POST-MENOPAUSAL OSTEOPOROSIS: ADVANCES IN PREVENTION

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The prevention of osteoporosis is key in the management of this common condition today. Microarchitectural deterioration is irreversible, and thus it is necessary for us to identify early those individuals at risk for osteoporosis and osteoporotic fracture. We now have a number of treatment options available which enable us to prevent bone loss as well as the development of osteoporotic fractures. Height loss, spinal deformity and fragility fractures which are commonly recognized as signs of aging are now preventable.

Key words: Osteoporosis, aging, menopause, fractures

OSTEOPOROSIS RESEARCH: FOCUS ON PREVENTION

Osteoporosis is a condition in which the bone mass is decreased, in association with microarchitectural deterioration resulting in increased bone fragility and an increased susceptibility to fracture (Fig. 1).[1] This paper will review those options approved by HPB for prevention of bone loss.

At the age of 50, women have a lifetime risk of sustaining a hip fracture of 17.5%, 15.6% for vertebral fractures, and 16% risk for Colles' fracture.[2] This is independent of a woman's **bone mineral density (BMD)**. The lifetime fracture risk increases at lower menopausal BMD values.[3] Men, however, have a lower risk of fracture at all three sites compared with women.[4] The estimated lifetime fracture risk for men is approximately 13.1% for any of the three sites: hip, spine or forearm.[4]

Fig. 1. Codfishing and wedging on lateral spinal xrays.

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Men are protected by achieving a higher peak bone mass. They also do not experience a menopausal equivalent period of androgen deficiency. They have a lower rate of bone loss and also have a shorter life-expectancy, resulting in the lower rates of osteoporotic fracture.[5-8]

Low bone mass and increased bone turnover post-menopause are important risk factors for fracture.[9] Other risk factors include a positive family history, being tall, low body weight <127 lb (57.7 kg) and lifestyle factors including inadequate calcium intake, smoking, excessive alcohol and excessive caffeine intake.[10] Following menopause, bone loss can reach 5-7% per year and this results in significant decreases in BMD over the subsequent 5 to 10 years. Prospective longitudinal studies have documented a strong relationship between low bone mass and increased risk of fracture.[11-13] BMD is the most objectively measurable predictor of osteoporotic fracture risk.[13,14] The risk of fracture doubles for each standard deviation decline in BMD. BMD thus allows the diagnosis of osteoporosis to be made in asymptomatic individuals before a fracture.

Previous fractures of the hip, wrist or spine also significantly increase the risk of future fractures, independent of BMD. The presence of one vertebral fracture increases the risk of future vertebral fractures by five-fold and the risk of future hip fractures by two-fold.[15]

A valuable predictor of fracture can be obtained by combining risk factors for fracture, including current BMD, markers of bone turnover and history of previous fractures.[16] Early intervention can thus be targeted to those at high risk and can prevent further bone loss and reduce lifetime fracture risk in women, particularly those who have never had an osteoporosis fragility fracture.

This article will review strategies which prevent

further declines in bone mass. Strategies which prevent fracture in individuals who have already experienced osteoporotic fracture are beyond the scope of this article.

A number of therapeutic options are now available for the prevention of bone loss. It is important to remember that these are in addition to lifestyle changes. Lifestyle changes include discontinuation of smoking, reducing alcohol intake, as well as embarking on a regular weight-bearing exercise program. Patients should ensure adequate calcium intake primarily from dietary sources. If this is not possible then calcium supplementation ensuring 1000 mg of elemental calcium per day for pre-menopausal women is recommended. Post-menopausal women who are not on estrogen replacement should take 1500 mg of elemental calcium a day. Women who are on hormone replacement require 1000 mg of elemental calcium per day. Both calcium and vitamin D have been shown in randomized controlled trials to increase bone mass and decrease fractures.[17,18]

IDENTIFICATION OF INDIVIDUALS AT RISK

Risk factors for bone loss as well as risk factors for fracture should be reviewed particularly at the time of menopause, before the onset of post-menopausal bone loss. In general, the greater the number of risk factors present and the greater the duration of presence, the higher the risk of subsequent fracture.

National and international guidelines recognize the need to identify individuals at risk for osteoporosis. Targetted bone densitometry screening is recommended for post-menopausal caucasian and asian women who have one or more risk factors for osteoporosis and for all post-menopausal women over age 65. The Osteoporosis Society of Canada guidelines recommend evaluation for individuals with risk factors for fracture as well as those on glucocorticoid therapy or menopausal women considering hormone replacement therapy.[19]

PREVENTION OPTIONS

1. Estrogen Replacement

Hormone replacement therapy (HRT) has been shown to prevent bone loss in post-menopausal women.[20] HRT has been associated with a decrease in the risk of hip, wrist and all non-spine fractures in a prospective cohort study evaluating more than 9,000 women.[21] HRT is also effective in preventing bone loss in elderly women.[22,23] Estrogen can improve muscle strength and neuromuscular function and may also contribute to a decreased risk of falls in elderly women. Estrogen users have been shown to have greater muscle strength than non-users.[24] In the **Heart and Estrogen/Progestin Replacement Study (HERS)**, 2,763 post-menopausal women with coronary artery disease were followed for 4 years. The study was not designed to assess fracture. There were, however, no differences in osteoporotic fractures between the HRT and the non-HRT group. As the incidence of fracture is low in women without osteoporosis and these women did not have to have low BMD to be enrolled in the study, it is difficult to draw conclusions from this prospective trial. The *Women's Health Initiative* will help to clarify the effect of HRT on fracture. Long-term HRT may be associated with an increased risk of breast cancer, as suggested by observational clinical trial data. Selection biases may, however, have contributed to these findings and definitive results are expected upon completion of the *Women's Health Initiative*.

Physicians must review the benefits and disadvantages of HRT in each patient, bearing in mind that all-cause mortality is decreased in women on HRT.[25] Currently HRT is strongly recommended for osteoporosis fracture prevention, due to positive effects on BMD at both cortical and cancellous bone sites. HRT appears to decrease fractures of the axial as well as the appendicular skeleton. Estrogen also has additional extra skeletal benefits and thus is recommended for osteoporosis fracture prevention.

2. Selected Estrogen Receptor Modulators

SERMs act through estrogen receptors and have estrogen agonistic effects on bone and LDL-cholesterol but estrogen antagonistic effects on breast and endometrium.

Tamoxifen is a first generation SERM and has estrogen agonistic effects on bone, with partial estrogen agonistic effects on the endometrium, leading to hyperplasia of the endometrium.

Raloxifene is the first of the second generation SERMs. Raloxifene is a benzothiophene derivative and has been shown to prevent bone loss and vertebral fractures. In addition, it has been shown to decrease the incidence of breast cancer without stimulating the endometrium.[26,27] In a randomized placebo-controlled trial, raloxifene was effective in

decreasing both total and LDL-cholesterol over 24 months.[28] In this trial raloxifene was effective in increasing BMD.[28] This trial evaluated 601 post-menopausal women randomly assigned to receive 30 mg, 60 mg or 150 mg of raloxifene or placebo over 24 months. Patients were supplemented with 400-600 mg of elemental calcium. Serum osteocalcin and excretion of urinary N-telopeptide, a marker of bone resorption, decreased significantly from baseline. The 60 mg dosage of raloxifene resulted in increase in BMD by 2.4% in lumbar spine and 2.4% in total hip, compared to the placebo arm. The 60 mg dosage of raloxifene also decreased LDL-cholesterol by 10.1% from baseline and total cholesterol by 6.4% from baseline. Raloxifene was well-tolerated, and there was no increase in endometrial thickness or breast pain.[28] An increase in the incidence of hot flashes was seen in phase II clinical trials. Raloxifene appears to have a comparable increase in the risk of venous thromboembolic events to HRT. Preliminary data also show a reduction in the risk of breast cancer development. Raloxifene thus is a valuable option in the prevention of post-menopausal osteoporosis.

Raloxifene has been approved for the prevention and treatment of post-menopausal osteoporosis.

3. Bisphosphonates

Bisphosphonates are another valuable alternative to HRT in the prevention of osteoporosis. Bisphosphonates are synthetic analogues of pyrophosphate. They bind to the calcium-phosphorus bone surface in the skeleton and inhibit osteoclast-mediated bone resorption.[29] Cyclical **etidronate** was evaluated for the prevention of bone loss in the early post-menopausal period.[30] Healthy post-menopausal women with BMDs between -2 and +2 standard deviations from young normal individuals were treated for 2 years with cyclical etidronate; 54 women were treated with etidronate 400 mg a day for 14 days followed by calcium for the subsequent 11 weeks. This double-blind randomized placebo-controlled trial showed a statistically significant increase in spine BMD at 2 years. An increase of 2.9% ($p < 0.02$) was seen in the treatment group in the spine. The femoral neck BMD increased by 2.02% ($p < 0.03$). There was evidence of inhibition of bone turnover, with suppression of the biomarkers including urinary cross-laps and osteocalcin. The serum osteocalcin decreased during the first year of treatment and subsequently normalized at 24 months. Etidronate was well-tolerated and effective in preventing vertebral and femoral bone loss in women within the first 5 years following menopause.[30] A larger study conducted by Pouilles confirmed these findings.[31]

Alendronate is a potent amino bisphosphonate which has been evaluated in the prevention of osteoporosis. A double-blind randomized placebo-controlled trial of 1,609 women who had been post-menopausal for at least 6 months and were below age 60 were followed.[32] Women treated with 5 mg of alendronate demonstrated an increase in the spine BMD of 3.5% ±2% compared to baseline and a 1.9%±0.1% increase at the hip compared to baseline. Compared with placebo, the increment in the lumbar spine was 5.24% and in the hip 3.3%. There was no significant difference between alendronate 5 mg compared with the conjugated equine estrogen and medroxyprogesterone acetate arm with respect to BMD with 2 years of treatment.[32] Alendronate was very well-tolerated, with a safety profile similar to that of placebo.[32] A 3-year double-blind randomized placebo-controlled trial evaluated 447 post-menopausal women.[33] BMD increased in comparison to baseline at the lumbar spine, femoral neck and trochanter by 1% to 4%. The placebo group lost 3% to 4% of BMD in the spine, femoral neck or trochanter.[33] A decrease in bone turnover was also seen, with a decrease in the markers of bone resorption by 3 months and a decrease in the markers of bone formation by 6 to 12 months. Bone biopsies demonstrated normal bone histology in patients treated with alendronate. Patients had all received calcium supplementation at 500 mg per day, unless dietary calcium intake was greater than 1000 mg per day. The placebo group did have evidence of bone loss in both the lumbar spine and hip sites, indicating that calcium supplementation is inadequate in preventing bone loss following menopause.[33] Alendronate is effective at 5 mg per day in preventing bone loss in the lumbar spine, hip and total body, with a safety and tolerability profile comparable to placebo.[33] Alendronate has been approved for the prevention and treatment of post-menopausal osteoporosis.

Risedronate, a third generation bisphosphonate, has been evaluated in the prevention and treatment of post-menopausal osteoporosis. Risedronate was evaluated in 383 early post-menopausal women randomized to receive 2.5 mg or 5 mg of risedronate or placebo in addition to calcium daily for

2 years.[34] The mean lumber spine T-score at baseline was -.4 in all treatment groups. At 24 months, risedronate 5 mg significantly increased BMD versus placebo by 4.5% in lumber spine, 3.3% in femoral neck and 4.3% in femoral trochanter. Risedronate was well-tolerated and the incidence of GI adverse events was comparable to placebo.[34]

Risedronate in combination with estrogen versus estrogen alone has been evaluated in the prevention of bone loss in post-menopausal women;[35] 524 women were randomized to receive risedronate 5 mg plus conjugated estrogens .625 mg/day for 12 months or placebo plus conjugated estrogen .625 mg/day for 12 months.[35] All individuals received 1000 mg/day of calcium and those with intact uteri were supplemented with medroxyprogesterone acetate. At 12 months there was a statistically significant increase in BMD in the femoral neck in the combination arm versus conjugated estrogen alone. Again risedronate was found to be well-tolerated.[35]

Risedronate is approved for both prevention and treatment of post-menopausal osteoporosis.

4. Other Agents

Salmon **calcitonin** is a valuable *treatment* option in post-menopausal osteoporosis and has been approved for this indication. It has not yet been approved for the *prevention* of osteoporosis.

Other agents being evaluated for prevention of post-menopausal osteoporosis include **tibolone**, a tissue-specific synthetic steroid with estrogenic, progestogenic and androgenic effects. Tamoxifen may also be effective in preventing post-menopausal bone loss.

CONCLUSION

Osteoporosis prevention requires identification of individuals at risk for bone loss and osteoporotic fracture. Lifestyle changes in addition to a number of preventive options are effective in arresting bone loss and development of osteoporosis. It is necessary to identify early the individual at risk for fracture, as we can now prevent osteoporosis and its significant morbidity and mortality.

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