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Brazilian guidelines for the diagnosis and treatment of postmenopausal osteoporosis

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ABSTRACT

Osteoporosis is the leading cause of fractures in the population older than 50 years. This silent disease affects primarily postmenopausal women and the elderly, and the morbidity and mortality rates are high. The main goal of treating osteoporosis is the prevention of fractures. The identification of populations at risk through early diagnosis and treatment is essential. The last Brazilian guideline for the treatment of postmenopausal osteoporosis was elaborated in 2002. Since then, new strategies for diagnosis and risk stratification have been developed, and drugs with novel action mechanisms have been added to the therapeutic arsenal. The Osteoporosis and Osteometabolic Diseases Committee of the Brazilian Society of Rheumatology, in conjunction with the Brazilian Medical Association and other Societies, has developed this update of the guidelines for the treatment of postmenopausal osteoporosis according to the best scientific evidence available. This update is intended for

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professionals in many medical and health specialties involved in the treatment of osteoporosis, for physicians in general and for health-related organizations.

Diretrizes brasileiras para o diagnóstico e tratamento da osteoporose em mulheres na pós-menopausa

RESUMO

A osteoporose é a principal causa de fraturas na população acima de 50 anos. É uma doença silenciosa que afeta especialmente as mulheres na pós-menopausa e idosos e tem elevada taxa de morbimortalidade. O principal objetivo do tratamento da osteoporose é a prevenção das fraturas. A identificação dessa população de risco através do diagnóstico e tratamento precoces é de fundamental importância. A última diretriz brasileira para tratamento da osteoporose em mulheres na pós-menopausa foi elaborada em 2002. Desde então foram desenvolvidas novas estratégias de diagnóstico da osteoporose, bem como fármacos com novos mecanismos de ação foram adicionados ao arsenal terapêutico. A Comissão de Osteoporose e Doenças Osteometabólicas da Sociedade Brasileira de Reumatologia em conjunto com a Associação Médica Brasileira e sociedades afins desenvolveu esta atualização da diretriz do tratamento da osteoporose em mulheres na pós-menopausa de acordo com as melhores evidências científicas disponíveis. Esta atualização é destinada aos profissionais das várias especialidades médicas e da área da saúde envolvidos no tratamento da osteoporose, médicos em geral e organizações relacionadas à saúde.

Palavras-chave:
Osteoporose
Mulher
Menopausa
Diretrizes
Diagnóstico
Terapia

Introduction

Osteoporosis is a disease characterized by bone fragility and changes in bone microarchitecture, and the primary clinical outcome is the occurrence of low-impact[1D] fractures. Osteoporosis affects more than 200 million people worldwide.[2D]

In the United States, more than 2 million osteoporosis-related fractures occur annually, particularly in women (70%), and the rates of morbidity and mortality are high. In addition, the annual overhead costs of addressing the outcomes exceed USD 25 billion.[3C]

Osteoporosis fractures occur more frequently in the vertebrae, distal radius, and proximal femur. These fractures cause pain, physical incapacity, and deformities, impair quality of life, and reduce life expectancy. Hip fractures are the most severe and increase the mortality rate by 12–20% within 2 years of fracture. More than 50% of individuals who survive a hip fracture cannot live independently, and many of them need to live in institutionalized centers.[4D]

Low bone mineral density (BMD), especially in the femoral neck, is a strong predictor of fractures. The risk of fracture increases 2–3 times with each reduction of one standard deviation in the BMD. In addition to low BMD, it is important to identify the clinical risk factors for osteoporosis and fractures because these factors help evaluate the absolute risk of fracture on an individual basis and select the patients who are eligible for treatment.[5C]

Several epidemiological studies published in the past decade have highlighted the importance of risk factors for osteoporosis and fractures in Brazil.[6A,7A,8A] The last Brazilian guideline on the treatment of postmenopausal osteoporosis was published in 2002.[9D]

Risk factors for postmenopausal osteoporosis and fractures

Osteoporosis does not present specific clinical manifestations until the occurrence of the first fracture. Therefore, a detailed medical history and physical examination should be performed in all patients to identify factors that may contribute to the bone mass loss, to evaluate predictive factors for future fractures, and to discard secondary causes of osteoporosis. Some risk factors may be reversed.[10D]

The most important risk factors associated with postmenopausal osteoporosis and fractures are age, being female, Caucasian or Asian ethnicity, previous individual and family history of fractures, low BMD of the femoral neck, low body mass index, and use of a prednisone dose $\geq$5.0 mg/day for more than 3 months, in addition to environmental factors, including smoking, abusive intake of alcohol ($\geq$3 units per day), physical inactivity, and low dietary calcium intake.[11D]

Because of the high prevalence of secondary causes of osteoporosis, many of which are subclinical, a minimum laboratory evaluation, including complete blood count, calcium, phosphorus, alkaline phosphatase, thyroid function, dosing of serum 25 (OH) vitamin D, 24-h calciuria, simple lateral radiographs of the thoracic and lumbar spine, and measurement of the BMD of the lumbar spine and proximal femur are recommended for all patients before starting any treatment. Other specific tests should be conducted only in patients

Table 1 – Initial investigation of postmenopausal osteoporosis. Modified from Papaioannou A et al.[10]

Routine tests
Complete blood count
Calcium, phosphorus, and alkaline phosphatase
Thyroid function tests
Vitamin D (25OH)
24-hour calciuria
Creatinine
BMD
Lateral RX of thoracic and lumbar spine
Specific exams
According to clinical suspicion

with clinical suspicion of associated diseases, including gastrointestinal diseases (intestinal malabsorption syndrome, inflammatory disease, and celiac disease), endocrine disorders (primary hyperparathyroidism, thyrotoxicosis, Cushing's syndrome, hypogonadism, and diabetes mellitus), rheumatologic diseases, and chronic pulmonary diseases (Table 1).[10D]

Bone remodeling markers are useful in assessing the effects of medications, aging, and diseases on the rates of bone resorption and formation in a period of time but should not be used for the diagnosis of osteoporosis or the choice of medication to be prescribed. The most used markers are serum CTx as a marker of bone resorption and serum P1NP as a marker of bone formation. Elevated serum CTx levels may indicate rapid loss of bone mass and have a moderate correlation as a risk factor for osteoporosis and fractures, regardless of the BMD.[12A,13B,14B] The use of CTx in clinical practice is limited by the high variability among trials and the poor predictive value in the same patient. The levels of CTx may change rapidly in response to drug treatment; therefore, this marker may be useful in specific situations, such as the assessment of bone adhesion, bone adsorption, or failure to respond to drug treatment.[15A,16A]

Aromatase inhibitors,[17B] GnRH analogs,[18B] antiretroviral therapy,[19B] and medroxyprogesterone,[20D] in addition to anticonvulsants and anticoagulants,[11D] have been listed as risk factors for osteoporosis.

The risk of falls should be considered in the evaluation of patients with osteoporosis because recurrent events constitute per se an independent risk factor for fractures, particularly in cases of neurological impairment, such as hemiparesis, Parkinson's disease, dementia, dizziness, alcoholism, and visual impairment.[21B] However, the importance of the risk of falls is often neglected. In comparative terms, one standard deviation in the decrease in BMD increases the risk of hip fracture by approximately 2- to 2.5-fold, and a fall to the side increases the risk of hip fracture 3- to 5-fold. The risk of hip fracture increases approximately 30-fold in cases in which this type of fall increases the impact on the trochanter compared with the proximal femur.[22B]

Recommendation

All patients diagnosed with osteoporosis should be evaluated for risk factors before the start of treatment for osteoporosis and fractures by conducting a careful medical history and physical examination, with minimal laboratory testing. In cases of clinical suspicion, specific laboratory tests should be requested to identify the causes of secondary osteoporosis.

Risk factors that are modifiable in postmenopausal women, including physical activity, smoking cessation, restriction of sedative and hypnotic medications, and other conditions that may reduce bone mass should be discussed. The correction of visual deficits and the implementation of measures to minimize the risk of falls, including the use of anti-slip stands and mats in the bathroom, care with slippery floors and loose carpets, improvement in lighting systems, and care with stairs and steps, are crucial.

Non-pharmacological treatment of postmenopausal osteoporosis

Evidence of the effectiveness of physical exercise in reducing the risk of falls and improving the quality of life of postmenopausal women with osteoporosis

Clinical trials have revealed that the indication of supervised physical activity programs improves functional capacity, muscle strength, balance, coordination, flexibility, and quality of life.[23A,24A] A study implemented an exercise program for the prevention of falls and randomized postmenopausal women (aged 55–75 years) with osteoporosis into two groups: the first group was used to evaluate progressive quadriceps strengthening and proprioception training associated with drug therapy, and the second group was used to assess drug therapy with bisphosphonate monotherapy for 18 weeks.[25B] The results of this program indicated that women subjected to the exercise program had a lower incidence of falls compared with the group subjected to pharmacological treatment during a 6-month follow-up (ARR = 0.38, 95% confidence interval [CI] = 0.18–0.52, NNT = 2).[25B] Similarly, another muscle-strengthening exercise program that aimed at improving postural control randomized postmenopausal women (72.8 ± 3.6 years) with osteoporosis into three intervention groups: (1) balance training with muscle strengthening; (2) balance training with stretching, and (3) controls (without physical activity).[26B] After 8 weeks, women in groups 1 and 2 had significant increases in dorsiflexion force and knee flexion and an increase in range of motion.[26B] A 12-month, randomized, controlled study examined the impacts of circuit exercise on mobility, balance, and the quality of life of postmenopausal women with established osteoporosis (previous vertebral fracture). Three months after the beginning of the intervention, there were significant improvements in mobility and in the quality of life domains analyzed using General Health Questionnaire-20 (GHQ-20) and Quality of Life Questionnaire issued by the European Foundation for Osteoporosis (QUALEFFO-41).[27B]

Recommendation

Resisted and supervised physical exercises that primarily involve quadriceps strengthening and weight-bearing exercises are recommended for postmenopausal women with a diagnosis of osteoporosis or osteopenia because these exercises can reduce the number of falls. The results of

randomized clinical trials demonstrated that the implementation of a physical activity program significantly improved flexibility, balance, muscle strength, and quality of life, thus reducing the risk of falls. However, there is still no robust evidence regarding the reduction of fractures with physical activity.

Evidence for the efficacy of calcium intake in the prevention and treatment of postmenopausal osteoporosis

Calcium is an essential nutrient for the regulation of bone tissue homeostasis. Adequate calcium intake is fundamental for the prevention and treatment of osteoporosis and general bone health at any age, although daily calcium requirements vary with age. The Institute of Medicine (IOM) established daily calcium requirements by age group in 2011.[28D] For adults older than 50 years, the recommended daily dose is 1200 mg, including dietary calcium and supplements (in cases of poor dietary intake).

Since the end of the twentieth century, several studies have shown the importance of calcium in the treatment of osteoporosis (most cases in association with vitamin D), with a modest effect on fracture prevention.[29A,30A]

In a recent meta-analysis published by the National Osteoporosis Foundation (NOF), the results indicated a 15% reduction in the overall relative risk of fractures (Summary Relative Risk Estimates (SRRE) = 0.85%, 95% CI = 0.73–0.98) and a 30% reduction in the risk of hip fracture (SRRE = 0.70, 95% CI = 0.56–0.87).[31A] In a 7-year follow-up study, the Women's Health Initiative Calcium/Vitamin D Supplementation (WHI CaD) study evaluated 36,282 postmenopausal women aged 50–79 years (mean age of 62.4 years) with a predominance of Caucasian ethnicity (83%) and randomized the study sample to receive a combination of calcium and vitamin D3 (1000 mg/day + 400 IU/day) or placebo. During follow-up, hip BMD was significantly higher in the supplemented group, although there were no significant decreases in the risk of hip fractures (hazard ratio [HR] = 0.88, 95% CI = 0.72–1.09), clinical vertebral fractures (HR = 0.90, 95% CI = 0.74–1.1), and total fractures (HR = 0.96, 95% CI = 0.91–1.02).[32A] With regard to adverse events, the occurrence of renal calculi was 17% higher in patients subjected to treatment (HR = 1.17, 95% CI = 1.02–1.34); however, no significant difference was observed for cardiovascular events, gastrointestinal disorders such as constipation, and neoplasms.[32A]

The evaluation of the effect of calcium supplementation on the reduction of bone loss is compromised in many studies because calcium supplementation involves vitamin D administration.[33C]

The optimal daily dose of calcium and the use of supplements are still controversial, particularly when considering adverse events. A Swedish cohort of patients with high daily calcium intake (>1500 mg/day considering dietary and supplemented calcium) showed a 40% increase in all-cause mortality (HR = 1.40, 95% CI = 1.17–1.67).[34B]

A meta-analysis involving a subpopulation of 16,718 WHI study patients who did not use calcium or vitamin D supplements at baseline and who were randomized to begin using them found significant increases in cases of acute myocardial infarction (AMI) and myocardial revascularization ($p = 0.004$).[35A] The use of low calcium doses (<700 mg/day compared with 1400 mg/day) increased the cardiovascular risk.[36B]

A recent meta-analysis involving controlled and randomized studies found no significant differences in hospital admissions and deaths in women with postmenopausal osteoporosis who received calcium supplementation.[37A]

The results of the 10-year Multi-ethnic Study of Atherosclerosis (MESA) involving a multi-ethnic cohort reported a slight decrease in the number of cases of coronary atherosclerosis by tomography (calcium score) in female patients who ingested dietary calcium (average of 1081 mg/day). The risk of coronary calcification in patients who received calcium supplementation was 20% higher than in those who did not receive calcium supplementation (relative risk [RR] = 1.22, 95% CI = 1.07–1.39).[38A]

With respect to the correlation between calcium supplementation and cardiovascular events, randomized, controlled, and prospective studies rather than meta-analyses and subgroup analyses should be conducted to improve the level of evidence for clinicians.[39C]

It is important to highlight that the daily dietary intake of calcium in Brazil is below the IOM recommendation (average of 400 mg regardless of region, sex, and age).[40A]

Women older than 50 years with osteopenia or osteoporosis should be encouraged to ingest calcium preferentially from their diet. Some calculators can help identify calcium-rich foods and determine the daily intake of calcium (https://www.iofbo).[41] Calcium supplementation should be considered for patients who are intolerant to lactose or who for other reasons cannot obtain the daily recommendation.

Several calcium supplements are commercially available. Calcium bioavailability is highest in calcium carbonate and tribasic calcium phosphate (approximately 40%). Calcium carbonate causes gastrointestinal problems such as constipation and should be ingested with meals. The calcium bioavailability from calcium citrate is lower (21%); thus, more tablets are needed to reach the desired dose. The latter is commercially available and is an option for patients with nephrolithiasis or a history of gastric surgery (gastrectomy) or bariatric surgery. Calcium supplementation should not exceed 500–600 mg per dose regardless of the formulation because fractionation increases absorption.[42D]

Recommendation

For women older than 50 years, it is recommended and safe to ingest up to 1200 mg of calcium per day, preferably in the diet by the consumption of milk and dairy products. In cases in which the dietary intake is not possible, calcium supplementation is advisable, and the risks and benefits should be assessed. Although calcium and vitamin D supplementation is essential for adequate bone mineralization, treatment of postmenopausal osteoporosis exclusively with calcium associated or not with vitamin D is not recommended.

Recommendations for the use of vitamin D in the treatment of postmenopausal osteoporosis

Vitamin D is a prohormone synthesized in the skin by exposure to ultraviolet B (UVB) rays from sunlight. The food sources of vitamin D are limited, and humans rely primarily on the production of this vitamin in the skin by UVB light. Vitamin D, either produced in the skin or ingested, undergoes chemical transformations to reach its active form (calcitriol), which has important functions in osteomineral physiology, particularly for intestinal absorption and calcium homeostasis.[43D,44D]

In addition to its role in the intestinal absorption of calcium, vitamin D has an important role in peripheral muscles and body balance and may affect the risk of falls. Vitamin D deficiency is common in patients with osteoporosis[45B] and hip fractures.[46B]

The plasma concentration of vitamin D can be determined by the dosing of 25 hydroxyvitamin D [25(OH)D].[47D,48D] Dosing of 25(OH)D is recommended in the suspicion of vitamin D deficiency, especially in high-risk populations, such as patients with osteoporosis and other potential osteopenia-inducing clinical conditions.[47D,48D] The United States Preventive Services Task Force found no evidence to support the dosing of vitamin D in the general population.[49A]

Serum concentrations of 25(OH)D lower than 20 ng/mL (50 nmol/L) are classified as vitamin D deficiency in the general population, and values between 20 ng/mL (50 nmol/L) and 29 ng/mL (74 nmol/L) are considered insufficient for individuals at risk of osteoporosis[28]; the ideal concentrations range between 30 ng/mL (75 nmol/L) and 100 ng/mL (250 nmol/L). These values are recommended by the Endocrine Society and the Brazilian Society of Endocrinology and Metabolism.[47D,48D]

A meta-analysis of studies on postmenopausal women reported significant reductions in the risk of femoral neck fractures and non-vertebral fractures with vitamin D supplementation using daily doses higher than 800 IU.[50A] However, the WHI group that received calcium and vitamin D supplementation presented a slight gain in bone mass in the femoral neck, but the reduction in the risk of fractures was not significant.[32A] In contrast, other studies found increases in muscle strength and body balance and reduction of falls with vitamin D supplementation.[51A,52A]

In adults with vitamin D deficiency [(25(OH)D < 20 ng/mL)], a loading dose of 7000 IU/day or 50,000 IU/week for 8 weeks is recommended, followed by a maintenance dose of 1000–2000 IU per day.[47D,48D] Inadequate levels of vitamin D are considered a potential cause of failure of drug-based treatments for osteoporosis (significant loss of BMD and fractures).[53D,54A] Despite the abundant evidence of the association between vitamin D deficiency and several diseases, high doses of vitamin D are not recommended because no phase III clinical trials with robust and consistent results are available. A study has shown that high doses of vitamin D equal to or greater than 500,000 IU given at once in annual regimens may increase the risk of falls and fractures,[55A] and another study reported functional worsening in supplemented patients.[56B]

Other studies did not demonstrate that vitamin D replacement reduced overall mortality[57A] or prevented cancer[58A] and cardiovascular diseases,[59A] even at high doses.

The available data are controversial. Therefore, more studies are necessary to establish cause and effect relationships between vitamin D deficiency and diseases and to determine whether vitamin D deficiency can predict worse clinical outcomes.

Recommendation

In women with postmenopausal osteoporosis, the determination of the plasma concentrations of 25(OH)D is recommended before the initiation of treatment. In vitamin D-deficient patients, replacement should be initiated at 50,000 IU per week for 8 weeks and then reassessed. As a maintenance dose, daily doses of 1000–2000 IU and serum levels higher than 30 ng/mL are recommended for the prevention of secondary hyperparathyroidism, improvement of bone mass, and reduction of the risk of falls. Treatments with high doses of vitamin D are not indicated.

Pharmacological treatment of postmenopausal osteoporosis

Indication of pharmacological treatment for women with postmenopausal osteoporosis

Osteoporosis is a significant public health problem worldwide and lacks effective therapies. Moreover, patients eligible for pharmacological intervention are not easily identified.[60C] Screening and case detection strategies using bone densitometry have high specificity (can identify high-risk patients) but low sensitivity (fail to characterize correctly the patients who will present fractures). Therefore, strategies that take into account clinical risk factors can help determine the individual risk of fractures regardless of BMD measures and thus better determine the absolute risk of fracture due to osteoporosis.[61C]

The Fracture Risk Assessment Tool (FRAX) is the first specific model of prediction of fractures in Brazil. It is based on the original FRAX methodology, which was externally validated in several independent cohorts and calibrated using consistent retrospective epidemiological data on hip fracture and mortality.[62B,63A,64A,65A,66A]

FRAX is a computer-based algorithm that calculates the 10-year probability of a major osteoporotic fracture (hip, spine, humerus, or wrist fracture) and hip fracture. The likelihood of fracture is calculated considering clinical risk factors (age, sex, and body mass index) and dichotomous risk factors (previous fragility fracture, parental history of hip fracture, current smoking, long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption). The BMD of the femoral neck can be optionally included to improve the prediction of the risk of fractures. The probability of fracture is calculated considering the risk of fractures and death. The use of clinical risk factors and BMD measures improves the sensitivity of fracture prediction without compromising specificity. The use of FRAX in clinical practice requires the determination of the probability of fracture in which to intervene for treatment (intervention threshold) and the BMD test (evaluation thresholds).[67B]

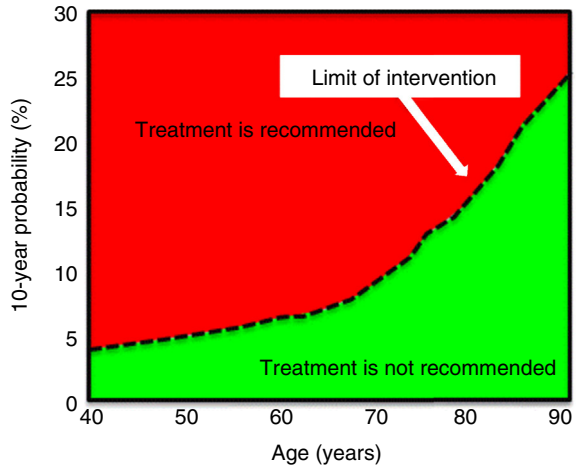

Fig. 1 – Limit of FRAX intervention with densitometry.[62]

Many guidelines recommend that women with a previous fragility fracture be considered for intervention without the need for a BMD test (except for treatment follow-up), and a previous fracture may constitute sufficient risk to recommend treatment.[68B,69B]

For this reason, the intervention threshold in women without previous fracture can be adjusted to the age-specific probability of fracture similar to that of women with a previous fragility fracture, i.e., the intervention threshold (Fig. 1) is set at the "fracture threshold." This approach was well validated and demonstrated to be cost-effective. With regard to the assessment thresholds for BMD measures, two limits (Fig. 2) were established. A threshold probability below which neither treatment nor a BMD test should be considered (lower limit of assessment) is based on a 10-year likelihood of osteoporosis fracture similar to that of women without clinical risk factors, with a BMI of 25 kg/m^2, and without BMD measurement. This approach is consistent with the recommendation, in most clinical guidelines, that individuals without clinical risk factors not be considered eligible for evaluation.

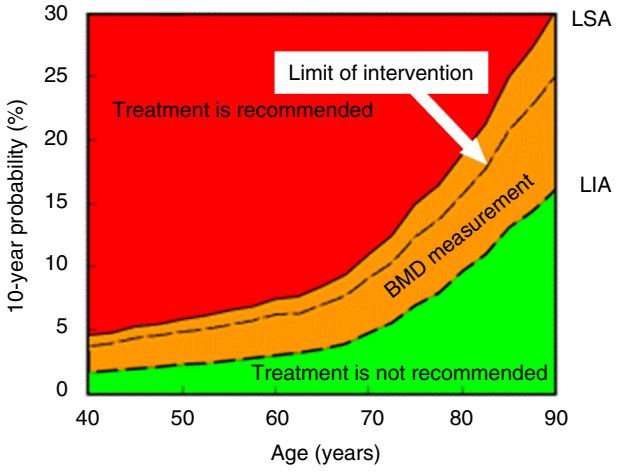

Fig. 2 – Limit of FRAX assessment without densitometry. ULE, upper limit of evaluation; LLE, lower limit of evaluation.[62]

A threshold probability above which treatment may be recommended, regardless of the BMD, is set at 1.2 times the intervention threshold because, in cases in which patients have a fracture probability of at least 20% of the intervention threshold, a few individuals are reclassified when the odds are recalculated with the inclusion of BMD to the FRAX (UK National Osteoporosis Guideline Group – NOGG).[70D] Moreover, an expert committee reviewed recent recommendations for the identification of patients at high risk for osteoporosis and fractures.[71D] In view of these considerations, the following approach is recommended for decision making in Brazil.[62B]

Preliminary data from the BRAVOS study—a multicenter prospective study on fractures in the north, southeast, and south regions of Brazil—were accepted for publication. The results of this study can improve the calibration and the capacity of FRAX Brazil to predict fractures according to the study "Incidence and mortality of hip fractures in Joinville, a community of the south of Brazil", by Silva DMW, Lazzareti-Castro M, Sejzenfeld VL, Zerbini C, Eis SH, Borba VCZ, accepted for publication in the Archives of Endocrinology and Metabolism).

Recommendation

- Patients with a history of previous fragility fracture should be considered for pharmacological treatment without the need for further evaluation by BMD measurement, although this evaluation may be appropriate, particularly in younger postmenopausal women and for treatment follow-up.
- Patients with *T*-scores equal to or less than −2.5 SD in the lumbar spine, femoral neck, total femur, or 33% radius should be considered for pharmacological therapy.
- In patients without previous fragility fractures, the treatment strategy should be based on a 10-year probability assessment using FRAX Brazil and NOGG recommendations.

What is the recommended interval to repeat the Bone Densitometry test?

In patients at high risk of fractures based on BMD or calculation, BMD should be repeated every 1 to 2 years by medical decision. In cases of significant loss of bone mass, patients should be re-evaluated for adherence to treatment, bone densitometry (equipment and acquisition and analysis protocols), and secondary causes, including vitamin D deficiency, presence of diseases, and medications.[53D,72C]

The drugs approved in Brazil for the treatment of osteoporosis in postmenopausal women are listed in Table 2.

Evidence for recommending the use of hormone therapy in postmenopausal women to reduce the risk of fractures

Estrogens play an important anti-resorptive role in the bone metabolism of premenopausal women. Hypoestrogenism, which occurs after menopause, accelerates the loss of bone

Table 2 – Approved treatments for postmenopausal women with osteoporosis.

Intervention	Vertebral fracture	Non-vertebral fracture	Hip fracture
HRT	A	A	A
Alendronate	A	A	A
Ibandronate	A	A[a]	NAE
Risedronate	A	A	A
Zoledronic acid	A	A	A
Denosumab	A	A	A
Raloxifene	A	NAE	NAE
Teriparatide	A	A	NAE

A, grade A recommendation; NAE, not adequately evaluated; HRT, hormone replacement therapy.
[a] In subsets of patients only (post hoc analysis).

mass but can be alleviated with the use of hormone replacement therapy (HRT).[73C] A meta-analysis from 2002 evaluated 57 randomized clinical trials and demonstrated a consistent increase in BMD in the lumbar spine (6.8% on average) and femur (4.1% on average) after 2 years.[74A]

The WHI study was not performed only in women with osteoporosis with an indication of pharmacological treatment in the estroprogestative arm but evaluated 16,608 menopausal women aged 50–79 years and performed bone densitometry in a subgroup of 1024 participants. After 5 years of follow-up, on average, HRT with progesterone associated with conjugated equine estrogens (CEE) significantly increased BMD in the lumbar spine and femur by 4.5% and 3.7%, respectively, compared with placebo.[75A]

The isolated estrogen arm evaluated 10,739 hysterectomized menopausal women aged between 50 and 79 years, and densitometry was performed in a subgroup of 938 participants. After an average of 6 years, there were significant increases of 7.1% in the lumbar spine and 1.8% in the femur of the participants who received CEE compared with a 1.9% increase in the spine and a loss of 1.95% in the femur of the placebo group.[76A]

The WHI study is the largest randomized trial of placebo-controlled HRT with fracture data. The HRT conducted with estrogen alone (CEE at 0.625 mg/day) and the estroprogestative combination (association of CEE at 0.625 mg/day and AMP at 2.5 mg/day) showed an approximate reduction of 30% in hip fractures and clinical vertebral fractures. Furthermore, there was a significant decrease of 24–29% of all osteoporotic fractures with statistical significance.[75A,76A] However, the beneficial effects on BMD were maintained only during HRT. After discontinuation, there was a loss of BMD after the first 12 months, and the rate of bone loss was similar to that of natural hypoestrogenism in postmenopausal women.[77A] Therefore, discontinuation of HRT should be followed by another therapeutic option.

The risk of thromboembolism during HRT is approximately 2-fold higher in users of conventional doses (CEE at 0.625 mg/day associated with 2.5 mg of medroxyprogesterone acetate in a combined or cyclic scheme), particularly in the first year of treatment, and decreases as HRT is extended.[78B] The prolonged use of HRT for more than 5 years associated estrogens and progestagens produces a small increase in the risk of breast cancer (eight cases per 10,000 women/year).[79B]

Recommendation

HRT should be considered for the treatment of postmenopausal osteoporosis, particularly in women with climacteric symptoms, before the age of 60 years or within 10 years of the onset of menopause. The discontinuation of HRT results in loss of bone mass and an increase in the fracture rate; these patients should adopt another therapeutic strategy. The patients subjected to HRT should be carefully evaluated on an individual basis, and this treatment should be prescribed only when the benefits outweigh the risks.

Evidence for recommending the use of bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid) in postmenopausal women to reduce the risk of vertebral and non-vertebral fractures

Nitrogen-containing bisphosphonates are the most prescribed class of drugs worldwide for the treatment of postmenopausal osteoporosis. These synthetic analogs of inorganic pyrophosphate bind to hydroxyapatite crystals at the sites of remodeling and inhibit osteoclast-mediated bone resorption.[80D]

Alendronate, risedronate, and ibandronate are administered orally at doses of 70 mg/week, 35 mg/week (or 150 mg/month), and 150 mg/month, respectively. Zoledronic acid is the only intravenous bisphosphonate approved for the treatment of postmenopausal osteoporosis at a dose of 5 mg per year. In 3- to 4-year placebo-controlled clinical trials, bisphosphonates significantly reduced the risk of osteoporotic fractures. The decrease in the absolute risk of fractures with bisphosphonates depends on the baseline risk and fracture site (vertebral versus nonvertebral fractures and hip fractures).[81A,82A,83A,84A,85A,86A]

In the above studies, the benefits of bisphosphonates outweighed the risks. Overall, randomized clinical trials with bisphosphonates reported a 40–70% reduction in the risk of vertebral fracture and a 40–50% reduction in the risk of hip fracture, always associated with calcium and vitamin D.[87D]

Oral bisphosphonates should be taken during fasting, 30–60 min before breakfast, and with a full glass of water to ensure the maximum absorption; the decubitus position

should be avoided after drug intake. A weekly presentation of risedronate can be taken during or shortly after breakfast.[88D]

Pivotal studies with bisphosphonates reported common adverse events, such as gastrointestinal disorders (nausea and esophagitis), flu-like symptoms, arthralgia, and mild myalgia. These events may be associated with poor adherence to treatment in many patients and affect the capacity of these drugs to reduce the risk of fractures.[89B]

Patients with esophageal and severe gastrointestinal diseases, such as hiatal hernia, stenosis, esophageal motility disorders (e.g., systemic sclerosis), esophageal varices, and Crohn's disease, should avoid these drugs. Patients with renal impairment with creatinine clearance lower than 35 mL/m, particularly elderly adults and individuals taking diuretics, should also avoid these drugs. Hypocalcemia should be assessed and corrected before the initiation of treatment.[90D]

Oral bisphosphonates (alendronate, risedronate, and ibandronate) are indicated for the reduction of vertebral and hip fractures in women with postmenopausal osteoporosis. In the study that led to the approval of ibandronate, this drug reduced only vertebral fractures. However, in a subgroup of patients with severe osteoporosis and BMD with *T*-scores lower than -3.0 SD in the femoral neck, the number of hip fractures decreased significantly.[91A]

Zoledronic acid is indicated for reducing vertebral, non-vertebral, and hip fractures in patients with postmenopausal osteoporosis.[92A]

Prolonged use of bisphosphonates

The optimal duration of treatment with bisphosphonates in patients with osteoporosis is unknown. Data from extension studies of larger clinical trials suggest that alendronate therapy for more than 5 years does not significantly reduce the risk of fractures except for the risk of clinically diagnosed vertebral fractures.[93A]

In addition, post hoc analysis of the data from the FLEX study revealed that non-vertebral fractures were reduced in patients treated with alendronate for 10 years (compared with those treated for 5 years) only in individuals in whom the femoral neck *T*-score remained lower than −2.5 SD after 5 years of therapy or those with a previous vertebral fracture.[94D]

In the 3-year study of zoledronic acid, similar effects were observed, with a significant reduction in the risk of vertebral fractures, but no significant difference in the risk of non-vertebral and hip fractures in patients treated for 6 years compared with those treated for 3 years.[95A]

The outcomes following discontinuation of treatment with risedronate after 2 or 7 years of treatment have also been reported. The discontinuation of treatment for 1 year increased the serum levels of bone remodeling markers in both groups to values close to the baseline and decreased the BMD of the total hip, whereas the BMD of the lumbar spine and femoral neck remained unchanged.[96A]

Because of the accumulation of bisphosphonates in bone and its prolonged use, serious adverse events have been reported since 2003, including osteonecrosis of the jaw and atypical subtrochanteric fractures. Osteonecrosis of the jaw has been reported primarily in patients with advanced cancer who use high doses of bisphosphonates. In randomized studies in patients with advanced cancer, the incidence of osteonecrosis of the jaw was 1–2% per year with zoledronic acid, which is 10-fold higher than in patients with osteoporosis treated with the same drug.

Another severe adverse event is the atypical fracture of the femur. A recent review reported that patients presented a prodrome of thigh pain in 70% of cases, bilateral fracture in 28% cases, and healing delay in 26% cases. The exact etiology and correlation of these events with the use of bisphosphonates are not entirely understood. The ASBMR has published recommendations on these severe events in two task forces over the past 3 years.[97D,98D]

The concerns about the potential side effects of bisphosphonate use, along with available data on the long-term efficacy, have led to a recent reconsideration of the appropriate duration of treatment with these agents. In some patients, a period of temporary discontinuation of bisphosphonate has been suggested by experts[99D] and was later endorsed by the American Association of Clinical Endocrinologists (AACE).[90D]

Advocates of the temporary discontinuation strategy argue that the efficacy of bisphosphonates has not been demonstrated after 5-year therapy for most low-risk patients and that the rates of side effects, such as atypical fracture of the femur and osteonecrosis of the jaw, increase with prolonged use. An ASBMR Task Force has developed an algorithm for recommending the long-term use of bisphosphonates (Fig. 3).[87D]

Patients continuously using corticosteroids (>7.5 mg/d), those older than 75 years, and those with previous hip fracture should be considered for oral bisphosphonate therapies longer than 5 years.[70D]

A study published in the Brazilian Journal of Rheumatology (Revista Brasileira de Reumatologia) suggested a modified algorithm of the ASBMR.[100] This algorithm includes bone resorption markers in decision-making in cases of non-response to treatment, which is not unanimously accepted in the literature.

Recommendation

Randomized clinical trials have demonstrated the efficacy of bisphosphonates in reducing vertebral, non-vertebral, and hip fractures in patients with osteoporosis and have considered these drugs as the first-line therapy for postmenopausal osteoporosis. All bisphosphonates are effective in reducing the risk of vertebral fractures. However, only alendronate, risedronate, and zoledronic acid significantly decreased the risk of non-vertebral and hip fractures. Patients taking bisphosphonates should have sufficient levels of calcium and vitamin D. The reassessment of the use of bisphosphonates after 5 years has been proposed considering the risks and benefits for each patient.

Evidence for the use of denosumab in the treatment of osteoporosis in postmenopausal women

Denosumab is a human monoclonal antibody (IgG2 isotype) with high affinity and binding specificity for the activator receptor of nuclear factor kappa B (RANK-L), a cytokine

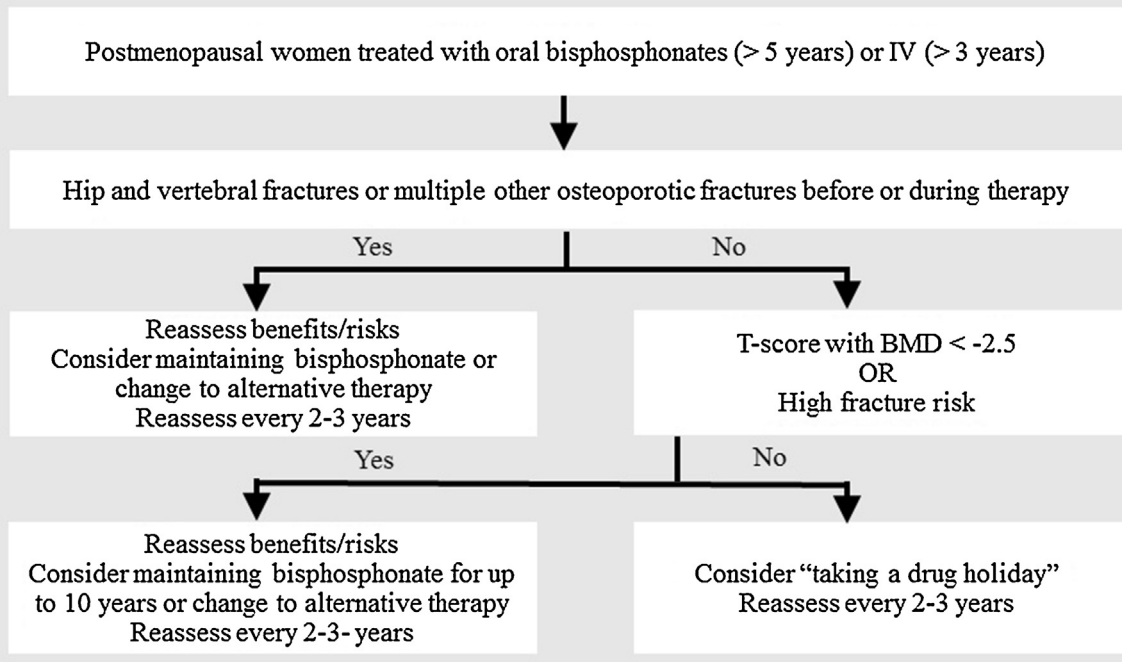

Fig. 3 – Recommendation algorithm on prolonged bisphosphonate use. Modified from Adler RA et al.[87]

belonging to the tumor necrosis factor (TNF) family. Denosumab blocks the binding of RANK-L to RANK, its natural receptor, and decreases bone resorption by inhibiting the formation, activation, and survival of osteoclasts and increasing BMD.[101] C

The pivotal phase III clinical trial "Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months" (FREEDOM) randomized 7808 women aged 60–90 years (72 ± 5.2 years) with *T*-scores between −2.5 and −4.0 SD (lumbar spine or femur) and treated with denosumab (60 mg every 6 months for 36 months) or placebo and observed a significant reduction (68%) in the risk of radiographic vertebral fractures in the intervention group. In addition, this treatment reduced the risk of all non-vertebral fractures by 20% (HR = 0.8; 95% CI = 0.67–0.95) and femur fractures by 40%. The risks of neoplasia, cardiovascular disease, delayed fracture healing, and hypocalcemia did not increase, and no cases of osteonecrosis of the jaw were observed. A few cases of cellulite were observed.[102] A

The long-term open-label extension study reported continuous increases in the BMD of the lumbar spine and hip (15.2% and 7.5%, respectively). A few cases of atypical femur fracture and mandible osteonecrosis were observed.[103] A,[104] A

In patients with renal impairment, denosumab was effective and safe, with no need for dose adjustment because of the absence of glomerular clearance. However, hypocalcemia should be evaluated and corrected before treatment initiation.[105] B

A 12-month non-inferiority multicenter comparative phase III study on alendronate reported that 1189 postmenopausal women with *T*-scores lower than −2.0 SD in the lumbar spine or total hip were randomized to treatment with denosumab (60 mg every 6 months) or alendronate (70 mg per week). There was a significantly higher increase in femur BMD in the first group (3.5%) compared with the second group (2.6%).[106] A Another randomized non-inferiority clinical trial found that the transition from alendronate to denosumab significantly increased the total femur BMD after a 12-month interval and resulted in reduced cortical porosity and resorption markers in patients treated with denosumab compared with those treated with alendronate.[107] A

Consistent with the mechanism of action, the discontinuation of denosumab therapy may reverse the benefits (i.e., BMD and risk of fracture). In cases of discontinuation of denosumab therapy, switching to another treatment for osteoporosis should be considered. The temporary discontinuation of treatment of osteoporosis does not apply to denosumab.[108] D

Recommendation

Denosumab is indicated for the treatment of postmenopausal osteoporosis. Pivotal studies have shown that this drug significantly reduced vertebral, non-vertebral, and hip fractures. Denosumab can be used in case of oral bisphosphonate failure, intolerance or contraindication, and in special situations as the first line of treatment, such as in patients with renal dysfunction. After 10 years of treatment, the available data indicated continuous gains in the BMD of the lumbar spine and the femur and reduction of fractures, with the same safety profile previously described, and in patients with renal dysfunction. Discontinuation of denosumab treatment may lead to reversal of the benefits obtained in BMD and increase the risk of fracture and, in this case, changing to another osteoporosis treatment should be considered.

Recommendation of raloxifene to postmenopausal women diagnosed with osteoporosis

Selective estrogen receptor modulators (SERMs) are a class of drugs that selectively act on selective estrogen receptors and exert agonistic or antagonistic effects on different target tissues. Raloxifene is a second-generation SERM with bone anti-resorptive activity.[109D]

The multicenter study "Multiple Outcomes of Raloxifene Evaluation" (MORE) evaluated 7705 postmenopausal women (average age of 66.5 years) with osteoporosis and without a history of breast or endometrial cancer and randomized the sample to treatment with placebo and either 60 or 120 mg of raloxifene per day.[110A] After 36 months, the risk of vertebral fractures in women subjected to raloxifene monotherapy was significantly decreased by 30% and 50% at doses of 60 and 120 mg/day, respectively (RR = 0.7, 95% CI = 0.5–0.8 and RR = 0.5, 95% CI = 0.4–0.7) but did not modify the risk of non-vertebral and hip fractures compared with the placebo group (RR = 0.9; 95% CI = 0.8–1.1).[110A] A significant increase was observed in BMD at the evaluated sites. With regard to adverse events, there was a higher risk of venous thromboembolism in the treated group compared with the placebo group (RR = 3.1; 95% CI = 1.5–6.2).[110A]

The increased risk of venous thromboembolism (1.5 to 3-fold higher) was the most severe adverse event of raloxifene therapy, and a previous history of thromboembolism was a contraindication to the use of this medication. The exacerbation of climacteric symptoms and a mild reduction of breast cancer risk were also observed in patients treated with raloxifene.[110A] The decrease in the risk of breast cancer was confirmed in another large clinical trial involving women at high risk of breast cancer. Raloxifene has been approved for the prevention and treatment of osteoporosis in postmenopausal women and reduces the risk of breast cancer in postmenopausal women with osteoporosis.[111B]

Recommendation

Raloxifene at a dose of 60 mg per day has been approved for the prevention and treatment of spinal osteoporosis in postmenopausal women without climacteric symptoms and significantly reduces vertebral fractures. This drug is also indicated for reducing the risk of breast cancer in postmenopausal women with osteoporosis. However, it is not recommended for nonvertebral and hip fractures.

Efficacy and safety of teriparatide in the treatment of postmenopausal osteoporosis

Teriparatide is homologous to the 34-amino-acid N-terminal sequence of the synthetic parathormone obtained via recombinant DNA technology (PTH 1–34). This drug has been approved for the initial treatment of postmenopausal osteoporosis in women at high risk of fracture or who have failed or not tolerated previous treatments for osteoporosis.

Teriparatide is considered an anabolic agent because it acts by increasing bone formation, in contrast to other drugs approved for the treatment of osteoporosis, with antiresorptive action. It has also been approved for glucocorticoid-induced osteoporosis. PTH 1–84 has also been approved in Europe.[112D]

The multicenter clinical trial that led to the approval of teriparatide evaluated the risk of osteoporosis fractures in 1637 postmenopausal women (average age of 69 years) with at least one moderate fracture or two mild non-traumatic vertebral fractures identified by spinal radiography. In this study, patients were randomized to treatment with teriparatide with subcutaneous doses of 20 or 40 μg per day or placebo.[113A] After 24 months (mean follow-up of 21 ± 3 months), there was a lower risk of new vertebral fractures (ARR = 0.096, 95% CI = 0.062–0.128, NNT = 10) and non-vertebral fractures (ARR = 0.037, 95% CI = 0.090–0.067, NNT = 26), but not femur fractures. The most frequent adverse events were headache, nausea, cramps, hypercalcemia, and hypercalciuria.[113A]

As with HRT, SERMs, and denosumab, the discontinuation of teriparatide monotherapy resulted in the loss of bone mass; thus, another treatment option for osteoporosis is recommended.[114B] Teriparatide has been indicated for atypical fractures due to bisphosphonate monotherapy.[115D]

Recommendation

Teriparatide is recommended for the treatment of postmenopausal osteoporosis in women at high risk of fractures, women with previous fractures, or women who experienced failure with or were intolerant to other forms of osteoporosis treatment. It is not indicated for treatment periods longer than 2 years. It may be recommended for atypical fractures caused by bisphosphonate monotherapy.

Evidence for recommending combined or sequential regimens for treatment of postmenopausal osteoporosis

Combined therapy

The results of clinical trials of the combination of drugs with different mechanisms of action, such as antiresorptive agents (HRT, bisphosphonates, denosumab, and SERMs) and anabolic agents (teriparatide and PTH1-84), differ depending on the evaluated associations, although these trials may have acceptable theoretical arguments from a scientific point of view.

The first double-blind, randomized study with this drug combination was conducted in 2003 by Black with 238 postmenopausal women (119 using PTH 1–84, 60 using alendronate, and 59 using the combined regimen) for 12 months. This study concluded that alendronate impaired the anabolic action of PTH 1–84 when the two drugs were combined.[116A] Opposite results were obtained in a randomized, double-blind, non-inferiority clinical trial with the combination of teriparatide and zoledronic acid compared with teriparatide monotherapy and zoledronic acid monotherapy in 412 postmenopausal women (average age of 65 ± 9 years) with osteoporosis. After 52 weeks, their respective BMDs increased

7.5%, 7.0%, and 1.4% in the lumbar spine and 2.3%, 1.1%, and 2.1%, in the femur. Therefore, teriparatide alone had a greater vertebral gain than zoledronic acid alone, and the combination promoted greater vertebral and femoral gains. However, the study did not have sufficient statistical power to evaluate fracture outcomes considering the sample size and treatment period.[117A] Short-term adverse events, including nausea, chills, fatigue, fever, arthralgia, myalgia, and headache, were more common in patients treated with zoledronic acid (both combined and isolated regimens) within the first 3 days of infusion, whereas the events were similar between the three groups after this period.[117A]

Robust data from combination therapy were obtained in the Denosumab and Teriparatide Administration (DATA) clinical trial, which also analyzed the effects of the combined regimen. In this initial study, 100 postmenopausal women with osteoporosis were randomized to receive either denosumab 60 mg or teriparatide in standard doses or in combination. After 12 months, there was a significant increase in vertebral BMD in the combined drug group (9.1%) compared with the teriparatide monotherapy (6.2%) and denosumab monotherapy (5.5%) groups. Moreover, there was a greater increase in total femur BMD in the combined drug group (4.9%) compared with the teriparatide monotherapy (0.7%) and denosumab monotherapy (2.5%) groups. Therefore, combined therapy may be useful in patients at high risk of fractures, although no data are available on the effect of this drug on fracture reduction.[118B]

It is important to note that, to date, the evidence points only to the benefits of the combined therapy on BMD outcomes and bone remodeling biochemical markers. However, no data are available on fracture reduction, adverse events, and costs.

Sequential treatment

Several studies have demonstrated the rapid loss of BMD after discontinuation of therapy with PTH 1–84 and teriparatide.[116A,117A] A study examined the BMD gain in women undergoing parathyroid hormone therapy followed by alendronate therapy. After 12 months, there was a significant increase in BMD with sequential therapy compared with monotherapy.[119B] Treatment with anabolic agents should always be followed by bisphosphonates, denosumab, raloxifene, or HRT because these drugs are used for periods of less than 2 years and there is loss of bone mass, especially in the lumbar spine shortly after treatment discontinuation.

Recommendation

The lack of studies with outcomes in fracture reduction, safety data, and the cost of drug combinations for the treatment of postmenopausal osteoporosis is still unknown and therefore cannot be recommended by this guideline. Evidence suggests that the administration of bone resorption inhibitors such as bisphosphonate after the interruption of teriparatide therapy and with denosumab maintains the benefit of bone mass gain. In patients at high risk of fractures, including those with previous or multiple fractures and inadequate responses to previous treatments, drug combination should be considered.

Importance of the prevention of secondary fractures

Patients with recent osteoporotic fractures are at high risk for secondary fractures and usually do not receive guidance and treatment after the first fracture. Reference services specializing in refracture prevention are increasing worldwide and have shown good results regarding cost-effectiveness, including in Brazil,[120B,121D] with the support of the IOF.[122D]

Recommendation

The IOF has a training and capacity building program for services for the prevention of secondary fractures (Capture the Fracture® (CTF) network; www.capturethefracture.org), and this program is growing worldwide. Specialized fracture treatment services should be encouraged to participate.

This study is an updated review (as of March 2017) of the guidelines for the treatment of postmenopausal osteoporosis. This study was conducted by the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia) with the collaboration of the Brazilian Medical Association (Associação Médica Brasileira – AMB), the Brazilian Federation of Gynecological Societies and Obstetrics (Federação Brasileira das Sociedades de Ginecologia e Obstetrícia – FEBRASGO), the Brazilian Society of Endocrinology and Metabology (Sociedade Brasileira de Endocrinologia e Metabologia – SBEM), the Brazilian Association of Bone Evaluation and Osteometabolism (Associação Brasileira de Avaliação Óssea e Osteometabolismo – ABRASSO), and the Brazilian Society of Orthopedics and Traumatology (Sociedade Brasileira de Ortopedia e Traumatologia – SBOT).

Conflicts of interest

The authors declare the following possible conflicts of interest (clinical research, consulting, speaker or others): Sebastião Cezar Radominski, Amgen, Sanofi, Medley; Ben-Hur Albergaria, Amgen, Sanofi, Organon, Eli Lilly, Novartis, Wyeth, GlaxoSmithKline; Cesar Eduardo Fernandes, Sanofi, Aché; Charlles H. M. Castro, Sanofi, Eli-Lilly, Novartis, Amgen; Cristiano A. F. Zerbini, Amgen, Novartis, Eli Lilly, Sanofi; Diogo S. Domiciano, Novartis, Aché, Sanofi; Laura M. C. Mendonça, Eli Lilly, Amgen; Luciano de Melo Pompei, Libbs, FMQ, Aché, Amgen; Marco Antônio R. Loures, Amgen; Maria C. O. Celeste Wender, Sanofi; Marize Lazaretti-Castro, Mantecorp, Aché, Sandoz, Sanofi, Eli Lilly; Rosa M. R. Pereira, Eli Lilly, EMS, Amgen; Sérgio Maeda, Aché, Hypermarcas, Sanofi, Eli Lilly; Vera Lúcia Szejnfeld, Mantecorp, Aché, Eli Lilly, Amgen, Sanofi; Victoria Z. C. Borba, Mantecorp, Aché, Eli Lilly, EMS. The other authors declare no conflicts of interest.

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