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CONSENSUS STATEMENT

First Ecuadorian statement consensus for the evaluation and treatment of osteoporosis

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Abstract

Summary Osteoporosis management has become more relevant as the life expectancy increases. In Ecuador, approximately 19% of adults over 65 years of age have been diagnosed with osteoporosis. There is no national consensus for the management and prevention of the disease being this proposal the first Ecuadorian consensus.

Introduction In Ecuador, it is estimated that around 19% of adults over 65 years of age have osteoporosis. Due to the increase in life expectancy in the world population, the evaluation and management of osteoporosis has become more relevant. Currently, there is no national consensus for the management and prevention of the disease. The Ecuadorian Society of Rheumatology presented the project for the elaboration of the first Ecuadorian consensus for the management and prevention of osteoporosis.

Methods A panel of experts in multiple areas and extensive experience was invited to participate. The consensus was carried out using the Delphi method. Six working dimensions were created: definition and epidemiology of osteoporosis, fracture risk prediction tools, non-pharmacological treatment, pharmacological treatment, calcium and vitamin D, and glucocorticoid-induced osteoporosis.

Results The first round was held in December 2021, followed by the second round in February 2022 and the third round in March 2022. The data was shared with the specialists at the end of each round. After three rounds of work, a consensus was reached for the management and preventionof osteoporosis.

Conclusion This is the first Ecuadorian consensus for the management and treatment of postmenopausal osteoporosis.

Keywords Ecuador · Osteoporosis · Osteopenia · Treatment

Introduction

Due to the increase in life expectancy in the world population, the evaluation and management of osteoporosis has become more relevant. In Ecuador, it is considered that around 19% of adults over 65 years of age have osteoporosis [1]. At the moment, there is no national consensus for the prevention and management of osteoporosis. Due to this, the Ecuadorian Society of Rheumatology presented the project for the elaboration of the first Ecuadorian consensus for the prevention and management of osteoporosis.

Methodology

It is not necessary for all the participants to reach an agreement in a consensus [2]. A specific range must be established prior to reaching the consensus. For the percentage of acceptance of 80% among the participants was taken as a measure [3]. We used 80% as the percentage of acceptance measure among participants.

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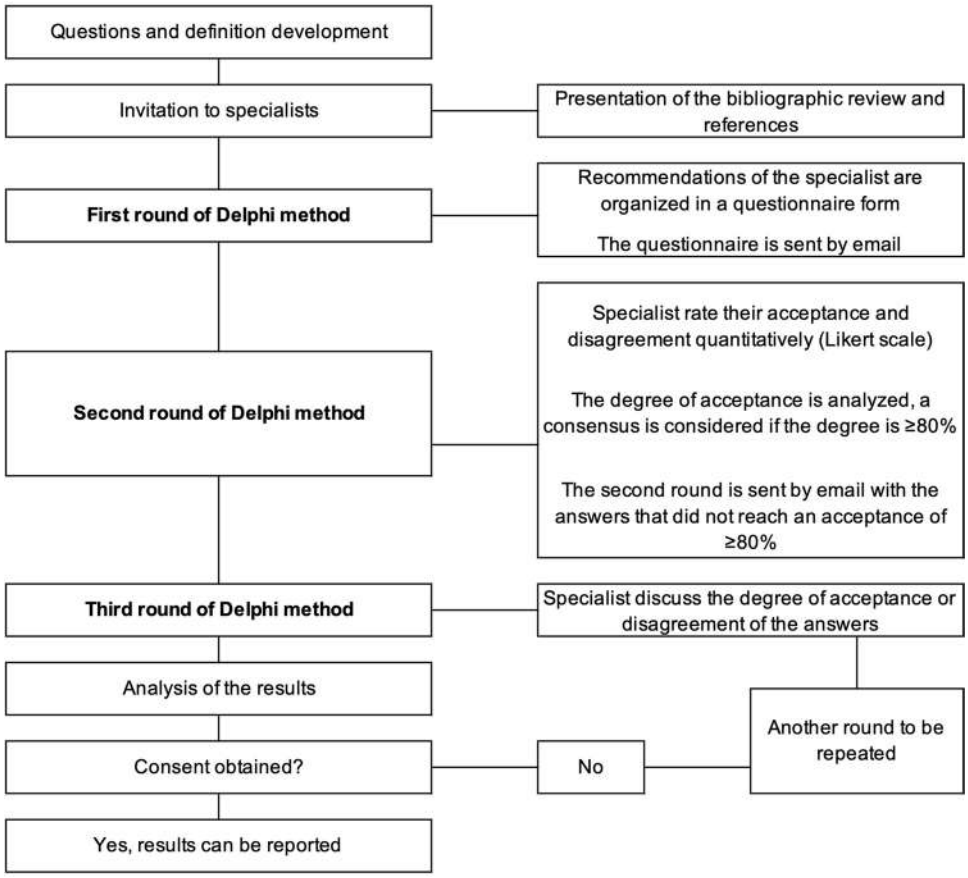

Fig. 1 Delphi methodology

Participants

Specialists in the field of rheumatology, endocrinology, traumatology, and gynecology were taken into consideration, because the heterogeneity of the group gives more credibility to the consensus methodology and the experience of each participant contributes immensely to an adequate discussion [4, 5].

Delphi method

First described in 1960, the Delphi method was developed to obtain a consensus about a specific topic in a systematic way [6]. The Delphi method is used when a consensus must be obtained from a large group of experts and they cannot be brought together in a specific place due to logistical or economic reasons [7]. The process is represented in Fig. 1. It was delineated based on five stages; stage 1 included the establishment of a steering committee, stage 2 was focused on the literature review and generation of draft checklist items, stage 3 reached a consensus on checklist items, stage 4 was dedicated to creating the report guideline and explanation and elaboration document, and lastly, stage 5 included dissemination [8]. Based on the Delphi principles, the consensus threshold was defined as at least 50% of the target panel respondents and 80% of responding experts able to answer voting "agree" or "strongly agree," with two rounds of statement revision and re-voting. The first round was held in December 2021, followed by the second round in February 2022 and the third round in March 2022. The data was shared with the specialists at the end of each round.

Search strategy

The systematic review was performed by the authors GM, CR, and MM, based on the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [9]. Search was made in EMBASE (OVID), PubMed and Cochrane Library without limits by year or language of publication. The authors GM, CR, MM, OM and JL reviewed independently the titles and abstracts retrieved for inclusion. Keywords used included "osteoporosis," "postmenopausal women," "management," "treatment," "guidelines," and others.

Table 1 Class (Strength) of the recommendations

Class (Strength) of the recommendations	
Class I (Strong)	Benefit > > > Risk
Evidence and/or general agreement on whether the usefulness/efficacy of the treatment or procedure is beneficial, useful, and effective	It is recommended, it is indicated
Class IIa (Moderate)	Benefit > > Risk
There is contradictory evidence and/or differing opinions on the usefulness/efficacy of the treatment or procedure given that the weight of the evidence/opinion is in favor of the usefulness/efficacy	Should be considered
Class IIb (Weak)	Benefit > Risk
The utility/efficacy is less established by evidence/opinion	Can be considered
Class III (No benefit)	Risk > Benefit
Evidence or general agreement that the given treatment or procedure is not useful/effective and, in some cases, may be harmful	Not recommended

Table 2 Evidence level based on quality

Evidence level based on quality	
Level A	Quality of evidence
-High-quality evidence from more than one randomized clinical trial -High-quality metanalysis based on randomized clinical trials -One or more corroborated randomized clinical trials with high-quality registries	High
Level B-R (Randomized)	
-Moderate quality evidence of more than one randomized clinical trial -Moderate quality metanalysis based on randomized clinical trials	Moderate
Level B-NR (Nonrandomized)	
-Moderate quality evidence from one or more nonrandomized trials, observational studies, or study registries -Metanalisis based on non-randomized observational studies	Moderate
Nivel C-DL (Limited data)	
-Randomized or non-randomized clinical trials with limitations in design or execution -Metanalysis from these studies	Low
Nivel C-OE (Expert opinion)	
-Based on expert consensus or clinical experience	Low
Nivel D	
-Any estimated effect is uncertain, based on expert opinion, without direct investigation evidence	Very low

Recommendations, classification system, and levels of evidence

The recommendation class indicates the strength of the recommendation, considering the magnitude and benefits in proportion to the risks. The level of evidence classifies the quality of the scientific evidence supporting the intervention based on the type, quantity, and consistency of randomized clinical trials and other sources [10] (Tables 1 and 2).

Definition and epidemiology of osteoporosis

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mineral density with alterations in its micro and macro architecture, which implies a decrease in bone resistance, increased fragility, and increased risk of fracture. It is multifactorial in origin, with genetic, biomechanical, and environmental factors participating in its etiology [11].

In Ecuador, 19% of adults over 65 years of age have osteoporosis (1). According to data from the Ministry of Public Health, forearm fracture is the tenth cause of hospital admission with 10,426 cases per year [12]. Lopez et al. reported a crude annual incidence of 123 cases per 100,000 inhabitants, 74.6 per 100,000 men and 165.8 per 100,000 women [13]. The hip fracture mortality rate has increased from 4.4% in men and 2.9% in women [14] to 5.1% in men and 3.8% in women [15].

Risk factors

Risk factors for osteoporosis are advanced age, history of previous fracture, glucocorticoid therapy, family history of hip fracture, smoking, alcohol consumption, established diagnosis of rheumatoid arthritis, systemic lupus erythematosus

[16–18], ankylosing spondylitis [16], secondary osteoporosis (hypogonadism, malabsorption syndromes, chronic liver disease, inflammatory bowel disease, diabetes mellitus types I and II, chronic kidney disease, and sickle cell anemia) [19]. In addition, gastrectomy and various forms of bariatric surgery such as gastric bypass have recently been identified as risk factors for osteoporosis and fractures [20].

Fragility fractures

Fragility fractures are those that occur spontaneously or due to minor trauma, such as a fall from a foot height or less, and that do not involve the hands, feet, face, or skull [11, 21, 22]. Brittle fractures are the result of mechanical forces that would not normally cause fractures. Decreased bone density is a major risk factor for fragility fractures. The most common sites of fragility fractures are the spine (vertebral compression fractures), the hip, and the wrist [11]. Fragility fractures also occur in the humerus, ribs, and pelvis. Stress fractures are not considered fragility fractures, since they are due to repetitive injuries [11, 21, 22].

It has been estimated that only one in three fragility fractures is identified and only a small percentage require hospitalization [22, 23]. Robinson et al. showed that white race, obesity, age between 70 and 79 years, and previous history of fracture after 50 years are risk factors for developing fragility fractures [24].

Fall risk evaluation

Falls are related to a lower quality of life, increased mortality, and morbidity [25]. According to WHO data, of all the years lived with disability, falls are the third most common cause of increased mortality and morbidity [26]. Approximately 30% of people over 65 years of age have at least one fall per year, 15% have more than two falls per year, and 5% of all falls result in fractures [27–29]. This emphasizes the importance of determining the risk of falling for fracture prevention (Table 3).

Table 3 Intrinsic and extrinsic factors for fall risk

Intrinsic factors	Extrinsic factors
Demographics Age > 70 Women White/Caucasian Systemic Gait and balance Muscle strength Vision Cognition Disease/symptoms Dizziness/vertigo Cardiovascular disease Dementia Depression	Medications • Opioids • Antidepressives • Anticonvulsants • Diuretics • Antihypertensives • Anesthesia • Inappropriate shoes • Household characteristics • Lack of security handrails • Bathrooms without anti-slip carpets • Presence of loose rugs • Unstable furniture • Dim lighting

Diagnostic methods

Bone densitometry

In clinical practice, DXA is the only exam that allows us to perform diagnostic classifications [30]; it is useful for monitoring changes in bone mineral density (BMD) and the radiation exposure is very low with current densitometers [31]. According to the International Society for Clinical Densitometry (ISCD), the indications for performing DXA in women are as follows [30]:

Age 65 or older
In postmenopausal women under the age of 65, a bone density scan is indicated if they have a risk factor for low bone mineral density, such as:

- Low body weight (BM ≤ 19 kg/m.^{2})
- Previous fragility fracture
- Use of high risk medications
- Illness / disease associated with decreased bone mass.

Women during the menopausal transition with clinical risk factors for fracture, such as low body weight (less than 57 kg), previous fracture, or use of high-risk medications.
Men aged 70 or older
For men < 70 years of age, a bone density scan is indicated if they have a risk factor for low bone mass, such as:

- Low body weight
- Previous fracture
- Use of high-risk medications
- Illness/disease associated with decreased bone mass.

Adults with a fragility fracture history*
Adults with a disease or condition associated with low bone mass or bone loss.
Adults taking medications associated with low bone mass or bone loss.
Any person considered for therapy against osteoporosis.
Anyone not receiving therapy where evidence of bone loss leads to treatment.
**In patients with a history of fragility fracture, it is not necessary to perform a densitometry to start treatment; however, it is necessary to establish the diagnosis, evaluate the response to treatment and determine the risk of fracture* [32].

Diagnostic criteria

The WHO has established a densitometry classification according to the *T*-score [31]. This classification can be applied to perimenopausal women, postmenopausal women,

and men older than 50 years of all races, and a *T*-score of − 2.5 or less is required for diagnosis.

There are three evaluation sites: hip, lumbar spine, and forearm [33]. Any hip can be measured if it has not been surgically intervened. Measurement of the forearm is recommended only when measurements of the lumbar spine and hip are not interpretable [34].

The WHO international reference standard for the diagnosis of osteoporosis is a *T*-score of − 2.5 SD or less at the femoral neck or lumbar spine L1–L4) [30]. Due to this, the *T*-score is used for postmenopausal women and men older than 50 years, since they better predict the risk of future fractures. The *Z*-score is used for the diagnosis of low bone mass for chronological age when the *Z*-score is equal to or less than − 2 SD in premenopausal women, men under 50 years of age, and children [30].

Clinical criteria

The clinical criteria for the diagnosis of osteoporosis can be made in the presence of a fragility fracture, regardless of bone mineral density. The National Bone Health Alliance establishes a clinical diagnosis of osteoporosis in patients with the presence of low-impact fractures with a *T*-score less than − 2.5.

Vertebral morphometry

The usefulness of bone morphometry lies in the evaluation of vertebral fractures [35]. Vertebral fractures are the most common type of fragility fracture. This modality can be performed at the time a conventional bone densitometry is performed; The advantages of this method are its lower cost, lower exposure to radiation compared to conventional spine radiography [36]. The sensitivity and specificity of bone morphometry for the detection of moderate to severe fractures are 87–93% and 83–93%, respectively [37].

According to the International Society for Clinical Densitometry (ISCD), the indications for performing bone morphometry are [30]:

Parameters: *T*-score < − 1.0 and one or more of the following criteria:

Feminine sex, ≥ 70 years of age
Masculine sex, ≥ 80 years of age
History of height loss > 4 cm in less than two years
Previous vertebral fracture
Glucocorticoid therapy (≥ 5 mg daily for ≥ 3 months)

Previous vertebral fracture not documented but reported by the patient.

X-rays

In osteoporosis, vertebral fractures are a common clinical problem. Due to this, the presence of vertebral fractures is a cause of morbidity and mortality and confers a risk of 5 to 12.6 times of other vertebral fractures and a risk of 2.3–3.4 times of hip fracture [38, 39]. Indications for obtaining a thoracolumbar spine radiograph include a history of hip fracture secondary to low-intensity trauma and/or patients with a *T*-score < − 1 associated with one or more of the following parameters [40, 41]:

o Women older than 70 years of age
p History of height loss > 4 cm in less than two years
q Previous vertebral fracture
r Glucocorticoid therapy (≥ 5 mg daily for ≥ 3 months)
s Hyperkyphosis
t Pain in the thoracic or lumbar spine of more than 15 days of evolution without apparent cause

Nuclear magnetic resonance imaging

In the presence of symptoms of lumbar compression, a magnetic resonance imaging (MRI) should be performed. MRI makes it possible to differentiate between a malignant or benign fracture and acute or chronic vertebral crushing [42, 43].

Clinical laboratories

Bone turnover markers

Routinely measuring bone turnover markers (BTMs) is not necessary in all patients [44]. However, it would be advisable to measure them in specific patients such as those where the absorption or efficacy of the drug is not adequate or those with poor adherence to treatment. Several essays are available, focused on measuring collagen breakdown products released by osteoclasts and osteoblasts during the process of bone resorption and formation. Bone formation markers include bone-specific alkaline phosphatase (BSAP), osteocalcin, and N-terminal propeptide of type I procollagen (PINP). Bone resorption markers include N-terminal telopeptide of type I collagen (NTX), C-terminal telopeptide of type I collagen (CTX), and pyridinoline cross-links [40, 45]. In Ecuador, the only available bone turnover marker is deoxypyridinoline or Pirilinks-D; this marker is excreted without metabolizing in the urine.

Serum calcium

Before starting antiresorptive therapy, it is necessary to exclude secondary causes of osteoporosis [11]. For the analysis of calcium, it is necessary to measure total serum calcium and in cases such as cirrhosis, nephrotic syndrome, malnutrition,

malabsorption syndromes, and paraproteinemia; the correction of calcium in relation to albumin should be performed [45].

Phosphorus

Phosphorus is an essential mineral that plays a vital role in bone health. It is an important element of the mineral matrix of bones, along with calcium, and is necessary for the formation and maintenance of bones. There is no evidence that the measurement of phosphorus alters the decision to start treatment, however, if there is a suspicion of an alteration in the phosphorus-calcium metabolism or secondary osteoporosis, it is necessary to carry out the measurement [11]. Special considerations include young patients with muscle and bone pain, history of multiple fractures, stress fractures, and suspicion of tumor-induced osteomalacia.

25-Hydroxyvitamin-D

Despite being located on the equator and with high levels of solar radiation, the population takes measures to avoid sun exposure. Due to this, there is a considerable vitamin D deficiency in Ecuador [46, 47]. Approximately 70% of Ecuadorians have levels below 30 ng/dL, with normal levels being above 30 ng/dL [48].

Creatinine

Most of the drugs of choice for the management of osteoporosis, such as bisphosphonates, are excreted by the kidney. Creatinine levels and glomerular filtration rate should be measured [11].

Alkaline phosphatase

In patients prior to treatment for osteoporosis, it is important to evaluate other causes of bone loss [49]. If there are elevated levels of alkaline phosphatase, the next step is to confirm the origin of the elevation, which can be hepatic or bone [50]. Furthermore, alkaline phosphatase is a nonspecific marker of bone resorption.

Miscellaneous

In patients with suspected secondary osteoporosis or unexplained causes of bone loss, the measurement of parathormone (PTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, thyroid profile, erythrocyte sedimentation rate, factor rheumatoid arthritis, iron, ferritin, iron-binding capacity, homocysteine, tissue transglutaminase antibodies to detect celiac disease, urinary and serum protein electrophoresis, markers of bone formation and resorption, and urinary excretion of cortisol [51].

Fracture risk assessment tools

The Fracture Risk Assessment Tool or FRAX, for its acronym in English, is a fracture risk model developed in 2008 by the University of Sheffield, it estimates the 10-year probability of the risk of fracture of the hip and major osteoporotic. Vertebral, proximal humerus, or forearm in patients between 40 and 90 years old using clinical risk factors for fractures and bone densitometry, when available [52]. It is available on its official website (https://www.sheffield.ac.uk/FRAX/) and on mobile devices through an application. In Ecuador, it was first developed in 2009 and updated in 2019 [53].

The FRAX tool can be used in all patients aged 40–90 years with suspected fracture risk. It is recommended that all postmenopausal women and men older than 50 years should be screened for osteoporosis [54].

FRAX intervention values are estimated based on the evaluation of the absolute risk of fractures and specific analyzes of each country [11]. International guidelines have established that treatment should be started when FRAX values exceed $\geq 20\%$ for major osteoporotic fractures and 3% for hip fractures [55, 56].

Additional guidelines are available from the American Association of Clinical Endocrinologist (AACE) which have been updated in 2020 and highlights the stratification of the patient according to high-risk and very-high-risk features [40].

Evaluation and intervention curves

The objective of using evaluation thresholds is to improve risk assessment in patients close to the threshold and reduce the number of required densitometries [57] (Fig. 2). Individuals with FRAX probability below the lower screening threshold do not require further intervention, whereas those above the upper screening threshold may be considered for treatment without densitometry. People with FRAX probability within the limits of the screening thresholds should undergo densitometry and their FRAX recalculated using BMD (orange color). However, clinical judgment based on risk factors should take precedence when evaluating each patient.

Trabecular bone score

The trabecular bone score or TBS for its acronym in English, is a complement to the densitometric analysis and evaluates the risk of fracture by evaluating the trabecular microarchitecture [58, 59]. The software uses data derived from densitometric images of the lumbar spine and generates a texture index of gray colors. TBS levels above 1.35 are considered normal and represent a strong microarchitecture resistant to fractures, while a low TBS reflects a weak microarchitecture prone to fractures [58, 59]. TBS is not validated for the Ecuadorian population.

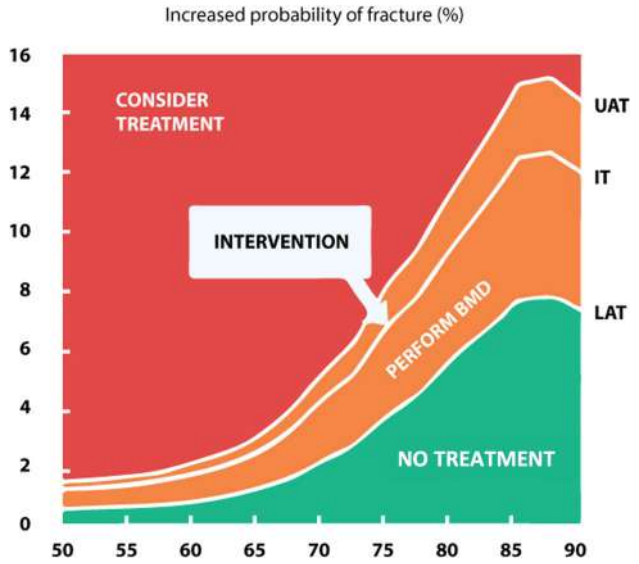

Fig. 2 Evaluation and intervention curves. UAT, upper assessment threshold; IT, intervention threshold; LAT, lower intervention threshold

Nonpharmacological measures

Nutrition and bone metabolism

In order to preserve muscle mass, the adequate intake of protein in adults is 0.8 g/kg/day, and in adults over 65 years of age in the absence of chronic kidney disease, the adequate intake is 1.0–1.2 g/kg/day [60]. Studies suggest that a higher protein intake may be associated with a lower risk of hip fractures [61] and bone loss [62–65].

Exercise

Resistance, balance, and coordination exercises have been shown to have positive effects on muscle mass, reducing the risk of falls. A meta-analysis by Cadore et al. demonstrated a decrease in falls of up to 58% in subjects who performed resistance exercises [66]. Due to the benefits of exercise to reduce the risk of falls, at least 30 min of exercise 3 times a week is recommended. Similarly, a meta-analysis by Kemmler et al. demonstrated a decreased risk of fractures in older adults [67].

The most effective exercise to increase femoral neck bone mineral density is high-force weight-bearing (progressive resistance strength training), while a combined program (more than one type of exercise) is more effective for the lumbar spine [66]. Regarding the intensity of the exercise, a regular weight-bearing exercise regimen that facilitates long-term compliance is recommended, since high-intensity exercises can lead to abandonment of the activity. In addition, some studies have shown the usefulness of Tai Chi as a complementary exercise in patients with osteopenia and osteoporosis [68].

Alcohol consumption

Alcohol increases bone remodeling and increases the risk of fracture. High alcohol consumption (more than 2 alcoholic drinks per day) results in an entity described as alcohol-induced osteopenia [69]. In addition, alcohol can interfere with calcium balance by decreasing calcium absorption, increasing PTH levels, decreasing 1,25-dihydroxyvitamin D production, and decreasing estrogen production. In older adults, the risk increases because alcohol increases the risk of falls [69].

Carbonated beverages

The consumption of carbonated beverages has increased in recent years, in young adolescents a decrease in bone mineral density has been shown due to the displacement of beverages with high nutritional value [70–73]. However, Samano et al. demonstrated that in adults, carbonated beverages are associated with bone loss due to their caffeine content [74], in addition, these beverages contain high levels of phosphoric acid, which interferes with calcium absorption and contributes to the risk of osteoporosis [75, 76]. However, there is not an official consensus regarding the consumption of carbonated beverages. Due to this, we recommend avoiding excessive consumption.

Caffeine

Consumption of up to 400 mg of caffeine per day appears to be safe in adults, with a cup of coffee containing approximately 133 mg of caffeine [77, 78]. Several studies have shown an inverse correlation between caffeine intake and bone density. Harris et al. determined that the consumption of five or more cups of coffee is associated with a decrease in bone mineral density [79]. In addition, Rapuri et al. showed that more than 18 oz of prepared coffee accelerate bone loss in the lumbar spine of elderly postmenopausal women [80]. Because of this, limited coffee intake (up to three cups per day) is recommended to prevent bone mineral loss.

Smoking

Smoking accelerates bone loss and is a risk factor for hip fracture in women [81–84]. Nicotine promotes osteoblast apoptosis and decreases its bone formation effect, in addition, it affects the proliferation and differentiation of osteoblasts, thus generating a risk factor for osteoporosis [85]. Smoking cessation can reverse bone mineral density loss and decrease excess hip fracture risk after approximately 10 years of quitting tobacco use.

Orthopedic corset

Several international studies and guidelines do not recommend the use of corsets as first-line treatment for osteoporotic vertebral fractures [86–89].

Pharmacological treatment

We recommend pharmacological intervention in postmenopausal women and men older than 50 years with [90]:

Previous fragility fracture
Risk factors for osteoporosis
T-score ≤ 2.5 in the femoral neck or lumbar spine
T-score between − 1 and − 2.5 in the femoral neck or lumbar spine and a FRAX ≥ 3% of hip fracture, and ≥ 20% in the lumbar spine [9, 91]
Patients with a prolonged use of glucocorticoid therapy (≥ 5 mg daily of prednisolone for ≥ 3 months)

Treatment should be started in patients who meet the previously discussed criteria (postmenopausal women or men older than 50 years with a history of fragility fracture, BMD between − 1.0 and − 2.5 risk factors for osteoporosis) [90] (Fig. 2).

Approved therapies for the treatment of osteoporosis are listed below in Table 4 [92]:

Bisphosphonates

Bisphosphonates are the first-line medications for the treatment of osteoporosis, since they inhibit osteoclastic action, adhering to hydroxyapatite binding sites [94, 95]. In addition, they decrease the growth and recruitment of osteoclast progenitor cells and promote osteoclast apoptosis [94, 95].

Alendronate

Alendronate is an oral bisphosphonate indicated for prevention and treatment of osteoporosis in men and postmenopausal women, prevention of glucocorticoid-induced osteoporosis, and Paget's disease [11, 90]. The indicated dose for treatment is 70 mg/week or 10 mg/day [91, 96].

Risedronate

Risedronate is an oral bisphosphonate indicated for the treatment of osteoporosis in postmenopausal women and men, prevention of glucocorticoid-induced osteoporosis, and Paget's disease [11, 22, 92]. There are different formulations: 5 mg/day, 35 mg/week, or 150 mg/month.

Ibandronate

Ibandronate is a bisphosphonate available orally (150 mg monthly dose) and intravenously (3 mg/3 mL every 3 months). It is indicated for the treatment and prevention of osteoporosis in postmenopausal women. Ibandronate has not been shown to prevent hip or non-vertebral fractures [40, 92, 93].

Zoledronic acid

Zoledronic acid is an intravenous bisphosphonate, which is administered once a year as an infusion lasting at least 30 min. Its effectiveness has been evaluated in several clinical trials. The HORIZON study (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) demonstrated a reduction in the risk of vertebral fracture by 70% in a period of 3 years compared to placebo and a reduction in the risk of hip fracture by 41% [97].

Because oral bisphosphonates are poorly absorbed (at least about 1% of the dose), they should be taken on an empty stomach. It should be taken with at least 240 mL (8 oz) of water. After administration, the patient should not eat, drink, or take vitamin supplements for at least 30 min (alendronate) or one hour (ibandronate) and should remain seated or standing.

Contraindications to the use of bisphosphonates include patients with a history of gastric and esophageal disorders, inability to follow dosing instructions (upright position for at least 30–60 min), or chronic kidney disease (glomerular filtration rate < 30 mL/min). In patients who have undergone bariatric surgery (surgical anastomosis, Roux-en-Y gastric bypass) bisphosphonates are also contraindicated.

The choice of initial medication will depend on the patient, treatment compliance, the nature of contraindications or intolerance, the severity of osteoporosis, and the risk of fracture. Intravenous bisphosphonates are an alternative (zoledronic acid, ibandronate) as well as the use of denosumab.

Therapeutic holiday

The therapeutic holiday is considered a temporary interruption of the drug for up to 5 years, which must be evaluated annually with BMD and bone turnover markers to verify the patient's progress. This period may be longer or shorter depending on the BMD and the clinical circumstances of each patient [92].

In postmenopausal women with osteoporosis on bisphosphonate therapy, it is recommended that fracture risk be reassessed after 3–5 years and women who continue to be

Table 4 Approved therapies for the treatment of osteoporosis

Class	Administered method and dosage	Reduction in fracture risk	Adverse effects	Use approved for osteoporosis
Bisphosphonates				
Alendronate	Oral: 70 mg/week	Vertebral, non-vertebral, and hip	Common: esophagitis, malaise Rare: ONJ, atypical femoral fractures	Treatment and prevention
Risedronate	Oral: 35 mg/week or 150 mg/monthly (in one dose or two doses of 75 mg in consecutive days)	Vertebral, non-vertebral, and hip		
Ibandronate	Oral: 150 mg/week; IV: 3 mg every 3 months	Vertebral		
Zoledronic acid	IV: 5 mg/annual	Vertebral, non-vertebral, and hip	Common: first dose acute reaction Rare: ONJ, atypical femoral fractures	Treatment and prevention
Biological: Denosumab	Subcutaneous: 60 mg every 6 months	Vertebral, non-vertebral, and hip	Possible: cellulitis at the administration site or skin reactions Rare: ONJ, atypical femoral fractures	Treatment
Biological: Romosozumab *(not available in Ecuador)*	Subcutaneous: 210 mg every month for up to 1 year	Vertebral	Common: arthralgia and headache Precautions: cardiac events (infarction, stroke), hypersensitivity, hypocalcemia, osteonecrosis, and atypical femoral fractures	Treatment
Anabolic: Teriparatide	Subcutaneous: 20 µg/day	Vertebral and non-vertebral	Common: nausea, cramps in lower limbs Rare: hypercalcemia and osteosarcoma	Treatment
Abaloparatide *(not available in Ecuador)*	Subcutaneous: 80 µg/day	Vertebral and non-vertebral	Common: nausea, cramps in lower limbs Rare: hypercalcemia and osteosarcoma	Treatment
SERM: Raloxifene (not available in Ecuador)	Oral: 60 mg/day	Vertebral	Venous thromboembolism, hyperthermia, leg cramps, nausea	Treatment and prevention
Bazedoxifene (not available in Ecuador)	Oral: 20 mg/day	Vertebral and non-vertebral	Venous thromboembolism, hyperthermia, leg cramps, nausea	Treatment and prevention
Estrogens				
Tibolone	Oral: 2.5 mg/day	Vertebral and non-vertebral	Increased recurrence of breast cancer [93]	Treatment and prevention
17 β-Estradiol	Oral 0.025–0.10 mg/day; transdermic: 2 times per week	No data from randomized studies	Venous thromboembolism, increased risk of breast cancer (not significant), and cardiovascular disease	
Ultra-low-dose 17 β-estradiol	Oral: 0.014 mg/day	No data from randomized studies		
Bazedoxifene-conjugated estrogen combination (not available in Ecuador)	Oral: 20 mg/0.45 mg daily	Vertebral, non-vertebral and hip		Prevention

at high fracture risk should continue therapy, while those at low fracture risk to moderate should be evaluated individually and depending on the risk factors present, the possibility of a therapeutic holiday [92].

Denosumab

Studies of the long-term use of denosumab are of 10 years [98, 99]. It has been shown that its use is associated with a decrease in the incidence of fractures and an increase in bone mineral density [100], in each of the 10 years of follow-up [101, 102].

An increased risk of fracture has been observed in patients who discontinue denosumab. Fractures occur 8–16 months after the last dose of denosumab, raising concerns about a rebound effect in fracture risk when the drug's effects wear off [98, 99, 103, 104]. They can occur because of the rapid increase in bone turnover and a temporary decrease in bone density. The frequency of rebound fracture varies depending on the length of treatment and other individual factors. The risk of rebound fractures may be higher in patients who have had multiple prior fractures or a history of high bone turnover.

In clinical trials, patients who discontinued denosumab after 3 years of treatment had a higher incidence of vertebral fractures than those who continued treatment with another osteoporosis medication. Hence, if denosumab is discontinued, sequential antiresorptive therapy should be performed in order to prevent bone loss [105, 106]. Some studies have shown that the use of bisphosphonates such as alendronate and zoledronic acid maintains bone mass levels and can be started from the sixth month after suspension [107, 108].

Hormone replacement therapy

Menopausal hormone therapy (MHT) is commonly used to treat vasomotor symptoms and genitourinary syndrome of menopause [109]. The benefits of MHT outweigh the risk of cancer in healthy, symptomatic women when started within the first 10 years of menopause or in those younger than 60 years. Contraindications for MHT are a history of breast cancer, coronary heart disease, history of thromboembolic or venous events, cerebrovascular accident, and/or active liver disease [109]. Menopausal hormone therapy medications that have benefits on bone metabolism are selective estrogen receptor modulators (Raloxifene and Bazedoxifene), tibolone, and estrogen/progestin therapy [92].

Raloxifene

Raloxifene inhibits bone resorption and reduces the risk of vertebral fracture [40, 110]. Due to 8-year safety and efficacy studies and breast cancer risk reduction, it may be considered an alternative treatment option to reduce the risk of vertebral fractures in patients for whom bisphosphonates and denosumab are not suitable, or in patients with an elevated risk of fracture and risk of breast cancer. Raloxifene therapy should be continuous, Siris et al. demonstrated that BMD levels increased during 7 years of raloxifene therapy in postmenopausal women with osteoporosis. BMD levels decreased 2 years after discontinuation of therapy.

The most common adverse effects of raloxifene are hot flashes, cramps in the lower limbs, and peripheral edema. In addition, there is an increased risk of venous thromboembolic events and cardiovascular risk.

Bazedoxifene

Bazedoxifene has similar efficacy to raloxifene in the prevention and treatment of osteoporosis in postmenopausal women [111]. In a three-year randomized trial of 6847 postmenopausal women with osteoporosis, the cumulative incidence of new vertebral fractures was lower in women treated with bazedoxifene (20 or 40 mg/day) or raloxifene (60 mg/day) compared to placebo, with a fracture rate for bazedoxifene of 2.3%, raloxifene 2.5%, and placebo 4.1% [112]. The most common adverse effects from the use of bazedoxifene were cramps and hot flashes, however, the incidence of deep vein thrombosis was lower with bazedoxifene compared to raloxifene [112]. Its use in the prevention of breast cancer has not been fully studied. It is not available in Ecuador.

Estrogen/progestin

Possible indications for estrogen/progestin therapy in postmenopausal women include persistent menopausal symptoms and women with an indication for antiresorptive therapy who are intolerant to the other drugs. The mechanism of action lies in the activation of estrogen receptors (ERα and ERβ), which produces a decrease in osteoclastic activity, by inhibiting the production of the RANKL receptor and increasing the synthesis of osteoprotegerin [113]. In the Women's Health Initiative (WHI) study, combined estrogen/progestin treatment reduced the risk of hip and vertebral fracture, even among women not selected for their risk of osteoporosis or for having that diagnosis [114]. Estrogen/progestin therapy is the first-line medication for the treatment of osteoporosis in postmenopausal women with climacteric symptoms.

Contraindications for MHT are a history of breast cancer, coronary heart disease, history of thromboembolic or venous events, stroke, and/or active liver disease [114].

Tibolone

Tibolone is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties.

It is approved in several countries including Australia, Canada, European Union countries, and some other countries. It reduces vasomotor symptoms compared to placebo, but has less evidence than estrogen therapy [115]. It also has a beneficial effect on bone mineral density (BMD) and may have a modest effect on symptoms of sexual dysfunction. The mechanism of action of tibolone is not fully understood, however, it is believed that the drug undergoes different selective metabolic transformations that lead to activation of estrogens, progestins, and/or androgens [115, 116]. The LIFT (Long-Term Intervention on Fracture with Tibolone) study analyzed the effect of tibolone on the risk of vertebral fracture in postmenopausal women [117]. The use of tibolone decreased the risk of vertebral fracture, with 70 cases versus 126 cases per 1000 person-years, and a lower risk of non-vertebral fracture, with 122 cases versus 166 cases per 1000 person-years [117].

Anabolic agents: Teriparatide

Teriparatide is a recombinant formulation of the first 34 amino acids of endogenous parathyroid hormone (PTH) [118]. The pharmacological activity is similar to the physiological activity of PTH and includes the stimulating function of osteoblasts, the increase in gastrointestinal absorption of calcium, and the increase in renal tubular reabsorption of calcium. It is now available in Ecuador.

The mechanism of action of teriparatide is similar to the physiological activity of PTH, including stimulating osteoblast function, increasing gastrointestinal calcium absorption, and increasing renal tubular reabsorption of calcium [118].

The use of teriparatide is recommended for the following conditions [119]:

- o Treatment of osteoporosis in postmenopausal women at high risk of fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture
- p Treatment to increase bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture [120]
- q Treatment of men and women with chronic systemic glucocorticoid-associated glucocorticoid-induced osteoporosis with a prednisone dose of ≥ 5 mg/day (or equivalent) at high risk of fracture [120]
- r Patients who have failed or are intolerant to other available osteoporosis therapy [92]
- s Modernly, it has been recommended as the start of sequential therapy in the long-term management of osteoporosis, followed by an antiresorptive [92]

Teriparatide used to have a safety label until 2021, due to the increase in the incidence of osteosarcoma in animal models, depending on the dose and duration of treatment. However, the label was removed after the 15-year US post marketing surveillance study by Gilsenan et al. which showed that the incidence of osteosarcoma associated with teriparatide was no different of what would be expected based on the background osteosarcoma incidence rates [121]. Teriparatide should not be prescribed in patients with a high baseline risk of osteosarcoma (Paget's disease and pediatric patients) [122].

The duration of teriparatide treatment should not exceed 2 years due to the cumulative length of half-life [118, 123]. Because the benefits of anabolic therapy are rapidly lost after discontinuation, initiation of antiresorptive therapy (bisphosphonate or denosumab as an alternative) is generally recommended to maintain bone density gains after a course of teriparatide [124].

Abaloparatide

Abaloparatide is an analog of parathyroid hormone-related peptide (PTHrP [1–34]). Its use is indicated only for the reduction of vertebral and non-vertebral fractures in patients at very high risk (severe vertebral fractures or multiple previous fractures), or as a therapeutic option in patients for whom first-line therapy is not tolerated or ineffective [119]. It is not available in Ecuador.

Abaloparatide acts as a PTH1 receptor (PTH1R) agonist, which results in the stimulation of osteoblastic function and increased bone mass [125, 126].

Fracture reduction efficacy has been demonstrated for a period of 18 months [127], therefore the duration of treatment with abaloparatide or any other parathyroid hormone therapy (teriparatide) should not exceed 2 years. Initiation of antiresorptive therapy (bisphosphonate or denosumab as an alternative) is recommended to maintain bone density gains after a course of abaloparatide.

Romosozumab

Romosozumab is a selective sclerostin inhibitor for the treatment of osteoporosis in postmenopausal women with a high risk of fracture; or patients who have presented intolerance or failure to other available therapies [128, 129]. The indicated dose is 210 mg SC monthly for 12 months.

It is contraindicated in patients with hypocalcemia, a history of hypersensitivity reactions including angioedema, erythema multiforme, and urticaria [129]. Patients receiving romozosumab should be informed of possible complications, major cardiac events, hypersensitivity reactions, hypocalcaemia, osteonecrosis of the lower jaw, atypical subtrochanteric and femoral fractures [129].

In the FRAME study, adverse events occurred in 2% of patients who received at least one dose of romozosumab.

These are characterized by arthralgia, headache, muscle spasms, peripheral edema, asthenia, insomnia, and paresthesia [128].

The anabolic effect of romozosumab decreases after 12 monthly doses, therefore, therapy should be limited to 12 months. If continued treatment for osteoporosis is required, the use of antiresorptive agents should be considered [128, 130].

Therapeutic response evaluation

The guidelines (ISCD/NOF) recommend carrying out a control densitometry (lumbar spine and hip) 1 or 2 years after the start or change of therapy, with longer intervals once the therapeutic effect is established [30]. In conditions associated with rapid bone loss, such as the use of glucocorticoids, more frequent densitometry is appropriate.

Therapeutic failure

Therapeutic failure is considered in a patient with osteoporosis, with an adequate intake of calcium and vitamin D, documented adherence to treatment, and low levels of bone markers, who presents any of the following scenarios [131]:

- o Presence of a major osteoporotic fracture within the first year of treatment
- p Multiple osteoporotic fractures
- q Reduction in bone mineral density when it is significant, that is, when it exceeds the minimum significant change, which is 0.03 g/cm.^{2}

Calcium and vitamin D

Calcium absorption at the intestinal level is low, approximately only 35% is absorbed from food. There are two types of calcium absorption mechanisms, by passive diffusion or by vitamin D receptors[132]. The absorption mechanism is mediated by PTH, which, when faced with lower calcium levels, increases the production of calcitriol, the renally active form of vitamin D.

The adequate intake of calcium through supplementation or diet should be 1200 mg of elemental calcium per day in adults[11]. A rough method to estimate dietary calcium intake is to add the number of dairy servings consumed per day and multiply by 250 mg. One serving is 8 oz (240 ml) of milk or yogurt or 1 oz (29 g) of hard cheese.

The NOF guidelines recommend that calcium supplementation be as follows: Women > 50 years: 1200 mg/day, men 50–70 years: 1000 mg/day, men > 71 years: 1200 mg/day. Doses above 1200 mg have been shown to have no positive effect on bone metabolism. Doses greater than 2000 mg increase the risk of nephrolithiasis; the meta-analysis by Lewis et al. did not demonstrate an increased cardiovascular risk [40].

The recommended dose of elemental calcium intake is 1.2 g daily. One gram of calcium carbonate is equal to 400 mg of elemental calcium. Calcium carbonate must be administered on an empty stomach since an acid medium is required for its absorption. It produces more gastrointestinal symptoms such as constipation and abdominal pain. In addition, it is associated with an increased incidence of nephrolithiasis.

Vitamin D

Data from studies from several countries show that serum concentrations of 25(OH)D should be between 25 and 50 ng/ml, which corresponds to a daily vitamin D intake of 400–800 IU (10–20 µg) [133, 134]. No pharmacological treatment against osteoporosis has been tested in a single clinical trial without the addition of different doses of calcium plus vitamin D to the treatment, so their participation is mandatory when starting any treatment for osteoporosis.

In patients with osteoporosis, supplementation will depend on the serum levels of each patient. The guidelines recommend a daily supplementation of 800–1000 IU of vitamin D [135].

Megadoses of vitamin D

Megadoses have been described as the consumption or administration of nutrients in supraphysiological doses that exceed the recommended dietary allowance by ten or more times [136]. A dose higher than 100,000 IU is considered a megadose of vitamin D [137]. There is a difference between high doses and megadoses, high doses correspond to 2–3 times more than the recommended dose and are used in special populations such as obese, patients using glucocorticoids, antifungals, or antivirals [138].

Several studies show that although megadoses of vitamin D are effective in increasing serum 25(OH)D values, they are not effective in reducing the risk of falls [137–139]. Smith et al. studied the frequency of falls at different doses of ergocalciferol (400, 800, 1600, 2400, 3200, 4000, and 4800 IU daily) for one year, it was evident that in the groups that received 1600–3200 IU of vitamin D, the frequency of falls was lower compared to the groups that received doses higher than 4000 IU, showing that high doses and megadoses do not reduce the risk of falling.

Guidelines recommendations published by the Clinical Society of Endocrinology [138]:

- o For adults deficient in vitamin D: 50,000 IU of vitamin D2 or D3 weekly for 8 weeks to reach target levels

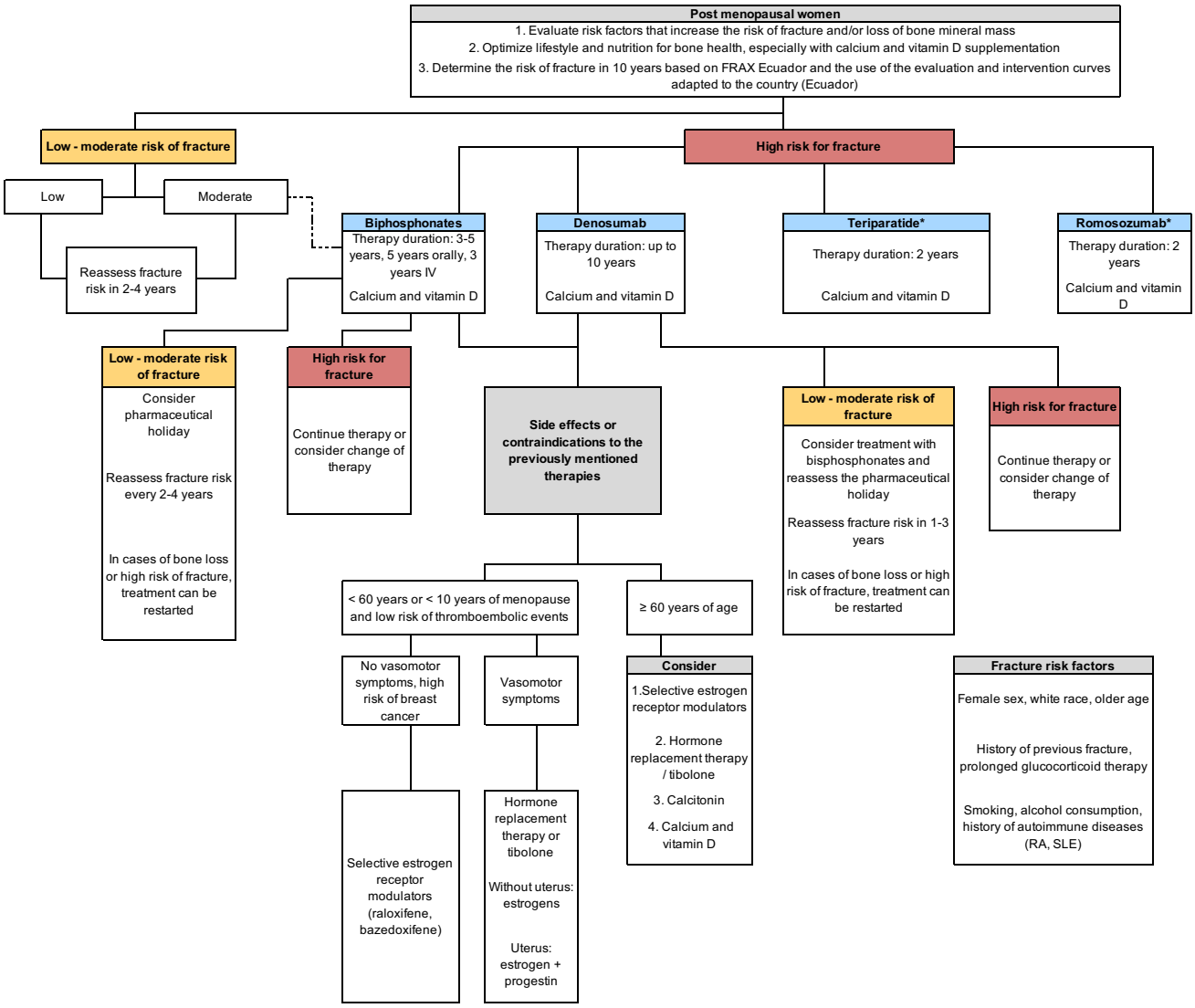

Fig. 3 Algorithm for the management of postmenopausal osteoporosis in the Ecuadorian population

of 25OH vitamin D followed by maintenance doses of 1500–2000 IU/day.

p For obese patients, patients with malabsorption, and patients treated with drugs that affect vitamin D metabolism: 6000 to 10,000 IU/day of vitamin D2 or D3 to reach target levels of 25OH vitamin D followed by maintenance doses of 3000–6000 IU/day.

Therapies not recommended

Calcitriol

Calcitriol is the most active metabolite of vitamin D, its use can cause hypercalcemia and/or hypercalciuria [140]. The use of calcitriol as a vitamin D supplement in osteoporosis is not recommended. The use of calcitriol is indicated in patients with hyperparathyroidism secondary to chronic kidney disease, in whom the control of calcemia and calciuria must be constant.

Androgens

The effect of the combination of androgens and estrogens on BMD does not appear superior to the effect of estrogen alone. In addition to having unwanted virilizing effects [141, 142] Fig. 3.

Conclusions

This is the first Ecuadorian consensus for the management and treatment of postmenopausal osteoporosis.

Recommendations

1. Central bone densitometry measur ed by DXA is the method of choice for the diagnosis of osteoporosis (I; A).
2. For the diagnosis of osteoporosis, a *T*-score value of − 2.5 or less should be observed in the femoral neck or lumbar spine (I; A).
3. Vertebral morphometry should be performed with a *T*-score less than − 1.0 and one or more of the following criteria: female, ≥ 70 years old, male, ≥ 80 years old, history of height loss > 4 cm in less than 2 years, previous vertebral fracture, glucocorticoid therapy (≥ 5 mg daily for ≥ 3 months) and/or previous undocumented vertebral fracture but reported by the same patient (I; A).
4. A thoracolumbar spine radiograph should be taken in patients with osteoporosis (I; B-R).
5. In the presence of symptoms of lumbar compression, a nuclear magnetic resonance should be performed (I; B-NR).
6. It is not recommended to measure bone turnover markers routinely (IIa; A).
7. Serum calcium should be measured in patients with osteoporosis before starting treatment (I; B-R)
8. 25-Hydroxyvitamin D should be measured in patients with osteoporosis before starting treatment (IIa; B-R).
9. Serum creatinine should be measured in patients with osteoporosis before starting treatment (I; B-R).
10. Serum alkaline phosphatase should be measured in patients with osteoporosis before starting treatment (IIa; C-OE).
11. FRAX should be used in all patients aged 40–90 years with suspected fracture risk (I; A).
12. FRAX Ecuador can be used for the evaluation of osteoporosis in Ecuadorian patients (IIa; C-DL).
13. It is recommended to apply the evaluation and intervention curves in Ecuadorian patients based on the FRAX Ecuador for the determination of fracture risk (IIb; C-DL).
14. Resistance, balance, and coordination exercises are recommended to increase muscle mass and reduce the risk of fractures (IIa; B-NR).
15. Complete suspension of alcohol and tobacco consumption is recommended in patients at risk of fracture and diagnosed with osteoporosis (IIa; B-NR).
16. It is recommended to reduce the consumption of carbonated beverages in patients at risk of fracture and diagnosed with osteoporosis (IIb; B-NR).
17. It is recommended to limit caffeine consumption (up to three cups per day) in order to prevent bone mineral loss (IIa; B-NR).
18. Bracing is not recommended as first-line treatment for osteoporotic vertebral fractures (IIa; C-DL).
19. Treatment with antiosteoporotic drugs should be started in postmenopausal women and men older than 50 years with a history of fragility fracture, risk factors for osteoporosis, *T*-score ≤ 2.5 in the neck of the femur or lumbar spine, *T*-score between − 1 and − 2.5 in the neck of the femur or lumbar spine and a FRAX ≥ 3% of hip fracture and ≥ 20% in the lumbar spine, and/or patients with prolonged use of glucocorticoids (more than 3 months) (I; A).
20. In the presence of contraindications to oral bisphosphonates, the use of intravenous bisphosphonates or the use of monoclonal antibodies such as denosumab (IIa; C-OE) should be considered.
21. Bisphosphonate treatment should be reassessed after 3–5 years, given the possibility of creating a therapy holiday (IIa; B-R).
22. After a bisphosphonate holiday, it is recommended to assess the risk of fracture at intervals of 1, 2, and 4 years (I; A).
23. Taking a holiday with denosumab is not recommended, due to the increased risk of fracture (III; A).
24. We recommend the use of hormone replacement therapy in patients without risk or history of breast cancer, coronary heart disease, or history of thromboembolic events with climacteric symptoms or within the first 10 years of menopause or under 60 years (IIa; B-R).
25. We do not recommend the use of combination therapy for the treatment of postmenopausal patients with osteoporosis (III; B-R).
26. We recommend evaluating the response to therapy with bone densitometry 1 or 2 years after starting or changing therapy (IIa; B-NR).
27. Supplementation of 1200 mg/day of elemental calcium is recommended in women over 50 years of age and men between 50 and 70 years of age (I; A).
28. The recommended supplementation of 800–1000 IU of vitamin D daily (I; A).
29. We do not recommend the use of calcitriol and androgens for the treatment of osteoporosis (I; A).
30. We recommend treatment for the management of osteoporosis in patients with prolonged use of glucocorticoids (≥ 5 mg/day for more than 3 months) (IIa; B-R).

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Declarations

Conflicts of interest None.

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