POSITION PAPER

Diagnostic, treatment, and follow-up of osteoporosis—position statement of the Latin American Federation of Endocrinology

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Abstract

Summary The Latin American Federation of Endocrinology position statement on osteoporosis was developed by endocrinologists from 9 countries. It encompasses the definition, diagnosis, treatment, and follow-up of the disease, the identification of barriers to healthcare, and proposals to improve the disease care in the region.

Introduction There is a gap in the understanding of osteoporosis in Latin America. The objective of this work is to state the position of the Latin American Federation of Endocrinology on osteoporosis care in postmenopausal women to better bridge this gap.

Methods An experts' panel was formed comprising of 11 endocrinologists from 9 countries. A data search was conducted with a conceptual approach and data selection was based on the hierarchy of the EBHC pyramid. Unpublished data was considered for local epidemiological data and expert opinion for the identification of barriers to healthcare. An expert consensus based on the Delphi methodology was carried out. Experts were asked to respond on a 5-point Likert Scale to two provided answers to guiding questions.

Results Consensus was agreed on the answer for the questions with the higher median on the Likert scale and synthetized on 16 statements covering the definition of osteoporosis, diagnostic approach, treatment options, and follow-up. Besides clinical topics, unmet needs in osteoporosis were identified in relation to local epidemiological data, barriers to treatment, and misclassification of programs within health systems.

Conclusions Through a process based on recognized methodological tools, FELAEN's position on osteoporosis was developed. This made it possible to state an optimum scenario for the care of the disease and helped to identify knowledge gaps. There is great variability in the approach to osteoporosis in Latin America and barriers in all the stages of healthcare persist.

Keywords Bone density conservation agents · Bone diseases · Densitometry · Health services · Osteoporotic fractures

Summary of statements

1. Osteoporosis is a systemic disease characterized by low bone mass, deterioration of the microarchitecture of bone tissue, and decreased bone quality that leads to an increase in bone fragility and susceptibility to fractures.

2. Adequate calcium intake, optimal vitamin D levels, physical activity including strength, balance, and endurance exercises, limiting alcohol intake, and avoiding tobacco are needed to protect bone health.

3. The risk of osteoporosis should be assessed in women 50 years of age or older or at the beginning of menopause with a detailed medical history, physical examination, and fracture risk assessment with FRAX®. Measurement of BMD should be considered according to the risk profile.

4. The diagnosis of osteoporosis is made in the presence of fragility fractures, or with a T-score less than or equal to -2.5 in the lumbar spine, femoral neck, total hip, or radius 33% in the adequate clinical context.

5. Initial evaluation for suspected secondary causes of osteoporosis can be supported by laboratory tests, such

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as blood count, levels of vitamin D, phosphorus, intact parathyroid hormone (PTH), creatinine, alkaline phosphatase, transaminases, serum and urinary calcium, and 24-h urinary creatinine excretion.

6. Measurement of BMD should be considered in women age 65 or higher and in women under 65 years of age who are at increased risk of developing osteoporosis. If done, it should be measured by DXA at the spine and hip.

7. There are additional diagnostic tools to DXA such as VFA, TBS, REMS, and FS that should be implemented in Latin American countries to improve the initial approach to osteoporosis.

8. In people with osteopenia without fragility fractures or in healthcare centers that do not have DXA, FRAX® is useful to assess the need to start treatment.

9. Calcium and vitamin D supplementation should be considered in patients with osteoporosis if their dietary calcium intake is less than 1200 mg per day and vitamin D levels are less than 30 ng/ml.

10. Bisphosphonates are indicated for the treatment of postmenopausal osteoporosis and patients with osteopenia and risk factors for fracture.

11. Denosumab is indicated as an alternative for the initial treatment of postmenopausal osteoporosis with a high risk of fracture.

12. Teriparatide is indicated for the treatment of osteoporosis with high or very high risk of fracture and osteoporosis with a history of vertebral fracture.

13. Romosozumab is indicated for the treatment of osteoporosis with a very high risk of fracture or multiple vertebral fractures and should be administered for one year.

14. Selective estrogen receptor modulators are indicated as an alternative for the treatment of osteoporosis with risk of vertebral fracture or for younger postmenopausal women at risk of breast cancer.

15. Estrogen replacement therapy is indicated as an alternative for the treatment of osteoporosis or osteopenia in women under 60 years of age, with intense vasomotor or climacteric symptoms, and who do not have any contraindication.

16. The follow-up of postmenopausal osteoporosis should be based on the characteristics of each patient, including the individual assessment of the risk of fracture and general health status.

Introduction

Morbidity due to osteoporosis is progressively increasing in Latin America, a situation possibly related to the accelerated aging of the population in most countries in the region

[1], leading to an increase in bone fragility fractures and complications.

According to the Economic Commission for Latin America and the Caribbean (ECAC) demographic data, the population of Latin America in 2020 was estimated at 652 million, 15.4% older than 50 years old ($\approx$ 100 million). The average estimated 2020 life expectancy in the region of 75.7 years is an increase of 5.7 years over life expectancy in 2000 with a corresponding increase in the total at-risk population [2]. On the other hand, there is considerable variation of up to 10 times in the risk of hip fracture and other osteoporotic fractures among countries of the region as found in the validation studies of FRAX® [3] and prevalence studies [4].

In the Latin American Vertebral Osteoporosis Study (LAVOS), which provides most of the known epidemiological data for osteoporosis in Latin America, a prevalence of 14.77% was estimated for all vertebral fractures in osteoporosis patients of all ages. This increased with age from 6.9% for the 50 to 59 years old group to 27% for those older than 80 years [4]. Aside from the LAVOS study, heterogeneous epidemiological data for vertebral and hip fractures, osteopenia, osteoporosis incidence and prevalence, and scarce mortality data is available from the International Osteoporosis Foundation (IOF) Regional Audit [5] and some local studies (Supplementary Table 1).

It is relevant to note that variations observed in the incidence of fractures between populations in Latin America are likely due to differences in their inhabitants' ancestry. For example, in southern Brazil in the municipality of Joinville, where 83% of the population is Caucasian, the annual incidence of hip fracture in women is 268.8/100,000 inhabitants and 153/100,000 inhabitants in men — higher than that of the north of the country where the population is primarily made of indigenous peoples — and increases significantly after age 75 [6].

Regarding the diversity in disease treatment, in Colombia the healthcare system includes 100% of all health technologies related to prevention, diagnosis, treatment, and rehabilitation of osteoporosis [7]. In the rest of the countries in the region, there is no complete covered access to some technologies as DXA, and for some drugs [8]. As a consequence of the diversity in the structure of health policies and systems in Latin America, the coverage of the expenses in the management of osteoporosis is diversely divided between state subsidized healthcare systems, private insurance systems, or out of pocket expenses, a scenario that leads to differences across the countries and to inequities in health care access [9]. According to a cost estimation study of four Latin American countries, based on the modeling of disease burden from the incidence rates of osteoporotic fractures, the lowest annual cost of care was estimated at $94,265,619 (USD) in Colombia and the highest at $410,739,402 (USD)

in Mexico, showing a high variability in the cost of care in the region [10].

There is a challenge in proposing a binding framework due to variability in the approach to the disease in Latin American countries. The objective of this work is to state the position of the Latin American Federation of Endocrinology (FELAEN) [11] on osteoporosis care in postmenopausal women. The position aims to reconcile clinical concepts on the presentation of the disease in Latin America, the relevance of the available tools in the identification of high-risk populations, and the use of diagnostic tools in addition to dual-energy X-ray absorptiometry (DXA), utilizing a multidisciplinary approach to fracture with the purpose of reducing the occurrence of the disease in the highest risk population.

Methods

The development of this consensus position followed a protocol based on the Methodological Guide for the Preparation of Clinical Practice Guidelines (CPG) of the Colombian Ministry of Health [12] and the Guideline Development Checklist of the Guidelines International Network (GIN) and McMaster University [13]. The process was divided into 5 stages: preparation, formulation, development, writing/preparation, and socialization.

The target population of the position includes postmenopausal women with an osteoporosis diagnosis, at-risk post-menopausal women, or post-menopausal women with a history of fragility fractures. The central clinical topics considered were the definition of osteoporosis and its diagnostic assessment, treatment, and follow-up. The target users of the position are the medical professionals in healthcare institutions of all levels of complexity who provide care to patients with osteoporosis.

Participants

The Developer Group (DG) was made up of a panel of endocrinology specialists who are members of FELAEN's affiliated associations. A coordinating team, which included two endocrinologists and an epidemiologist, supervised the process through all the stages. The participation of the experts was considered after potential conflicts of interest were declared individually. None of the professionals had any impediments to participate in the process.

Evidence

A search for CPG was made in the databases of organizations that collect or produce CPG, including the GIN repository, the official publications of non-Latin American

endocrinology societies and governmental agencies. The official CPG repositories and publications of the health care authorities and medical associations from Latin American countries were also screened. The identification of relevant literature was complemented with manual screening of the reference list of the CPG identified and suggestions from the DG members. Following the hierarchy of the evidence-based healthcare information pyramid [14], sources identified as being of good quality after applying the quality assessment tools of the Scottish Intercollegiate Guidelines Network (SIGN) [15] and the CPG quality assessment tool of the International Center for Allied Health Evidence (iCAHE) [16], were selected (Supplement 1).

Consensus process

An expert consensus was made based on the Delphi methodology [17]. A set of guiding questions was proposed by the coordinating team and refined by discussion with the whole DG. The list covered the definition, diagnostic, treatment and follow up of osteoporosis with questions such as "What healthy lifestyle habits should be promoted to maintain bone health?", and "How long should bisphosphonate therapy last?". Each panel member was asked to respond anonymously on a Likert scale to two provided answers to the guiding questions. Consensus was agreed after three rounds of discussion for the answer with the highest median score provided that it was greater than or equal to 4.

Results

The development of the position statement began with the preparation of the protocol and ended after the discussion of the findings among panel members (socialization) and the review and approval of the final draft of the manuscript by the DG. Statements regarding the most relevant aspects of the diagnosis, treatment, and follow-up of postmenopausal osteoporosis were derived from the information appraised and agreed upon by the DG.

Position statement

The position of FELAEN on postmenopausal osteoporosis is supported by the statements presented and discussed below:

1. Osteoporosis is a systemic disease characterized by low bone mass, deterioration of the microarchitecture of bone tissue, and decreased bone quality that leads to an increase in bone fragility and susceptibility to fractures.

The definition of osteoporosis as a disease characterized by a reduction in the quality of bone tissue has been

promoted by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the European Foundation for Osteoporosis and Bone Disease, and the American National Osteoporosis Foundation 1991 consensus [18] and updated to include the consideration that it is a systemic disease as a fundamental concept in its approach [19]. The increase in bone fragility is attributable to the deterioration of the bone microarchitecture, which translates to a decrease in its biomechanical resistance function and is associated with an increase in the occurrence of fragility fractures, defined as fractures due to falls from one's own height or less or by low-energy mechanical forces that do not normally cause fractures [20, 21].

The most common anatomical sites for osteoporotic fractures in postmenopausal women are the spine, forearm, and femur/hip, with an estimated incidence density of 1250/100,000 people/year (95% confidence interval [95% CI] 648–2173), 703/100,000 person/year (95% CI 411–1381), and 325/100,000 person/year (95% CI 106–757) respectively [22].

2. Adequate calcium intake; optimal vitamin D levels; physical activity including strength, balance, and endurance exercises; limiting alcohol intake; and avoiding tobacco are needed to protect bone health.

Bone health is reflected in the integrity and mineral density of the bone. These characteristics are derived from the coordinated action of bone deposition and resorption, a process depending on mineral accretion patterns related to sex and age, which begins from the fetal stage and culminates towards the end of the second decade of life with epiphyseal fusion [23].

To maintain bone health, it is advisable to follow healthy lifestyle habits that allow for optimal skeletal development, maximizing peak accretion, minimizing loss of bone mass, and preservation of structural integrity. The main factors related to bone health are the intake of calcium (following age-specific recommendations), the maintenance of 25-hydroxyvitamin D (vitamin D) levels, and physical activity. Some specific recommendations are:

- Maintain a total calcium intake between 800 and 1200 mg per day, defined by age and risk of fracture. This level can be achieved with dietary calcium intake and supplements if necessary [24].
- Maintain vitamin D levels equal to or greater than 30 ng/ml. Promote safe exposure to sunlight as the primary natural source of vitamin D and supplement when needed [25, 26]. Exposing bare skin to the sun is recommended for 10 to 15 min a day [27].
- Although there is no specific exercise regimen recommended, resistance training has a positive osteogenic

effect when associated with mechanical loads between 3.5 and 4.2 g. This effect has been best observed in studies with exercise routines performed at least 3 days a week with at least 100 repetitions per session, primarily with jumping-involved activities [23].

3. The risk of osteoporosis should be assessed in women 50 years of age or older or at the beginning of menopause with a detailed medical history, physical examination, and fracture risk assessment with FRAX®. Measurement of BMD should be considered according to the risk profile. The risk of osteoporosis should be assessed in women 50 years of age or older or at the beginning of menopause with a detailed medical history, physical examination, and fracture risk assessment with FRAX®. Measurement of BMD should be considered according to the risk profile.

Women identified as being at high risk of fracture should undergo an evaluation of factors contributing to low bone mass, risk of falls, causes or history of fragility fractures, secondary causes of osteoporosis, decreased height, low back pain, and deformity of the spine such as dorsal hyperkyphosis. Medical history is the primary instrument for the initial diagnostic approach. It must include a detailed physical examination and may be complemented with laboratory tests to assess bone metabolism and secondary causes of osteoporosis, lateral spine radiography, determination of the risk of fracture by FRAX® and DXA according to the risk profile of the patient [24].

Factors that contribute to low bone density and increased risk of fracture that should be considered during patient evaluation are the use of systemic glucocorticoids, age (being 65 or older), previous fractures, family history of osteoporosis, history of falls, family history of hip fracture, secondary osteoporosis, body mass index (BMI) < 18.5 kg/m^2, smoking, alcoholism, reduced vision, mobility problems, and sarcopenia [20].

4. The diagnosis of osteoporosis is made in the presence of fragility fractures, or with a T-score less than or equal to − 2.5 in the lumbar spine, femoral neck, total hip, or radius 33% in the adequate clinical context.

Osteoporosis is clinically diagnosed in the presence of fragility fractures, regardless of the presence of alterations in bone metabolism and BMD. Thus, patients with T-scores in the range of osteopenia and fragility fractures should also be diagnosed with osteoporosis. In addition, the diagnosis should be made when a T-score is reported less than or equal to − 2.5 in the lumbar spine, femoral neck, total hip, or 33% radius, even in the absence of

fracture. The radius should be evaluated only when it is not feasible to test the hip or spine, especially if hyperparathyroidism is suspected, or at the request of the patient. The diagnosis should also be considered in people with osteopenia and an increased risk of fracture based on the country-specific FRAX® threshold [24, 28].

If one or more fractures (fragility or otherwise) occur in patients with a reported T-score lower than -2.5, the diagnosis is severe osteoporosis [29].

The risk of fracture is classified according to the presence of risk factors in addition to the diagnosis of osteoporosis or the presence of fractures. Patients may be considered very high risk with any of the following characteristics: osteoporotic fractures in the last 12 months, fractures while in pharmacological treatment for osteoporosis, multiple fractures, use of drugs that alter bone quality, very low BMD (T-score < -3), high risk or history of falls, or high probability of fracture according to FRAX®. Patients with a diagnosis of osteoporosis without any of the aforementioned characteristics are considered at high risk of fracture [30].

5. Initial evaluation for suspected secondary causes of osteoporosis can be supported by laboratory tests, such as blood count, levels of vitamin D, phosphorus, intact parathyroid hormone (PTH), creatinine, alkaline phosphatase, transaminases, serum and urinary calcium, and 24-h urinary creatinine excretion.

Factors that cause or contribute to low BMD have been reported in more than 50% of postmenopausal women, the identification and treatment of which has an important effect on the course of osteoporosis [31]. Since these factors have been identified in up to 40% of women diagnosed with primary osteoporosis who do not have clinical evidence of secondary causes, their systematic evaluation is recommended in postmenopausal women with a diagnosis of osteoporosis and people with risk factors for fracture regardless of their age [24].

Due to the diversity of secondary causes of osteoporosis, including alterations of endocrine, gastrointestinal, rheumatological, hematological, respiratory, metabolic, or renal systems, associated with the consumption of drugs and related to immobility, basic laboratory tests should be supplemented with additional testing according to the findings from the clinical assessment.

6. Measurement of BMD should be considered in women age 65 or higher and in women under 65 years of age who are at increased risk of developing osteoporosis. If done, it should be measured by DXA at the spine and hip.

The measurement of BMD is the main criterion used for the diagnosis and monitoring of osteoporosis. It is reported in g/cm^2 and is measured by DXA at different points of the skeleton. The most common measurement sites are the lumbar spine and hip. The hip is preferred due to decreased measurement accuracy in the lumbar area in the presence of scoliosis and vertebral deformity. The discriminating power of the test across the disease risk range (area under the curve) is 65% (95% CI 62–67%) for any major osteoporotic fracture in treatment-naïve patients [20].

In women with osteoporosis without a history of fracture, measurement of BMD has been shown to be a good predictor of osteoporotic fractures. Adjusted for age, a decrease of 1 standard deviation (SD) in the BMD measured at the hip is associated with a relative risk (RR) of fracture of 1.4 (95% CI 1.4–1.6) in the forearm, 2.6 (95% CI 2.0–3.5) in the hip 1.8 (95% CI 1.1–2.7) for vertebral fractures and 1.6 (CI of 95% 1.4–1.8) for all sites [32]. Conversely, a 40% decrease in the risk of fracture has been observed for each 1 SD increase in BMD at the hip (Hazard Ratio [HR] 0.60; 95% CI 0.52–0.69) [33].

For the interpretation of the measurement of BMD by DXA in postmenopausal women, the evaluation of the T-score and the WHO densitometric classification are preferred [29, 34]:

- Normal: A BMD that is not more than 1 SD below the average normal value for a young adult.
- Low bone mass or low bone density (osteopenia): BMD with a T-score between -1 and -2.5 SD of the normal value for a young adult.
- Osteoporosis: A BMD value that is below -2.5 SD of the normal value for a young adult.

7. There are additional diagnostic tools to DXA such as VFA, TBS, REMS, and FS that should be implemented in Latin American countries to improve the initial approach to osteoporosis.

Vertebral Fracture Assessment (VFA) is a DXA diagnostic technology that allows imaging of the thoracic and lumbar spine to search for the presence of vertebral fractures. It is a convenient and reliable low-cost, low-radiation method ($\approx$3 μSv) [35]. VFA is indicated when the T-score < -1 and one or more of the following are present: a woman of 70 years or older, decrease of more than 4 cm in height, a self-reported but not documented vertebral fracture, and corticosteroid therapy in doses equivalent to prednisone 5 mg or more per day for 3 or more months [36]. It can be repeated if the patient continues to be at high risk of fracture or the risk factors for its indication persist [35].

As women 70 years of age and older have a higher risk of developing vertebral fractures, the panel considers it appropriate to evaluate the spine for fractures, regardless of the presence of additional risk factors and the result of the BMD measurement. This can be done using the VFA or lateral lumbar and thoracic spine X-ray if this is not available.

Trabecular Bone Score (TBS) is a texture index that evaluates the variations in the gray scale of the image obtained by DXA of the lumbar spine. It reflects the trabecular quality and serves as an approximation for the evaluation of the bone microarchitecture correlated with the density of connectivity of trabecular bone, its number, and the trabecular separation. It is interpreted by determining the variogram of the projected image of the region of interest, calculated as the sum of the difference of squares of the gray scale between pixels at a given distance. A reduced TBS indicates that the bone microarchitecture may be deteriorated and is associated with risk of major osteoporotic, hip, and vertebral fracture in postmenopausal women [37]. Used together with FRAX®, TBS has shown an improvement in the classification of fracture risk, especially in patients with results close to the treatment threshold and women under 65 years of age [38].

Radiofrequency Echographic Multispectrometry (REMS) is an ultrasound technique based on the analysis of unfiltered ultrasound raw signals obtained during an ultrasound scan of the lumbar spine and/or the femoral neck [39] whose result is reported as the ultrasonographic BMD expressed in g/cm^2 [40]. In a prospective study of 1516 Italian women ages 30 to 90, the REMS vertebral T-score was significantly lower in patients with fragility fractures (median [Me] = −2.9; quartile 1 [Q1] = 3.6—Quartile 3 [Q3] = −1.9), compared to those without fracture (Me = −2.2 [C1 = −2.9—C3 = −1.2]). The sensitivity was 65.1% and the specificity 57.7% for the identification of incident vertebral fractures (OR = 2.6; 95% CI 1.77–3.76) and 40.2% and 79.9% respectively for femoral fractures (OR = 2.81; 95% CI 1.80–4.39). The corresponding DXA was 84.8% for vertebral fractures and 84.2% for femoral fractures [39].

Fragility Score (FS) is an ultrasound parameter that estimates skeletal fragility based on a transabdominal ultrasound scan of the lumbar vertebrae. It has shown a good correlation with the risk of fracture estimated by FRAX® for any major fracture (r = 0.51) or hip fracture (r = 0.46). This is especially true when the measurement of the BMD of the femoral neck by DXA is added (r = 0.71 for major fracture; r = 0.70 for hip fracture), showing that the FS is directly proportional to the estimated risk of fracture [41].

To properly use these diagnostic aids, an adequate implementation of each technology and knowledge of its interpretation methods is required (Table 1).

8. In people with osteopenia without fragility fractures or in healthcare centers that do not have DXA, FRAX® is useful to assess the need to start treatment.

FRAX® is an algorithm that considers factors other than BMD to estimate the 10-year risk of fracture. It is a complementary tool to the measurement of BMD that can be useful to select the best therapeutic intervention according to the magnitude of the risk. It can also be considered as an educational instrument to improve the patient's knowledge about the disease and its risk factors [21].

Using FRAX® as a screening tool in community settings for women between 70 and 85 years of age from seven regions of England, the proportion of osteoporotic fractures found was similar in screened and unscreened women (12.9% vs 13.6%; adjusted HR = 0.94; 95% CI = 0.85–1.03). However in a prespecified secondary analysis, this strategy was associated with a 28% relative reduction in hip fractures when compared to standard care (2.6% vs 3.5%; aHR = 0.72; 95% CI = 0.59–0.89) [43].

Epidemiological data from countries with specific fracture risks and mortality and fracture rates was used to develop FRAX® [21]. For its proper use, the appropriate country model should be considered. In seven Latin American countries (Argentina, Brazil, Chile, Colombia, Ecuador, Mexico and Venezuela), thresholds for evaluation and treatment have been established [3].

9. Calcium and vitamin D supplementation should be considered in patients with osteoporosis if their dietary calcium intake is less than 1200 mg per day and vitamin D levels are less than 30 ng/l.

Table 1 Interpretation of new diagnostic technologies in osteoporosis

Technique	Interpretation
VFA	Genant's semi-quantitative visual method [36]
TBS	Determination of the variogram of the projected image of the region of interest [37]
REMS	Spectral analysis of transformed US radio frequencies by comparison to BMD [42]
FS	US radio frequency spectral analysis compared to healthy and fragile bone models [41]

VFA Vertebral Fracture Assessment, *TBS* Trabecular Bone Score, *REMS* Radiofrequency Echographic Multispectrometry, *FS* Fragility Score, *US* ultrasound

There exists a controversy in the definition of vitamin D sufficiency based on measured plasma concentration, specifically in reference to the positions adopted by the Endocrine Society (ENDO) and the Institute of Medicine (IOM) — both US institutions — reflecting different therapeutic approaches and appraisals of evidence [44].

IOM issued a response to the recommendations for vitamin D supplementation of the ENDO CPG, in which they recognize the commonalities between both approaches, such as that vitamin D and calcium are essential for bone health and that it is not necessary to perform routine screening in the general population. However, it warns of a fundamental difference of the plasma level at which supplementation should be considered: The IOM considers maintaining vitamin D levels greater than 30 ng/ml does not provide any additional benefit to maintaining a level greater than 20 ng/ml [45].

The Brazilian Society of Endocrinology and Metabolism (SBEM) and the Brazilian Society of Clinical Pathology/Laboratory Medicine (SPBC) issued a consensus on the reference values of the plasma level of vitamin D. It states that values between 20 and 60 ng/ml are sufficient for the general population under 65 years of age and ideally should remain between 30 and 60 ng/ml in older adults, people with a history of recurrent falls, people who have had bariatric surgery, pregnant women, patients treated with drugs that interfere with the metabolism of vitamin D, and patients diagnosed with osteoporosis, secondary hyperparathyroidism, osteomalacia, type 1 diabetes mellitus, cancer, chronic kidney disease, or malabsorptive diseases. The level of deficiency was defined as less than 20 ng/ml, and for levels greater than 100 ng/ml, risk of toxicity must be considered [46].

In light of the additional benefits to at-risk populations such as postmenopausal women with osteoporosis on which this document focuses, as proposed by ENDO [47] and the Brazilian consensus of SBEM and SPBC [46], a plasma level less than 30 ng/ml was adopted as a cut-off point to evaluate the need to start vitamin D supplementation in this population. For the general population, as proposed by the IOM, the value of 20 ng/ml is accepted as sufficient to maintain bone health in healthy individuals [48]. During the discussion to select this cut-off point, one of the panelists said 20 ng/ml should be considered as a threshold for treatment in postmenopausal osteoporosis (AARA).

In addition to people treated for osteoporosis, supplementation should also be considered if calcium intake is less than 1000 mg per day in adults under 50 years of age or less than 1200 mg per day in adults over 50 years of age. The use of supplements should be considered as additional to the daily calcium intake and be taken in doses of 500 to 600 mg (in any preparation) to optimize absorption. If the patient requires a greater daily supplement, dosing should be divided. Vitamin D supplementation can be started with doses of 1000 to 2000 IU per day titrating until sufficiency is reached [30].

Calcium and vitamin D supplementation reduces secondary hyperparathyroidism, bone remodeling, has a slight effect on BMD [21], and has been associated with a decrease in the risk of hip fracture (RR = 0.84; 95% CI 0.74–0.96) and any type of fracture (RR = 0.95; 95% CI 0.90–0, 99) when co-administered [49].

However, calcium and vitamin D supplements have been associated with an increased risk of kidney stones (RR = 1.17; 95% CI 1.03–1.34). They can also cause abdominal distention and constipation (RR = 1.04; 95% CI 1.00–1.08), and although no significant effect on mortality has been linked to high doses of these supplements, some studies have shown an unclear association with an increased risk of myocardial infarction [49]. Verifying the effect of exclusive calcium supplementation, no evidence of increased incidence of renal lithiasis has been found when compared to placebo (Absolute Risk Reduction [ARR] = 0.00%; 95% CI − 0.88% to 0.87%), and it has been suggested that there is no association with this event (RR = 0.68; 95% CI 0.14–3.36) [50]. It is important to note that in adults older than 70 years who had a history of falls, vitamin D supplementation with monthly doses of 60,000 IU or 24,000 IU plus calcidiol was associated with a greater number of falls compared to supplementation alone with 24,000 IU [51].

10. Bisphosphonates are indicated for the treatment of postmenopausal osteoporosis and patients with osteopenia and risk factors for fracture.

Bisphosphonates are the treatment of choice for osteoporosis in postmenopausal women in most countries where there is extensive experience with these medications [52].

Compared with placebo, bisphosphonates significantly reduce the risk of vertebral fracture (OR = 0.54; 95% CI 0.45– 0.65), non-vertebral fracture (OR = 0.78, 0.72–0.84), hip fracture (OR = 0.70; 95% CI 0.60–0.81), and any type of osteoporotic fracture (OR = 0.70; 95% CI 0.65–0.76) [53]. Differences in bisphosphonates may guide the therapeutic choice according to the risk profile of the patient: alendronate reduces the risk of vertebral, hip, and wrist fractures, risedronate can reduce the risk of vertebral and non-vertebral fractures, zoledronic acid can reduce the risk of any osteoporotic fracture and vertebral fractures, and ibandronate may reduce the risk of vertebral fractures, but not non-vertebral or hip fractures [54].

Treatment with bisphosphonates should last between 3 and 5 years, with periodic fracture risk assessment to define the optimal treatment duration for the patient. If the patient's risk of fracture persists, therapy should be continued. For women deemed at low to moderate risk, a supervised, temporary suspension of therapy should be considered [52].

Oral bisphosphonates can be associated with adverse gastrointestinal reactions such as esophagitis and dyspepsia. The most frequent adverse effect of parenteral application of zoledronic acid is a flu-like syndrome, which approximately one in four patients experience primarily after the first dose. Adverse effects with less frequency include osteonecrosis of the jaw and atypical fractures. In both cases their presentation depends on comorbidities, time, and dose of treatment [52]. As they are cleared by the kidneys, their use is recommended in patients with a glomerular filtration rate (GFR) > 30 ml/min for oral bisphosphonates and > 35 ml/min for zoledronate. Rapid intravenous administration may cause temporary or permanent decrease in GFR, especially in the elderly or patients using diuretics or potentially nephrotoxic drugs. Use is contraindicated if there is evidence of hypersensitivity or hypocalcemia [30].

11. Denosumab is indicated as an alternative for the initial treatment of postmenopausal osteoporosis with a high risk of fracture.

Denosumab reduces the risk of hip fracture (RR = 0.56; 95% CI 0.35–0.90) as well as non-vertebral (RR = 0.80; 95% CI 0.67–0.96) and vertebral fractures (RR = 0.32; 95% CI 0.22–0.45) [55]. It is safe to use in patients with chronic kidney disease (CKD) in all stages, including patients with GFR $\leq$ 35 ml/min/1.73 m^2. In patients with CKD stages I to III, the drug has increased BMD and reduced the occurrence of fractures at all sites. In patients with stage IV CKD, an increase in BMD in the hip has been observed without reducing the rate of fractures [52].

The therapeutic effect of denosumab has been observed early during treatment (after the first year) and has remained stable up to 10 years, showing a reduction in the risk of fracture, a sustained increase in BMD, and a low fracture rate at all sites, especially at the hip (0–0.61% per year) [30, 56]. There is no data for a treatment time greater than 10 years, so the risk of fracture and the response in BMD should be periodically reassessed to decide whether to continue therapy [52]. The suspension of denosumab should be followed without delay by the administration of another antiresorptive agent. An oral bisphosphonate is generally recommended after treatment with denosumab, due to regression of the effect on BMD to the baseline level at 12 months, progressive increase in the risk of vertebral fracture, and risk of subsequent fractures after the first fracture [57].

Although adverse drug reactions are infrequent, redness and infections at the application site have been reported with use of denosumab, as well as a low risk of hypocalcemia ($\approx 0.05\%$). No significant increase in the incidence of systemic infections, malignancy, or skeletal alterations has been observed in comparison with placebo [52]. The incidence

of atypical fractures and osteonecrosis of the jaw is low and may be related to the presence of additional risk factors [56].

12. Teriparatide is indicated for the treatment of osteoporosis with high or very high risk of fracture and osteoporosis with a history of vertebral fracture.

In a network meta-analysis, teriparatide reduced the risk of non-vertebral fractures (RR = 0.62; 95% CI 0.47–0.80) and vertebral fractures (RR = 0.27; 95% CI 0.19–0.38), with no evidence of a significant effect on hip fractures (RR = 0.64; 95% CI 0.25–1.68) compared to placebo [55]. Another meta-analysis that evaluated its effect on the incidence of hip and upper limb fractures in women and men with osteoporosis showed a reduction in the risk of hip fracture (OR = 0.44; 95% CI 0.22–0.87) after treatment for an average of 18 months, with no evidence of a reduction in the risk of fracture in the upper limb [58].

It is indicated for the treatment of osteoporosis patients who have a very high risk of fracture, such as those with a history of vertebral fracture or multiple vertebral fractures [52] or patients who have high risk factors, such as those with a history of corticosteroid treatment, those who have had a new fracture during treatment with antiresorptive agents, or those in whom antiresorptive agents are contraindicated [21, 30].

Treatment with teriparatide should be administered for 2 years, the duration for which the greatest benefit has been observed in terms of increased BMD [59]. In patients receiving teriparatide treatment, an extension regimen with an antiresorptive agent should be considered to prevent decrease in BMD and loss of efficacy in preventing fractures [60].

The most common adverse reactions have been reported with a frequency of less than 5% and include dizziness, cramps in the lower limbs, application site reactions, and headache. They are usually mild and do not require the suspension of treatment [21]. Mild transient hypercalcemia, mild increases in renal uric acid, and calcium excretion may occur. No cases of osteosarcoma in humans have been reported in association with teriparatide [60].

13. Romosozumab is indicated for the treatment of osteoporosis with a very high risk of fracture or multiple vertebral fractures and should be administered for one year.

Romosozumab has been indicated for the treatment of severe or very high-risk osteoporosis and in patients who have had treatment failure with antiresorptive agents [52]. It has been considered as a retreatment option in patients who have received anabolic therapy with teriparatide or abaloparatide [30]. Compared with placebo, romosozumab has

been shown to reduce the risk of hip fracture (RR = 0.44; 95% CI 0.24–0.79), non-vertebral fractures (RR = 0.67; 95% CI 0.53–0.86), and vertebral fractures (RR = 0.33; 95% CI 0.22–0.49) [55]. This effect is maintained for vertebral fractures (HR = 0.27; 95% credibility interval [CrI] 0.13–0.52) and for hip fractures with romosozumab followed by an extension therapy with alendronate (RR = 0.39; 95% CI 0.21–0.72) in subsequent analyses [61]. To maintain the gain in BMD and reduce the risk of fracture, treatment with romosozumab can be followed by an extension regimen with an antiresorptive agent [52].

The most common adverse effect, reported in up to 5% of patients, is application site infection [52]. No significant differences were observed in the frequency of presentation of adverse reactions when compared with teriparatide (RR = 1.03; 95% CI 0.80–1.34), placebo (RR = 1.00; 95% CI 0.98–1.02), or alendronate (RR = 0.96; 95% CI 0.93–1.00) [62]. Uncertainty persists in relation to the effect of romosozumab on cardiovascular risk [30, 52]. The Food and Drug Administration (FDA) issued a warning for its use in patients with cardiovascular risk, it is contraindicated for patients who have had a heart attack or stroke in the last year and should be discontinued if the patient experiences either of these events during treatment [63].

14. Selective estrogen receptor modulators are indicated as an alternative for the treatment of osteoporosis with risk of vertebral fracture or for younger postmenopausal women at risk of breast cancer.

Selective estrogen receptor modulators (SERMs) are an option for the treatment of osteoporosis patients in whom vertebral fractures are considered the highest risk, such as women with low BMD in the spine or a history of vertebral fracture, and may be especially useful in women with early menopause at risk of vertebral fracture and breast cancer [21]. The risk of vertebral fracture decreases both with the use of raloxifene (HR = 0.60; 95% CI 0.52–0.69) and bazedoxifene (HR = 0.61; 95% CI 0.48–0.77). Their use is recommended in women with osteoporosis who are at low risk of venous thromboembolism, at high risk for breast cancer, or who are not suitable for treatment with other antiresorptive agents. Other adverse effects that limit the use of SERMs are the appearance of cramps in the lower limbs and hot flashes. The use of raloxifene has been associated with a lower risk of breast cancer during and up to 5 years after finishing treatment [52].

15. Estrogen replacement therapy is indicated as an alternative for the treatment of osteoporosis or osteopenia in women under 60 years of age, with intense vasomotor or climacteric symptoms and who do not have any contraindication.

Estrogens are a treatment alternative for women with osteoporosis who have associated climacteric symptoms. The results on the risk of fracture observed with estrogen therapy come mainly from studies with women who were not at high risk of fracture. Risk reduction has been evidenced for vertebral fracture (HR = 0.66; 95% CI 0.49–0.89), hip fracture (HR = 0.71; 95% CI 0.52–0.98), and non-vertebral fracture (HR = 0.79; 95% CI 0.70–0.90), with an additional effect on climacteric symptoms. Potential adverse effects include venous thromboembolism, stroke, myocardial infarction, breast cancer, endometrial cancer, ovarian cancer, dementia, gallbladder stones, and urinary incontinence. The results of the Women's Health Initiative (WHI) study have shown that most of these risks subside when treatment is stopped [30, 52]. During the first 6 years of menopause, estrogen therapy has been associated with a decrease in the progression of subclinical atherosclerotic disease. This result has not been evidenced when therapy is started in women who have been postmenopausal for greater than 10 years [64].

16. The follow-up of postmenopausal osteoporosis should be based on the characteristics of each patient, including the individual assessment of the risk of fracture and general health status.

Several scientific associations agree that reducing the risk of fracture is the main objective of the treatment of osteoporosis. However, they have accepted in their CPG the difficulty of determining universal parameters of surveillance and response to therapy [21, 30, 52, 65, 66].

This difficulty is due to the fact that osteoporosis is a complex disease caused by the interaction between genetic, metabolic, and environmental factors that depend on the individual characteristics of each patient [67].

As a general follow-up for patients with postmenopausal osteoporosis, the following plan is proposed:

- The frequency of follow-up should be established according to the risk of fracture and changes in the health status of each patient.
- In the initial consultation and follow-up, the risk of fracture should be assessed, and the adoption and maintenance of lifestyle habits favorable to bone health should be emphasized.
- The occurrence of back pain and decrease in stature should be monitored.
- For patients with osteoporosis with fractures and those receiving drug treatment, check-ups could take place every 6 months for clinical evaluation and basic laboratory tests to evaluate bone metabolism may be requested.
- The assessment of the response to pharmacological treatment includes review of the prescription, verification of

the administration of the drug, and evaluation of adherence.

- Suspicion of therapeutic failure or deterioration of the patient's initial condition should be followed by evaluation of secondary causes of osteoporosis.
- As the follow-up of these patients can last for up to 30 years of life for postmenopausal women, the need for sequential pharmacological treatments should be considered.
- In patients with osteopenia or osteoporosis without fractures, DXA monitoring could be performed every 2 to 3 years.
- In patients with osteoporosis with fractures, DXA monitoring could be performed every 1 to 3 years.

DXA densitometry cannot be considered as the sole decision parameter due to the inherent measurement error of the technique and the variability of the response to therapy within the patient. For this reason, calibration of the equipment following the guidelines of the ISCD is recommended [34] along with comparison of repeated measurements of the patients, taking into account the minimum significant change of the measurement for the equipment and the course of the disease. A greater speed of modification in the gain of BMD has been observed with pharmacological treatment compared with the decrease in BMD observed in different prepathological stages [59, 65].

Within the approach to patients with osteoporosis, the use of bone remodeling markers can be included. These are an indirect measure of osteoblastic and osteoclastic activity that provide an estimate of the rate of bone remodeling, considered as a dynamic index that allows evaluating the short-term therapeutic response [68]. These markers have an inversely proportional relationship with BMD but given the low strength of association of this relationship, they are not considered as a suitable diagnostic strategy. The bone formation markers, N-terminal propeptide of type I

protocollagen (P1NP) and bone resorption β-isomer of the carboxy-terminal telopeptide of collagen I (βCTX-1), have been recommended to identify patients with relatively high or low rates of bone remodeling and to detect secondary causes of osteoporosis due to their availability, biological and analytical validation, bone specificity, and characteristics that can facilitate standardization [69]. To assess adherence to bisphosphonates, obtaining a measurement of P1NP and βCTX-1 is recommended before starting treatment along with monitoring at 3, 6, and 12 months [69, 70]. The measurement of P1NP can be useful in evaluating adherence to anabolic therapies and should be measured before starting, with the first assessment at 1 to 3 months and then at 6 and 12 months [70]. However, it should be noted that tests for bone remodeling markers may be expensive or unavailable in most Latin American countries.

Biosimilar drugs

Whereas the treatment of osteoporosis is also subjected to the use of biosimilar drugs and their inclusion on national lists of medicines, the existence of an operational definition of biosimilars was investigated in the regulations or communications issued by the competent bodies in each country (Supplementary table 2).

Barriers to healthcare of osteoporosis in Latin America

The barriers to disease care perceived by the panel members were discussed during the consensus process. Acknowledging that a formal methodology was not used to ensure representativeness of their responses, based on their extensive professional careers, they lay the groundwork to explore areas for improvement within the disease intervention process (Table 2).

Table 2 Perception of barriers to osteoporosis care

Area	Barrier
Diagnosis	Unidentified fragility fractures
	Low availability of densitometers and uneven geographical distribution within each country
Treatment	Lack of secondary fracture prevention programs
	Poor communication between services that care for patients with fractures Centralization of resources
	Not all drug treatment options are covered by healthcare systems
Burden of disease	It is not recognized as a public health problem
	It is not recognized as a preventable disease
	Lack of knowledge of the general population
	May go undetected by health professionals
	Low access to health services

The barriers stated by the panel have been previously acknowledged. Other structural issues previously acknowledged for the region have been related to the lack of administrative integration of actions needed to implement comprehensive country-wide approaches to osteoporosis [8].

These problems can begin to be resolved with the creation of well-articulated treatment programs within the countries' health systems, health education for patients and health professionals, and the collection of local epidemiological information.

Discussion

FELAEN is a non-profit organization that brings together endocrinology associations in Latin America and seeks to increase the visibility of osteoporosis and the generation of public policies to mitigate its impact [11]. FELAEN's position is summed up in 16 statements that are intended to serve as a summary of what the federation suggests as the basis for comprehensive treatment programs of osteoporosis in the countries of the region.

The review of epidemiological data makes it possible to establish variations in the incidence of fractures in the Latin American region not explained by the sources of error in the capture of cases. That variability must be analyzed in a heterogeneous way to implement local measures and strategies for the prevention of osteoporotic fractures.

There is great concern for the structural barriers to the care of osteoporosis that arise from situations of a political, economic, and social nature that lead to differences in the care of osteoporosis in Latin America. Such barriers hinder the timely care of the disease and the achievement of the objective of reducing the incidence of osteoporotic fractures and the morbidity and mortality associated with them.

The low availability of bone densitometry is perceived as the main diagnostic barrier. Even more serious, there is a perception of weakness in the institutional protocols that can lead to fragility fractures related to osteoporosis not being recognized as such and flaws in the communication between the professionals that treat patients with fractures. Secondary prevention is also perceived as deficient.

Differences in the availability and coverage and disparities in access to antiosteoporotic drugs also exist. A new concern appears from the introduction to the market of innovative biotechnological drugs as romosozumab, recently included in the treatment recommendations of the ENDO [71] and AACE/ACE CPG [30], and the arrival of competing biotech drugs, taking into account the approval of teriparatide biosimilar drugs by the European Medicines Agency (EMA) in 2017 [72] and the FDA in 2019 [73], as well as the launch of a study to determine the comparability of a denosumab biosimilar that has been in the recruitment phase since July 2019 [74].

One limitation in the development of this position statement is that the experts panel consisted only of endocrinologists, leading to a possible view on the disease guided by the experience and the context in which these professionals make their practice. This situation arises from the selection of the experts only through the national endocrinology associations affiliated to FELAEN. Nevertheless, the position was developed to be headed toward all the health professionals involved in the treatment of patients suspected or diagnosed with osteoporosis.

To contribute to the satisfaction of unmet needs in osteoporosis, FELEAN makes its consensus position for the diagnosis and treatment of postmenopausal osteoporosis available to the entire Latin American community as a calling on action to curb the burden of the disease. To achieve this goal, the panel advises to update the available information on the disease, to encourage the health care professionals in the region to make use of current clinical practices and asks for governmental policies that have the potential to improve the health care of osteoporosis. Such actions include the commission of studies to gather local epidemiological data, the development of context-specific CPG, the allocation of resources guided by EBM and best clinical practices, the implementation of detection programs for early diagnosis, and the creation of Fracture Liaison Services (FLS) to treat patients with osteoporotic fractures and to prevent subsequent fractures. FLS have proved to reduce subsequent fractures in patients from Argentina, Brazil, Colombia, and Mexico [75].

Regarding the differences in the initial diagnostic approach, mainly owing to the uneven distribution of DXA between countries and between the administrative divisions in some countries, the panel proposes the use of FRAX® to reduce the delay in diagnosis and the beginning of treatment.

Lastly, this position statement is also intended to serve as a starting point to achieve less fragmentation in the patient journey of osteoporosis in Latin America by highlighting the current evidence-based practices acknowledged by international medical associations. This also sets the conceptual basis to achieve a common framework for treating patients in the region.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest *PNR* has received support from Lilly for an academic event and has been a speaker for Lilly and Sanulac. *APT* assisted to academic events with the support of Amgen and Novo Nordisk and has received lecture fees from MSD. *MBZ* has been sponsored in an academic event by Amgen; has been a speaker for Lilly, Takeda, and Amgen; and received a grant from Ultragenyx. *MM* assisted to academic events with the support of Amgen and Aché and has received research grants from Shire and Alexion. *CAM* attended academic events with support from Amgen and Ultragenyx and has received research and academic grants from Ultragenyx. *CC* received support for an academic event and has received lecture fees from Tecnofarma and was previously employed as Medical Director at Clínica Universidad de Los Andes. *AMO* attended an academic event sponsored by Amgen and has received lecture fees from Lilly, Amgen, and Farma. *SC* has received support from MD Pharma, Janssen Cilag, Asofarma, and Pfizer and has been a speaker for Asofarma and MD Pharma. *PDP* has been a speaker in academic events for Lilly and Amgen and received research grants from Lilly. *AARA* assisted to an academic event with the support of Merck. *CV* attended academic events supported by Lilly, Grupo Mallen, and Asofarma; has been a speaker for Asofarma, Lilly, and Novartis; and received research grants from Novartis and Astellas. *BM* received support for attending academic events from Gador and research grants from Urufarma. *LRUO* has nothing to declare. *OG* attended academic events with the support of GSK and Roche and consults for Pharmalab.

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