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ARTÍCULO ESPECIAL

Epidemiology of osteoporosis in Mexico. Present and future directions

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ABSTRACT

This position paper has been written by a multidisciplinary group of experts appointed by the National Institutes of Health (NIH). Its aim is to present the state of the art of knowledge about osteoporosis in Mexico. A review of the scientific papers in Mexico and information about diagnostics tools and treatment is discussed along with some research recommendations for the future.

Key words. *Osteoporosis. Epidemiology. Impact.*

Epidemiología de la osteoporosis en México. Dirección presente y futura

RESUMEN

El presente artículo define la postura y recomendaciones de un grupo multidisciplinario de expertos de la Coordinación de los Institutos Nacionales de Salud de México en relación con la osteoporosis como un problema de salud pública creciente en el país. Para esta publicación se realizó la revisión de la evidencia científica de los datos de impacto de esta enfermedad, así como de los recursos de diagnóstico y tratamiento disponibles. Ofrece recomendaciones para futuras investigaciones en el área que permitirán llenar huecos del conocimiento actual para un mejor entendimiento de los factores de riesgo, prevención y tratamiento de esta entidad que apoyen de forma sustancial la optimización de los recursos de la investigación y asistencia y sirvan de marco referencial para epidemiólogos, tomadores de decisiones y autoridades en el diseño de futuros programas de salud enfocados a la osteoporosis y sus complicaciones.

Palabras clave. *Osteoporosis. Epidemiología. Impacto.*

PREAMBLE

The Commission of the National Institutes of Health (NIH) in Mexico recently recognized osteoporosis (OP) as a public health concern. The head of the commission formed a multidisciplinary team from NIH, the Instituto Mexicano del Seguro Social (IMSS), and the Faculty of Medicine of the Universidad Nacional Autónoma de México (UNAM). This team was tasked with evaluating the magnitude of the problem and establishing an agenda to set priorities for research and policy programs that will evolve into large-scale preventive and interventional programs for OP and the fractures associated with it. The team is composed of epidemiologists, clinical researchers in several specialties related to bone metabolism (rheumatologists, nephrologists, rehabilitation medicine, gynecologists, and orthopedic surgeons,

among others), health economists, and policy decision-makers. They meet regularly to integrate available scientific evidence, synergizing the knowledge and the resources available in each institution. They are establishing a feasible work plan that includes measuring the burden of disease, developing human resources and infrastructure for timely diagnoses and treatment, and establishing future directions for research and development of programs with measurable indicators for intermediate and long-term periods for prevention, diagnoses, education, and cost-effective treatment.

INTRODUCTION

Changes in demographic dynamics in Mexico present new challenges for health care. The growing number of elderly and the continuing rise in life expectancy will have an impact on the incidence of fragility fractures in the coming decades. Worldwide, hip fractures are projected to increase from 1.2 million in the 1990s to 2.6 million by 2025 and to 4.5 million by 2050, assuming no change in age- and sex-specific incidence. The vast majority of hip fractures in the 21st century will occur in developing countries; Asia and Latin America are estimated to be the two regions that will have the largest increases.[1]

According to the 2010 census, the national population in Mexico in 2010 was slightly over 112 million people; according to the National Council Population projections, it will increase by 8.6% and 14.8% for the years 2020 and 2050 respectively. When the same estimates are projected for those 50 years and older, the figures increase more steeply: the current 2010 population for this age group is over 19 million people, and projections are that it will increase 57% and 200% for the same periods.[2,3]

As in many developing countries, the Mexican health-care system is a mixture of governmental and private institutions. Three main types of health-care providers have roughly a similar share of the market. They are:

- Social security institutions created for persons with formal employment and their families.
- Social assistance institutions for persons with no employment, run by the Ministry of Health.
- Private sector.

The IMSS provides health care for 35% of the Mexican population; similar social security institutions for government employees (ISSSTE, SEDENA, PEMEX, SEMAR) provide care for another 18% of the population. Persons with no formal employment, peasants, and indigenous groups, almost half the population, seek health care either at Ministry of Health facilities or in the private sector. Even at the Ministry of Health facilities, these individuals frequently have to cover out-of-pocket expenses, mainly for drugs or other forms of treatment. As might be expected, the costs and impact of OP and fragility fractures greatly differ among the subsystems of this complex health care system.

To overcome the health care inequities of persons with no formal education and employment and the financial consequences for them in the early years of this decade, the national congress approved a major constitutional reform to grant the necessary conditions for all Mexican citizens to obtain health equity services. This mandate led to modifications to the General Health Law. Based on the mandate, the Ministry of Health created a funding agency (CNPSS) to cover the basic health-care needs of the Mexican population with no social security. This was called Seguro Popular.[4] This public insurance system currently covers 1,400 diseases and 275 health interventions for nearly 50 million beneficiaries.[5]

The Seguro Popular uses all the types of health-care facilities mentioned above through agreements between the Ministry of Health and the other health systems (private or governmental). However, although the Seguro Popular includes OP detection, diagnosis, treatment, and surgical repair of osteoporotic fractures, the infrastructure and process for attention and treatment is not well developed and is far from being optimal to cover the needs for OP and fragility fractures.

Background

The study of OP in Mexico was formally initiated in 1992 when the first association related to the field was founded: the Mexican Association for Study of Climatric (AMEC). From then to 1994, AMEC was the only medical association devoted to the study of OP; results from its collaborative work with the National Institute of Public Health were published and used as a reference for many. In 1994, two organizations directly involved in OP were founded: the Mexican Association for Bone and Mineral Research (AMMOM), a medically oriented organization, which focuses its efforts on medical education, organizing different types of activities and holding an annual scientific meeting, and the Mexican Committee for Prevention of Osteoporosis, which focuses on OP awareness by the population, prevention, and early

identification of high-risk populations. Both are affiliated as full members to the International Osteoporosis Foundation.

Some consensus documents and guidelines for the diagnosis and treatment of OP have been elaborated by AMMOM, AMEC, and other specialty groups such as endocrinology.[6,7] However, even when these consensuses and guidelines could help with diagnosis and treatment, little is known about their dissemination and use from health-care providers since they have not yet been evaluated. The same problem arose when the official norm was published in 2002 for diseases for the perimenopausal and climateric periods: OP in women is mentioned, but information about these conditions has not been disseminated adequately or followed by an official clinical guideline.[8]

This position paper summarizes what it is known in this field in Mexico, presents what resources we have, and sets up a meaningful agenda to help health authorities allocate resources needed for OP and fragility fractures according to the needs in three different strategic areas:

- OP burden and health economics approach.
- Diagnoses, patient-oriented health care, and clinical guidelines.
- Prevention and public health policies.

Each area contains specific recommendations and directions for future research. This position paper could also be used by researchers in other countries in the developing world to direct their efforts and infrastructure planning.

OSTEOPOROSIS BURDEN AND ECONOMIC APPROACH

Epidemiology of OP in Mexico

Epidemiological studies have recently reported on the burden of hip and vertebral fractures in Mexico.[9,10] It is estimated that 1 in 12 Mexican women and 1 in 20 Mexican men will have a hip fracture after the age of 50 (lifetime risk probability of 8.5 and 3.8%, respectively).[11] Compared to other countries, Mexico shows intermediate hip fracture incidence rates12 (age-standardized incidence rates of 203 and 108 per 100,000 person years in women and men, respectively). However, the absolute number of hip fractures in the Mexican population has been increasing and is expected to increase even more in the next decades due to increased life expectancy and the consequent aging of the population.

Accordingly, data from the Division of Information in Health at IMSS show the age-specific incidence increased significantly in both sexes by 1% per year. In 2005, there were an estimated 29,732 hip fractures in Mexico. Assuming no change in the age- and sex-specific incidence of hip fractures, the number will increase to 155,874 by the year 2050. But assuming that the age-specific incidence continues, the number of hip fractures in men and women would increase by a further 46% to 226,886 in 2050.[9]

Vertebral fracture prevalence rates for Mexicans over 50 years of age are 19.2% for women and 9.8% for men.[13,14] The figure for women is the highest in Latin American countries and very similar to what is found in women from Asian and some European countries. There is limited information regarding the incidence of other fragility fractures that usually do not require hospitalization. However, the IMSS fracture registry show that in 2005, wrist fractures were the most common reported fracture in persons aged 50 and older, followed by hip, humerus, and pelvis fractures. As in many countries, vertebral fractures are largely undiagnosed and therefore underrepresented in this registry.

OP prevalence has been measured in some studies.[15] A recent study was carried out in a community-wide random sample of 820 men and women with bone mineral density (BMD), performed by central DXA, and using the World Health Organization (WHO) operational criteria for OP. A prevalence of OP at the lumbar spine of 9% of men and 17% of women was found in this survey, whereas 30% of men and 43% of women had osteopenia. At the femoral neck, OP was found in 6% of men and 16% of women, and osteopenia in 41% men and 56% of women in the same sample.[16]

Epidemiological studies in the Mexican population indicate that fragility fractures and OP are frequent conditions among the elderly and an imminent threat for the health system in the near future as our population continues to age and its life expectancy continues to increase.

In 2008, the WHO implemented the fracture risk assessment tool FRAX®[17] to evaluate the absolute fracture risk of individual patients based on clinical risk factors. Additionally, if available, the BMD at the femoral neck can be introduced to the model to enhance its prediction to the risk. This simple instrument allows identification of high-risk groups through a cost-effective case-finding strategy. Thus, it is useful to primary-care physicians, the first level of those attending patients; however, it is also a

useful tool for specialists. The Mexican model has been available since 2010, so anyone can access it through the Internet (http://www.shef.ac.uk/FRAX). Two things are still needed to take advantage of the Mexican model of the FRAX® tool. First, we have to develop a cost effectiveness analysis with our specific needs to set the threshold for deciding which patients to treat. Second, we have to initiate a program that informs primary-care physicians about the importance and use of this tool.

The information is now restricted to some types of fractures. Mexico must develop a national registry of fragility fractures, which would provide more detailed incidence and mortality figures with regard to types of fractures, age groups, and regions. Also needed are large-scale epidemiological studies to determine the prevalence of OP and vertebral fractures, the status of vitamin D, determination of the quality of life of persons who have suffered OP-related fractures, and assessments of the role of environmental and genetic risk factors on the etiology of OP and their consequences.

Health economics approach

OP has serious physical, psychosocial, and financial consequences, placing a significant burden on individuals, their families, and society as a whole.[18] Osteoporotic fractures are associated with pain and loss of well-being; they typically entail a number of serious complications and disabilities, which, in turn, lead to enormous expense and often death.[18-20] The socioeconomic burden of OP and related fractures is expected to further increase due to the aging of the population.[21]

Cost of illness (CoI) analysis is a descriptive method to assess the amount of both resources consumed and resources potentially lost because of a particular disease or a group of diseases, attempting to identify and measure all cost components. Along with epidemiological data on morbidity and mortality, CoI may help in ranking diseases according to global burden.[22]

Few CoI analyses for OP and fragility fractures have been conducted in Mexico. In a population-based study, Clark, *et al*.[23] estimated that the direct medical cost of diagnosis and one-year treatment for a patient with OP ranges from US$ 595 to US$ 2,236. This amount included the cost of DXA measurements, laboratory bone-markers, and image tests performed during diagnosis and follow-up as well as the average yearly pharmacological treatment for 275 patients.

The economic burden related to acute medical attention of different osteoporotic fractures at governmental institutions and private settings in Mexico has been published. For 2006, total direct and indirect costs incurred during the acute event of hip fractures in Mexico were estimated to be more than US$ 97 million. This figure is comparable to the expenses incurred in 2005 for covering the cost of insulin for one million insulin-dependent diabetics across the country, and was based on the occurrence of about 22,000 hip fracture cases, with a global cost of US$ 4,365.50 per case.[23] The average cost of acute treatment for a hip fracture differs according to the type of institution where the patient receives medical attention, ranging from US$ 1,613 (for those treated at a public institution) to US$ 13,778 (for those treated at a private hospital).[23]

A recent publication estimated a direct medical cost of US$ 3,315 for acute treatment of hip fracture cases in the Seguro Popular de Salud.[24] By combining the proportional distribution of three Diagnosis Related Group (DRG) reported by Velasco-Murillo, *et al*.[25] with the most recent technical costs of these DRG at IMSS,[26] the weighted average cost of a hip fracture in this institution during 2008 was around US$ 9,500 per case. A fourth study focused on different types of fractures attended at a tertiary hospital of IMSS. The estimated cost of acute treatment by case (all 2000 year values) was US$ 3,333 for hip fractures, US$ 2,063 for forearm and hand fractures, and US$ 4,180 for knee fractures.[27]

There is little information on the medical and non-medical costs of follow-up for osteoporotic fractures. However, a protocol to estimate the costs and health-related quality of life associated with different types of osteoporotic fracture in a sample of Mexican patients followed since the time of fracture to a maximum of 18 months post-fracture has been funded by CONACyT (National Council for Science and Technology). This study is part of ICUROS (International Costs and Utilities Related to Osteoporotic Fractures Study) and will allow us to compare our data with those from other countries using a common methodology.

Economic evaluations provide important information about the value of alternative therapies that may assist decision makers seeking to allocate limited resources to achieve maximum health-care benefits.[28] Economic factors are important when justifying allocation of health-care resources and identifying patients to receive drugs used for the treatment and prevention of chronic medical problems such as OP.[29]

International evidence shows that OP screening and treatment is a cost-effective intervention for most available drugs, especially for postmenopausal women at moderate or high risk.[28,30-32] Virtually all evidence on cost-effective analysis of OP medication was derived in high-income countries.[33] It is important that health economics studies be done in developing countries, where health problems are far greater than available resources. Well-designed economic evaluations are mandatory to help decision makers and health authorities make meaningful decisions about how and where to allocate budgets for OP and fragility fractures and to set priorities among other health threats that the Mexican population is facing.

As previously stated, the absolute fracture risk is more important in determining cost-effectiveness than is the relative risk.[29,34] Therefore, the use of instruments such as FRAX® for developing management algorithms for OP is becoming widespread.[31,35] Cost-effectiveness analysis to set up the intervention thresholds for OP management is the next step, since the FRAX® instrument is already calibrated to be used with the Mexican population.

Future research and recommendations

A special effort must be made to:

- Gather current statistics for the number of fractures and common sites and the direct and indirect costs related to fragility fractures, quality of life, types of disability, and death rates in affected individuals.
- Estimate disability adjusted life years (DALY) lost due to OP and its fractures; develop sound economical modeling studies to estimate the burden of this entity in Mexicans to help the government prioritize this health condition and allocate the resources needed to treat and prevent OP.
- Determine the absolute risk of fractures in Mexicans through the WHO FRAX® tool and conduct a case-finding strategy and cost-effectiveness analysis to help Mexican authorities set up reasonable treatment thresholds for the Mexican population.

CLINICAL GUIDELINES FOR PREVENTION, EARLY IDENTIFICATION, DIAGNOSIS, TREATMENT, AND PATIENT CARE

During the last 20 years, criteria to classify an initial BMD result obtained by DXA of an individual person were established in 1994 by the WHO. The use of a T-score of -2.5 SD below the mean of the reference population has been adopted worldwide as the gold standard. These criteria were frequently misused: They were validated only for central DXA equipments, but were also used to classify results obtained with peripheral devices and for other purposes such as case-finding strategies, diagnoses, as a treatment threshold to set up pharmacological interventions, or as an entry criterion for pharmacological studies.

During the last decade, well-designed epidemiological studies and meta-analyses have shown the importance of clinical risk factors being powerful tools to predict the probability of fracture in an individual. New, robust, and scientifically validated algorithms developed by the WHO expert panel combine central DXA BMD results with clinical risk factors. These algorithms provide more accurate assessments of fracture probability using the absolute risk of fracture over a period of 10 years. Many countries have been changing their guidelines to incorporate these new algorithms in order to become more efficient in selecting the high-risk groups that need to be treated.[28,31,36] This approach will redirect how infrastructure and resources should be allocated from the public health perspective. The calculation will also be useful at the individual patient-care level.

The strategy will help us define more accurately the size of the problem and the infrastructure and human resources required. Through evidence-based studies, we will be able to select the treatment opportunities and prevention programs for our population's bone health.

There are insufficient clinical care units or centers focused in metabolic bone diseases (MBD) and OP. This is partly because our public health system had not included MBD and OP in its priorities. Therefore, available resources for diagnosis and treatment are limited to research centers and private practices and do not cover the needs of the general population, even in the tertiary health institutions.

The first Whole Body DXA instruments were introduced in Mexico in the early 1990s when just a few private laboratories were able to determine biochemical markers of bone turnover. The situation has improved, and although it is still insufficient to cover the country's needs, the medical community now has access to the following validated equipment to determine bone mass:

- Dual photon, low energy x-ray bone absorptiometry (DXA) represented by the central whole

body, spine, and femur as well as peripheral anatomical sites equipments.
- Quantitative bone ultrasound (QUS).
- Quantitative bone X-ray computed tomography (BQTc).
- Non-mineralized quantitative, dynamic bone histomorphometry (BHM).

Most of these diagnostic capabilities are restricted to some private and public health institutions or to some research facilities. Several peripherical devices are also available.

In the case of central DXA, the gold standard for the diagnosis of OP, a recent survey with the distributors of the two more common DXA whole body or two regions (lumbar and hip) equipments revealed a total of 397 instruments sold to private or public health facilities since their inception in 1990, of which apparently only 300 are in use. Thus, there are around 1.8 to 2.3 pieces of DXA equipment per million people over 50 years of age. This number is insufficient to cover the needs of the general population, not to mention the imbalance in the allocation of this resource. The majority of Mexicans go to public health facilities where the DXA equipment is scarce (only 15% has been sold to public health institutions). If we accept the recommendation made for Europe in 2005 by Kanis,[37] Mexico, with a current population of 112 million people, should have at least 1,190 DXA instruments and optimal almost 1,600. A second problem that we face with this technology is the lack of official regulatory rules and too few qualified technicians who can use this diagnostic tool.

The picture is also poor when we look at the ability of determining biochemical markers of bone turnover, calciotropic hormones, Vitamin D3 and its metabolites, the numerous citokynes, and prostaglandins involved in bone turnover. They are determined in numerous private clinical laboratories and in only a few public institutions. We have only one center with updated technology to perform bone histomorphometry in iliac crest biopsies, which is accepted internationally as the gold standard technique for specific diagnosis of MBD. This laboratory, located at one national institute of our public health system, is predominantly devoted to research and has enough capacity to solve the cases in which this diagnostic methodology has a clinical indication.

In the last two decades, growing scientific evidence shows that the majority of cases of primary OP have polygenic and multifactorial genetic determinants modulated by different hormonal and environmental factors. Many of these genes are responsible for the bone phenotype, contributing to the genetic control of bone mineral density (BMD), bone turnover, skeletal dimensions, bone microarchitecture, osseous fragility, femoral neck geometry, and fracture risk. Familial and twin studies suggest that between 50% and 85% of the variance in peak bone mass is determined genetically as is increased risk of fragility fractures independently of bone mineral density.

Several international studies have investigated the association between polymorphisms potentiality related with genetic predisposition to OP and fracture risk in different anatomic regions (spine, hip, and distal forearm). These genes included: ESR1, ESR2, VDR, CT, CALCR, IL6, COL1A1, LRP5, RANK, RANK-L among others.[38-41]

Recent genetic studies in Mexican population suggest a relationship between polymorphisms localized in CT, ESR1, IL6, and COL1A1 genes.[42-44] Although these results are preliminary, these findings have the potential to become useful markers for detecting subjects at higher risk of OP, for whom measures of early prevention and opportune treatment should be indicated. Another future promising application of genetic studies is pharmacogenomics research. This research makes it possible to design new genetically targeted therapeutic options and develop a genetic prognostic test for OP.

In sum, Mexico has up-to-date technology and equipment for diagnosis and follow-up patients with OP and/or MBD. However, these resources are clearly insufficient, unevenly distributed, and unregulated by the health authorities. Therefore, there is no universal access to timely diagnosis and opportune treatment. Our group recommends strongly development of a joint strategy in which the research community, the public, and private health institutions collaborate with industrial developers to define the infrastructure needed to give the whole population access, quality assurance, and cost-effective results for OP diagnosis and treatment.

Future research and recommendations

- The infrastructure for prevention, diagnosis, and treatment of OP, fragility, fractures, and other less-frequent MBD is clearly insufficient. There is a need to allocate economic and human resources to develop this infrastructure.
- We need to increase the number of DXA machines to cover the needs of the elderly and to distribute them wisely within governmental institutions.

- Better detection, treatment opportunities, and education programs need to be facilitated for primary-care physicians.
  Special programs have to be implemented to help clinicians detect vertebral fractures since timely diagnosis and treatment will prevent other fragility fractures in the elderly.
- There is a need to expand the genetic investigations for identification of new genes related to bone metabolism in Mexicans. This will allow better understanding of some aspects of bone metabolism not yet entirely explored. This knowledge will eventually drive us to open newer therapeutic windows for treatment of this disease.

Prevention and Public Health Programs

Currently, there is no organized large-scale government program in Mexico to prevent OP and its fractures in adults or to maximize peak bone mass in children and adolescents through aggressive promotion of healthy life-styles (physical activity, adequate diet, and reduction and avoidance of smoking and alcohol). Vitamin D deficiency is a recognized epidemic in several counties, but there have not been any published studies about it for Mexico. Regarding the nutritional status of calcium, there are some isolated reports about Mexicans in which the average calcium intake in children and adults is suboptimal.[45,46]

Although Mexico lacks an inventory of both public and private health-care facilities for OP diagnosis, treatment, and rehabilitation, experts agree that OP health care is mainly directed at diagnosis, with limited access to treatment and rehabilitation. Although medical schools have no formal OP educational programs, AMMOM has generated a virtual advanced course in OP and metabolic bone diseases from which 35 doctors have graduated over a 6-year period.

Most interested physicians have access to the basic diagnostic methodology around the country. However, we need to expand the number of sites as well as develop standardization procedures and create our own regulatory criteria. These will facilitate the allocation of government funds to finance the different actions involved in the health care for OP. In addition, most well-recognized treatment options for OP are available in Mexico but, because of lack of funding, they are not accessible to most high-risk people.

Future research and recommendations

- Carry out more research on vitamin D and calcium status in Mexicans to better estimate the extent these nutritional supplements are needed in older Mexicans.
- Increase awareness and education programs for consumers and health professionals using as many avenues as possible to reach as many people of influence as possible (medical centers, periodicals, newspapers, government departments, business community groups, and media campaigns).
- Increase awareness of OP at all levels (authorities, physicians, and the general public).
- Allocate resources to fund large-scale research projects that are evidence based and provide tools for early identification, recognition, and post-fracture treatment and management of OP both by the health-care profession and the community.

We should promote continuity in the areas where OP research is currently being done and synergize the available resources to build up a critical mass of researchers to integrate new teams who can work with the current ones.

Finally, we should promote prevention programs to build bone mass through promotion of healthy life-styles, increase education about OP at all levels of education and training, and generate the infrastructure needed for timely diagnosis and treatment.

APPENDIX

The collaborative group from the National Institutes of Health and high specialty hospitals of Mexico.

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Recibido el 23 agosto 2012.
Aceptado el 14 de febrero 2013.