Osteoporose pós-menopausa: aspectos clínicos

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Abstract

Postmenopausal osteoporosis is a highly prevalent worldwide skeletal disease. It is characterized by low bone mass, leading to extensive bone fragility. Osteoporosis diagnosis is made on the basis of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA). The major complications are fractures. The prevention and treatment of osteoporosis are aimed at reducing substantially the fractures. Calcium and vitamin D supplementation may slow the rate of bone loss or mildly increase BMD. Bisphosphonates are currently the most used drugs, they reduce osteoclast activity and are potent inhibitors of bone resorption. Strontium ranelate is an alternative to bisphosphonates. Raloxifene, a selective estrogen receptor modulator, prevents bone loss, like estrogen, but probably without prejudicial side effects of estrogen. Estrogen alone, or in combination with progesteron, is now seldom used. Calcitonin, a peptide produced by thyroid C cells, inhibits bone resorption, but its clinical efficacy is moderate. Teriparatide, a parathyroid hormone analogue, is an potent bone anabolic agent that increases bone formation; however, this medication is reserved for severe cases. Balanced nutrition with adequate calcium and vitamin D intake, physical activity and load-bearing exercise seem to be effective in maintaining or increasing BMD. Also, it is necessary to instruct the patients, concerning the prevention of osteoporotic fractures.

Key words: osteoporosis, bone mineral density, bisphosphonates, calcium and vitamin D, raloxifene, calcitonin, teriparatide.

INTRODUCTION

Postmenopausal osteoporosis[1-6] is the most commonly found metabolic bone disease all over the world. According to the World Health Organization (WHO), osteoporosis belongs to the ten important diseases with worldwide 75 million osteoporotic subjects, of whom 30% are postmenopausal women. It affects 25 million people in the United States, primarily postmenopausal women, and is the underlying cause of 1.5 million fractures annually. Approximately 7.8 million Germans older than 50 years are estimated to be affected by osteoporosis, of whom 83% are women, and, around 333,000 fractures are attributed to osteoporosis in Germany each year. Of this total, about 50% are vertebral fractures and 20% each are hip, wrist, and other fractures. Less than 30% of the cases of osteoporosis have been diagnosed, and only 15% of women with osteoporosis receive treatment. Optimal management of this disease, including prevention, early diagnosis and treatment should be aimed at reducing substantially osteoporotic fractures which are mainly responsible for the mortality, morbidity, and cost of medical care. This article provides a short overview about postmenopausal osteoporosis, its diagnosis, prevention and treatment.

PATHOGENESIS

The pathogenesis[6,7] explains the causes, risks and mechanisms, concernig this affection. Bones are dynamic living tissues. During our childhood and teenage years the body builds up bone mass through adulthood. The bone mass is primarily determined by genetics, female and male sex hormones, estrogen and testosterone. However, it may be negatively influenced by factors outlined in Table I. It reaches its peak around the age of 30 years. Thereafter, we steadily lose bone mass. Nevertheless, osteoporosis is not part of the natural process of aging.

As we age, our bones continuously renew themselves. Bone cutter cells, osteoclasts, resorb portions of old bone, and bone builder cells, osteoblasts, follow to form an organic matrix of minerals that become new bone.

Osteoporosis occurs when the balance of this cycle is upset, causing bone to break down faster than it can be replaced by new bone. Our bones become less dense and more fragile as this imbalance progresses.

At menopause, bone remodeling becomes unba-

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This work is dedicated to my wife with love and gratitude.

Received for publication on the 29th July 2008
Accepted for publication on the 1st December 2009

lanced and results in bone loss at each remodeling site. An increase in number of bone turnover sites results in an accelerated bone loss throughout the entire skeleton. Bone loss is most rapid during the first postmenopausal decade. The factors mentioned in Table I may accelerate bone loss independent of the effects of estrogen reduction.

In early postmenopausal years, bone loss averages yearly 1 to 2%. The rate of turnover is greater in cancellous bone, such as the lumbar spine, than in cortical bone.

In most cases, osteoporosis is diagnosed, after bone fractures, often from a small accident or fall. Vertebral, hip, and wrist fractures are common, sometimes even without trauma. Fragility fractures may occur spontaneously. Therefore, osteoporosis is known as a "silent killer" or "silent epidemic disease".

Bone loss leads also to lose height or become kyphosis or stooped as vertebrae particularly in the thoracic and thoracolumbar regions of the spine collapse. Following to body shortening, the ribs may drop downward towards the hips, squashing internal organs and protruding the abdomen; the lungs can not expand properly, breathing can become difficult.

DEFINITION

The word osteoporosis is from the Greek for "porous bones".[7] Postmenopausal osteoporosis is a chronic, progressive disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and decreased bone strenght, leading to increased bone fragility and a consequent susceptibility to fracture.[2] The WHO has estabilished an operational definition of osteoporosis on the basis of bone mineral density (BMD), commonly expressed as T-score.[2] The WHO criterion for BMD is generally accepted as standard.[2,6]

DIAGNOSIS

Anamnesis should include age of menarche, age of menopause and conditions listed in *Table I*. The examination should include measurement of height; a 2 cm height decrease over three years is suspicious of osteoporosis.[8]

In current clinical practice, the diagnosis is made on the basis of either a health outcome (low-impact or fragility fracure) or an intermediate outcome (low BMD). A low-impact fracture occurs after a fall from standing height or less; a fragility fracture happens spontaneously or with no trauma (cough, sneeze, sudden movement).[2,7]

Dual energy X-ray absorptiometry (DXA) of the lumbar spine and proximal femur remains the gold standard for the diagnosis of osteoporosis. This methode is noninvasive, accurate, reproducible, and predictive of short- and long-term fracture risk. It has a reported precision of about 1.0-1.5% at the spine and approximately 3% at the proximal femur. BMD data are reported as T-scores and Z-scores. T-scores represent the number of SDs from the mean BMD values in normal sex-matched young adults.T-scores are used for the diagnosis of normal BMD, osteopenia, or osteoporosis in postmenopausal women *(Table II)*. Z-scores represent the number of SDs from the normal mean value for age- and sex-matched control subjects. A Z-score of –1.0 or lower (for some experts, –2.0 or lower) may suggest the presence of a secondary cause of osteoporosis, although no definitive data supports this hypothesis. Z-scores are used preferentially to assess bone loss in premenopausal women. A Z-score of –2.0 or lower is defined as "below the expected range for age"; a Z-score above –2.0 is "within the expected range for age".[2,6,8-10]

Serial biochemical marker of bone turnover can be measured in serum and urine.[2,11,12] These markers include those associated with bone formation (bone

TABLE I

Risk factors for postmenopausal osteoporosis

Family history of osteoporosis
Hip fracture in a first-degree relative
Advancing age
Premature menopause
Previous fragility fracture
Low calcium intake
Body mass index 19 kg/m2 or lower
Immobility
Lack of exercise, eating disorders, nicotin abuse, alcohol excess
Prolonged glucocorticoid therapy
Malabsorption
Hyperthyroidism, hyperparathyroidism, hypercorticism
Rheumatoid arthritis
Chronic liver disease
Chronic renal disease

TABLE II

WHO definition of osteoporosis based on hip BMD assessed with DXA

Normal	T-score >–1
Osteopenia	T-score between –1 and –2.5
Osteoporosis	T-score <–2.5

alkaline phosphatase, osteocalcin and the type I collagen propeptides) and those associated with bone resorption (urinary calcium, tartrate-resistant acid phosphatase, bone sialoprotein, type I collagen cross-linked-telopeptides, and pyridinium derivates), however its precise role in the clinical management of osteoporosis has not been established.[2,6] Nevertheless, these markers may be useful [6,13] for assessing fracture risk, monitoring response to antiresorptive therapy, and for determining probability to accelerated decrease of bone mass.

The Institute for Clinical Systems Improvement (ICSI) recommends following laboratory testing in patients with newly diagnosed osteoporosis: [2]

Serum creatinine, liver function tests, serum calcium, alkaline phosphatase, serum phosphorus, thyroid studies (thyrotropin and thyroxine), erythrocyte sedimentation rate or C-reactive protein, complete blood cell count, urinary calcium excretion, serum 25-hydroxyvitamin D and serum intact (whole-molecule) PTH. The same Institute suggests in case of Z-score below –1.0 or premature osteoporotic fracture (patients at higher risk of having secondary causes of osteoporosis) following additional tests:[2]

Serum estradiol, tissue transglutaminase antibodies, 24-hour urinary free cortisol and overnight dexamethasone suppression test, and serum and urin protein electrophoresis with immunoelectrophoresis; the serum testosterone (total and free) analysis, mentioned in these guidelines, is indicated in men, and is inapplicable for postmenopausal women.

SCREENING AND PREVENTION

Postmenopausal osteoporosis has a long preclinical course before the onset of fracture.

Therefore, the screening of asymptomatic individuals may be beneficial.[2] The U.S. Preventive

Services Task Force (USPSTF)[14] recommends that women 65 years of age and older should be screened

TABLE III

Summary of USPSTF recommendations for osteoporosis screening in postmenopausal women

All women 65 years of age and older
Women 60 to 64 years of age who are at increased risk for osteoporotic fractures
No studies have evaluated the optimal intervals for repeated screening; a minimum of 2 years may be needed to find a reliable change in BMD; longer intervals may be adequate for repeated screening to identify new cases of osteoporosis
No data are available to indicate the appropriate age to stop screening

routinely for osteoporosis. This routine screening should begin at 60 years of age for women at increased risk for osteoporotic fractures. Among different BMD measurement tests performed at various anatomic sites, BMD measured at the femoral neck by DXA seems to be the best predictor of hip fracture and fractures at other sites. Screening more often than every 2 years is not likely to be helpful, and even longer intervals, such as 5 years, are probably adequate for women with normal BMD (*Table III and IV*). Women with low BMD should receive osteoporosis treatment to prevent further decline in BMD and osteoporosis-related fractures. The USPSTF guidelines 2002 are formulated from evidence-based literature review, and they are essentially in conformance with those of "Dachverband Deutschsprachiger Wissenschaftlicher Gesellschaften für Osteologie" (DVO), Germany, 2006,[15] and Practice Guidelines, USA, 2007.[16]

The risk for osteoporosis and fractures increases with age; the short-term risk for fracture can be estimated by BMD and risk factors; fracture risk can be reduced with treatment; the role of risk factor assessment and different BMD techniques, frequency of screening, and identification of subgroups for which screening is most effective remain unclear. Therefore, many authors emphasize that further research is necessary to determine the benefits and harms of this screening more accurately. The final decision about when and how often to perform BMD testing is ultimately at the discretion of the physician and the patient.[2]

An algorithm based, on 11 clinical factors (age, self-reported health, weight, height, race/ethnicity,

self-reported physical activity, history of fracture after age 54 years, parental hip fracture, current smoking, current corticosteroid use, and treated diabetes) has been found to be useful to predict the 5-year risk of hip fracture among postmenopausal women. This prediction was measured by the area under the receiver operator characteristic (ROC) curves. Also, this methode is at present not unobjectionable; further studies are needed to assess the clinical implication of this calculator.[17]

FRAX[18,19] is a new computer tool for fracture risk assessment developed by the WHO. Individual risk factors, such as age, sex, weight, height and femoral neck BMD if available are entered into the FRAX™ website, along with information on prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term use of glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and daily alcohol consumption. The Web-based FRAX™ algorithm then provides a figure indicating a 10-year fracture probability as a percentage. The FRAX use may be helpful for the treatment decision. Prospective studies are necessary to test the validity of this methode.

The new Clinician's Guide for the Prevention and Treatment of Osteoporosis (www.NOF.org) of the National Osteoporosis Foundation (NOF)[19] pertains to women and men of all races/ethnic origin, 50 years of age and older, who are not currently on a pharmacological agent for the prevention or treatment of osteoporosis. Its main recommendations are outlined in *Table IV*. The fracture prediction algorithm (FRAX) has been calibrated by the NOF, in collaboration with the WHO, for use in the U.S.

A similar approch has also been applied in the UK.[18]

Furthermore, falling is an important risk factor for osteoporotic fracture. This factor is preventable through strength and balance training, hip protectors, and other instrumental devices.[20] Weight-bearing exercise increases BMD at lumbar spine and hip in postmenopausal women, but there is no evidence that it reduces fractures.[2,6,8]

Lifestyle risk factors, like nicotin abuse, alcohol excess, lack of exercise or excessive exercise should be avoided. A regular exercise program including load-bearing exercise and fitness trainig is recommended. Smoking over a long period may modify estrogen metabolism and have toxic effects on osteoblats; cigarette smokers undergo ealier menopause and have more fractures. Excessive alcohol consumption may cause bone loss, because of poor nutrition and increased risk of falls.[2,6,8,16,19]

Finally, calcium and vitamin D supplementation [2,7,19] may prevent bone loss or even mildly increase BMD. Furthermore, vitamin D is necessary to stimulate calcium absorption. According to the consensus statement of the U.S. National Institutes of Health, women should optimize their elemental calcium intake to 1000 mg/d until menopause and increase it to 1500 mg/d thereafter. Recently, the NOF advises at least 1200 mg/d calcium *(Table IV)*. Dietary calcium sources include yogurt, milk, cheese, and other dairy products. The U.S. National Academy of Sciences recommends 400 to 600 IU/d vitamin D intake for all adults older than age 50. The NOF suggests 800-1000 IU/d vitamin D intake for those at risk of deficiency, such as elderly, chronicaly ill, housebound, or institutionalized individuals *(Table IV)*. Natural vitamin D sources include milk, eggs, salt water fish, fish oils, liver, and sun exposure. About 10 minutes of sun exposure 4-6 times per week is required to get the necessary daily intake of vitamin D.

PHARMACOLOGICAL MEASURES

The prevention and treatment of osteoporosis should be aimed at substantially reducing fractures.[1] All postmenopausal women should be considered as potential targets for pharmacological intervention *(Table IV)*. Currently used drugs *(Table V)* include antiresorptive and anabolic agents. All these substances except teriparatide and parathyroid hormone are antiresorptive agents. The antiresorptive drugs reduce bone resorption more than promote bone formation and thereby block bone turnover and loss. The anabolic drugs stimulate bone formation more than reduce bone resorption.[1,2,6,8,10,11,21,22]

Bisphosphonates

Bisphosphonates reduce vertebral and nonvertebral fractures, including hip fractures by 50% to 60% in postmenopausal women.These drugs include risedronate, alendronate, ibandronate, etidronate and zoledronic acid. Risedronate and alendronate are probably the most potent oral bisphosphonates. They are first-line options for osteoporosis management, and therefore are most frequently used. Ibandronate can be administered oral or intravenous, but etidronate

TABLE IV

Summary of the main recommendations in the NOF Guide for men and postmenopausal women age 50 yr and older

Counsel on the risk of osteoporosis and related fractures
Check for secondary causes
Advise on adequate amounts of calcium (at least 1200 mg/d, including supplements if necessary) and vitamin D (800-1000 IU/d of vitamin D for individuals at risk of insufficiency)
ecommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures
Advise avoidance of tobacco smoking and excessive alcohol intake
In women age 65 and older and men age 70 and older, recommend BMD testing
In postmenopausal women and men age 50-70, recommend BMD testing when you have concern based on their risk factor profile
Recommend BMD testing to those who have suffered a fracture, to determine degree of disease severity
Initiate treatment in those with hip or vertebral (clinical or morphometric) fractures
Initiate therapy in those with BMD T-scores -2.5 and less at the femoral neck, total hip, or spine by DXA, after appropriate evaluation
Initiate treatment in postmenopausal women and in men age 50 and older with low bone mass (T-score –1 to –2.5, osteopenia) at the femoral neck, total hip, or spine if 10-yr hip fracture probability is 3% and more or 10-yr major osteoporosis-related fracture probability is 20% and more based on the U.S.-adapted WHO absolute fracture risk model (FRAX; www.shef.ac.uk/FRAX)
Current FDA-approved pharmacological options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, ibandronate, risedronate and zoledronate), calcitonin, estrogens and/or hormone therapy, raloxifene, and PTH 1-34
BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed 2 yr after initiating therapy and every 2 yr thereafter. However, testing after 1 yr may be warranted in certain clinical situations

only oral, and zoledronic acid only intravenous. Oral bisphosphonates should be taken fasting, with a full glass of water and at least 30 minutes (60 minutes with ibandronate) before the first meal, beverage, or medication of the day, avoiding lying flat during this time; thus, the risk of upper gastrointestinal side effects (abdominal pain, dysphagia, gastroesophageale reflux, flatulence) may be reduced. Furthermore, calcium should not be taken at the same day because bisphosphonate interferes with calcium absorption. In cases of difficult or painful swallowing, retrosternal pain and new or worsening heartburn, or severe muskuloskeletal pain, eye inflamation or jaw osteonecrosis, this medication should be stopped; otherwise, oral bisphosphonates are generally well tolerated; if one oral bisphosphonate is not tolerated, occasionally, other oral bisphosphonates may be tolerated; also, intravenous formulations (ibandronate, zoledronic acid) could be indicated in such situations; however, serious atrial fibrillation occurred more frequently in zoledronic acid group. Contraindications to bisphosphonates are hypersensitivity, hypocalcemia, esophageal irritation or stricture and renal insufficiency (creatinine clearance <30-35 mL/min). Therapeutic efficacy of alendronate has been demonstrated for 7 years; of risedronate and zoledronic acid for 3 years. Efficacy and safety beyond these periods have not yet been established.[2,6,10,21,22]

Strontium ranelate

This substance is a new class of medication, a non-radioactive form of strontium, which reduces all osteoporotic fractures in postmenopausal women. It is an alternative to bisphophonates in cases of contraindication or intolerance. Side effects are mild and include diarrhoea and headache.[7,10]

Raloxifene

Raloxifene is a benzothiophene, a selective estrogene receptor modulator, which decreases vertebral fractures by about 50%, but without evidence yet of reduction of fractures at other sites; it is regarded

TABLE V

Pharmacological therapy of postmenopausal osteoporosis

Agent	Dosing regimen	Route of administration
Risedronate	5 mg/d; 35 mg/wk	Oral
Alendronate	5 mg/d; 10 mg/d; 70 mg/wk	Oral
Ibandronate	2.5 mg/d, or 150 mg/mo 3 mg /3 mo	Oral Injection, i.v.
Etidronate	400 mg/d for 2 wk every 3 mo	Oral
Zoledronic acid	5 mg/yr	Infusion, i.v.
Strontium ranelate	2 g/d	Oral
Raloxifene	60 mg/d	Oral
Calcitonin	200 IU/d 100 IU/d	Nasal spray Injection, s.c. or i.m.
Teriparatide	20 µg/d	Injection, s.c.
Parathyroid hormone	100 µg/d	Injection, s.c.

as a second-line option in younger postmenopausal women with vertebral osteoporosis. This substance acts as an estrogen agonist on bone, and as estrogen antagonist on breast, endometrium and cardiovascular system. Raloxifene should reduce breast and endometrium cancer risk and protect against cardiovascular diseases, although this has not yet been demonstrated definitively in clinical trials. Its use in breast cancer women is not recommended at this time. Side effects include hot flushes, leg cramps, and a threefold increase in the relative risk of venous thromboembolism. Efficacy and safety have been determined for up to 40 months.[1,2,6,10]

Hormone replacement therapy

Estrogen alone, or in combination with progesterone decreases significantly vertebral, hip and other fractures in randomized placebo controlled studies. However, the use of these hormones remains controversial. Estrogen therapy alone is associated with an increased risk of stroke and venous thromboembolism. Combination therapy (estrogen and progesterone) increases risk of breast cancer, stroke and coronary heart disease. Considering the risk-benefit balance, hormon replacement therapy is generally not recommended. Nevertheless, some experts believe that this treatment is an appropriate option in younger postmenopausal women; in these rare cases, it is recommended in doses as low as possible for as short a time as possible.[1,2,10,11]

Calcitonin

Calcitonin is a peptide produced by thyroid C cells. This agent is administered as salmon calcitonin nasal spray or in injectable formulation. Its use is limited by the need for subcutaneous or intramuscular injection and because of poor tolerance (nausea, facial flushes, diarrhoea in about 20% of subjects). Nasally administered calcitonin is better tolerated (nasal symptoms and rhinitis in approximately 12% of patients). This drug reduces the rate of vertebral fractures by about 30% by comparison with placebo, but it is not effective for the prevention of nonvertebral or hip fractures. Calcitonin is not considered first-line treatment for osteoporosis because of better efficacy of other medications. Also, the optimal duration of therapy with calcitonin is unknown.[1,2,6]

Teriparatide

This is a recombinant human parathyroid hormon analogue. It is the first anabolic agent which is reserved for treatment of severe cases of postmenopausal osteoporosis (unresponse or contraindication to other drugs, and severe bone loss with preexisting fractures or with high risk for fracture). Teriparatide (PTH) reduces vertebral fractures by 65% and nonvertebral fractures by 53%. Side effects are mild and transient, and include light-headedness, dizziness, nausea, arthralgias, leg cramps, and occasionally an asymptomatic hypercalcemia. In long-term toxicological studies, high dosis of PTH induced osteosarcomas in rats but not in monkeys. Therefore, PTH should not be used in sujects with a history of bone malignancy, Paget disease of bone, unexplained hypercalcemia, or skeletal radiation exposure or those younger than 18 years. Nevertheless, clinical trials with PTH medication for up to 3 years did not demonstrate an increase of tumours in bone or other tissues. The efficacy and

safety of PTH have been assessed for up to 2 years and are unknown thereafter.[1,2,6,10]

The full 1-84 parathyroid hormon peptide has been recently approved for cases with severe osteoporosis who are unable to tolerate or are unresponsive to other treatments.[10]

In addition to pharmacological intervention, all these subjects need an appropriate lifestyle including adequate calcium and vitamin D supplementation, weight-bearing and muscle-strengthening exercises, and elimination of tobacco use and excessive alcohol intake.[2,6,16,19]

Yet, adherence (compliance and persistence) to osteoporosis treatment is low with poor health outcomes. Multiple reasons may be responsible for this like fear of possible side effects, dosing requirements, and unwillingness to therapy. Considering these factors, many trials have been attempted to enhance this adherence, however, with controversial results. Active patient education, including discussion of therapy benefits and feedback of treatmenr effects, use of better tolerated and less frequently dosed medication and trustful relationship between physician and patient should be conducted to improve adherence and reduce fracture rates.[23-25]

CONCLUSION

Postmenopausal osteoporosis is a highly prevalent bone disease, characterized by low bone mass, leading to extensive bone fragility. Major complications are vertebral, hip and other fractures. The management of postmenopausal osteoporosis is based on a correct diagnosis by DXA, avoidance or reduction of factors associated with increeased risk of osteoporosis and fraktures, and an individual nonpharmacological and pharmacological intervention. The targets are the prevention or reduction of fractures.

Acknowledgment

The author would like to thank Dr. Ritá Dessai, Lisbon, and Professor Till Talaulicar, Witten/Herdecke, for reading and improving the manuscript.

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