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Osteoporosis Drug Treatment Update

Atualização do tratamento medicamentoso da osteoporose

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Abstract

The Brazilian population is aging and the prevalence of chronic degenerative diseases, including osteoporosis, is increasing. The diagnosis and treatment of osteoporosis have made significant advances in the last decade. The orthopedist and traumatologist can no longer be detained only in the surgical treatment of osteoporotic fracture. It is extremely important that we know: 1) what risk factors to evaluate, and the Fracture Risk Assesment Tool (FRAX) can be used; 2) which complementary tests should be requested, such as densitometry, radiography of the spine and pelvis, blood and urine tests, and even bone biopsy; 3) which supplements to use, such as calcium and magnesium, vitamins D and K; 4) which medications to prescribe, antiresorptives or trainers, therapeutic windows and adverse events.

Keywords
- aging
- osteoporosis/diagnosis
- osteoporosis/therapy

Resumo

A população brasileira está envelhecendo, e com isso aumenta a prevalência de doenças crônico-degenerativas, dentre elas a osteoporose. O diagnóstico e tratamento da osteoporose teve avanços significativos na última década. O ortopedista e traumatologista não pode mais se deter apenas no tratamento cirúrgico da fratura osteoporótica. É extremamente importante que saibamos: 1) quais fatores de risco avaliar, podendo ser utilizada a ferramenta Fracture Risk Assesment Tool (FRAX, na sigla em inglês); 2) quais exames complementares solicitar, como densitometria, radiografia da coluna e bacia, exames de sangue e urina, e até mesmo biópsia óssea; 3) quais suplementos utilizar, como cálcio e magnésio, vitaminas D e K; 4) quais medicamentos prescrever, antirreabsortivos ou formadores, janelas terapêuticas e eventos adversos.

Palavras-chave
- envelhecimento
- osteoporose/diagnóstico
- osteoporose/terapia

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Introduction

When we intend to treat a patient with osteoporosis, some questions come to mind. The first is: why treat? And the answer is because we want to avoid the high prevalence of complications caused by this disease. Approximately half of the population > 50 years old will have osteopenia or osteoporosis, half of which will suffer at least one fracture by minimal trauma. Around the world, we have an osteoporotic fracture every 3 seconds, and the tendency is for that number to increase as the population ages.[1,2]

Osteoporosis in the United States results in 1.5 million fractures per year, mostly in postmenopausal women. Hip fractures can result in worsening quality of life, loss of independence and increased risk of death. Vertebral fractures, also associated with risk of death, can result in chronic pain, kyphosis and loss of quality of life.[1,2]

In Brazil, the number of people who have osteoporosis reaches 10 million, and the cost of treatment and care in the Brazilian Unified Health System (SUS, in the Portuguese acronym) is high. In 2010 alone, the SUS spent ~ BRL 81 million for the care of patients with osteoporosis and victims of falls and fractures.[3] Considering population aging, and because the reporting of fractures is not mandatory, the Brazilian real number is much higher. Friedman et al,[4] in 2007, called to attention that orthopedists missed the first opportunity to treat osteoporosis when treating patients with wrist fractures. The scenario has changed little among orthopedists when dealing with the clinical manifestation of osteoporosis, which is the fracture. The orthopedist has a duty to indicate treatment or refer patients for treatment, and in Brazil this attitude is still rare.[2,3]

In several cities in Brazil, there are services organized to treat osteoporosis and prevent refracture, a worldwide trend with the so-called Fracture Liaison Services (FLSs), one of them being in Brazil, the PREVREFRAT.[3] There is always a professional dedicated to this type of activity, who can be the orthopedist. With the treatment of osteoporosis, we want to avoid high mortality after fractures due to frailty in the first year after the fracture (30%), in addition to avoiding high morbidity such as dependence to walk (60%) or the loss of some ability to perform activities of daily life (90%). Treating osteoporosis patients, mortality decreases, and this should be our main concern.[1–6]

For Whom To Indicate Treatment of Osteoporosis

The second question is: how to identify who needs to be treated? According to the National Osteoporosis Foundation (NOF), the recommendations for the treatment of osteoporosis in women and men > 50 years old are as follows:[1–6]

1. Presence of vertebral or femoral fracture due to frailty (minimal trauma);
2. Bone densitometry with a T-score ≤ - 2.5, that is, osteoporosis;
3. Patients with a T-score between - 1.1 and - 2.4 (osteopenia), and with positive Fracture Risk Assessment tool (FRAX).

Before instituting treatment, the patient should be evaluated for differential diagnosis of osteoporosis, such as: osteomalacea, multiple myeloma, malnutrition, gastrointestinal diseases or kidney diseases, among others. In the suspicion of any disease that occurs with bone loss, tests for diagnosis of secondary osteoporosis should be requested. The comorbidities in treatment should be checked. In the clinical history, risk factors should be sought. The most important risk factors are: age, female gender, white and eastern ethnicities, family history of anticipated and personal fracture, low bone mineral density (BMD), use of glucocorticoids (dose ≥ 5.0 mg/day of prednisone for > 3 months), environmental factors, smoking, alcoholism (≥ 3 doses per day), sedentary lifestyle, low vitamin D and low calcium intake. Lactose intolerance and low sun exposure are relevant as risks.[6]

For the initiation of treatment, the modifiable risk factors should be eliminated, for example: low weight, alcoholism, smoking, sedentary lifestyle, nutritional deficiencies, and others of possible action. Women have a higher incidence of osteoporosis and osteoporotic fractures than men, but in postfracture mortality, men have a higher incidence. The causes of secondary osteoporosis can be identified in ~ 40 to 60% of men, especially in those with osteoporotic fractures. The most common are hypogonadism and prolonged corticosteroid therapy, followed by gastrointestinal diseases, vitamin D deficiency, alcoholism and anticonvulsants. Blood and urine tests help us to carry out these diagnoses, the main ones being: blood count, glycated hemoglobin, thyroid-stimulating hormone (TSH), creatinine, calcium and phosphorus, type 1ASS and 24-hour calciuria, parathyroid hormone (PTH), 25-OH-Vitamin D, C-telopeptide of type I collagen (CTX-1), alkaline phosphatase and protein electrophoresis.[7] With these tests, we were able to diagnose > 80% of secondary causes and establish drug treatment safely. In rarer cases, bone biopsy may be required, including histomorphometric evaluation.

The clinical evolution of osteoporosis is similar between genders in the senile phase > 70 years old. There is a new concept, for rapid action, called imminent risk of fractures, which is the greater possibility of refractures that can occur in the first and second year after the first fragility fracture, osteoporosis with the presence of important risk factors and preexisting diseases.[8]

Bone densitometry is the current gold standard test for the diagnosis of osteoporosis, with normal results: T-Score from 0 to - 1, low bone mineral density (tendency to abolish the name osteopenia) from - 1.1 to 2.4, and densitometric osteoporosis ≤ - 2.4. The lowest value site in the exam is considered for reading. Presence of fragility fracture and clinical diagnostic risk factors of osteoporosis, and indicate treatment. A Z-Score value ≤ - 2 indicates research to investigate the possible existence of a causal factor for secondary osteoporosis. Presence of fragility fracture with other risk factors is clinical diagnosis of osteoporosis regardless of the value in densitometry, with formal indication for treatment.[2–6]

Fracture due to mild trauma (fall from one's own height) or bone fragility is already an indication for treatment. Several guidelines indicate treatment in T-Score < - 2.4 and

presence of risk factors in the absence of fractures. It is important for the physician to keep in mind the risk factors at the time of the consultation; several mathematical algorithms have been developed to aid the diagnosis and assess the risk of fracture. Currently, the most used algorithm for calculating the risk of fractures in 10 years is FRAX, a tool that uses the more important risk factors for calculation, such as age, sex, alcoholism, body mass index (BMI) and others, such as bone mineral density (BMD) of the femoral neck. Fracture Risk Assesment tool Brazil can be searched at the www.shef.ac.uk/FRAX website and at ABRASSO https://abrasso.org.-br/calculadora/calculadora. The FRAX predicts osteoporosis fracture with risk factors even without BMD. It can be used in men and women with osteopenia (low bone mineral density) or osteoporosis, and it is validated in Brazil.[6–9]

Supplements Used for Osteoporosis

All patients with bone loss, or potential risk for loss, should be advised for dietary use of calcium and vitamin D or supplements. Calcium absorption decreases with age. Between 30 and 50% of the calcium ingested by adults are absorbed by the intestine. Vitamin D, being a hormone, activates intestinal calcium absorption and it is necessary to supplement elderly, sedentary or hospitalized individuals.[3–6]

Calcium carbonate, the most common in capsules, contains 40% calcium, so for 500 mg of the element, one requires 1,250 mg of carbonate, best used when ingested next to a meal. Calcium carbonate can cause intestinal constipation, being reported as a cause of kidney stones. For patients with gastrectomy, history of calculosis and bariatric surgery, calcium triphosphate or calcium citrate, whose molecule has $\sim$ 20% of the element, but with absorption in greater quantity, are best indicated. Consumption of calcium supplements $>$ 2,000 mg per day is related to increased risk of cardiovascular events and kidney stones, but the calcium ingested from the diet is safer regarding side effects.[10–12]

Evidence indicates that daily feeding including dairy, fruit, vegetables and adequate amount of meat, fish and poultry contributes to bone health.[11,12] The International Osteoporosis Society (IOF) has a program to calculate calcium intake with diet https://www.iofbo diet.[13]

Vitamin D is a pro-hormone synthesized in the skin exposed to ultraviolet B (UVB) rays from sunlight. Food vitamin D sources are scarce, and humans depend primarily on skin stimulation by solar UVB rays. Vitamin D, stored in the subcutaneous fat of the skin, undergoes chemical transformations, changing into its active form (calcitriol), with important functions in bone-mineral physiology, especially regarding intestinal absorption and calcium homeostasis.[6]

In addition to its role in intestinal calcium absorption, vitamin D exerts important action on peripheral musculature and balance, potentially decreasing the risk of falls. Vitamin D deficiency is common in patients with osteoporosis and hip fractures. For vitamin D dosage, hydroxyvitamin D (25[OH]D), which is the circulating form, is considered normal for adults at 30 ng/ml. In adults with vitamin D deficiency (25[OH]D $<$ 20 ng/ml), it is recommended the administration of an attack dose of 7,000 IU/day or 50,000 - IU/week for 8 weeks, followed by the maintenance dose between 1,000 and 2,000 IU per day. It is recommended to dose vitamin D in the clinical follow-up after 4 months.[12]

Magnesium helps in stabilizing calcium phosphate in hydroxyapatite, and its recommended daily dose is 320 mg. Vitamin K2, which is found in green foods, carboxyla to osteocalcin, a bone protein that aids in bone mineralization, in addition to decreasing vascular calcification. The most commonly used protein supplements are whey protein (WP), branched-chain amino acids (BCAA) and hydrolyzed collagens for muscle and bone mass gain.[13,14]

Drugs Used to Treat Osteoporosis

From a pharmacological point of view, we have two classes of drugs for osteoporosis: antiresoprtive (anticatabolic) and stimulators of bone formation (anabolic). Osteocytes are the cells responsible for controlling the entire process of skeletal renewal by perceiving microfractures in their canaliculi. Antiresoprtives act by inhibiting osteoclasts, which are the cells responsible for initiating bone remodeling, reabsorbing areas of microfractures or fragile bone, leading to the formation of Howship gaps. Trainers are those that stimulate osteoblasts to produce bone mass, filling these gaps with renewed osteoid matrix, which will be subsequently mineralized, improving the physical (deformity under load) and biological (tissue histomorphometry) properties of the bone to prevent fractures. Bone is a living tissue that needs to be renewed continuously, at a rate of 10% per year. Bone that does not renew fractures easier because it loses its viscoelasticity.[6]

The antiresorptives are subdivided into: 1) hormonal: hormone replacement therapy (HRT) (estrogens and testosterone); calcitonin (thyroid hormone), raloxifene (selective inhibitor of estrogen receptors [SERM]); 2) bisphosphosates: non-nitrogenous or nitrogenous; alkyl or heterocyclic; 3) biological: denosumab (anti-RANKL). Anabolics act by stimulating bone formation and are therefore stimulators of bone metabolism. Currently, we have in use teriparatide, a PTH analogue. Recent launch in the USA and Europe of Abaloparatide (similar to PTH), and a biological – Romosozumab (human monoclonal anti-sclerostatin) antibody, esclerostina approved in the USA and Japan. Both awaiting release in Brazil by ANVISA[13–33] (►**Table 1**).

Hormone Replacement Therapy

Female HRT should be indicated by the gynecologist in the presence of symptomatic menopausal disorders. It can be considered as preventive treatment of osteoporosis in the prevention of fractures, when the risks of use in the patient are lower than the benefits, and to treat vasomotor disorders of menopause. Male hormone replacement with testosterone may be indicated with evaluation by the urologist in the existence of osteoporosis by hypogonadism.[7]

Table 1 Drugs approved by ANVISA for the treatment of osteoporosis

Drugs approved by ANVISA for osteoporosis treatment				
Class	**Posology**	**Fractures reduction**	**Adverse effects**	**Approved use**
Alendronate	700 mg/week	Vertebral, nonvertebral and hip	Common: esophagitis, musculoskeletal pain; Rare: MON, atypical femur fracture[§]	Treatment and prevention
Risedronate	Oral: 35 mg/week or 150 mg/month	Vertebral, nonvertebral and hip	Common: esophagitis, musculoskeletal pain; Rare: MON, atypical femur fracture[§]	Treatment and prevention
Ibandronate	Oral: 150 mg/month Intravenous: 3 mg/ each 3 months	Vertebral	Common: intravenous local reaction, esophagitis, musculoskeletal pain; Rare: MON, atypical femur fracture[§]	Treatment and prevention
Zoledronic acid	Intravenous: 5 mg/year	Vertebral, nonvertebral and hip	Common: most frequent answer, first dose flu-like symptoms[æ]; Rare: MON, atypical femur fracture[§]	Treatment and prevention
Biologic: denosumab	Subcutaneous: 60 mg/semester	Vertebral, nonvertebral and hip	Common: cellulitis or skin reactions; Rare: MON, atypical femur fracture[§]	Treatment
Anabolic: teriparatide	Subcutaneous: 20 µg/day	Vertebral, nonvertebral and hip	Common: nausea, cramps. Hypercalcemia, osteosarcome not confirmed	Treatment
Salmon calcitonine	Intranasal: 200 IU/day	Vertebral	Nasal congestion	Treatment
SERM: raloxifen	Oral: 60 mg/day	Vertebral	Deep vein thrombosis, rubor, cramps, MMII, nausea	Treatment and prevention

Abbreviations: MON, mandible osteonecrosis; SERM, selective estrogen receptor modulator.
Bisfosfonats are reabsorbtion inhibitors.
[§]MON: mandibule osteonecrosis and atypical femur fracture are rare complications that can occur after long treatment with antiresoprtives; benefits are greater than risks.
[æ]Flu-like syndrome: general sickness, muscle pain and ocasionatl fever, most common in people $<$ 60 years old and new to the treatment.

Calcitonin

In Brazil, salmon calcitonin was approved for the treatment of postmenopausal osteoporosis at a nasal dose of 200 IU per day, with evidence of reduction of vertebral fractures, with no documented action on cortical bone. It has analgesic effect on pain of vertebral fracture and indication for treatment in algoneurodystrophy or Sudeck atrophy. Available for dispensation in the SUS network. The Prevent Recurrence of Osteoporotic Fractures (PROOF) study in 2000 demonstrated efficacy in preventing vertebral fractures in postmenopausal osteoporosis, with no evidence of action on cortical bone. It is a second-line alternative in the treatment of osteoporosis, as studies of other medications have shown better results in fracture reduction.[25]

Raloxifene

Raloxifene is approved for the treatment of postmenopausal osteoporosis, available for dispensing in the SUS network. It is a drug of the SERM group, which acts antagonistically in some organs and as agonist in others, and has a beneficial effect on the bones. Indicated for prevention and treatment of postmenopausal osteoporosis, affecting more trabecular bone (spine), with significant reduction of vertebral fractures. Presentation in capsules at a dose of 60 mg per day. Raloxifene is also indicated for breast cancer reduction in postmenopausal women with osteoporosis. It has no action demonstrated in cortical bone, therefore without demonstrated efficacy in the prevention of hip fractures. Its main side effect is deep vein thrombosis (DVT), and it should be avoided in women with a previous and family history of DVT.[6,18,25]

Bisphosphonates

Bisphosphonates are the most commonly used antiresorptive drugs worldwide for the treatment of osteoporosis.[15,16] They are synthetic analogues of pyrophosphate that bind to hydroxyapatite in the bone, inhibiting the resorptive action of osteoclasts. Due to its incorporation into bone tissue during the remodeling process,[16] it can be recycled under the surface of the bone resulting in prolonged action of the drug.[16] Bisphosphonates can remain for up to 10 years in the bones, those that have amino chain, containing nitrogen, in the molecule has greater power of action. The most potent are: zolendronate, risedronate, alendronate and ibandronate.[17,18] These drugs, which can cause hypocalcemia and muscle pain occasionally, are safe to use.[16]

Two serious adverse events occur rarely in prolonged use: atypical fracture of the femur, in the subtrochanteric region, of noncominutive transverse trait, with lateral

cortical thickening, which may be bilateral,[16] and usually after 8 years of continuous use. Mandibular osteonecrosis is the other event, defined by maxillofacial gingival bone exposure.[16] Mandibular osteonecrosis occurs more in people treating severe forms of cancer, with an incidence of 1/10,000 to 1/100,000 patients per year; the risk factors are invasive dental procedures and poor oral hygiene.[19] The website of the Brazilian Association of Orthopaedics in Osteometabolism (ABOOM, in the Portuguese acronym) (https://www.aboom.com.br/) brings important information about jaw necrosis, as well as FRAX Brazil. The use of these drugs should be avoided in patients with creatinine clearance $<$ 35 ml per minute.[16,18] People with low serum level of 25-hydroxyvitamin D develop hypocalcemia using bisphosphosnates.[16]

Oral daily doses of alendronate 10 mg and risedronate 5 mg are rarely used. Alendronate 70 mg and risedronate 35 mg are administered weekly (available in SUS pharmacies). Risedronate 150 mg and Ibandronate 150 mg are for monthly use. Oral bisphosphonates are absorbed into the intestine from 1 to 5%, and 50% of this amount binds to the bone, the remainder being excreted by the kidneys.[18] The tablets should be ingested with pure water, in the morning fasting, 60 minutes before breakfast, and it is recommend not to lie down to avoid possible gastroesophageal reflux. In the case of gastric intolerance, zolendronic acid or zolendronate may be used in annual intravenous infusion.[18] The main side effect of injectables is flu-like syndrome due to the release of cytokines in the acute phase causing fever and muscle pain.[1,6,18]

This effect decreases or ceases continuing treatment. The authors suggest hydrating the patient with 6 glasses of fluids for 3 days before and 3 days after the infusion, using in this period calcium 500 mg 3 times a day, and 3 days after, and adding on the day of infusion acetaminophen 500 mg every 8 hours up to 3 days if necessary.

There is no definite consensus on how long to use these drugs. Bisphosphonates are not exactly the same, so there should be specific individual studies. Alendronate, risedronate and zolendronate are well evaluated. It is recommended the use for 3 years of injectable (zolendronate) when the patient is at low risk for fractures, and for 5 years of oral use.[6,16,20] Black et al[20] define that patients with low BMD , T-Score $<$ - 2.5 in the femoral neck, after 3 to 5 years of treatment, have a high risk of vertebral fractures, as well as those with preexisting vertebral fractures, even with a T-Score - 2.0, continue to benefit from the continuity of treatment. Low risk are patients with a T-Score $>$ - 2.0, with no benefits with continued treatment after 5 years of oral or 3 of the injectable.[20] The data from studies of bisphosphonates for limit of use are 10 years; each patient should be evaluated with their risk factors, side effects and existing comorbidities for decision-making of stopping or continuing the treatment. Bisphosphonates are also suitable for men.[7,21]

Bisphosphonates can be used in the acute fracture period.[22] Zolendronic acid showed increased bone callus in rats.[22] There is evidence to discontinue the use of bisphosphonates in fractures in patients that are in prolonged use, and in cases of atypical fractures.[22] In a study of wrist fractures, conservative treatment demonstrated to avoid loss in mineral density by immobilization, with the use of risedronate, and did not demonstrate superiority in fracture consolidation time over placebo (use of calcium and vitamin D).[23]

Denosumab

Denosumab is the first approved biological treatment for the treatment of osteoporosis, both female and male.[6,7,16] It inhibits bone resorption by binding to the RANKL of the tumor necrosis activating factor group, decreasing osteoclast differentiation (TNF).[16] It can be used in patients with renal impairment. It is presented in subcutaneous injectable form with 60 mg/ml, semiannual dose, with syringes ready for use with 1 ml. It is a similar biological osteoprotegerin molecule that inhibits the formation of osteoclasts, blocking the ligand of the RANK L that activates RANK for the formation of the multinuclear giant cell – osteoclast, responsible for bone resorption. Denosumab is the first biological drug approved for the treatment of osteoporosis. Indicated for the treatment of postmenopausal women and of patients with bisphosphonate intolerance.[6] Also suitable for use in men.

Unlike bisphosphonates, denosumab can be used in patients with impaired renal function.[1,6,16] A large trial involving women with densitometry score between - 2.5 and - 4.0 in the lumbar spine or total femur in treatment with denosumab showed a decrease of 68% in the incidence of vertebral fractures, of 40% in femoral fractures, and of 20% in nonvertebral fractures.[1,16] Rare cases of atypical fractures of the femur and osteonecrosis of the mandible have been reported.[1,16] Data from 10 years of treatment showed continuous gains in BMD without limit with the time of use, sustained reduction of fractures, and good safety profile, even with renal dysfunction.[2,6] Discontinuation of treatment with denosumab may lead to the reversal of the gains obtained, verified in bone densitometry tests in the clinical follow-up; if it occurs, it should be exchanged for another drug.[6,16,24] Denosumab is also approved for use in men, and in corticosteroid-induced osteoporosis.

Bone Anabolic

Osteoanabolics are indicated in four patient groups: 1 - severe osteoporosis with fractures, or high risk of fractures; 2 - insufficiency of treatment, maintaining low BMD or occurrence of fractures; 3 - intolerance or contraindications to other alternatives for treating osteoporosis; 4- osteoporosis induced by corticosteroids.[27]

Teriparatide

Teriparatide is a PTH analogue with a sequence of 34 amino-acids (PTH 1–34), and it stimulates bone metabolism with predominance of formation, increasing trabecular and cortical bone mass. It is administered in daily subcutaneous

injections of 20 µcg.[2,6,28] Teriparatide presented a reduction in the risk of fractures in the spine by 65%, and in non-vertebral fractures by 54%.[28] The sample studies did not show a significative number of reduction of hip fractures,[28] perhaps due to the sample size, but in clinical practice its use has demonstrated protection. The treatment period was limited to 2 years due to the appearance of osteosarcoma in rats.[28]

There is great gain of bone mass, more evident in trabecular bone (spine). To maintain gains, an antiresorptive is used in the follow-up. Teriparatide is safe for use. It may cause asymptomatic hypercalcaemia, occasional nausea, dizziness, cramps, or headache.[6,18] Teriparatide is contraindicated for use in patients at high risk for osteosarcoma, such as children and adolescents, patients with Paget disease, bone metastases, postskeletal radiotherapy, and with unexplained increases in alkaline phosphatase.[6,18,27] For prudence, its use is avoided in any type of diagnosed cancer, and in primary and secondary hyperparathyroidism. In vitamin D deficiency, secondary hyperparathyroidism may occur, corrected with vitamin D replacement, in which case teriparatide may be used. It is indicated for treatment of severe osteoporosis induced by corticosteroids, both in women and men.[29] A comparative study with bisphosphonates showed improvement in the consolidation of vertebral fractures with teriparatide.[29]

Anabolic Drugs Not Yet Approved by Anvisa

Abaloparatide

Abaloparatide is an analogue of human PTHrP$^{1-3334}$ developed for the treatment of osteoporosis. The sequence of aminoacids is identical to that of PTHrP in the first 20, while the remaining are different.[31] In the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) study, with 80 µgr subcutaneous

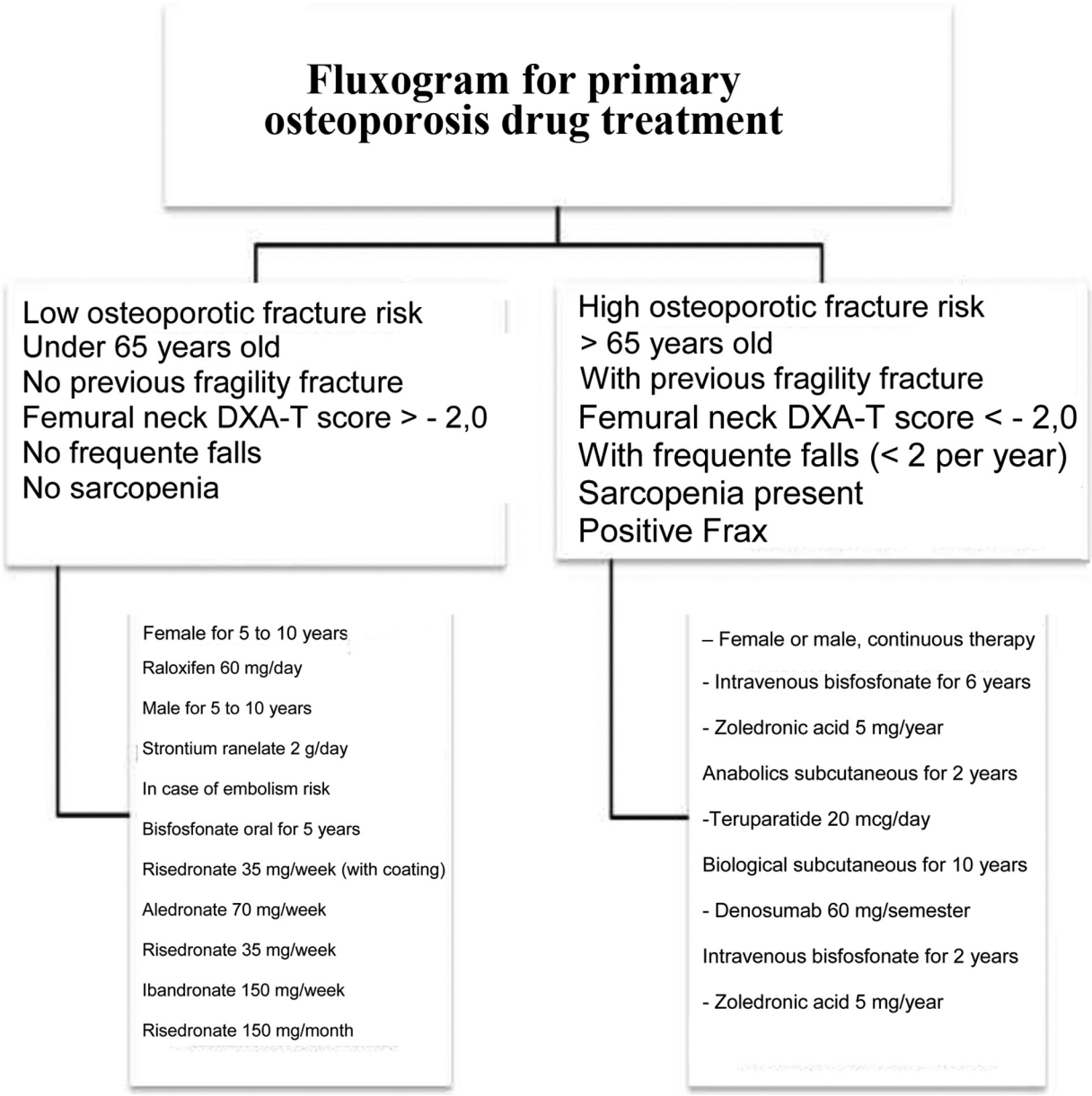

Fig. 1 Flowchart of primary osteoporosis drug treatment.

abalaparatide daily for 18 months, reduced the risk of new vertebral fractures by 86% and of nonvertebral fractures by 43%, and also reduced by 70% major osteoporotic fractures (vertebral clinics, proximal humerus and hip) compared with placebo.[32] It has the potential to reduce the incidence of vertebral and nonvertebral fractures, and increases bone mineral density (BMD) in women with postmenopausal osteoporosis, regardless of age, history of anterior fracture or low BMD.[32] No significant difference was found in vertebral fractures between abaloparatide and teriparatide.[27] It is indicated in patients at high risk of fractures, failure with previous treatments and intolerance to the usual drugs. Use of abaloparatide and teriparatide are restricted for up to 2 years.[27] It has the same contraindications as teriparatide. It is approved in the United States, Europe and other countries.

Romosozumab

Romosozumab was developed after study of the rare, genetic disease, with high bone mass, scleroosteosis, due to mutation with functional loss in the sclerostine gene (*SOST*). Sclerostine is secreted by osteocytes and inhibits formation and stimulates bone resorption. Romosozumab is a humanized monoclonal antisclerostatin antibody.[27] The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) study, with a monthly subcutaneous injection of 210 mg for 12 months, compared with placebo, showed 75% reduction in the incidence of new vertebral fractures.[27] The increase in bone mineral density (BMD) was faster and higher than with placebo, alendronate, denosumab and teriparatide in the spine and hip.[33]

To optimize the use of drugs according to the risk of fracture, we suggest the flowchart below (►**Figure 1**).

Final Considerations

Thus, we consider that osteoporosis is a chronic-degenerative disease of the skeleton, of extreme importance, because it is developing in a pandemic, due to the aging of the population. Its consequence is fragility fracture, which increases morbidity and mortality, especially in hip and spine fractures. In orthopedics and traumatology worldwide, there is lack of knowledge about the disease, which leads to decreased diagnosis and nonsurgical and drug treatment, focusing on secondary prevention of fractures. In the present article, we demonstrate the various treatment options available with their indications, adverse events and treatment flowchart suggestions. The orthopedist and traumatologist should recognize the severity of this disease and its consequences, and if they do not feel qualified for this treatment, they should refer the patient to colleagues who deal with this situation.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Black DM, Rosen CJ. Clinical Practice. Postmenopausal Osteoporosis. N Engl J Med 2016;374(03):254–262
2 de Souza MP. Osteoporosis Diagnosis and Treatment. Rev Bras Ortop 2010;45(03):220–229
3 Stolnick B, Oliveira LG. Para que a primeira fratura seja a última. Rev Bras Ortop 2016;51(02):121–126
4 Freedman BA, Potter BK, Nesti LJ, Cho T, Kuklo TR. Missed opportunities in patients with osteoporosis and distal radius fractures. Clin Orthop Relat Res 2007;454(454):202–206
5 Souza BGSE, Carvalho LGVA, Oliveira LFMM, Ferreira AG, Amaral RCSD, Oliveira VM. Primary and secondary osteoporotic fractures prophylaxis: evaluation of a prospective cohort. Rev Bras Ortop 2017;52(05):538–543
6 Radominski SC, Bernardo W, Paula AP, Albergaria BH, Moreira C, Fernandes CE. Diretrizes brasileiras para o diagnóstico e tratamento da osteoporose em mulheres na pós-menopausa. Rev Bras Reumatol 2017;57(Suppl 2):s452–s466
7 Oliveira LG, Guimarães ML. Male osteoporosis. Rev Bras Ortop 2015;45(05):392–396
8 Banefelt J, Åkesson KE, Spångéus A, et al. Risk of imminent fracture following a previous fracture in a Swedish database study. Osteoporos Int 2019;30(03):601–609
9 Sousa CJ, Oliveira ML. Ferramenta FRAX no Brasil: revisão integrativa da literatura após sua Validação. Rev Bras Geriatr Gerontol 2018;21(01):111–118
10 Bauer DC. Clinical practice. Calcium supplements and fracture prevention. N Engl J Med 2013;369(16):1537–1543
11 Peters BS, Martini LA. Nutritional aspects of the prevention and treatment of osteoporosis. Arq Bras Endocrinol Metabol 2010;54 (02):179–185
12 Chen LR, Wen YT, Kuo CL, Chen KH. Calcium and Vitamin D Supplementation on Bone Health: Current Evidence and Recommendations. Int J Gerontol 2014;8:183–188
13 Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019;30(01):3–44
14 Maeda SS, Borba VZ, Camargo MB, et al. Brazilian Society of Endocrinology and Metabology (SBEM). Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D. Arq Bras Endocrinol Metabol 2014;58(05):411–433
15 Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med 2017;166(11): 818–839
16 Matzkin EG, DeMaio M, Charles JF, Franklin CC. Diagnosis and Treatment of Osteoporosis: What Orthopaedic Surgeons Need to Know. J Am Acad Orthop Surg 2019;27(20):e902–e912
17 Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010;95(04):1555–1565
18 Maeda SS, Lazaretti-Castro M. An overview on the treatment of postmenopausal osteoporosis. Arq Bras Endocrinol Metabol 2014;58(02):162–171
19 Khan AA, Morrison A, Hanley DA, et al. International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30(01):3–23
20 Black DM, Bauer DC, Schwartz AV, Cummings SR, Rosen CJ. Continuing bisphosphonate treatment for osteoporosis–for whom and for how long? N Engl J Med 2012;366(22):2051–2053
21 Zanatta LB, Marcattoa C, Ramosa CS, Manasa N, Moreira C, Borba V. Uso de pamidronato para tratamento da osteoporose no sistema público de saúde no Brasil. Rev Bras Reumatol 2017;57 (06):514–520

22 Kates SL, Ackert-Bicknell CL. How do bisphosphonates affect fracture healing? Injury 2016;47(01, Suppl 1):S65–S68
23 Oliveira LG, Eis SR, Neto HM, de Moraes FB, Pires LA, Vasconcelos JW. Use of risedronate for consolidation and callus formation in Colles fractures in postmenopausal women: SOLID study. Rev Bras Ortop 2015;50(03):274–282
24 Cummings SR, Ferrari S, Eastell R, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res 2018;33(02):190–198
25 Protocolos clínicos e diretrizes terapêuticas: volume 3 / Ministério da Saúde, Secretaria de Atenção à Saúde. – Brasília: Ministério da Saúde;2014. Disponível em: http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais- ominister io/840-sctie-raiz/daf-raiz/cgceaf-raiz/cgceaf/l3-cgceaf/11646-pcdt
26 Chesnut CH III, Silverman S, Andriano K, et al; PROOF Study Group. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. Am J Med 2000; 109(04):267–276
27 Haas AV, LeBoff MS. Osteoanabolic Agents for Osteoporosis. J Endocr Soc 2018;2(08):922–932
28 Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344 (19):1434–1441
29 Pereira RM, Carvalho JF, Paula AP, et al. Diretrizes para prevenção e tratamento da osteoporose induzida por glicocorticoide. Rev Bras Reumatol 2012;52(04):569–593
30 Iwata A, Kanayama M, Oha F, Hashimoto T, Iwasaki N. Effect of teriparatide (rh-PTH 1-34) versus bisphosphonate on the healing of osteoporotic vertebral compression fracture: A retrospective comparative study. BMC Musculoskelet Disord 2017;18(01): 148
31 Gonnelli S, Caffarelli C. Abaloparatide. Clin Cases Miner Bone Metab 2016;13(02):106–109
32 Cosman F, Hattersley G, Hu MY, Williams GC, Fitzpatrick LA, Black DM. Effects of Abaloparatide-SC on Fractures and Bone Mineral Density in Subgroups of Postmenopausal Women With Osteoporosis and Varying Baseline Risk Factors. J Bone Miner Res 2017;32 (01):17–23
33 McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014;370(05):412–420