

Osteoporosis in Relation to Menopause

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Abstract

With an ageing population in Singapore, it is anticipated that postmenopausal osteoporosis and related fractures will be an increasingly important health issue in the coming decades. Oestrogen replacement therapy has a long history of use to treat postmenopausal problems including osteoporosis. The availability of other potent agents such as bisphosphonates, calcitonin and selective oestrogen receptor modulators has enriched the therapeutic options. This article reviews the evidence for the choice of appropriate agents, and strategies to prevent and treat postmenopausal osteoporosis.

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Introduction

Singapore has a rapidly ageing population. In 1990, only 6% of the population was above the age of 65 years but this percentage of elderly citizens will rise rapidly to 17% by the year 2030. As Singaporean women achieve longer life expectancy and live a greater portion of their lives in the postmenopausal years, it is anticipated that the problem of postmenopausal osteoporosis and related fractures will rise dramatically.

In Singapore, as well as the rest of Asia, osteoporotic fractures are increasingly common. Hip fracture admissions in Singapore showed a linear increase between 1991 and 1998.¹ After the age of 60 years, women had significantly more hip fractures than men. The hip fracture rate in Singapore amongst women between 50 and 54 years was estimated to be 12 in 100,000 of the population, but this rose steeply to 1352 in 100,000 for women aged 75 years and above.

The impact of osteoporotic fractures is tremendous. It affects the financial, physical and psychosocial aspect of the patient as well as the family and community. An analysis of patients who had sustained osteoporotic hip fractures in Singapore² demonstrated a mortality risk of 26% in the first year. Amongst the survivors, the quality of life can be profoundly affected. Nine per cent were bedridden and 24% were wheelchair bound. Additionally, osteoporotic fractures can also be associated with chronic disabling

pain, with subsequent effects in the mental and emotional lives of affected patients. In the United States today, over 10 million individuals have osteoporosis. The financial expenditure for treatment of osteoporotic fractures is estimated at US\$10 to US\$15 billion annually. This does not even include the loss of earnings or productivity of the individual or the caregiver.³

Physiological Basis of Postmenopausal Osteoporosis

Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of fracture. Bone strength is dependent on 2 features: bone density and bone quality. Although bone mineral density (BMD), as measured by absorptiometry, is the most accurate measure of bone mass and thereby represents the strongest predictor of future osteoporotic fracture, it does not take into account the bone quality.⁴ Bone quality refers to the architectural integrity of the bone, and is less amenable to non-invasive quantification.

After linear growth ceases during the mid to late teens, bone remodelling serves to keep the bone dynamic and elastic while maintaining an adequate source of calcium for extracellular purposes. This involves the osteoclasts and osteoblasts in a constant cycle of bone resorption and new bone formation. During the reproductive years of a woman, bone is constantly being remodelled but the amount of bone laid down corresponds to that which was removed,

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maintaining a relatively stable equilibrium. Following menopause, loss of oestrogen results in loss of inhibition of osteoclastic activity. More bone remodelling units are being activated, with more bone resorption than new bone formation taking place. The net effect is a reduction in bone mass and this is the fundamental basis of postmenopausal osteoporosis.

Rationale for Oestrogen Replacement

Hormone replacement therapy (HRT) in the postmenopausal woman works on the simple principle of replacing the oestrogen, which is no longer being produced by the atrophic ovaries, thus reversing the many different processes associated with the loss of oestrogen. One of this is the very important effect that oestrogen has on reducing bone resorption. Indeed, oestrogen has been used for the prevention and treatment of postmenopausal osteoporosis for a long time. However, up to recently, most of the evidence is derived primarily from observational, case-control or cohort studies.

Some of the early studies highlighted the importance of oestrogen on bone metabolism and how postmenopausal oestrogen replacement may affect the risk of osteoporosis.

Lindsay et al⁵ studied 100 women after oophorectomy for periods of up to 12 years. There was a significant reduction in bone mineral content of the mid-radius and the third metacarpal of women who were not on oestrogen replacement as compared with those who were treated with oestrogen (mestranol, mean dose 23 mg/day) at the end of the 12 years. Only 4% of the 58 women who received oestrogen lost stature as compared to 38% of the 42 women who received placebo.

An early, though small, prospective randomised controlled trial reported by Nachtigall et al⁶ studied 168 patients for 10 years. Women were randomly assigned to either oestrogen plus cyclical progestin or placebo. Women who were not on hormonal treatment lost about 10% of their BMD, as measured by single photon absorptiometry of the radius, compared to an increase of 8% in those who started HRT within 3 years of menopause. There was no difference in BMD in those who started HRT beyond 3 years of menopause. In addition, among the 128 women who completed the study, there was only one fracture in the HRT group compared to seven fractures (hip, spine, radius) in the placebo group.

In a double-blind, placebo-controlled trial, Lufkin et al⁷ reported that bone density improved by 3% after 1 year of treatment with transdermal oestrogens. There was a two-third reduction in the occurrence of new vertebral fractures among osteoporotic women treated with transdermal oestrogen just after 1 year, although this was not the primary end point of the study.

Although BMD is the most useful tool we have at the present time to determine the fracture risk, it is but one of many determinants of fracture risk. Oestrogens may prevent bone loss by one mechanism and prevent fractures in other ways. For example, it may improve the muscle strength and coordination thus reducing the number of falls. It is uncertain if change in BMD during hormone replacement is enough to explain the strong protective effect of oestrogen on fracture risk.

Using incidence of fractures as an end point, Komulainen and co-workers⁸ investigated the incidence of new non-vertebral fractures during HRT in 464 early postmenopausal women (age range, 47 to 56 years) without osteoporosis for a period of 5 years. The estimated risk of new non-vertebral fractures among women treated with HRT was 0.29 (95% confidence interval, 0.10-0.90). The fracture sites involved mainly the radius, ankle and humerus. None involved the hip, which has more impact on the patient's quality of life. This perhaps could be attributed to the relatively young population in the study.

Grady et al⁹ performed a meta-analysis of HRT trials. The conclusion from 6 case-control and 5 cohort studies was that ever-use of oestrogen was associated with a reduced risk of hip fracture (relative risk, 0.75; 95% confidence interval, 0.68-0.84) when compared with never-use of oestrogen. The relative risk of hip fracture for women currently receiving oestrogen was considerably lower than for ever-users.

The methodology of the non-randomised and controlled studies mentioned above was subject to selection bias, such as the "healthy user effect", which can distort the conclusions drawn from such studies. Indeed, one of the limitations in recommending oestrogen replacement for osteoporosis treatment has been that until recently, there is little evidence from prospective randomised clinical trials.

The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial¹⁰ is a prospective, randomised, placebo-controlled trial which studied the use of premarin and premarin/progestin combinations in postmenopausal women. The study showed an increase in BMD by about 6% in the spine and 2.8% in the hip after 3 years, but there was no significant reduction in fracture rates. However, osteoporotic fracture was not the primary end point of this study and the trial was conducted in relatively young women (age range 45 to 64 years) who have a low incidence of osteoporotic fractures.

More recently, the Danish Osteoporosis Prevention Study,¹¹ a prospective, controlled, comprehensive cohort trial involving 2016 women for a duration of 5 years, published rather interesting results. There were two main study arms: a randomised arm and non-randomised arm. Results of the preliminary study (duration of 5 years)

showed reduction in overall fracture risk (relative risk, 0.61; 95% confidence interval, 0.39 to 0.97) and the risk of forearm fractures (relative risk, 0.24; 95% confidence interval, 0.09 to 0.69) in the group randomised to HRT. In the non-randomised arm, the overall fracture risk reduction of patients on oestrogen replacement was of borderline statistical significance (relative risk, 0.45; 95% confidence interval, 0.22 to 1.05) while the forearm fracture risk was significantly reduced (relative risk, 0.61; 95% confidence interval, 0.22 to 0.90).

We await the results of other prospective controlled studies, such as the “Women’s Health Initiative” presently conducted in the United States, to add to the body of evidence regarding the role of oestrogen replacement in prevention of fractures secondary to postmenopausal osteoporosis.

It should be highlighted that besides prevention of osteoporosis, oestrogen replacement therapy in the postmenopausal women has numerous other indications, the primary being the improvement in quality of life. For a woman who has symptoms of menopause like hot flushes, palpitations, mood instability and vaginal dryness, oestrogen replacement would improve the quality of life by alleviating these symptoms. It lowers the low density lipoprotein (LDL) level and increases the high density lipoprotein (HDL) levels. This may then reduce the risk of cardiovascular events. Although the recent Heart and Estrogen/Progestin Replacement Study (HERS)¹² and the Estrogen Replacement and Atherosclerosis Study¹³ suggested that women with established cardiovascular disease may not stand to benefit from oestrogen replacement, the role of oestrogen replacement in the primary prevention of coronary events in women without established coronary artery disease appears to be promising.¹⁴ It also has a beneficial effect on the genitourinary system and may reduce the risk of Alzheimer’s disease and colorectal cancer.^{15,16} Overall, oestrogen replacement therapy has the potential to improve both the quality as well as the quantity of life of postmenopausal women.

Limitations of Oestrogen Replacement Therapy

Studies have repeatedly shown that the two main reasons for a patient’s failure to embark or continue on HRT are the return of cyclical or unscheduled bleeding and the fear of breast cancer.¹⁷

The Collaborative Group on Hormonal Factors in Breast Cancer¹⁸ is a re-analysis of 51 epidemiological studies involving 52,000 women with breast cancer and over 100,000 without. It was estimated that the cumulative incidence of breast cancer among women 50 to 70 years of age is about 45 per thousand among non-HRT users. If the same cohort of 1000 takes HRT for 5 years, the cumulative

excess risk is just 2 cases per 1000 (95% confidence interval, 1 to 3). For 10-year and 15-year exposures, the cumulative excess is 6 per 1000 (95% confidence interval, 3 to 9) and 12 per 1000 (95% confidence interval, 5 to 20), respectively. After the cessation of HRT, the relative risk of breast cancer returns back to baseline 5 years later, irrespective of the duration of exposure. If cancer was diagnosed, there was a tendency for the tumour to be less advanced at diagnosis and there was no increase in the mortality from breast cancer.

Though the data remain largely reassuring for treatment of shorter than 10 years, constant media dramatisation of the association between HRT and breast cancer risk has resulted in this risk being perceived out of proportion to the true risk.

Timing and Maintenance of Oestrogen Replacement Therapy

The previous recommendation was that oestrogen replacement should be commenced as soon as menopause was diagnosed to maximise protection against osteoporosis. This was based on the rapid bone loss observed at menopause and the expectation that even if bone loss resumed after discontinuing oestrogen, the delay in bone loss would reduce fracture risk. However, Lindsay and co-workers¹⁹ showed that after withdrawal of oestrogen, the bone loss is quite rapid and the rapid rate of decline lasts for about 3 to 4 years. Ettinger and Grady²⁰ also showed that once a woman stops HRT, bone loss accelerates and BMD rapidly falls to the level of a group that has never used postmenopausal oestrogen.

Cauley and co-workers examined the relative risk for fracture among older postmenopausal women in the Study of Osteoporotic Fracture,²¹ a prospective cohort study of 9704 women aged more than 65 years old. The study found that current oestrogen use was associated with a significant reduction in the relative risk of wrist fractures (relative risk, 0.39) and all non-spinal fractures (relative risk, 0.66). The initiation of oestrogen soon after menopause among current users was associated with the lowest risk of hip fracture (relative risk, 0.29), wrist fractures (relative risk, 0.29) and all non-spinal fractures (relative risk, 0.50) when compared to women who had never used oestrogens.

Observational data indicate that women may be able to start HRT 10 years after menopause and achieve a BMD almost equal to women using HRT continuously since menopause. Quigley and colleagues²² have shown that initiation of HRT to elderly osteoporotic women resulted in a 5% to 10% increase in spine BMD. On the other hand, when HRT was discontinued, bone loss began anew at a rate approximating immediate perimenopausal loss. Maximal increases in BMD are thought to occur during the

first few years of oestrogen treatment.

The clinical implication is that while greatest benefit is seen when oestrogen replacement is started soon after menopause, if this treatment is discontinued even after more than 10 years of use, it would have little substantial effect on the subsequent risk of fractures. The protective effect of oestrogen is seen mainly in current users, and it is never too late to start on oestrogen replacement therapy, even many years after menopause.

Dose and Response

For many years, it has been widely accepted that the minimum effective dose for preventing bone loss is 0.625 mg of conjugated equine oestrogens or the equivalent in other oestrogen products.

There is increasing evidence, however, that suggest lower doses of oestrogens may be adequate for many women. Oral estradiol, 0.5 mg; transdermal oestradiol, 0.025 mg; esterified oestrogens, 0.3 mg; and conjugated oestrogens, 0.3 mg, have been shown to halt bone loss.²³⁻²⁶ One small study using an oestradiol vaginal ring that did not raise systemic oestrogen levels above the menopausal range reported a 2.1% increase in BMD of the forearm, compared with a 2.7% loss in non-users.²⁷ It is possible that in the elderly, a small increase in oestrogen could produce a benefit in bone density, whereas the same dose would not be so effective during the rapid bone loss phase of early menopause.

Lower doses of oestrogen for bone protection have the potential benefit of reducing the adverse side effects. This can be a crucial factor to oestrogen compliance.¹⁷ Besides fewer side effects, the lower dose of oestrogen did not produce a significant increase in triglycerides.²⁵ However, there is a need to examine if this dose would be cardioprotective.

Diagnosis and Assessment

According to the recommendations of the WHO task force, osteoporosis is defined as a BMD that lie 2.5 standard deviations or more below the average for the young healthy female population.²⁸

Bone Mineral Density

Bone densitometry, with coefficients of variation in the range of 1% to 2%, is one of the most precise measurements in clinical medicine.⁴ Prospective studies have shown that the risk of fracture increases with lower prevailing BMD. For each standard deviation decrease in BMD, fracture risk approximately doubles. The preferred site for diagnostic assessment is the hip. This emphasis on the hip measurement arises from the relative clinical importance of hip fracture and the strength of the relationship between hip BMD and hip fractures.²⁸

Universal screening by BMD, however, has not been shown to be cost-effective at present but should be applied to individuals identified by the presence of one or more strong risk factors.

There is a lack of uniformity in the presentation of BMD values, in part due to technical difference in equipment, differences in normal ranges, and the complexity of the computer output. Uniform criteria should be used for diagnostic purposes utilising the T-score or other standardised approaches and appropriate reference ranges.

Other Techniques

The other techniques, like qualitative ultrasound and computed tomography, for assessing skeletal status are less validated than absorptiometry.

Biochemical indices of skeletal turnover for assessment of fracture risk and monitoring of treatment may be useful but further research is needed to determine its precise value in clinical practice.

Strategies

Besides the usual indications for BMD measurement, we recommend that BMD should be performed for postmenopausal women who are considering the use of oestrogen replacement for prevention or treatment of osteoporosis as the results may be critical to help them make the correct choice of treatment.

Patients with osteoporosis defined as BMD values more than 2.5 standard deviation (SD) below the young normal mean should be offered the appropriate anti-resorptive treatment,²⁹ which includes agents such as oestrogen, bisphosphonates, calcitonin and selective oestrogen receptor modulators (SERMs) such as raloxifene. Choice of drug is often based on the physician's preference and the patient's medical background.

Those with BMD values between -1 and -2.5 SD (osteopenia) should consider oestrogen replacement therapy to reduce the risk of developing osteoporosis, particularly if they have other concurrent indications for use of oestrogen replacement. If they are undecided or unsuitable, BMD should be repeated after a period of time to assess the rate of bone loss.

In the group of women who have normal BMD, are relatively young and have no background risk factor for osteoporosis, the risk of fracture is low. In order to have an impact on future fracture rates, these women would have to be on oestrogen replacement therapy for a long period of time. Advocates of prevention emphasize early intervention, especially in those who enter menopause with risk factors for osteoporosis, for example low body weight, family history of osteoporosis, smoking, etc, to reduce lifetime fracture risk. However, the issue of breast cancer risk

clouds the strategy of long term or lifetime oestrogen replacement therapy. If these women have no menopausal symptoms or have other indications for HRT, it may be prudent to reinforce a healthy lifestyle, modify risk factors for osteoporosis and defer intervention till a later date. Even at the age of 60 to 65 years, if they do decide to begin HRT, they can still obtain significant benefit, without the concern about having to consider prolonged use.

Alternatives: Bisphosphonates, SERMs, Calcitonin, Calcium and Vitamin D Supplementation

When the use of oestrogen replacement is not appropriate, there are several other options for the prevention and treatment of osteoporosis.

Bisphosphonates

These are synthetic compounds that bind to hydroxyapatite and inhibit bone resorption. The second-generation bisphosphonates, like alendronate and risedronate, inhibit osteoclast-mediated bone resorption at doses that have little or no effect on osteoblast-mediated bone mineralisation. They are currently one of the most potent agents that we have for the treatment of osteoporosis.

The Fracture Intervention Trial^{30,31} is a large, randomised, blinded, placebo-controlled trial assessing the effect on alendronate on risk of fracture. Women aged between 55 and 81 years with low femoral neck BMD were enrolled in 2 study groups based on the presence or absence of an existing vertebral fracture. In the group with existing vertebral fractures, there was a 50% reduction in vertebral fractures (both clinically apparent and morphometric). The risk of any clinical fracture, the main secondary end point, was lower in the alendronate than in the placebo group (relative hazard, 0.72; 95% confidence interval, 0.58 to 0.90). The relative hazards for hip and wrist fracture for alendronate versus placebo were 0.49 (95% confidence interval, 0.23 to 0.99) and 0.52 (95% confidence interval, 0.31 to 0.87).³⁰ In the group without pre-existing vertebral fractures, alendronate significantly increased the BMD at all sites and reduced clinical fractures by 14% although this end point was not significant (relative hazard, 0.86; 95% confidence interval, 0.73 to 1.01). Alendronate reduced clinical fractures by 36% in women with baseline osteoporosis at the femoral neck.

One drawback with alendronate is that its dosing regimen can be rather tedious. As its absorption profile is poor, it needs to be taken on an empty stomach with plain water. One of the side effects is oesophageal irritation and patients need to be advised against lying down again after taking the medication. The introduction of a once weekly dosing of alendronate (70 mg/week) may help in increasing the compliance with the medication.

Intravenous bisphosphonate therapy such as pamidronate³² is an interesting and useful new development. The use of an intravenous regime ensures that the drug is delivered to the bone. It is given over 2 hours every 3 months and can result in fever and myalgia lasting 24 to 48 hours. It is important to ensure adequate calcium and vitamin D intake before infusion as it can cause hypocalcaemia especially in patients with chronic renal failure.

There may be some synergy, which may be achieved by the combination of oestrogen and alendronate, even though both are anti-resorptive agents. A recent randomised trial demonstrated that combination therapy with oestrogen/progestogen and alendronate in women with osteoporosis increased the BMD of the spine and femoral neck more than either therapy alone.³³

Selective Oestrogen Receptor Modulators (SERMs)

SERMs are molecules designed to have oestrogenic effects in certain tissues of the body such as the bone and the blood vessels, but with little oestrogenic effects on other tissues such as the breast and endometrium. One of the goals of these agents is to maximise the beneficial effect of traditional oestrogen replacement such as the prevention and treatment of osteoporosis, while minimising the deleterious effects on the breast or endometrium.

The Multiple Outcomes of Raloxifene Evaluation (MORE)³⁴ is a multicentre, double-blind, randomised, controlled trial involving 7705 postmenopausal women. It reduced the risk of vertebral fractures in osteoporotic postmenopausal women with or without pre-existing fractures by about 30%. Of particular interest is that the trial also found a 76% reduction in the risk of breast cancer in women treated with raloxifene compared to placebo.³⁵ While this was a secondary end point and awaits further confirmation, it certainly holds great attraction for women who are concerned about the issue of breast cancer and oestrogen replacement therapy. It also has a mildly beneficial effect on the lipid profile.

It should be highlighted that raloxifene does not relieve hot flushes, vaginal dryness or any of the menopausal symptoms associated with oestrogen deficiency. Therefore, it is not a good option for recently postmenopausal women with menopausal symptoms who seek oestrogen replacement for improvement in quality of life, in addition to osteoporosis prevention.

Calcitonin

Calcitonin is another option for treating osteoporosis. It is a peptide normally secreted by the C cells of the thyroid. It inhibits osteoclast and decreases bone resorption.

In the Prevent Recurrence of Osteoporotic Fractures

Study,³⁶ there was a reduction in the risk of recurrent vertebral fractures by 35% with the 200 IU dose of nasal calcitonin. The subjects were postmenopausal women with pre-existing osteoporotic fractures studied over a period of 5 years. Calcitonin also has an analgesic effect. It comes in the form of a nasal spray, and therefore may not be suitable for patients with allergic rhinitis.

Calcium and Vitamin D

Regardless of the choice of therapeutic agent, adequate calcium and vitamin D intake is essential. The current recommendation for calcium intake in Singapore is 700 to 1000 mg/day.²⁹

Randomised trials studying the effect of calcium monotherapy have shown a reduction in vertebral fractures. These studies involved mainly elderly women. However, fracture was not a primary end point of these studies. It was also noted that the effect of calcium was greatest in the first year of treatment.³⁷

In a landmark study by Chapuy et al,^{38,39} more than 3000 women aged 69 to 106 years were randomly allocated to 1.2 g of elemental calcium plus 800 IU of vitamin D daily or placebo. There was a 32% reduction in non-vertebral fractures and 43% reduction in hip fractures in the patients receiving active treatment at 18 months. At the end of 3 years of treatment, these figures were reduced to 24% and 29%, respectively.

Dawson-Hughes and colleagues⁴⁰ also found an increase in BMD and reduction in non-vertebral fractures in subjects given 500 mg of elemental calcium plus 700 IU of vitamin D per day. Most of this difference occurred in the first year of treatment.

Vitamin D supplementation is not necessary for the young. However in the elderly, vitamin D deficiency is common and supplementation would be useful in reducing the risk of non-vertebral fractures.

Future Therapy

All therapies currently available are anti-resorptive, which limit the magnitude of the increase in bone mass. Parathyroid hormone (PTH) is one agent that stimulates bone formation and thereby has a potential for larger BMD increases. Instead of bone loss observed with chronic elevation of PTH in primary hyperparathyroidism, PTH given intermittently and in small doses has been shown to produce a large increase (10%) in spinal BMD after 2 years.⁴¹ Recently, it has been reported that in 1637 women with prevalent vertebral fractures, 21 months of therapy with PTH reduced vertebral fractures by 65% and non-vertebral fractures by 54%.⁴²

Monitoring of Treatment

For patients who are taking oestrogen replacement, calcitonin or SERMS, repeat BMD test may be performed every 2 to 4 years to evaluate the treatment. For patients on bisphosphonates, repeat BMD examinations are recommended at intervals of 1 to 2 years.⁴³

In using BMD to measure response of treatment, it is useful to keep in mind the principle of regression to the mean; individuals who have measurements that differ from the mean for a population tend to have repeat measurements that are closer to the mean. This tendency is greatest for measurements that are farther from the mean. This explains why most who lost the most BMD in the first year also gained the most the next year of treatment. Therefore, effective treatments for osteoporosis should not be changed because of loss of BMD during the first year of use.⁴⁴

Conclusions and Recommendations

With an ageing population and sedentary lifestyle, postmenopausal osteoporosis is becoming an increasingly important problem. Regardless of whether a woman uses oestrogen replacement therapy or other treatment options, it is important to maintain a healthy lifestyle that includes adequate calcium intake and regular weight-bearing exercise. Exercise is also essential in preserving muscle tone and balance, which is important for preventing the falls that are responsible for most fractures.

Oestrogen replacement therapy is indicated for the *prevention* of osteoporosis in postmenopausal women at risk. Although prospective data supporting its use for the *treatment* of established osteoporosis remain weak, vast numbers of controlled studies have indicated its probable therapeutic benefit. The availability of other anti-resorptive agents such as bisphosphonates, SERMs and calcitonin has enriched our options, and allowed us to tailor the most appropriate therapy for the patient, taking into account the risk profile, medical history and preferences of the individual.

REFERENCES

1. Koh L K, Saw S M, Lee J J, Leong K H, Lee J, National Working Committee on Osteoporosis. Hip fracture incidence rates in Singapore 1991-1998. *Osteoporos Int* 2001; 12:311-8.
2. Leong K H. Osteoporosis—the need for a paradigm shift. *Ann Acad Med Singapore* 1998; 27:100-4.
3. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement 2000 March 27-29; 17:1-45.
4. Grampf S, Genant H K, Mathur A, Lang P, Jergas M, Takada M, et al. Comparisons of noninvasive bone mineral measurements in assessing age-related loss, fracture discrimination, and diagnostic classification. *J Bone Miner Res* 1997; 12:697-711.
5. Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomized women. *Lancet* 1980; 2:1151-4.
6. Nachtigall L E, Nachtigall R H, Nachtigall R D, Beckman E M. Estrogen replacement therapy I. A 10-year prospective study in the relationship to osteoporosis. *Obstet Gynecol* 1979; 53:277-81.
7. Lufkin E G, Wahner H W, O'Fallon W M. Treatment of postmenopausal

- osteoporosis with transdermal estrogen. *Ann Intern Med* 1002; 117:1-9.
8. Komulainen MH, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, et al. HRT and vit D in prevention of non-vertebral fractures in postmenopausal women: a 5-year randomized trial. *Maturitas* 1998; 31:45-54.
 9. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; 117:1010-37.
 10. Marcus R, for the PEPI Trial Investigators. Effects of hormone replacement therapies on BMD: Results from the Postmenopausal Estrogen and Progestin Interventions Trial. *J Bone Miner Res* 1995; 10:276.
 11. Mosekilde L, Henning BN, Ole HS, Stig PN, Peder C, Vestergaard P, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women—results of the Danish Osteoporosis Prevention Study. *Maturitas* 2000; 36:181-93.
 12. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; 280:605-13.
 13. Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, et al. Effect of estrogen replacement on the progression of coronary artery atherosclerosis. *N Engl J Med* 2000; 343:522-9.
 14. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; 335:453-61.
 15. Purdie DW. Consequences of long-term hormone replacement therapy. *Br Med Bull* 2000; 56:809-23.
 16. Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, et al. Effect of estrogen during menopause on risk and age of onset of Alzheimer's disease. *Lancet* 1996; 348:429-32.
 17. Ravnika V A. Compliance with hormone therapy. *Am J Obstet Gynecol* 1987; 156:1332-4.
 18. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997; 350: 1047-59.
 19. Lindsay R, Hart DM, MacLean A, Clark AC, Kraszewski A, Garwood J. Bone response to termination of estrogen treatment. *Lancet* 1978; 1:1325-7.
 20. Ettinger B, Grady D. Maximizing the benefits of estrogen therapy for prevention of osteoporosis. *Menopause* 1994; 1:19-34.
 21. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black B, Cummings SR, et al. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1995; 122:17-23.
 22. Quigley ME, Martin PL, Burnier AM, Brooks P. Estrogen therapy arrests bone loss in elderly women. *Am J Obstet Gynecol* 1987; 156:1516-23.
 23. Ettinger B, Genant HK, Steiger P, Madrig P. Low dosage micronized 17beta-estradiol prevents bone loss in postmenopausal women. *Am J Obstet Gynecol* 1992; 166:479-88.
 24. Evans SF, Davie MW. Low and conventional dose transdermal estradiol are equally effective at preventing bone loss in spine and femur at all postmenopausal ages. *Clin Endocrinol* 1996; 44:79-84.
 25. Genant HK, Lucas J, Weiss M, Akin M, Emkey R, McNaney-Flint H, et al. Low dose esterified estrogen therapy: effects on bone, plasma estradiol concentration, endometrium and lipid levels. *Arch Intern Med* 1997; 157:2609-15.
 26. Recker RR, Davies KM, Dowd RM, Heaney RP. The effect of low dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. *Ann Intern Med* 1999; 130:897-904.
 27. Naessen T, Berglund L, Ulmsten U. Bone loss in elderly women prevented by ultralow doses of parenteral 17beta-estradiol. *Am J Obstet Gynecol* 1997; 177:115-9.
 28. Genant HK, Cooper C, Poor G, Reid I, Ehrlich G, Kanis J, et al. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. *Osteoporos Int* 1999; 10:259-64.
 29. Practice Guidelines from the Osteoporosis Society (Singapore). Singapore: Osteoporosis Society, 1998.
 30. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996; 348:1535-41.
 31. Cummings SR, Black DM, Thompson DE, Applegate WB, Connor EB, Muslinor TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. *JAMA* 1998; 280:2077-82.
 32. Peretz A, Body JJ, Durmon JC, Rozenberg S, Hotimski A, Praet JP, et al. Cyclical pamidronate infusions in postmenopausal osteoporosis. *Maturitas* 1996; 25:69-75.
 33. Tiras MB, Noyan V, Yildiz A, Yildirim M, Daya S. Effects of alendronate and hormone replacement therapy, alone or in combination, on bone mass in postmenopausal women with osteoporosis: a prospective, randomized study. *Hum Reprod* 2000; 15:2087-92.
 34. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999; 282:637-45.
 35. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999; 281:2189-97.
 36. Chesnut CH, Silverman S, Andriano K, Genant HK, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporosis fractures study. PROOF Study Group. *Am J Med* 2000; 109:267-76.
 37. Reid IR. The roles of calcium and vitamin D in the prevention of osteoporosis. *Endocrinol Metab Clin North Am* 1998; 27:389-98.
 38. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994; 308:1081.
 39. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992; 327:1637.
 40. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age and older. *N Engl J Med* 1997; 337:670.
 41. Hodsman AB, Fraher LJ, Watson PH, Osthie T, Stitt LW, Adachi JD, et al. A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 1997; 82:620-8.
 42. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344:1434-40.
 43. McGarry KA, Kiel DP. Postmenopausal osteoporosis: Strategies for preventing bone loss, avoiding fracture. *Postgrad Med J* 2000; 108: 79-89.
 44. Cummings SR, Palermo L, Browner W, Marcus R, Wallace R, Pearson J, et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. *JAMA* 2000; 283: 1318-21.