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A SYSTEMATIC REVIEW ON DIAGNOSIS AND MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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ABSTRACT: The aim of this review is to assess the efficacy of treatments for postmenopausal osteoporosis in women with low bone mass or with an existing vertebral fracture. Osteoporosis is a worldwide health problem related to the aging of the population, and it is often under diagnosed and undertreated. It is related to substantial morbidity, mortality and impairment of the quality of life. Estrogen deficiency is the major contributing factor to bone loss after menopause. Postmenopausal osteoporosis is a silent disease in most cases, with no symptoms until fractures occur. It is characterized by low bone mineral density (BMD) and changes in bone micro architecture that reduce bone strength and increase fracture risk. The objective of this study was to present a systematic review of drugs for treatment of osteoporosis, focusing on the adequacy of clinical protocols based on existing evidence in the scientific literature. So, our study recommends that postmenopausal women should be screened for osteoporotic fracture risk which may be important strategy in the management of postmenopausal osteoporosis.

INTRODUCTION: Osteoporosis is defined as impairment in bone strength due to an abnormal quantity and / or quality of bone. Quantity is evaluated by measuring BMD. Quality is affected by many factors, including the degree of mineralization, the rate of bone remodelling the connectivity of the bony trabeculae, the quality of the collagen fibers, and the health of the bone cells. The 3 types of bone cells are osteoblasts, osteoclasts, and osteocytes [1]. Statistics show that the mean age of natural menopause is 51 years in industrialized nations, compared to 48 years in poor and non-industrialized nations [2].

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Menopause is a natural physiological phenomenon resulting from primary ovarian failure secondary to apoptosis or programmed cell death. Ovarian function declines with age. The onset of menopause features the decreasing production of estradiol, as well as increasing levels of follicle-stimulating hormone (FSH) [3]. Various drugs are available for the treatment of osteoporosis and prevention of osteoporotic fractures [4].

Information on drug efficacy for the treatment of osteoporosis is necessary in the public health sphere to evaluate adequacy and support the updating of clinical protocols, based on the available scientific evidence. An improved understanding of the pathophysiology of osteoporosis has led to the development of treatments with effects on bone mineral density (BMD), bone turnover and / or fracture. The objective of the current study was to present a

systematic review of the available drugs for treatment of osteoporosis, with a focus on evaluating their efficacy [5].

Pathophysiology: The major factors that determine whether a person develops osteoporosis are the maximum (peak) bone density that is achieved and the amount that is subsequently lost [6, 7]. Low bone mass and skeletal fragility in adults may be the result of low peak bone mass in early adulthood, excessive bone loss in later life, or both [8, 9].

Approximately 70% to 80% of peak bone mass is genetically determined [10 - 13]. There is a direct relationship between the lack of estrogen after menopause and the development of osteoporosis. After menopause bone breakdown overtakes the building of new bone. Early menopause (before age 45) and any long phases in which the woman has low hormone levels and no or infrequent menstrual periods can cause loss of bone mass [14, 15]. The hormonal changes occurring at menopause are a major factor leading to osteoporosis in woman. An abrupt reduction in ovarian function results in rapid decrease in 17 β-estradiol secretion which leads to an increased secretion of cytokines that activate osteoclasts, including RANKL, interleukin - 1β, interleukin-6 and tumor necrosis factor α [16].

Secondary hyperparathyroidism due to Vitamin D and calcium deficit also contributes to bone loss in elderly men and woman. Intestinal calcium absorption decreases with age. Decreased synthesis of endogenous Vitamin D results from aging of the skin and from lower sunlight exposure [17]. Lifestyle factors that increase the risk of low BMD and fracture include alcohol abuse, smoking, low calcium intake, and lack of physical activity. These factors are interrelated: smokers tend to drink more alcohol, often have a poorer diet and take less physical activity. They also tend to be thinner. Lifestyle factors also interact with other factors; for example, components of tobacco smoke influence enzymes involved in the metabolism of steroid hormones [18 - 21].

Many factors including nutrition, Vitamin D, exercise, smoking, and the presence of other diseases and medications (**Table 1**), can influence the rate of bone loss and the risk of fractures in individuals. Nutrition is important during aging as well as during bone growth. In particular, Vitamin D deficiency, whether isolated or associated with more generalized under-nutrition, has reached almost epidemic proportions throughout the world. Although severe Vitamin D deficiency impairs mineralization of the skeleton, even mild to moderate Vitamin D deficiency reduces calcium absorption and can lead to parathyroid (PTH)-mediated bone resorption. Vitamin D deficiency also causes impairment of muscle strength and balance, leading to an increased risk of falling.

TABLE 1: SOME FACTORS THAT MAY ACCELERATE BONE LOSS

Disease	Medications
Endocrine disorders	Corticosteroids
Hyperthyroidism	Proton pump inhibitors
Hypopituitarism	Antiepilepsy drugs
Hypogonadism	Medroxyprogesteroneacetate
Cushing disease	phosphate (Depo-Provera)
Primary	Selective serotonin reuptake
hyperparathyroidism	inhibitors
Gastrointestinal disorders	Thiazolidinediones
Celiac disease	Thyroxine in
Short bowel syndrome	supraphysiologic doses
Hematologic disorders	Excess Vitamin A
Multiple myeloma	Aromatase inhibitors
Systemic mastocytosis	Androgen deprivation
Renal disorders	therapy
Chronic renal failure	Nutritional deficiency
Idiopathic hypercalciuria	Calcium, Vitamin D
Neuromuscular disorders	Protein

Most osteoporosis-related fractures are the result of falls, which probably have important a role in the pathogenesis of osteoporosis-related fractures. Risk factors for falls are summarized in **Table 2** [22].

TABLE 2: SOME FACTORS THAT INCREASE RISK OF FALLING AND FRACTURE

Neurologic disorders	Environmental factors	Medications
Parkinson disease	Poor lighting	Sedatives and
Proximal	Stairs	hypnotics
myopathy	Slippery floors	Antihypertensive
Peripheral	Wet, icy, or	agents
neuropathy	uneven pavement	Narcotic
Prior stroke	Uneven roadways	analgesics
Dementia	Electric or	
Impaired gait or	telephone cords	
balance (or both)	Pets-small or	
Impaired vision	large	
Impaired hearing	Throw rugs	
Frailty and	Positioning in a	
deconditioning	wet or dry bath	
Sarcopenia	tub	

In determining risk factors, it is important to distinguish between risk factors for primary and secondary causes) and risk factors for osteoporotic fracture. For BMD - defined osteoporosis, major risk factors in postmenopausal women are advanced age, genetics, lifestyle factors (*e.g.*, low calcium and Vitamin D intake, smoking), thinness, and menopause status. In the absence of other risk predictors such as BMD, clinical risk factors can be used to assess fracture risk or help make the decision as to which women should be screened with dual-energy X-ray absorptiometry (DXA). Such risk factors increase the risk of fracture 1.5- to 3-fold over that seen in unaffected individuals. Women with multiple risk factors are at greater risk of fracture if they have a lower BMD. The use of BMD T-scores to assess fracture risk can be markedly improved by combining BMD with information about other risk factors, particularly the women age and fracture history [23].

Diagnosis: Malignancies with skeletal muscle and metastases and multiple myeloma may cause vertebral fracture or, less commonly, fracture at other sites. The diagnosis is usually suggested by the severity of the pain or the general physical findings and is confirmed by laboratory tests, roentgenograms, or bone scintigraphy. In some cases, the diagnosis may be more difficult, necessitating a computed topography scan, magnetic resonance imaging, or histologic examination of a bone specimen [24, 25].

TABLE 3: WHO CRITERIA FOR CLINICAL DIAGNOSIS OF OSTEOPOROSIS [26]

BMD T-score	Diagnosis
T-score ≥ -1	Normal
-1 > T-score > -2.5	Low bone mass
T-score ≤ -2.5	Osteoporosis
T-score ≤ -2.5 with existing fracture	Severe osteoporosis

The World Health Organization (WHO) defines osteoporosis as a BMD 2.5 standard deviations or more below the mean value for young adults (a T score < −2.5), and severe osteoporosis as a BMD below this cut-off and one or more fragility fractures 1. The WHO defines osteopenia as a BMD T score between −1.0 and −2.5. It should be remembered that whilst osteoporotic fracture incidence is highest in those with the most pronounced osteoporosis, a substantial number of fractures occur in women who do not have very low bone density [27, 28]. A new algorithm from the WHO for the definition of osteoporosis treatment thresholds, which includes other factors such as age, is currently awaited [29, 30].

Treatment: Bone strength is determined by both bone quantity and bone quality. Bone densitometry provides information on BMD, which is a reflection of bone quantity. Bone quality is determined by a number of factors; including the rate of re-modelling, bone mineralization, function of the bone cells, and quality of the collagen fibres [31]. Peak bone mass is achieved during the third decade of life, and it is mainly determined by genetic influence and, to a lesser extent, by the modifiable aspects in life style and health status. Factors such as nutrition, hormonal status, physical exercise, medical conditions, drug abuse, alcohol or tobacco can interfere with the peak of bone mass. Patients should be encouraged to smoking and reduce excessive alcohol and caffeine intake [32].

Several effective medicines are approved for the prevention and treatment of osteoporosis. These agents have been demonstrated to reduce vertebral, and in some cases non-vertebral, fracture risk in women with osteoporosis. They can be broadly divided into two categories: anti-resorptive (or anti-catabolic) or anabolic agents. Anti-resorptive agents, which include estrogen, the selective estrogen receptor modulator raloxifene, bisphosphonates and the human monoclonal antibody to receptor activator of NFκB ligand (RANKL) reduce bone resorption (and subsequently bone formation), leading to an increase in BMD to varying degrees. In comparison, anabolic agents, which include full-length parathyroid hormone (PTH1-84) and teriparatide (PTH1-34) stimulate bone formation (and subsequently bone resorption), thereby increasing BMD. Strontium ranelate is another agent that reduces fracture risk. It has only weak effects on bone remodeling and probably improves bone strength mainly through effects on bone material properties [33, 34].

Calcium: Prolonged low calcium intake leads to a negative calcium balance with compensatory secondary hyperparathyroidism, which increases bone resorption and the risk of fractures. According to the US Institute of Medicine (IOM), the

recommended daily calcium intake for post-menopausal women is 1,200mg, with an upper limit of 2,000mg, preferentially obtained from the diet [35].

Vitamin D: The Contribution of diet as a source of Vitamin D is very limited and its concentrations are mainly dependent on the skin formation after URB radiation. The aging of the population, the rise in obesity, the more reclusive habits in large cities, and the indiscriminate use of sunscreen have caused a currently generalized inadequate Vitamin D status. Lower concentrations of Vitamin D are associated with elevated levels of PTH and, consequently, high resorption rate, and high risk of fractures. The IOM recommends a Vitamin D daily dietary allowance of 600 IU for 51-70 years old women, and 800 IU for those older than 70 years old, with and upper limit of 4,000 IU [35].

Hormone Replacement Therapy (HRT): There is evidence that bone loss starts 2-3 years prior to the last menses, and it is accelerated with menopause due to estrogen deprivation. This process continues for up to 5-10 years. Estrogen deficiency is associated with an increase in the life span of the osteoclasts and concomitant decrease in osteoblast lifespan. There is considerable evidence that even the low residual levels of estrogen present in postmenopausal women are important in reducing bone resorption, and that women with breast cancer treated with aromatase inhibitors are at increased risk of bone loss [36].

More recent studies show that even low doses of HRT may protect bone by decreasing BTM levels (Bone turnover marker) and preventing bone loss [37, 38]. The anti-fracture efficacy of these regimens has not been studied. Currently, HRT is regarded as an acceptable treatment for osteoporosis only after all other treatments have been considered and when all the risks and benefits are carefully explained to the patient. Women who decide to take HRT to relieve menopausal symptoms should use the lowest effective dose and for the shortest possible time [39].

Selective Estrogen Receptor Modulators (SERMS): Selective estrogen receptor modulators (SERM) are synthetic molecules that have the ability to bind to estrogen receptors throughout the body and act as estrogen agonists or antagonists depending upon the target organ. The concept of SERM is based on the observation that tamoxifen, used as an anti-estrogen in the treatment of breast cancer, acts as an estrogen agonist on bone in postmenopausal women. Raloxifene (60 to 120mg daily) slows down bone turnover (decrease in the BTM levels by 35%) and increases BMD by 2 to 3% at the lumbar spine and femoral neck [40, 41]. It reduces the incidence of vertebral fractures by 40 to 50%. No effect was observed on non-vertebral fractures, except a 22% decrease in the incidence of major osteoporotic fractures in women with prevalent vertebral fractures, mainly severe vertebral fractures [42, 43].

Raloxifene markedly reduces the risk of invasive estrogen - receptor positive breast cancer [44 - 46]. In most studies, raloxifene did not influence the risk of cardiovascular (coronary) events [44, 47] and, in some groups, may even decrease the risk of myocardial infarction or unstable angina [48]. It increases the risk of venous thromboembolism to the same extent as HRT and increases the risk of fatal stroke mainly in women with high risk of stroke at baseline [44, 49, 50, 51].

Tissue-selective estrogen complexes, which combine a SERM with 1 or more estrogens, constitute a new class of agents in development for the treatment of women with menopausal symptoms and at risk of osteoporosis. The goal of this combination is to provide relief of menopausal symptoms and prevent bone loss while protecting the breast and the endometrium. Bazedoxifene with conjugated estrogens is the first such agent in clinical development. Dosages of 20mg of bazedoxifene with either 0.45 or 0.625mg of conjugated estrogens have been shown in phase-III clinical trials to significantly reduce vasomotor symptoms [52] and vulvo-vaginal atrophy [53] in postmenopausal women aged 40 to 65 years and to prevent bone loss in those women at risk for osteoporosis [54].

Bisphosphonate Therapy: Bisphosphonates are the most used anti-resorptive agents in the world for the treatment of osteoporosis and are in use for three decades. They are synthetic analogues of pyrophosphate, with high affinity for hydroxyapatite. They strongly bind to the mineralized tissue,

especially in the active remodeling sites. They are removed from bone by osteoclasts during resorption and are not metabolized for excretion. Therefore, they can be rebound by the mineralized tissue again. Because of their characteristics, they can remain as long as 10 years in the skeleton. Variations in the structure of the amino side chains of these drugs affect their pharmacological activity in terms of bone affinity and potency. The most potent molecules have a nitrogen-containing chain, such as alendronate, risedronate, ibandronate, and zoledronate. Skeleton-binding affinity increases in this rank order: risedronate, ibandronate, alendronate, and zoledronate [55].

Bisphosphonates (BP) are potent inhibitors of bone resorption and inhibit the activity of osteoclasts. All approved bisphosphonates have been shown to reduce vertebral fracture risk and increase BMD, while some have also demonstrated reductions in non-vertebral and hip fracture risk. They are available as oral and IV formulations, with weekly, monthly and annual dosing schedules, depending on the specific agent. Bisphosphonates bind to bone mineral, and consequently have a long skeletal retention. Orally administered BPs has a poor intestinal absorption and can induce mild intestinal disturbances [56].

Alendronate: Alendronate, taken orally, has been approved for the prevention of osteoporosis at a daily dose of 5mg and for the treatment of osteoporosis at a daily dose of 10mg or a weekly dose of 70mg. Alendronate reduces the risk of vertebral fractures in postmenopausal woman with and without previous vertebral fractures, as has been demonstrated in the FIT study [57 - 59]. Several trials have shown that alendronate use reduces bone resorption and improves BMD [59, 60]. A combined analysis of the data for 3658 patients in the FIT osteoporotic cohort that had a pre-existing fracture or a femoral neck BMD T-score of -2.5 or less at baseline demonstrated a significant decrease in the incidence of symptomatic vertebral fractures of 55% (P = 0.003). The incidence of hip fractures was reduced by 63% at 18 months (P = 0.014) and by 54% at 36 months (P = 0.005) [61].

Risedronate: Risedronate decreases the incidence of new vertebral and peripheral fractures by the same extent as alendronate in women with low BMD and in women with prevalent vertebral fractures [62, 63]. In osteoporotic women 70 to 79 years of age, risedronate decreased the incidence of hip fracture by 40%. Bridging studies have shown that alternative doses of risedronate (35mg once a week, 75mg on two consecutive days a month, 150mg once a month) decrease BTM levels and increase BMD to a similar extent as the daily regimen [64 - 66]. In men with low BMD, risedronate decreased bone turnover and increased BMD [67]. The efficacy of risedronate has also been shown in the prevention and treatment of glucocorticoid - induced osteoporosis [68].

In a post-hoc analysis carried out in data combined from four phase III studies, risedronate reduced the incidence of fractures within 6 months of treatment [69]. Some, [70] but not all, [71] observational studies suggest that the anti-fracture efficacy of risedronate appears earlier than that of alendronate. However, these analyses are based on the retrospective analyses of the databases of the healthcare providers and no randomized head to head studies permitting direct comparisons were performed [72, 73].

Zoledronic Acid: Zoledronic acid is the most potent bisphosphonate available [74, 75]. It contains 2 nitrogen atoms in the R2 side chain [76]. Zoledronic acid administered intravenously to postmenopausal women with osteoporosis at a dose of 5mg once-yearly induced a sustained decrease in bone turnover, a progressive increase in BMD and a significant decrease in the incidence of vertebral fractures by 70% and in the incidence of non-vertebral fractures by 25% (including a significant 40% decrease in the incidence of hip fractures) [77]. In older men and women with recent low trauma hip-fracture (two weeks or later but less than 90 days after surgical repair) zoledronic acid increased BMD at the hip, decreased the incidence of clinical fractures (including a significant decrease in the incidence of hip fracture) and reduced the mortality rate by about 30% [78, 79].

In men and women treated with oral glucocorticoids, zoledronic acid induced a greater decrease in the rate of bone turnover and a greater increase in BMD compared with risedronate [80]. In men receiving androgen deprivation therapy for prostate cancer, zoledronate slowed bone turnover and prevented bone loss [81].

Advantages and Disadvantages: The major advantage of oral bisphosphonate therapy is ease of administration and excellent tolerability. The most common side effects are abdominal pain and dysphagia. However, in the RCT's (Randomized controlled trial) conducted to date, the incidence rates of upper gastrointestinal side effects with alendronate and risedronate have been comparable to those of placebo [82].

Intravenous administration of bisphosphonates has a number of advantages, including less frequent dosing and less potential for gastrointestinal side effects as compared with oral administration. Intravenous therapy also has assured compliance if the patient attends the physician's office for the annual infusion [83].

Calcitonin Therapy: Calcitonin, a hormone produced in the thyroid gland, inhibits osteoclastic bone resorption. Its poor oral absorption necessitates either subcutaneous or intranasal administration. Administration of 200 IU by nasal spray was approved in Canada for the treatment of postmenopausal osteoporosis. Recently, however, the European Medicines Agency [84] reviewed all available post marketing safety data for nasal spray calcitonin as well as information from experimental cancer studies and found a 0.7% to 2.4% increase in the rate of cancer among those using this therapy long term [85].

Calcitonin directly suppresses the activity of osteoclasts and also inhibits their recruitment. It has been isolated from a large number of animal species. Calcitonin from fish is the most resistant to degradation in humans and, thus, has the greatest potency per unit weight. It is not yet known whether calcitonins from other species will be more effective. Daily intramuscular salmon calcitonin at a relatively high dosage (100 IU) has been shown to prevent bone loss and slightly increase skeletal mass in women with osteoporotic fractures [86]. In healthy women, a much lower dose (20 IU) of synthetic human calcitonin, given subcutaneously three times a week in the early postmenopausal period, was as effective as estrogen in preventing spinal trabecular bone loss [87]. The inconvenience of injectable calcitonin led to the development of alternative methods of administration. Reports of the use of salmon calcitonin suppositories have failed to show effects on spinal or femoral bone mineral density or on markers of bone turnover, [88] and the suppositories are reported to have poor tolerability [89].

Denosumab Therapy: Denosumab is a fully human monoclonal antibody against RANKL; it binds to human RANKL, thus preventing osteoclast activation and consequently reducing bone resorption. In the estrogen - deficient woman there is upregulation of RANKL, resulting in an increase in osteoclast formation, function, and survival, which leads to significant bone loss after menopause. By binding to the RANKL, denosumab reduces binding to the RANK receptor on osteoclasts, thereby reducing the rate of bone remodelling. Denosumab is cleared through the reticulo endothelial system rather than the kidneys. Unlike bisphosphonates it can be used in those with stage IV chronic kidney disease and has been shown to be effective in reducing fracture risk in this patient population [85].

Teriparatide: Intermittent administration of low-dose PTH enhances osteoblast activity and bone formation. Two PTH peptides have been approved for the treatment of osteoporosis: teriparatide (PTH 1-34) and PTH 1-84, but only teriparatide is available in Brazil. It is administered as a 20-mcg subcutaneous daily injection. There was a 65% and 54% reduction in fracture risk in vertebral and non-vertebral fractures. Due to a small number of hip fractures, no significant fracture risk reduction was demonstrated [90]. The concomitant use of bisphosphonates may attenuate bone mass improvement seen with PTH alone, but the administration of an anti-resorptive agent has to be considered after the treatment in order to maintain the bone gain achieved [91].

Maximum treatment duration of 2 years is recommended because preclinical studies showed the development of osteosarcoma in rats [90]. Asymptomatic hyper-calcemia, occasional nausea, dizziness, leg cramps, and headache were associated with teriparatide use. Teriparatide is contraindicated in clinical situations with high risk of osteosarcoma, such as children and adolescents, Paget's disease, bone metastasis, skeletal irradiation, or unexplained elevations of alkaline phosphatase. The use of teriparatide is limited to

severe osteoporosis because of the high cost of the treatment [91].

Strontium Ranelate: Strontium ranelate (2g daily) slightly inhibits bone resorption, slightly stimulates bone formation and progressively dose-dependently increases BMD [91, 92]. It decreases the incidence of vertebral fractures by about 40% [91]. During long-term treatment (4 years), strontium ranelate decreased vertebral fracture incidence by 33% [93]. Strontium also decreases the incidence of vertebral fractures by 35% in younger postmenopausal women (aged 65 or less) and by 32% in the elderly women aged 80 and over [94, 95]. Strontium ranelate decreases the incidence of non-vertebral fractures by about 15% and even more (31%) in the oldest women [95 - 97]. Post-hoc analyses demonstrated that strontium ranelate decreases the incidence of hip fracture by approximately 40% in high risk elderly women with severe osteoporosis [96, 97].

Aim of Therapy: The aim of such therapy is to reduce osteoporosis - related morbidity and mortality by safely reducing the risk of fracture. Consequently, an important clinical goal is to identify patients with osteoporosis or at high risk of developing the disease. Although fractures tend to occur relatively late in life, they result from the bone loss and micro-architectural deterioration that occur from menopause onward. The purpose of therapy is to maintain or increase bone strength to prevent fractures throughout the patient's lifetime [98].

CONCLUSION: In summary, osteoporosis is a very common clinical situation, with an expected trend to and increasing incidence in the next decades due to the worldwide aging of the population. Bone loss and fractures follow the decrease in estrogen levels in the postmenopausal period, which increases osteoclast activity and, subsequently, bone resorption. The adequacy of calcium intake and Vitamin D status are priority measures before starting osteoporosis treatment with specific drugs, as well as encouraging physical activity and prevention of falls. Several drugs are already available with proven efficacy against fractures and excellent safety profiles. The challenge today is to improve the detection of osteoporosis and convince healthcare professionals to refer at-risk patients for treatment.

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