Preventing Osteoporosis in Postmenopausal Women: Treatment Approaches for Family Practitioners

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Abstract

Osteoporosis is defined as a systemic skeletal disorder that reduces the strength of bone, resulting in an increased risk of fracture. Fractures occur, even if an individual is subjected to minimal trauma such as a fall from own body height. The most common osteoporotic fractures are fractures of the vertebrae, femur neck and distal forearm but other peripheral fractures also play an important role. Osteoporotic fractures are common and will affect at least a third of women over the age of 50 years.[1] It not only leads to significant morbidity, but also increased mortality. Osteoporosis is an age-related disease. In view of expectations that life expectancy is on the rise, the scope of the problem and the burden of the disease will escalate in future. The incidence of osteoporotic fractures in South Africa has not been recorded and most of our calculations are derived from Europe and North America. A false impression has been created that Black South Africans are not prone to osteoporosis. It is true that ethnic Blacks have a lesser tendency to fracture at equivalent bone mineral density (BMD) values than do Europeans. This should however not distract from the fact that many Blacks suffer from the avoidable consequences of osteoporotic fractures. The prevention of osteoporotic fractures is a national priority for all our people. It is therefore obvious that the modern family physician needs to have a basic knowledge of the disease condition and a strategy for the prevention of fractures.

Pathophysiology

A continuous process of remodelling maintains normal bone health and bone strength. Osteoclasts remove old bone (resorption). Osteoblasts replace this with new bone (formation). Under circumstances of normal bone turnover these two processes are closely linked and do not result in any loss or gain of bone. In osteoporosis, bone turnover is increased and resorption is favoured, resulting in loss of bone strength. Natural aging in men and women leads to a loss of about 0.5% in bone mass per year after the age of 35. In women, lack of oestrogen after menopause results in acceleration of resorption and associated bone loss. Pharmacological compounds used in osteoporosis either *inhibit absorption* or *stimulate formation*. Various medical conditions such as hyperparathyroidism or drugs such as glucocorticoids, alcohol or nicotine may influence bone turnover and cause osteoporososis.

Prevention and treatment

In most aspects of life, prevention is better than cure. This is certainly also valid in the field of osteoporosis. Until the first fracture occurs, osteoporosis is a silent disease, without any symptoms or increased morbidity. Once the first fracture has occurred the risk of subsequent fractures doubles with every new fracture, with a resultant increase in morbidity and mortality.[2] The aim of any osteoporosis prevention strategy must be the prevention of fracture. The aim should never be the treatment (or improvement) of a single risk factor, such as bone BMD. As the disease affects such a large proportion of the postmenopausal female population a broad-based approach of all menopausal women seems attractive. This is only possible when using non-pharmacological strategies such as life-style changes and exercise. When using pharmacological strategies, cost-effectiveness, compliance and possible adverse events dictate that a case-specific approach be followed. This means that only the patient at significant risk of fracture must be targeted

Preventative measures for all postmenopausal women

1. Lifestyle changes

Management of the first visit after the last menstrual period (menopause) should always include reference to lifestyle changes that can promote bone health. All possible bone toxic substances should be avoided. The most common bone toxic substance is nicotine derived from cigarette smoking.[3] The excessive intake of alcohol is also a source of bone toxicity.[4] Medical history should search for the presence, and review the use, of any chronic medication toxic to bone, such as high dose systemic glucocorticoids or anticonvulsants.

Inactivity favours osteoclastic activity, with a resultant loss of BMD. Weight-bearing exercise on the other hand stimulates osteoblastic activity, with a resultant gain in BMD. Daily walking as well as specific weight bearing exercise have been found to slow down the normal bone loss associated with aging and should be encouraged in all postmenopausal women.[5] Patients in institutions need special evaluation by a physiotherapist.

Postmenopausal women should be encouraged to implement changes that can reduce the risk of falling.[6] Special attention must be given to all household flooring surfaces as well as the choice of appropriate footwear. Balance can be improved by the correction of

eyesight and treatment of middle ear pathology. Special attention should be given to medication that can promote falls such as antidepressants and tranquilizers. This can in some instances be addressed by reducing the dose to appropriate levels.

2. Diet and supplementation

Caregivers and patients are well aware of the important role of calcium and vitamin D in bone health. The role of a well balanced diet is often overlooked. Bone has an extensive protein matrix that needs to be maintained. Normal muscle mass around bone acts as fracture protection. Normal muscle function is needed to keep balance intact and depends on a well balanced diet, which is often lacking in the older patient. All postmenopausal women should concentrate on a diet rich in fruit and vegetables, with minimum fat intake. Protein supplementation should be considered, especially in the frail, and after fracture.

Normal body homeostasis depends on the maintenance of appropriate serum calcium levels. Bone acts as a reservoir of calcium. In the event of low availability of calcium (such as low dietary intake or absorption), it is mobilised from bone by, amongst others, the effect of parathyroid hormone (secondary hyperparathyroidism). This leads to increased bone fragility. Postmenopausal women need a total recommended dietary allowance (RDA) of 1200 mg of elemental calcium.[7] The best dietary source of calcium is dairy products because of the favourable elemental calcium content, the ability to be absorbed, and cost-effectiveness. Routine dietary supplementation is only needed when dietary sources are inadequate, in patients older than 60 years or in patients on treatment for osteoporosis. Depending on the routine dietary content, daily supplementation with 500 mg of elemental calcium carbonate or citrate will be sufficient. There is no routine blood test that can detect calcium insufficiency, but low levels of 24-hour urinary secretion may be indicative of low calcium intake. Daily supplementation of less than 1 500 mg of elemental calcium will not promote the formation of renal calculi.

The role of vitamin D in bone homeostasis has recently been redefined.[8] It has always been known that vitamin D is essential for calcium absorption and the RDA for vitamin D was set at 400 international units (IU). It is possible to directly determine vitamin D status by measuring the blood level of 25-hydroxyvitamin D and indirectly by observing the inverse relation with parathyroid hormone levels. Using these tools, the optimal 25-hydroxyvitamin D level has been set at 30 ng/ml or greater. In order to achieve this target the RDA has been raised to 800IU. If this is not done, about 60% of older patients will have inadequate levels of vitamin D. This is caused by age-related inability of the skin and kidney to produce the active form of vitamin D. Supplementation is the only option as it is impossible to correct the deficit by normal dietary measures. Vitamin D supplementation has been shown to independently lower the risk of falling in elderly patients.[9] In conclusion, it is recommended that all patients above the age of 60 years receive as supplement 500 mg of elemental calcium and 800IU of vitamin D daily.

Identifying the postmenopausal women at risk of fracture

A case-specific approach is based on the accurate identification of any validated risk factor for future fracture. An integrated risk analysis model has been commissioned by the World Health Organization

(WHO), based on the placebo groups of recent large randomised clinical trials (RCTs), that will express risk as a percentage over 5 or 10 years.[10] The following risk factors are relevant:

1. The presence of a fracture or the history of fracture after age 50 years

Any prevalent vertebral fracture doubles the risk of subsequent fracture. The risk of a subsequent fracture is 20% in the first year after vertebral fracture and is increased by the presence of multiple fractures. Vertebral fractures may be asymptomatic and only detectable by lateral X-ray of the lumbar and cervical spine or by lateral vertebral assessment by dual X-ray absorpsiometry (DXA). The semi-quantitative method of Genant should be used for the evaluation of the vertebral body. This requires at least a 20% decline in the anterior, mid or posterior height of the body

2. BMD estimation by DXA

The diagnosis of osteoporosis historically required the presence of a fracture. Bone densitometry by DXA, available since 1990, has provided us with a non-invasive, reliable and reproducible index that is validated as a good risk factor for fracture.[11] A loss of BMD of one standard deviation doubles the risk of fracture. The diagnosis of osteoporosis using DXA requires a DXA BMD value of 2.5 standard deviations below the peak value for a young Caucasian female (T-score –2.5). Although this definition is useful as an epidemiological tool, it is not a good clinical intervention threshold value, as it is based on a single risk factor for fracture. The need for treatment should also consider other risk factors. A routine DXA examination is advised for all postmenopausal women considered to be at risk of fracture and all women above the age of 65 years.

3. Advanced age

The risk of fracture increases with age for any given BMD value. A BMD T-score of –2.5 at age 75 years implies a greatly increased risk of fracture when compared to the same value at age 50 years.

4. Family history of osteoporosis or fractures in first-degree relatives

The peak bone mass of an individual is largely determined genetically. The history of a fragility fracture in a first degree relative is highly significant of a personal risk of fracture.

5. Low body mass index (BMI)

A low BMI (< 21 kg/m^2) is associated with a low BMD, an increased risk of fracture, and may be indicative of dietary deficiencies.

6. Bone toxins

These include glucocorticoids, nicotine, alcohol and aromatase inhibitors.

7. Secondary causes of osteoporosis

The following conditions are associated with osteoporosis:
a. Osteogenesis mperfecta
b. Haemochromatosis
c. Vitamin D deficiency
d. Cushing's disease
e. Premature menopause
f. Primary hyperparathyroidism
g. Malabsorption syndromes (Celiac disease, Chrohn's disease and total gastrectomy)
h. Multiple myeloma

i.   Lymphoma and leukemia
j.   Anorexia nervosa
k.   Chronic renal disease

No validated model is available that weighs and integrates risk factors to provide clear indications for a case specific approach. The best practice in menopausal women at present would be to classify patients in two groups, namely those with absolute indications and those with possible indications for therapy. (See box 1)

Box 1: Indications for therapy

Absolute indications for prevention/therapy would be any one of the following:
1. DEXA BMD of spine: T score of • ≤ –2.5 at 3 vertebrae L1–L4
2. DEXA BMD of hip: T score • ≤ –2.5 at femur neck or total hip
3. The presence of a fragility fracture irrespective of BMD.

Possible indications for therapy:
1. Low BMD, also called osteopenia (T score < –1 > –2.5) at any of the abovementioned sites plus additional risk factor(s).

The clinical work-up of a patient with osteoporosis

Evaluation entails history taking and physical examination. Biochemical assessment to exclude secondary causes of loss of bone strength comprises:

a.   Raised serum free calcium is an indication of hyperparathyroidism
b.   Raised serum parathyroid hormone (PTH) is indicative of primary hyperparathyroidism.
c.   Low levels of 25-hydroxyvitamin D is indicative of a vitamin D deficiency
d.   A low calcium level in a 24-hour urine sample is indicative of poor calcium intake or absorption
e.   Nutritional status may be reflected in a full blood count
f.   A raised erythrocyte sedimentation rate may raise suspicion of an underlying malignancy
g.   Abnormal serum protein electrophoresis may point to myelomatosis
h.   Paget's disease is suspected if the serum alkaline phosphatase level is raised
i.   Lateral X-rays of the thoracic and lumbar spine are used to exclude prevalent vertebral fractures

Pharmacological agents available for the prevention of fracture

Box 2 summarises the different treatment modalities according to their pharmacological action. The next section will review each of these therapies.

Box 2: Pharmacological classification of preventative therapies

1. Agents that inhibit resorption (anti-osteoclastic activity)
   a.   Oestrogen/Progestin hormone therapy (EPHT)
   b.   Selective oestrogen receptor modulators (SERM)
   c.   Bisphosphonates

2. Agents that stimulate bone formation
   •   Teriparatide (PTH 1-34)

3. Combination of anti-resorption and formation
   •   Strontium Ranelate

1. Agents that inhibit resorption (anti-osteoclastic activity)

   a. Oestrogen/Progestin hormone therapy (EPHT)
   The accelerated bone loss associated with the start of menopause is directly related to the abrupt loss of oestrogen caused by ovarian failure. It is known that this accelerated loss can be prevented by

the use of EPHT. It is also known that EPHT increases BMD in patients with osteoporosis. Results of the Women's Health Initiative Study (WHI) presented the first evidence in a large RCT that EPHT or oestrogen alone (EHT) reduces the risk of all osteoporosis related fractures, even in patients at low risk of fracture. Based on the initial interpretation and publication of the WHI data, the impression was created that any of the advantages of EPHT or EHT were overshadowed by possible adverse events. A later subgroup analysis in 2007 confirmed the presence of a window of opportunity if EPHT is initiated soon after the start of menopause.[12] The initiation of treatment before the age of 60 years pose very little risk and may even offer cardiovascular protection.[13] It is generally not recommended to initiate EPHT after the age of 60 years. The continuation of EPHT after the age of 60 years should take into account the following:

1.   An increased risk of venous thromboembolism (VTE). The excess risk is 18 cases per 10 000 women treated annually and the risk increases with age. The effect is maximal in the first year of treatment. Risk factors include a previous episode of DVT, or a family history of DVT. The risk can be diminished by the use of transdermal EPHT, as this avoids the first-pass effect on the liver.
2.   An increased risk of stroke of approximately 8–12 events per 10000 women annually. This risk is maintained after the first year of treatment. Using lower doses can minimise the risk.
3.   The risk of the diagnosis of breast cancer is slightly increased after five years of EPHT (not with oestrogen alone). It is unlikely that HT causes breast cancer, but HT may modify the behaviour of preexisting breast cancer. This effect increases with duration of treatment, as the natural occurrence of breast cancer increases.

The choice of EPHT for bone protection should take into account that the effect of HT on BMD is rapidly lost after cessation of therapy. EPHT is typically used in the younger patient at risk of fracture, who may also suffer from vasomotor symptoms, and may be replaced by another agent after the age of 60 years. The fact that all menopausal women experience accelerated bone loss at the start of menopause as a result of oestrogen loss begs the intuitive question of whether all menopausal women should not receive oestrogen replacement therapy. It has been calculated that such a population base approach is not feasible and that a case specific approach is far superior.

   b. Selective oestrogen receptor modulators (SERMs)
   The only SERM registered in South Africa for fracture protection is Raloxifene. Various newer SERMs are presently being developed. This complex group of synthetic molecules mimics the good effects of oestrogen on bone and lipids, without stimulating the oestrogen receptors in breast and endometrium.

   Raloxifene was shown to reduce the risk of vertebral fracture by 34–51% in a large RCT, in spite of a very modest increase in BMD.[14] Subgroup reanalysis confirmed that vertebral fracture risk reduction also applies to osteopenic patients. The risk of invasive oestrogen receptor positive breast cancer was reduced by 76%.[15] (Raloxifene© is registered for the prevention of breast cancer in osteoporotic patients in South Africa.) A recent RCT proved that the drug is as effective as tamoxifene in the prevention of breast cancer in non-osteoporotic patients.

   The disadvantage of SERM is that the drug does not treat the vasomotor symptoms of menopause and may cause hot flushes. Present studies have failed to demonstrate a protective effect on

non-vertebral fractures (hip fracture in particular). The RUTH trial failed to show that Raloxifene offers protection against coronary heart disease in patients at high risk.[16] In this trial, patients on Raloxifene were at higher risk of venous thrombotic events and stroke (risk comparable to that posed by oestrogen). Raloxifene is typically used in the patient at risk of vertebral fracture and breast cancer.

c. *Bisphosphonates*

Alendronate and risedronate are registered in South Africa as daily and weekly formulations for the prevention of both vertebral and non-vertebral fractures in menopausal osteoporosis, as well as in glucocorticoid induced osteoporosis, Paget's disease and osteogenesis imperfecta. Zoledronic acid, ibandronate and pamidronate are available as intravenous formulations, but are not yet registered for fracture prevention. These drugs share a common bisphosphonate structure (P-C-P), with different side chains distinguishing the different drugs. Alendronate is the most commonly used drug in postmenopausal osteoporosis.

Oral bisphosphonates are poorly absorbed (less than 1%) and must be taken fasting with a glass of water. The patient must remain upright and fasting for 30 minutes. Failure to do so may cause gastrointestinal side effects or inadequate absorption of the drug.

The bisphosphonates act against bone resorption by inhibiting osteoclast function and reducing bone turnover. Unlike oestrogen and raloxifene, the suppression of bone turnover may last for long periods after cessation of therapy. The level of suppression varies between different bisphosphonates. Bisphosphonates bind tightly to hydroxyapatite and are retained in bone for long periods of time. When bone is resorbed, metabolically active bisphosphonate is again released. This poses a potential risk of oversuppression of bone turnover with possible increased fracture risk, but 10 years of data on alendronate supports at least a maintained effect on BMD without any indications of compromised bone quality

The decision as to when to start bisphosphonate therapy is clear. When to stop therapy is however less clear. The Fracture Intervention Trial Long-term Extension (FLEX) study provides some answers with regards to alendronate. It has been suggested that alendronate can be stopped after five years for a drug-free holiday in patients that exhibit a good increase in BMD, with a T-score of >−3.5 and no additional risk factors for fracture such as a prevalent vertebral fracture.[17] It has further been suggested that these patients be followed-up by serial BMD, to detect possible fast-losers of BMD.

Osteonecrosis of the jaw (OJN) is a condition described as an area of exposed alveolar bone in the mandible or maxilla. A recent analysis of 368 reported cases provides insight into risk factors associated with ONJ.[18] Ninety-four per cent of cases had been treated with intravenous bisphosphonates at much higher doses than used for fracture protection, 84% suffered from multiple myeloma or metastatic breast cancer, and 60% were preceded by tooth extraction or other dental procedures.

Another risk factor is poor oral hygiene. Although the risk of ONJ in the management of menopausal osteoporosis is very rare (1:100 000) patients should be counselled and dental examination

is advised prior to commencing bisphosphonate treatment. Generic forms of Alendronate are available in South Africa, with the advantage of cost savings. The National Osteoporosis Foundation of South Africa has expressed concern about the lack of clinical evidence to support the use of these generic drugs. The issue is further confounded by the fact that Alendronate to date remains on the list of non-substitutable drugs. The bisphosphonates have a proven track record in osteoporosis and are commonly prescribed for the prevention of fractures.

2. *Agents that stimulate bone formation*
Teriparatide (PTH 1-34)
PTH 1-34 is presently the only pure anabolic agent available in South Africa. It is administered daily as a subcutaneous injection. If given in this intermittent fashion, PTH improves bone strength by stimulation of osteoblast activity (in contrast to the opposite effect if high doses of PTH prevail continuously as in hyperparathyroidism). When compared with the antiresorptives, PTH causes greater increases in BMD. It also improves microarchitecture. Vertebral fractures are reduced by 65% and non-vertebral fractures by 40%. Side effects are generally mild and include hypercalcemia and raised uric acid levels, as well as leg cramps, nausea and headaches. Early concerns regarding the induction of osteosarcoma in rats have not been substantiated in humans.

The use of PTH is limited by high costs. NOFSA has provided the following guidelines for the use of teriparatide:[19]

* Severe established osteoporosis as defined by low BMD and at least two prevalent fractures
* Failed antiresorptive treatment as defined by an incident fragility fracture while compliant to antiresorptive treatment for at least 12 months or unacceptable loss of BMD on two occasions while on treatment
* Duration of therapy is presently limited to 18 months and should be followed by maintenance therapy with an antiresorptive drug

The anabolic effect of PTH is blunted by prior treatment with bisphosphonates. It is hoped that the cost of PTH will be reduced in future, in order to be able to use this excellent drug in a less restrictive way.

3. *Combination of anti-resorption and formation*
Strontium ranelate
Strontium ranelate is registered in South Africa for the treatment of menopausal osteoporosis. This agent has a unique double action. Based on bone marker studies, strontium ranelate decreases resorption and increases formation. This action is mediated by the RANK ligand system as well as by a calcium sensing receptor. Two large randomised controlled trials (SOTI and TROPOS), as well as extension studies, have yielded robust data over 5 years.[20] The eight year results are expected soon. Strontium ranelate treatment results in significant increases in BMD and reductions in the risk of vertebral fractures (41%) and hip fractures (36%) in patients with osteoporosis. Significant fracture reduction was also demonstrated in patients with osteopenia, patients with or without prior fracture, patients older than 80 years, and in peripheral fractures. Strontium ranelate is provided as a 2 g powder that is dissolved in water. Adherence to therapy is good without any significant adverse side effects. Strontium ranelate can be considered as first line

therapy for the prevention of osteoporosis related fractures in all postmenopausal patients at risk of fracture.

Monitoring of therapy

Any patient on therapy should be monitored for the occurrence of any asymptomatic incident vertebral fracture. This can be done very effectively utilising VFA by DXA. Monitoring is mostly done by serial BMD, but results should be interpreted with caution. Monitoring intervals should not be shorter than one year (except in patients on high doses of glucocorticoids). It is better to compare vertebral values in cases where changes occur faster than in the hip. In spite of very similar fracture reduction abilities, the various agents have different effects on BMD. Raloxifene has a very modest effect on BMD, whereas strontium ranelate causes a disproportional raise in BMD levels as DXA also measures the strontium salt deposited in bone. Oestrogen, bisphosphonates and PTH have a more predictable effect on BMD. Comparative BMD measurements should take into account inter-device variability as well as inter operative variability. A BMD report should comment on whether any change in BMD satisfies the least value of significant change as calculated for the specific device and operator. The routine monitoring of treatment by biochemical markers of bone turnover is presently not recommended in routine clinical practice. ⴶ

Conclusion

All menopausal patients need to be educated about non-pharmacological ways of improving bone health. It is important to identify menopausal patients at high risk of fracture, as a variety of drugs is available with proven anti-fracture efficacy.

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■ Classifieds