ruled out in patients without apparent hemorrhage, but with prolonged aPTT that is not corrected with normal plasma and who are not positive for lupus anticoagulant.[8]

Almost 94 % of patients have hemorrhage, which is associated with a mortality of 9 to 33 %.[7] The hemorrhage appears upon unrecognizable ("spontaneous") stimuli or is post-traumatic. Severe hemorrhages account for 80 to 90 % of events and the most common sites are the central nervous system, gastrointestinal, prostate, retroperitoneum and lung. Sometimes, bleeding is caused by diagnostic or therapeutic interventions. Death from bleeding usually occurs within the first weeks of evolution; late mortality is associated with the primary disease and immunosuppressive treatment.[4] Although AH is a rare disease with high risk of morbidity and mortality, clinical experience is limited because most evidence comes from isolated cases.[9] When AH is associated with a primary pathology, its characteristics impose its clinical hallmark.

At first-contact services (emergency department, obstetrics & gynecology, family medicine, internal medicine and oncology),[10] the disease is not suspected and invasive maneuvers are indicated for

comprehensive care, but since this is a hemostatic problem, they turn out being counterproductive as they increase the risk and intensity of hemorrhage or bring the situation to critical states due to massive or vital organ bleeding. Final diagnosis is usually late (up to 30-day delay).[8] The responsibility is huge because there should be a high index of suspicion in order to establish an early therapy that improves the prognosis, since acute treatment almost always falls on these specialists, while the stable and definitive resolution phase depends more on the hematologist.

Unlike congenital hemophilia, AH occurs with large, diffuse, painful ecchymoses that can generate anemia. Other manifestations include muscle and gastrointestinal and genitourinary mucous membrane hematomas. Hemorrhage also complicates the situation of the postoperative patient or patients with wounds. There may be retroperitoneal hemorrhage,[9,11] but joint or intracranial bleeding is less frequent.[11] Muscle hemorrhage can lead to large blood loss and, if not properly and promptly treated, it generates vascular or nervous ischemia due to compression.[12] Large hematomas in the legs can be misdiagnosed as deep vein thrombosis;[12] if antithrombotic agents are indicated, they will induce massive hemorrhages. Abscess formation is another complication if treatment is delayed. Deep muscle hemorrhage, as in the psoas, is difficult to diagnose and is confused with acute abdomen, indicative of subsequent surgery. Any surgery is complex due to high hemorrhagic risk and can result in death even with dental extractions, biopsies or central catheter placement.

Screening or confirmatory tests can be misinterpreted. Any mild or moderate hereditary coagulopathy can go unnoticed but manifest itself lately as bleeding. This is ruled out by anamnesis and hemostatic tests correction by mixing the patient's plasma with normal plasma. Correction suggests factor deficiency and rules out the presence of inhibitors. Another confounding condition is lupus anticoagulant, auto-Ab associated with prolonged aPTT and a pattern of non-correction with normal plasma. There are differences between the AH auto-Ab, which requires time and temperature to fully manifest itself, and lupus anticoagulant, which requires neither time nor temperature, in addition to being associated with thrombosis.[13] A highly complicated scenario occurs when both auto-Abs coexist. Although disseminated intravascular coagulation should be considered in differential diagnosis, it is ruled out if coagulation tests show a multiple factor deficiency profile, in addition to data consistent with consumption, such as D-dimer increase and thrombocytopenia.[14]

Acquired hemophilia and pregnancy

Symptoms are heterogeneous in terms of presentation and intensity. Hemorrhage is always moderate or severe, and in 50 % there is no triggering factor.[15] Up to 75 % of pregnancy-associated AH occurs in primigravid women.[16] Hemorrhages are almost always subcutaneous, mucosal or retroperitoneal, and hemarthrosis is very rare. Occasionally, bleeding appears up to six weeks after delivery. AH rarely complicates pregnancy; it has a better prognosis because spontaneous remissions occur (maternal auto-Ab can disappear even without treatment) and the mortality rate is lower (up to 6 %).[17,18] When prenatal monitoring is adequate, diagnosing AH is feasible with aPTT as part of the preoperative workup or if mild bleeding appears, by assessing whether aPTT is prolonged in isolation. Up to one third of patients do not require treatment;[19] however, serious bleeding may occur any time until the inhibitor is eradicated.[17]

There are cases of in-utero transfer of the inhibitor to the fetus, although bleeding in the child is rather unusual.[18] When the fetus clears the maternal auto-Ab, the clinical picture disappears if it occurred; there is no chance of this problem coming back. The most effective and least expensive way to monitor the child is with aPTT, which shortens until normalizing in a maximum of six weeks.

Laboratory diagnosis

Testing begins with aPTT, a simple test that is available in almost any hospital, which is quick, standardized and economical. In the emergency department, any prolonged aPTT should always be studied. It is prolonged in relation to the normal control and is not corrected by adding a plasma mixture (also called pooled or control plasma), which suggests the presence of an inhibitor that blocks the flow of enzymatic reactions reflected in the aPTT (Figure 4). Almost always, aPTT is prolonged in isolation and if so, the patient should be rigorously interrogated looking for data consistent with bleeding.

The next step for laboratory diagnosis is to measure functional FVIII:C, which will be below normal range. The third and final step is to quantify the potency of the inhibitor using the Bethesda or Nijmegen-Bethesda tests, which evaluate the inhibitor titer in Bethesda units (BU). Variation of these tests is high, which translates into false positive and negative results. There is an ELISA test for these anti-FVIII auto-Abs, although it also yields false negative results.[20,21] Other more specific tests are

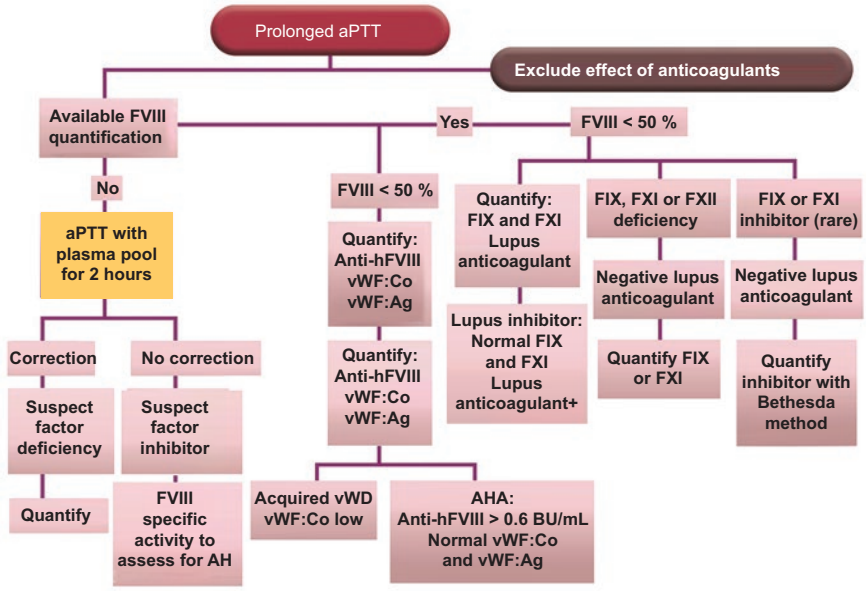

Figure 4. *Approach to the patient with prolonged activated partial thromboplastin time.*

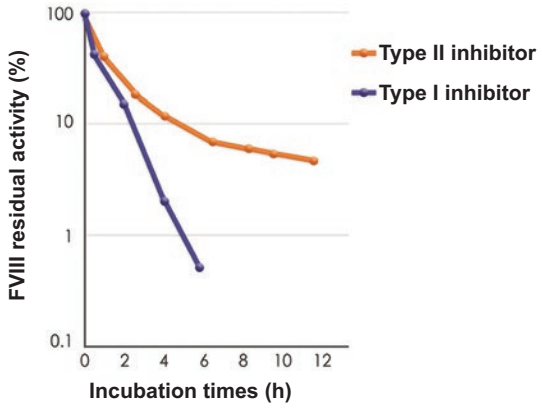

Figure 5. *Type 1 and 2 inhibitor kinetics.*

complex, expensive and poorly accessible in most hospitals.[22]

There are several techniques for measuring FVIII:C and its inhibitor: functional and antigenic methods. The former include two classes: coagulometric and chromogenic. The ELISA technique is generally used for antigenic testing. Chromogenic tests have some advantages: they are technically robust, easy to use and the lupus anticoagulant does not interfere. Its disadvantages include its cost and interference of heparin, lipemia, hemolysis and direct oral anticoagulants. This technique usually yields lower FVIII:C results than coagulation testing, which resolves some inconsistencies of the latter. The coagulation testing technique is based on aPTT and has indisputable advantages: it is the most widely used and is automated and therefore it is the most recommendable. It has drawbacks: it is affected by the quantity and quality of phospholipids used and requires activators. In addition, FVIII:C residual level may not be as accurate (FVIII:C quantification may be 50 to 100 % higher than with chromogenic testing). Any technique to measure inhibitors has variation. Once a method has been chosen, disease surveillance should be carried out with it.

Inhibitors should be assessed using the Bethesda method, which measures FVIII:C residual amount in a mixture of pooled plasma and patient plasma that is serially diluted (1:2, 1:4, 1:8, and so on and so forth), incubated for 2 hours at 37 °C.[23] FVIII increases with dilution. The inhibitor quantification ratio (1.0 BU) is reciprocal to a patient plasma dilution value that allows 50 % inhibition. Thus, 1 BU is the amount of inhibitor that neutralizes 50 % of circulating FVIII:C (2 BU neutralize 75 %, 3 BU 87.5 % and so on and forth).

The Nijmegen modification is more accurate if inhibitor levels are very low; a buffer is added to the Bethesda test to keep the control plasma at physiological pH for 2-3 hours and allow FVIII stabilization.[21]

Although these tests are useful in congenital hemophilia, the determination of auto-Ab in AH is more difficult because of its type II kinetics (see below). Ideally, the concentration of the auto-Ab bound to FVIII should be measured in order to better evaluate the inhibitor[24] by ELISA, agarose gel, immunoprecipitation or with fluorescent microbeads.[25] The latter seems better because it is not affected by residual FVIII:C, lupus anticoagulant or heparin.

FVIII inhibitors in AH and congenital hemophilia A are different (Figure 5). Congenital hemophilia allo-Abs are type I inhibitors (first-degree kinetics) that inhibit FVIII in a linear relation to their concentration and fully inhibit the factor at high concentrations. FVIII:C residual activity drops with incubation time, by saturation and in a straight line until FVIII:C is zero. That is, inactivation by allo-Ab is linear and dependent on temperature and time. AH auto-Abs are nonlinear (type II), initially inhibit FVIII rapidly, but then are balanced and residual FVIII activity can be found, even after incubating with maximum inhibitor concentrations for an adequate period. That is, AH inhibitors induce an initial straight drop, such as type I kinetics, but then they acquire a plateau behavior and residual FVIII:C concentration does not drop to zero (Figure 5).[17]

Residual activity is not correlated with inhibitor titers or with bleeding tendency. In AH, the level of residual FVIII:C is not interpreted as in congenital hemophilia. A patient with AH and residual FVIII:C of 20 % behaves as congenital hemophiliac with much lower FVIII concentration;[13] the patient with AH has more severe hemorrhages than a congenital hemophiliac at comparable levels of FVIII:C. Incubating FVIII in excess does not neutralize the type II inhibitor in vitro and high doses of FVIII are inefficacious in AH if the inhibitor titer is too high, which makes treatment difficult.

There are measurement and interpretation errors. For the former, it is important to remember that the inhibitor is a self-Ab that becomes evident by incubating at 37 °C; if this is omitted, the result is mixed up with lupus anticoagulant or with the effect of heparin or other anticoagulants. In interpretation, if the doctor requests other hemostatic factors (FIX, FXI or FX) coagulation activity measurement because aPTT is prolonged, their levels will be low, since the measurement of factors is based on aPTT, which is affected by the FVIII inhibitor; the result is falsely positive, with multiple factor deficiency being wrongly diagnosed. Since it is uncommon for an Ab to target several factors, antigenic or chromogenic functional measurement can be revealing. Another misinterpretation resulting from AH auto-A type II kinetics is to assume that a high level of FVIII:C (15-30 %) protects the patient; this is valid in congenital hemophilia (type I kinetics), but not for AH, where a FVIII:C of 20 % can be associated with severe bleeding.

In our experience, the main factor that delays diagnosis is the lack of knowledge about this pathology due to its low prevalence and because it is not taught during medical training. First-contact doctors usually have no information about it. Even in hematology residence, AH is not characterized with the dimensions of a diagnostic and therapeutic emergency. In addition, there is a need for laboratories specialized in hemostasis that have good quality control, a profile that often is not met by tertiary care centers either.

Complications and prognosis

Delaying the diagnosis worsens the prognosis. This depends on the course of the disease, which is parallel to hemorrhagic severity and underlying disease. Complete “spontaneous” remissions occur in 25-36 % of cases, especially in those associated with pregnancy and medications.[19,26] Overall survival is 69 to 78 %, and once remission is reached, it is similar to that of the general population or that of individuals affected by the primary disease. Up to 8 % die soon (median: 19 days post-diagnosis), usually due to uncontrollable bleeding.[19] Death within the first week post-diagnosis is almost always due to gastrointestinal or pulmonary hemorrhage. Intracranial and retroperitoneal hemorrhage is associated with later mortality.[27] Death is associated with AH, concomitant disease or with side effects secondary to the management of primary disease. Mortality due to primary disease treatment is similar to or higher than mortality due to hemorrhage.[16] Pregnancy-associated AH is the exception, since survival reaches 13 months in 100 %.[16]

The factors associated with poor prognosis for remission and survival are: FVIII:C < 1 IU/dL at diagnosis, a score > 2 on the performance status scale of the World Health Organization, association with neoplasms and not achieving a complete remission. Age older than 65 years at diagnosis decreases survival.[4,8] The factors of good prognosis include achieving complete remission, having FVIII activity > 1 IU/dL and an inhibitor titer < 16 BU.[8] In general, AH is potentially curable with immunosuppressants or immunomodulators, which eradicate the auto-Ab.

If remission is achieved, clinical and laboratory monitoring should be frequent due to the risk of recurrence; 20 % relapse within the first two years.[8,28] Inhibitor and FVIII:C titers are measured weekly while immunosuppressants are indicated. Once remission has been achieved, assessments are monthly for the first six months, every two or three months the following six months and every six months during follow-up for two years.[1,29] For pregnancy-associated AH, recurrence in subsequent pregnancies is low and the patient should

Table 2. First-line hemostatic agents for acquired hemophilia

Agent	Recommended dose	Comments
Replacement therapy		
rpFVIII	–If there is no anti-rpFVIII inhibitor: 50-100 U/kg every 2 to 3 hours and adjust dose as needed. –If there is anti-rpFVIII inhibitor: 200 U/kg for severe hemorrhage. –50-100 U/kg for moderate hemorrhage. –Adjust dose as needed.	–First-line treatment (if available), especially in most severe cases. –Can be monitored with aPTT. –Replaces the deficient component. –Proven efficacy. –Less effective if there are cross-reacting antibodies. –Potential generation of antibodies –Requires close monitoring. –First line if there are no anti-rpFVIII antibodies, if there is FVIII quantification and hemorrhage puts limb at risk.
Bypassing agents		
Activated prothrombin complex concentrate	–50-100 U/kg every 8 to 12 hours. –200 U/kg/day should not be exceeded.	–Proven efficacy. –No tests for monitoring. –Thrombotic potential. –First line if there is no rpFVIII, if anti-rpFVIII Ab titer is > 10 BU, if there is no FVIII quantification and in non-severe hemorrhage.
Recombinant activated FVII	–70-90 μg every 2 to 3 hours until hemostasis is achieved. –Subsequently, adjust dose as needed.	–Proven efficacy. –No tests for monitoring. –Short half-life. –Thrombotic potential. –First line if there is no rpFVIII, if anti-rpFVIII Ab titer is > 10 BU, if there is no FVIII quantification and in non-severe hemorrhage.

Simultaneously with the treatment, immunosuppressive therapy should be started. FVIII activity should be continuously monitored. There are no studies comparing all these therapeutic alternatives, and thus the choice of the agent is based more on availability, on physician experience and on economic issues. Hemostatic efficacy is based on clinical assessment, and change to another agent should be considered after 12 to 24 hours. Once hemostasis is achieved, the dosing frequency of any treatment should be reduced as much as possible to prevent thrombosis. These treatments should not be indicated if the level of FVIII is increasing, if there is no high risk of bleeding or if there is no active bleeding. It is very important to consider antithrombotic prophylaxis if FVIII level is higher than 50 %. rpFVIII = recombinant porcine factor VIII.

be informed of this possibility. Relapse is managed with the initially instituted treatment.

Treatment

Achieving a favorable outcome in AH depends on expedite diagnosis and selection of the best management. Treatment rests on two pillars:

- Control the hemorrhage if its present or prevent its occurrence.
- Eradicate the inhibitor.[17]

Since the patient can die rapidly,[26] prompt hemostatic treatment should be indicated depending on the severity and location of the bleeding. Invasive procedures such as evacuation of hematomas should not be performed unless they are absolutely necessary, preferably until the inhibitor has been eradicated,[8] since there is no reliable test to assess the coagulant response and minimal hemostasis cannot be ensured.[19] Many life-threatening hemorrhages are caused by medical interventions: venous punctures, insertion of catheters and tubes, biopsy taking and other invasive diagnostic or monitoring procedures such as frequently taking blood pressure.[30] We suggest avoiding any invasive procedure that is not strictly necessary. If required without postponement, only if hemostatic treatment is already implemented. This simple action reduces iatrogenic hemorrhages.[31]

The patient should be informed about the appearance of early hemorrhagic symptoms and on trauma prevention and on especially avoiding non-steroidal analgesic medications. It should be emphasized that he/she must seek attention in case of unjustified bleeding.

Between 20 and 30% of patients do not require hemostatic treatment at diagnosis, e.g., extensive ecchymosis. Immediately eradicating the inhibitor should be attempted and, unless there is obvious hemorrhage or hemodynamic decontrol due to hypovolemia, no hemostatic treatment is started immediately. Patients with inhibitors and FVIII:C functional deficiency but without bleeding do not require treatment either.

Patients who must receive immediate hemostatic treatment are those with high hemorrhagic risk or with clinical or paraclinical hemorrhage: muscular, genitourinary, gastrointestinal, retroperitoneal, articular, pulmonary or central nervous system. If the patient undergoes a major or minor invasive procedure, he/she must receive hemostatic treatment before and after it.[28]

Since the treatment is limited by availability of resources, the considerations hereafter may seem utopian, although it is necessary to know the existing options. Hemostatic treatment intensity is defined by hemorrhagic location and severity.[1,14] Although the treatment of choice is with bypassing agents and recombinant porcine FVIII, if they are not available and if inhibitor titer is < 5 BU and FVIII:C recovery can be frequently monitored (maintaining it at > 5%), it is enough to provide oxygen, general support and increase FVIII concentration with desmopressin.[32] Tranexamic acid is recommended in some mucosal hemorrhage guidelines. If activated prothrombin complex concentrate (aPCC) is used, tranexamic acid should never be indicated within the first 12 hours.[1]

Unfortunately, most hemorrhages in AH are severe and even fatal, with anemia being another factor that influences on treatment. As the hemorrhage progresses, more hemostatic therapy and monitoring of its efficacy is required, with clinical improvement and hemoglobin level being assessed.

Severe hemorrhage initial treatment is with bypassing agents. aPCC contains factors II, VII, IX and Xa, which are able to bypass FVIII to generate thrombin[33] (Table 2). The dose is 50 to 100 IU/kg every 8 to 12 hours or even 35 to 80 IU/kg every 8 to 24 hours[34] (200 IU/kg/day should never be exceeded); it is useful in 76 to 89 % of cases.[34] In patients with chronic and mild bleeding, 50 % of the dose is used prophylactically. Recombinant activated FVII (rFVIIa) allows bypassing hemostasis from the extrinsic pathway, thus avoiding the intrinsic one.[35,36] Evidence of rFVIIa as first line treatment in AH is large. Ninety to 120 μg/kg are used every two to three hours and the dose is decreased according to the response.[1,14,8] Its efficacy reaches 100 % (81 to 100 %).[1,37] Effectiveness and safety are slightly higher with rFVIIa vs. aPCC, but higher with both than with FVIII or desmopressin (93.3 versus 68.3 %, p = 0.003).[5] There are no studies that make either one preferable.[8,38] It should be borne in mind that the doses for AH are extrapolated from congenital hemophilia with inhibitors, that treatment optimal duration is unknown although it can be maintained until bleeding is controlled, that, empirically, additional doses are recommended to prevent the reappearance of hemorrhage,[14] and that there are no laboratory tests to monitor it (clinical evaluation is the best surveillance tool). Finally, rFVIIa and aPCC can be alternately administered in severe hemorrhages resistant to monotherapy at maximum doses and frequency.[14,32,38] It is an option in hospitalized patients under the supervision of a doctor with experience in coagulopathies.

Table 3. Risk of thrombosis in patients treated with bypassing agents

Study	Treatment	n	%
Summer[1]	rFVII	139	2.9
Ingerslev[2]	Combined or alternate agents	9	55
Baudo[3]	rFVII	174	2.9
	aPCC	63	4.8
	FVIII/desmopressin	70	0
Seita[4]	rFVII	132	2.3
Borg[5]	rFVII	28	0
	aPCC	6	0
Tiede[6]	rFVII	63	5
	rFVII/tranexamic acid	21	10

rFVII = recombinant factor VII, aPCC = activated prothrombin complex concentrate.

Direct adverse effects of bypassing agents are scarce but assessment for severity is justifiable. Thrombosis is the most dreaded complication. A significant number of patients with AH have prothrombotic primary pathologies, and thus it is crucial to adhere to the recommended dosage and stop the treatment at the right moment, as, for example, in elderly patients with high atherothrombotic risk and cancer or postpartum women, i.e., with prothrombotic states. Although thrombogenicity of both aFVIIr and aPCC is low, thrombosis should always be considered[5,39] (Table 3). Due to the rarity of AH, there is no evidence for indicating thromboprophylaxis or antithrombotic treatment. This is a decision-making problem, since patients often have thrombogenic risk factors for total anticoagulation but are candidates for potent hemostatic treatment for the management of AH. There are only expert recommendations suggesting general thromboprophylactic lines: elastic stockings or intermittent pneumatic compression as long as FVIII:C is < 50 %, since, once this level is reached, the patient can receive thromboprophylaxis or therapeutic

Table 4. First-line options for immunosuppressive therapy

First-line immunosuppression	Recommended dose	Comment
Steroids	–Prednisone 1 mg/kg/day. –Dexamethasone 40 mg/day/4-7 days.*	–Unlikely to be effective before 3 weeks in patients with FVIII < 1 % or with inhibitor titer > 20 BU at diagnosis. –Monitor for adverse events.
Steroids and Cyclophosphamide	–Steroids at similar doses to those above. –Oral cyclophosphamide 1-2 mg/kg/day. –Intravenous cyclophosphamide 5 mg/kg every 3-4 weeks.*	–Quicker responses but higher likelihood of adverse events. –Higher likelihood of complete responses. –Monitor for myelosuppression.
Steroids and rituximab	–Steroids at similar doses to those above. –Intravenous rituximab 375 mg/m^2/week for 4 weeks. –Rituximab 100 mg/week for 4 weeks.*	–Rituximab is not recommended as initial monotherapy unless the other therapies are contraindicated.

Average time to response (FVIII > 50 %) is 5 weeks. Patients with FVIII < 1 % at diagnosis require significantly longer periods to achieve remission in comparison with patients with > 1 % FVIII activity and maybe rather require combined therapy. FVIII activity, as well as that of inhibitors, should be monitored at least once a week according to clinical evolution. The therapy is individualized according to patient clinical status , primary disease, concomitant conditions and prognostic factors (FVIII < 1 %, inhibitor > 20 BU, presence of anti-rpFVIII antibodies, etc.), if available. *Poor evidence in acquired hemophilia, but with published data in other autoimmune pathologies.

anticoagulation.[5,36] Obviously, treatment should always be customized.

Laboratory monitoring of AH is difficult and therefore clinical response is the most applicable strategy.[40] In the patient with hemophilia A and inhibitors, calculating FVIII effect is hypothetically possible because inhibitors are type I. In AH, inhibitors are type II, which hinders laboratory surveillance evaluation. The problem is more evident in patients with high inhibitor titers (> 16 BU) and, therefore, the most effective alternative is to frequently monitor clinical status and quantify FVIII and aPTT.

The next therapeutic step is to seek the cure by eradicating the inhibitor with immunosuppressant agents. The patient achieves complete remission if inhibitor titers are < 0.6 BU and FVIII:C is > 50 %.[8] Relapse is defined when, upon immunosuppressant discontinuation, the inhibitor reappears at increasing titers associated with a progressive decrease in FVIII:C.[5] Stable remission is the persistence of complete remission after therapy is discontinued.

It should be mentioned that the ideal option is not known. The most commonly used first-line treatment is steroid administration (1 mg/kg/day), alone or associated with low-dose cyclophosphamide (1 to 2 mg/kg/day), for three to five weeks[1] (Table 4). Evidence is based on small, retrospective series. Only two small prospective studies showed almost 60 % of responses with the combination, which was better than with steroids alone (42 %).[41] Other registries show a non-significant advantage of the combination over steroid monotherapy (80 versus 70 %).[1] Apparently, there is no significant difference for overall and disease-free survival between both treatments.[28] Immunosuppression, together with patient comorbidities (age, multiple pathologies, current imbalance), entails the risk of cytopenia and secondary infections (33 to 53 %);[28] between 11 and 12 % of AH-associated mortality is attributed to these complications.[8] In pregnancy-associated AH, cyclophosphamide may have a leukemogenic effect and perhaps an effect on fertility.[28] The second-line treatment of choice is rituximab (Table 4), if first-line therapy fails.[1,14,28] Its effect is believed to be due to a decrease in anti-FVIII auto-Abs. It is started at 375 mg/m^2/week for four weeks,[8] with weeks or months of treatment being required. Eradication is achieved in 78.6 % of patients, regardless of the previous use or not of another immunosuppressant.[42] It is a good alternative if inhibitor titer is > 200 BU;[43] however, evidence is scarce and, therefore, combined treatment should be started in these cases.[44]

In general, the eradication rate is 60 %,[36] and it is higher in patients treated with rituximab and other immunosuppressants versus monotherapy, although, in some series, rituximab was no better than steroids (77 versus 61 %) and time to remission was longer (median: 32 versus 64 days). The relapse rate with rituximab appears to be lower than with steroids plus cyclophosphamide or steroids alone (4, 14 and 19 %, respectively). There is positive evidence for rituximab at a dose of 100 mg/m^2.[45] In pregnancy-associated AH, rituximab appears to be efficacious, although the cases involved correspond to treatments after failure to steroids and high inhibitor titers.[46]

There is no evidence that any immunosuppressant is superior or for choosing any based on hemorrhagic status or inhibitor titer. First-line therapy depends on assessment of the underlying disease and probable adverse events.[32] Infections are not negligible and can

lead to death[47] and, as in any patient with prolonged immunosuppression, close immunological surveillance is necessary. In addition to immunosuppressants, azathioprine, cyclosporine, cyclophosphamide, mycophenolate, 6-mercaptopurine, tacrolimus, cladribine, azathioprine and vincristine are also used. Prednisone is used as monotherapy or combined with cyclophosphamide with important responses.[28,32,41] High doses of intravenous Ig are also used.[4] Combined chemotherapy treatment (cyclophosphamide, vincristine and prednisone) is indicated if the other options have failed. In AH associated with systemic lupus erythematosus, cyclosporine at a dose of 10-15 mg/kg/day seems useful.[48]

There are two treatments that are not globally accepted or widely available: immunoadsorption and immune tolerance. In the former, patient plasma is passed through a sepharose column with adhered staphylococcus A protein, capable of eliminating auto-Abs; it is generally used in very acute and severe cases,[49] it is an expensive, complicated, scantily available treatment and whether eradication is sustained is not known. Immune tolerance, which is useful in congenital hemophilia, is expensive, its availability is limited and it does not ensure inhibitor sustained eradication either. FVIII chronic and high-dose administration induces immune regulation and increased auto-Ab-producing clone sensitivity to the immunosuppressant, thus modulating the generation of auto-Abs.[6] Maybe it is only applicable in relapsing AH and its widespread use is unlikely.[14,27]

Conclusions

The main problem with AH is delayed diagnosis due to lack of knowledge about the disease. Mid- and long-term educational strategies are imperative in order to raise awareness on this potentially curable entity in doctors so that they can include it in their diagnoses. It is not difficult to suspect AH; basic hemostatic tests and interpretation of clinical signs and symptoms in at-risk populations is sufficient. The next challenge is hematological laboratories at second and tertiary care levels, which should be made aware on their diagnostic role and the need to refine their processes to improve the quality of their tests. Another problem is the lack of a national hemophilia registry. We have advanced, although insufficiently, in congenital hemophilia (underreporting is 18 %); for AH, we only have the experience of large reference centers. We almost completely ignore AH epidemiology in Mexico; we need data that provide feedback to the health system in order to develop really effective therapeutic policies and guidelines. As for treatment, patient fragility is a challenge, since he/she is sensitive to secondary immunosuppression and infection, which are factors that can cause death by sepsis. Since individuals with AH have several comorbidities (some require antithrombotic treatment), and are prescribed medications that generate thrombin (bypassing agents, high doses of FVIII, DDAVP and antifibrinolytic agents), some patients will require antithrombotic prophylaxis.

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BRIEF COMMUNICATION

Clinical experience with Tolvaptan outpatient use. Cost and effectiveness in 9 cases

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Abstract

Introduction: *Tolvaptan introduction has constituted the main therapeutic novelty in the management of hyponatremia in recent years.* **Objective:** *To describe the experience with this drug at Complejo Asistencial Universitario de León, Spain.* **Method:** *Retrospective, observational study of tolvaptan outpatient use in a tertiary care hospital from March 2014 to August 2017.* **Results:** *A total of 9 patients were treated with tolvaptan in the outpatient setting. Eunatremia was reached in 24 hours by 23.1 %. After tolvaptan administration, a reduction in days of hospitalization was recorded (361 vs. 70; p = 0.007), especially in those days of hospitalization that were attributable to hyponatremia (306 vs. 49; p = 0.009).* **Conclusions:** *Long-term use of tolvaptan appears to be safe and is associated with a decrease in days of hospitalization.*

KEY WORDS: *Tolvaptan. Hyponatremia. Sodium. Syndrome of inappropriate antidiuretic hormone secretion.*

Experiencia clínica con el uso ambulatorio de tolvaptan. Costes y efectividad en nueve casos

Resumen

Introducción: *La introducción de tolvaptan ha supuesto la principal novedad en el tratamiento de la hiponatremia en los últimos años.* **Objetivo:** *Describir la experiencia con tolvaptan en el Complejo Asistencial Universitario de León, España.* **Método:** *Estudio observacional retrospectivo de utilización ambulatoria de tolvaptan en un hospital de tercer nivel, de marzo de 2014 a agosto de 2017.* **Resultados:** *Fueron tratados con tolvaptan de forma ambulatoria nueve pacientes, 23.1 % alcanzó eunatremia en 24 horas. Posterior a la administración de tolvaptan se registró reducción en días de hospitalización (361 versus 70, p = 0.007), especialmente por hiponatremia (306 versus 49, p = 0.009).* **Conclusiones:** *El uso a largo plazo de tolvaptan parece ser seguro y se relaciona con descenso en los días de hospitalización.*

PALABRAS CLAVE: *Tolvaptan. Hiponatremia. Sodio. Secreción inadecuada de hormona antidiurética.*

Introduction

Hyponatremia, which is a decrease in serum sodium concentration below 135 mmol/L, is the most prevalent electrolyte disorder in the outpatient and hospital setting.[1] Its main cause is inadequate secretion of antidiuretic hormone, pathophysiologically caused by inability to suppress vasopressin secretion.[2]

Mild or moderate hyponatremia (serum sodium [SNa] = 120-135 mmol/L), which in many cases is chronically maintained, is associated with an increase in hospital[3] and outpatient mortality,[4] as well as with

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Table 1. Characteristics of patients receiving tolvaptan in the outpatient setting, according to hyponatremia etiology

Variable	Pharmacological SIADH n = 3 (33.3 %)		Paraneoplastic SIADH n = 2 (22.2 %)		SIADH 2nd neurological condition n = 2 (22.2 %)		SIADH 2nd respiratory condition n = 1 (11.1 %)		Dilutional hyponatremia (cirrhosis) n = 1 (11.1 %)		Total n = 9 (100)	
Males/females (%)	33.3/66.6		100/0		0/100		100/0		100/0		55.6/44.4	
	Me	DQ1-Q3	Me	DQ1-Q3	Me	DQ1-Q3	Me	DQ1-Q3	Me	DQ1-Q3	Me	DQ1-Q3
Age (years)	79.1	17.1	70.2	20.23	67.8	6.2	86.4	0	56.9	0	70.9	15.6
Baseline SNa (mmol/L)	123	5	121	8	125.5	7	131	0	113	0	123	6
Final SNa (mmol/L)	139	5	138.5	3	138.5	5	142	0	124	0	139	4
TV initial dose (mg/day)	7.5	0	11.25	7.5	11.25	7.5	7.5	0	7.5	0	7.5	0
TV maintenance dose (mg/day)	7.5	7.5	7.5	0	2.95	1.61	7.5	0	15	0	7.5	0
Treatment duration (days)	770	500	92.5	79	596.5	985	730	0	61	0	277	630

SNa = natremia, TV = tolvaptan, SIADH = syndrome of inappropriate diuretic hormone secretion, Me = median, DQ1-Q3 = diference between quartile 1 and quartile 3.

an increase in instability, falls and fractures.[5] The need to address its treatment has been emphasized in various consensus documents and clinical practice guidelines,[6] which propose water restriction or increasing aquaresis with loop diuretics, urea or vasopressin V2 receptor antagonists, which constitute the main therapeutic novelty in its management; in Europe, tolvaptan (TV) is available.[7]

Contribution to the scientific literature

The purpose of this study was to assess costs and effectiveness of tolvaptan outpatient use at *Complejo Asistencial Universitario de León*, Spain, between March 2014 and August 2017, with the purpose to contribute some knowledge on the use of TV.

The hypothesis was proposed that hospitalization episodes and emergency department visits decrease with the use of TV with regard to the period without TV treatment. The elevated cost of this drug and the fact that it constitutes the main novelty in the treatment of hyponatremia in recent years motivated this report.

Method

Retrospective, observational study on the use of TV on an outpatient basis in a tertiary care hospital. All patients older than 18 years that were treated with tolvaptan between March 2014 and August 2017 were included. Data were collected from patient medical records. The information was anonymously handled.

The study variables were age, gender, reason for admission or visit to the emergency department, hospitalization and emergency department visit episodes before and after outpatient treatment, cause of hyponatremia, initial and maintenance dose, baseline and last available SNa measurement, treatment duration and treatment-related direct costs, calculated based on the manufacturer retail price, dispensed doses and number of days of treatment.

Statistical analysis was performed with Stata, version 14. The variables without normal distribution were described as medians and interquartile ranges and were compared using Mann-Whitney's U-test or Kruskal-Wallis test. Categorical variables were summarized as percentages and compared using the chi-square test. For all tests, statistical significance was considered with a p-value < 0.05.

This study was carried out in accordance with the guidelines established in the Fortaleza Declaration and all procedures performed on human subjects were approved by the Ethics and Clinical Research Committee of the hospital. Since this was a retrospective study, and given the difficulty to obtain informed consent of each patient, this was not applied.

Results

In total, nine patients received TV on an outpatient basis; their characteristics are summarized in Table 1.

The maintenance dose was lower than indicated in the summary of product characteristics (15 mg/day) in seven patients, with eunatremia being achieved with

Table 2. Cost of hyponatremia outpatient treatment with tolvaptan by etiology

Variable	Pharmacological SIADH n = 3 (33.3 %)	Paraneoplastic SIADH n = 2 (22.2 %)	SIADH 2nd neurological condition n = 2 (22.2 %)	SIADH 2nd respiratory condition n = 1 (11.1 %)	Dilutional hyponatremia (cirrhosis) n = 1 (11.1 %)	Total n = 9 (100)
Treatment cost (DQ1-Q3), €	30 766.1 (27 912.9)	3 236.3 (994.9)	16 880.6 (30 759.8)	27 387.1 (0)	8 714.5 (0)	17 930.6 (27 033)
Total cost, €	94 540.3	6 472.5	3 3761.3	27 387.1	8 714.5	170 875.7
Total cost-day of treatment, €	163.7	79.9	44.1	37.5	142.9	39.9
Total cost-admission episodes D, €	10 504.5	0*	11 253.8	13 693.6	0*	21 359.5
Total cost-hospitalization days D, €	844.2	106.1	767.3	912.9	181.6	587.2
Total cost-emergency department visits D, €	13 505.8	0*	33 761.3	13 693.6	0*	24 410.8

D = DQ1-Q3 = difference between quartile 1 and quartile 3. *Difference between the periods of outpatient treatment with TV and equivalent periods of time prior to the start of treatment, SIADH = syndrome of inappropriate antidiuretic hormone secretion.

2.1 mg/day (15 mg/seven days) in 11.1 %, with 3.75 mg/day (7.5 mg/48 hours) in 22.2 % and with 7.5 mg/day (7.5 mg/24 hours) in 55.6 %.

There were no episodes of hypernatremia (Na > 145 mmol/L) or acute renal failure during the follow-up.

When the periods of outpatient treatment with TV were compared in each patient with regard to equivalent periods of time prior to the start of treatment, we found a reduction in total days of hospitalization (361 versus 70, p = 0.007) at the expense of hospitalizations due to hyponatremia (306 versus 49, p = 0.009), with a trend towards a reduction in the number of total hospitalization episodes (19 versus 7, p = 0.072) and especially in those attributable to hyponatremia (14 versus 4, p = 0.051), as well as in episodes of aid at the emergency department for all causes (18 versus 11, p = 0.302) and in those directly attributable to hyponatremia (15 versus 5, p = 0.076).

Outpatient treatment total cost during the analyzed period was € 170,875.7 and mean cost per patient was € 17,930.6 (3,733.7-30,766.1).

Table 2 shows the itemized expenditure per diagnosis and lists the cost and the recorded difference in assessed events: admission episodes, days of hospitalization and episodes requiring visits to the emergency department.

Discussion

In the analyzed patients, TV outpatient use was shown to be safe and efficacious in the reduction of clinical events, even with doses lower than those indicated in the summary of product characteristics. Owing to the SALTWATER[8] study, we have data available on the safety and efficacy of TV chronic use with regard to the evolution of natremia; however, experience is limited in terms of clinical benefits associated with the correction of natremia, which is restricted to the publication of clinical cases.[9] In our patients, a follow-up of 3,993 days was accumulated, with a median of 277 days and a maximum individual follow-up of 1,089 days (2.98 years), which constitutes one of the strengths of the study. The use of TV appears to be associated with a significant decrease in days of hospitalization associated with hyponatremia and, overall, with any pathology; in addition, we identified a decrease in emergency department visits and admission episodes in patients treated with tolvaptan.

Of note, the majority of patients maintain eunatremia with the use of doses lower than those indicated in the summary of product characteristics. Along the same lines, the San Carlos Clinical Hospital group[10] reported their follow-up results in 16 patients on outpatient treatment with TV for at least three years; they found reductions in hospital admissions, days of stay and visits to the emergency department.

It should be taken into account that the results vary significantly depending on the etiology of hyponatremia; for example, cancer patients attend the emergency department more often once they are treated, probably due to progression of the underlying disease. On the other hand, this is a non-randomized retrospective study and the number of patients is small,

which constitutes the most important limitation of our study.

In the cost analysis, the expenses generated by ambulatory follow-up of the treated patients (medical appointments, laboratory tests, transportation, etc.) have not been taken into account, and neither have those related to admission or care at the emergency department; therefore, studies specifically designed to analyze the cost-effectiveness of this treatment would be necessary.

Conclusions

Long-term use of tolvaptan appears to be safe and could be related to a decrease in days of hospitalization due to hyponatremia.

Funding

This investigation did not receive public or commercial sector subsidy.

Conflicts of interest

David E. Barajas Galindo and Emilia Gómez Hoyos declare having received honoraria from Otsuka Pharmaceutical Co. Ltd. for other works unrelated to this report.

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Comments on the book *Las muertes que no deben ser*

Comentarios del libro Las muertes que no deben ser

Teresita Corona-Vázquez,[1] Alberto Lifshitz[2] and Elizabeth Luna Traill[3]*

[1]*Academia Nacional de Medicina de México;* [2]*Asociación de Médicos Escritores;* [3]*Universidad Nacional Autónoma de México, Philological Research Institute, Mexico City, Mexico*

On June 19, in the auditorium of the National Academy of Medicine, the presentation of the book *Las muertes que no deben ser. Natalidad y Mortalidad en México* (Deaths that should not be. Natality and mortality in Mexico), whose author is Dr. Mario Luis Fuentes, was carried out.

About the author

Dr. Mario Luis Fuentes is professor at the Faculty of Political and Social Sciences of the National Autonomous University of Mexico (UNAM – *Universidad Nacional Autónoma de México*) and academic coordinator of the Social Development specialization of the Single Program of Postgraduate Specializations at the Faculty of Economics of the same university. He has a degree in economics at ITAM and a Master in Regional Development by the Institute of Social Studies at The Hague University, The Netherlands. He did doctoral studies at the University of East Anglia, United Kingdom.

Dr. Mario Luis Fuentes is a distinguished researcher of the University Program for Development Studies, where his ability to analyze and use statistical information in Mexico has earned him recognition by the National Institute of Statistics and Geography (INEGI – *Instituto Nacional de Estadística y Geografía*) and the National Council for the Evaluation of Social Development Policy (CONEVAL); in addition, he received the "Gilberto Rincón Gallardo" Faces of Discrimination National Award, granted by the National Council to prevent Discrimination.

To present "*Las muertes que no deben ser. Natalidad y Mortalidad en México*" notable academicians were invited.

About the work

Las muertes que no deben ser. Natalidad y Mortalidad en México was published in December 2018 by *Fondo de Cultura Económica* as part of the Economics/Finance collection. It has six main chapters in 270 pages and a print run of 2000 copies, it is a paperback edition and the cover design is credited to Laura Esponda Aguilar and Irene Castro Nava (Figure 1).

Herein, we present the comments made during the presentation of the work.

Comments by Dr. Teresita Corona Vázquez, President of the National Academy of Medicine of Mexico

As a result of the incomplete transitions, both demographic and epidemiological, our country is crossing, Mexico has problems that are inherent to developing countries, such as infectious and contagious diseases and maternal and child complications.

In his book *Las muertes que no deben ser*, Mario Luis Fuentes refers that these diseases essentially depend on socioeconomic factors: they are linked to an absence or insufficiency of basic public services, deficiency in public policies for prevention, poverty, inequality, consumption and life habits or anthropogenic structural factors, such as climate change.

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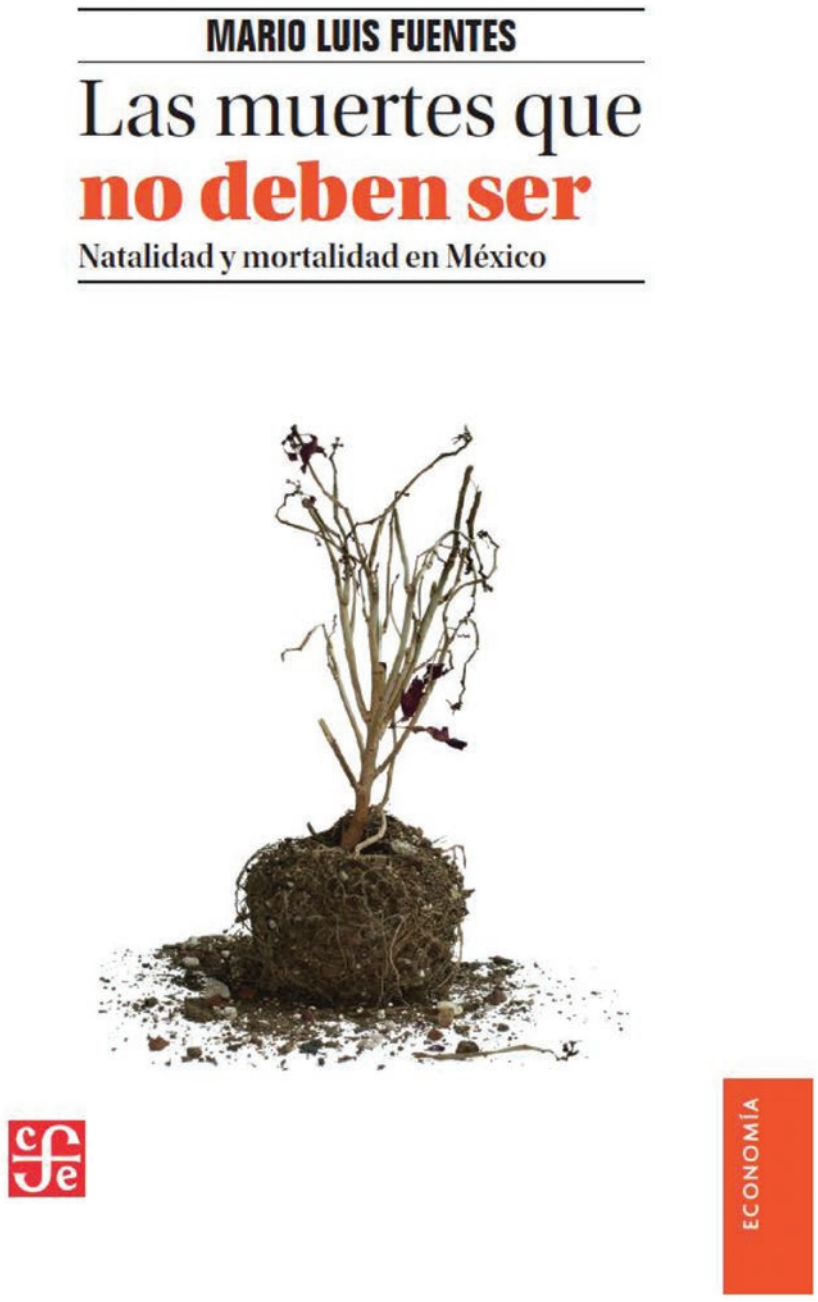

Figure 1. *Cover of the book Las muertes que no deben ser. Natalidad y mortalidad en México (Deaths that should not be. Natality and mortality in Mexico), published on December 2018.*

On the other hand, population circumstances generate health problems that are similar to those of developed countries. In Mexico, life expectancy of the population is currently 14 times higher than in 1970; however, it is the lowest among the Organization for Economic Cooperation and Development (OECD) country members, since it slowed down since the 1970s, which is explained by the limitation of resources directed to health, which impacts on access and quality of care.

With the increase in life expectancy, there is aging of the population and an increase in the prevalence of chronic-degenerative diseases.

Developed countries are considered to be aging when 10 % or more of their population is aged 60 years or older. Currently, in Mexico nearly 10 % of the population is at that stage of life, which means that very soon we will be an aged society. This aging, together with environmental and social factors, such as education, wealth distribution, access to sanitary and health

services, among others, is a cause of significant disability, which in Mexico affects almost 48 % of older adults; among them, women, the elderly (more than 85 years), the poorest and least educated are the most affected, which generates economic, family, labor and community consequences, which determines for them to be familial and social diseases. In addition, the World Health Organization notes that at least 10 % of the population has some disability, 70 % of them concentrated in developing countries.

Mexico is one of the countries with the highest prevalence and rates of obesity and overweight, but also with relevant data consistent with undernourishment, especially in vulnerable communities, in pregnant women and older adults.

The divergence in epidemiology in our country will have to be addressed focusing on public health, but also from the perspective of scientific research, technology, health innovation and education.

In Mexico, family out-of-pocket expenditure is rather high, more than 40 % in general, which is the second highest among OECD countries and twice the average of member countries. Population-based satisfaction surveys regarding basic services range from 44 to 56 %. Indicators of health working force distribution, such as the number of doctors and nurses per inhabitants, should be evaluated in order to ensure the minimum indispensable for the care of the population, as well as access to health systems.

The obesity rate, which has increased in recent years, is one of the highest and permeates adolescents and children, which explains, in part, why Mexico has the highest diabetes rate among OECD countries; in addition, both are important risk factors for prevalent diseases, such as cardiovascular, cerebrovascular and degenerative diseases.

Efforts have been made aimed at population health education, the sugary drinks tax, programs for elementary schools related to the sale of low-calorie foods; however, they have not yet been sufficient.

On the other hand, data on violent deaths, road traffic deaths and homicides are very high and are growing, not to mention the problems of mental health care of the population: more than 9 % suffer from any affective disorder and, among them, depression is the most prevalent, although these figures should be updated. In addition, there are addictions and reproductive health problems, such as unwanted pregnancies and increased pregnancies in girls and adolescents.

The challenge is enormous and the most prevalent diseases should be privileged, not forgetting those that are not and that affect people as well, such as the so-called rare diseases.

Las muertes que no deben ser. Natalidad y mortalidad en México, analyzes the social determinants of health, from vulnerability, interpretation of the evidence on natality, diseases of inequality and poverty, but also diseases of power. It addresses death with dignity, the perspective of violence, including crime and the avoidable future, in relation to all the above factors. It is a reference for scholars of the health-disease phenomenon that will surely be addressed in many forums on the subject.

Comments by Dr. Alberto Lifshitz, president of the Association of Medical Writers

I appreciate the opportunity to comment on this interesting book, wisely written by an expert on social issues and also a protagonist of Mexico's recent history. My comment obviously has the bias of a clinician, in an attempt to make a dialectical reading. Before undertaking the exploration of the text, I dared to try an exercise: I wondered, which would the "deaths that should not be" be for me? to then contrast the answers with that which is discussed in the book.

I identified several: premature, avoidable, undignified, painful (with unnecessary suffering), prolonged, desolate, lonely, isolated, technified, hospitalized, violent, utilitarian, pollution (atmospheric and microbial)-related deaths.

All this, I insist, prior to reading the book.

The book addresses several of these descriptors, some with a more original and, of course, more informed vision than mine. For example, with regard to premature death, it mentions that "death always arrives at the wrong time" and that, in any case, what is the timing of death? Avoidable death is "that due to conditions. that should not occur if there is access to health services of adequate quality". It also speaks of "avoidable excess death such as that which is due to conditions of deprivation, poverty and inequality, which restrict, limit or hinder compliance with human rights, particularly for the weakest and neediest of society". It also refers to dignified death, which it links as a reflection or consequence of a dignified life. Much of what it says about death also applies to disease.

The edition is impeccable, as usually are the books of *Fondo de Cultura Económica*, whose seal is accompanied by the seals of UNAM and its University

Program for Development Studies. The cover by Laura Esponda and Irene Castro shows a bush extracted from the earth with roots and everything, a very appropriate metaphor. The book consists of 270 pages, perfectly readable, and six sections: one dedicated to vulnerability, a central concept for this analysis; another on the birth rate, which encompasses, for example, a certain determinism and the question of who the mothers are, as well as the challenges of adolescent pregnancy and maternal mortality; diseases of inequality and poverty and the provocative concept of "diseases of power"; the inescapable violence among the causes of deaths that should not be and, finally, a section on the avoidable future. A good number of graphs illustrate very well the statistical arguments.

The author notes that "this is not a book about demographics; neither does it circumscribe to the field of public health; strictly speaking, it is a book on political economy that seeks to show that disease and death are determined today by structural inequalities, poverty and marginalization..."

As this one, he says many other important things. I would not like for my comment to wander in the large number of ideas the reading of this text raises, hence, I am going to focus only on that on which I might have a more educated opinion as a clinician.

Disease and death are phenomena that are obviously difficult to interpret, since they constitute authentic "complex systems", i.e., composed of a huge number of interacting components, capable of exchanging with each other and with environmental matter, energy or information and to adapt their states as a result of such interactions occurring in parallel. Particularly pertinent here is the multi-causality paradigm: disease and death are never governed by a single cause. The text clearly recognizes this and privileges social determinants with an emphasis on economic aspects, and not only monetary poverty but "dimensions linked to social rights". The concept of vulnerability is subject to a careful dissection, since it is considered central to understanding the issue. It is also clear that interventions that might modify current situation would not be able to attack a single cause.

Morbidity and mortality "that should not be" include nutrition problems, diabetes, hypertension, cardiovascular disease, digestive and respiratory diseases, mental health disorders and external causes; lack or insufficiency of public services, deficiencies in public prevention policies, poverty, inequality, consumption and life habits, structural changes of an anthropogenic nature, such as climate change.

Much has been said for a long time about the pathology of poverty, which undoubtedly represents a high proportion of "deaths that should not be", but the author speaks of the "pathology of power" as an additional or complementary entity, since he identifies a certain intentionality, linked to ideology, which results in a development model deliberately designed for inequality. The pathology of poverty and the pathology of power have effects that are rather due to relations of domination than to biological or physical determinants.

Avoidable mortality is "that which is caused by conditions that produce unnecessary and premature deaths that, given the advances in medical knowledge, should not occur if there is access to health services of adequate quality". Avoidable "excessive" deaths.

It is about reinterpreting disease and death as a result of asymmetries and deprivations in access to the guarantee of human rights. Birth and disease are part of these surroundings.

As a physician, I can avoid some deaths that should not be (or at least postpone them); but it is very clear that the challenge transcends the profession. Raising our voice, as this text does, is undoubtedly a contribution that can clarify the pathways.

Something that cannot be denied, then, is that this is a provocative book, capable of raising debate and controversy, but based on solid arguments. It will surely give a lot to talk about. Congratulations to the author and the publisher.

Comments by Dr. Elizabeth Luna Traill, researcher at UNAM Philological Research Institute

I will address the first chapter, which is entitled "For an apologia of the vulnerable. A proposal to approach the phenomenon". From the preface, I quote the author's warning:

> ...this is not a book about demographics; neither does it circumscribe to the field of public health; strictly speaking, it is a book on political economy that seeks to show that disease and death are determined today by structural inequalities, poverty and marginalization, and that it is necessary to build a different perspective on the social determinants of health, but especially, in the face of our own way of thinking and questioning these phenomena.

A first point refers to the problem presented by the dominant views of political theory and economic theory with regard to the analysis of social issues, since their categorical apparatuses restrict categorical

discussion to the scope of economy and its classic variables.

Thus, it is valid to maintain that most theories about poverty and inequality have been constructed based on the analysis of "the causes". The human development index has been widely accepted among governments because it allows them to design actions and programs whereby they have the "ability" to positively influence the modification of indicators. A central topic of the work at hand is the concept of "human dignity". At this stage of the Introduction, the author addresses the concept of vulnerability, and it would be therefore necessary to leave the Introduction; however, I will still refer to some issues that allow me to access the threshold of the chapter that is the subject of this presentation.

The world, not only our country, opened up to the discussion of the concept of social vulnerability, which was also related to the "social risk" category.

This clearly explains why Mario Luis Fuentes concludes that it is urgent to generate explanatory proposals that, on one hand, without renouncing the power of scientific method and statistical analysis (i.e., to the construction of evidence-based hypotheses), have the capacity to produce a change, a "turn" in the dimensions assumed as the main explanatory factors of social problems; and, on the other, put ethics ahead of technique as an irreducible declaration of principles.

The author starts by addressing the concept of vulnerability with an approach to its definition in the Mexican legal order. He points out that the "emergence" of this concept occurred only after the consolidation of the Mexican State and within the framework of an incipient institutional system. Although in 1936 the Ministry of Public Assistance was created, the vulnerability category began to have a greater presence in theoretical and institutional discussion since the 1970s, when the National System for Comprehensive Development of the Family was created and, later, in 1986, when the Statute of Social Assistance was enacted (which was deeply amended in 2004).

In our author's opinion, the concept of vulnerability is associated with the notions of "risk or discrimination", which substantially differ from that which is generically established by the Statute of Social Assistance, where the "conditions that prevent full physical, mental or social development of individuals" are addressed.

The constant link that is made in the legal and institutional framework between the notion of vulnerability and insufficiency of access to public goods and services and monetary income of people and their families, whereby, let's not forget, whether they live or not in conditions of poverty is determined.

To that end, Mario Luis Fuentes delves into the labyrinth of language to reinterpret the concept of vulnerability. It is not a "semantic concern" of a dilettante; the importance of elucidating the concept is incontrovertible.

In the matter in question, language is a mere instrument for data and information transmission that seeks to be efficient as operational thinking is, that which is able to contribute to the efficiency of the system and, especially, to enhance the efficacy of processes that are underway. From this point of view, people are conceived as agents of political and economic processes, without greater possibility of intervention regarding their capability of insertion into different spheres of functionality.

Another important element that should be noted is the application of natural sciences' evolutionism to social sciences, and a linear-thinking logic has been constructed that assumes that societies adopt the natural evolution of species. Posed this way, it is not surprising that several theorists have accepted that in the world of economics only the most suitable stand out: economic success is obtained by those who have more skills to interact with the market based on its rules.

All of the above drives Mario Luis to scrutinize the original notion of the concept of vulnerability in order to re-signify that which we should understand by human vulnerability, carrying out a fine philological analysis.

> Being vulnerable is finding out of what consists the humanity we are carriers of. Carrying the wound is not what determines our humanity, but the other way around: while we are humans (and we always are) we are possessors of that particularity, that is why the human being is not sometimes vulnerable and sometimes not; we are always vulnerable because we are humans.

Allow me a simple example: it is not because we live in the *Sierra de Guerrero* with the drug traffickers that we are vulnerable, but, in any situation, in our historicity, we are vulnerable because we are humans.

Vulnerability thus understood cannot be "overcome" in the sense given by the positivist or functionalist vision of reality, we cannot leave it behind and not even "protect ourselves", as it was intended with the theories of development of the 20th century. Then, what to do?:

> The responsibility we would have to assume would be the construction of a continuous process of generation of solidarity

> ties, because we cannot escape the reality that when poverty and inequality afflict some, they actually afflict us all.
>
> Invoking this feeling shared by every person brings us first to the dimension of that which is deeply human and, in second place, it will be the guideline for the construction of a social order different from the one we have and that would be oriented not to "social protection" but to the construction of a welfare model based on the recognition of shared human vulnerability.

The chapter closes with the promise that everything that allows us perceiving the "traces of our vulnerable being" is the task that is to be undertaken in the following pages. To accomplish this, Mario Luis Fuentes proposes addressing three of the fundamental phenomena of human existence that can allow us understand that the vulnerability we are exposed to is constitutive of our being humans, but at the same time, since we are such, it allows us thinking about a welfare model focused not on the generation of "capabilities", but on the construction of a humanity capable of seeing itself as the carrier of the already referred "original wound".

Editor's note

Dr. Elizabeth Luna Traill's valuable contribution was her posthumous work and will be published in its entirety elsewhere.

I thank Dr. Teresita Corona, coordinator of the symposium, for allowing me to shorten the original presentation in order to comply with *Gaceta Médica de México* editorial guidelines.

To the memory of Doctor Francisco Olvera Esnaurrizar

In memoriam del doctor Francisco Olvera Esnaurrizar

*Alejandro Treviño-Becerra and Francisco Espinosa-Larrañaga**

Gaceta Médica de México, Academia Nacional de Medicina de México, Mexico City, Mexico

Dr. Francisco Olvera Esnaurrizar passed away on October 15, 2019 at the age of 91. He was born on June 17, 1928 in Mexico City. His parents were Mrs. Angela Esnaurrizar Iriarte and Mr. Francisco Olvera Castillo.

Dr. Olvera Esnaurrizar was admitted to the National Preparatory School in 1944, where he showed skills in writing and good command on grammar, which is why some of his classmates gave him the nickname "grammar professor" and was invited as an assistant to Professor Erasmo Castellanos Quinto's class.

Since his adolescence, he showed dedication and commitment with work. He was invited by Arcady Boytler, owner of the Arcadia cinema at the time of the "golden age of Mexican cinema", to collaborate in the creation of scripts for movies.

Dr. Olvera belonged to the 1946-1951 generation of the National School of Medicine, which he chaired twice. On second year he was assistant to professor and forensic doctor Tarquino González, whom he aided in the autopsy room of former Juárez Hospital in the afternoons. At third undergraduate year, he also was admitted as a numerary member to the Green Cross Central Relief Post, in the streets of Revillagigedo and Victoria.

Early in the the 1950s, he was accepted at General Hospital of Mexico Pavilion 16, where he joined the Peripheral Vascular team, which was formed by doctors Manuel Castañeda, David C. Díaz Gutiérrez, Xavier Domínguez Estrada and Héctor Izquierdo Delgado. This group carried out the first aortic artery grafts in Mexico. In the middle of that decade, Dr. Olvera was responsible for the General Hospital "artery bank". He was a faculty member at the Faculty of Medicine of the National Autonomous University of Mexico.

At the National Academy of Medicine of Mexico (ANMM – *Academia Nacional de Medicina de México*) he was invited by Dr. Rubén Vasconcelos as secretary of the organizing committee from the first to the fifth National Medical Sessions, which allowed Dr. Olvera to interact with great personalities of the ANMM, including Dr. Luis Méndez, with whom he had a close friendship. When Dr. Luis Méndez was appointed Deputy Director General of the Mexican Institute of Social Security, he invited Dr. Olvera as one of his advisors and head of the Department of Medical Publications and Editions of the Institute, which produced essential medicines lists, newsletters, instruction manuals, regulations, continuing medical education fascicles and even books.

In 1960 and 1961 he was associate editor of *Gaceta Médica de México,* official dissemination journal of the ANMM, where he joined academicians Oswaldo Arias, Guillermo Montaño, Carlos Vejar Lacave, José Laguna and Herman Villarreal.

Dr. Olvera was *Revista Médica del IMSS* first editor, a publication founded in 1962, which he directed for more than one decade. In the celebration of 50 years of existence of that journal, the authorities of the Mexican Institute of Social Security made a well-deserved recognition to Dr. Olvera. As part of these celebrations, Dr. Francisco Espinosa Larrañaga, who then served as editor for that publication, proposed to develop the Journal's editors gallery, which was opened by Dr. Alberto Lifshitz, head of the Health, Research

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and Medical Education Policy Unit, and by doctor Francisco Olvera himself, who during the last 10 years he worked at the Institute was responsible for scientific events.

Dr. Francisco Olvera had many qualities, but he was characterized by a purist handling of language and writing, by his great talent for print publishing, his joy of living, his loyalty, honesty, courtesy, gratitude and the ability to cultivate friendship and, above all, knowing how to preserve it.

His departure leaves an absence that will be notable and felt by his family, by the survivors of his generation and by those of us who enjoyed his friendship and advice.

Thanks to reviewers

Agradecimiento a los revisores

In modern times, the publication of scientific or review papers requires the assessment of peers, who will provide the editors with judgments, observations and comments based on scientific relevance in order for a work to be accepted or rejected, as well as precise observations to the authors supporting the decision, or suggestions to improve the manuscript. The task of reviewers is arduous, difficult, repeated, anonymous, technical, and even criticized, but essential to determine the quality of a publication.

In the case of *Gaceta Médica de México*, peer-reviewers may be academicians or non-academicians, belong or not to the Editorial Committee, some are more requested than others, others are highly accurate and precise, some evaluations even exceed the quality of the reviewed article, others are frugal or drastic, but all carry out this peer-review work in favor of the quality of *Gaceta*, and for these reasons, herein we express our gratitude for their collaboration and professionalism as reviewers. We look forward to your continued support.

Best regards.

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