Review Article: The role of hormone therapy in the treatment of osteoporosis

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Keywords: osteoporosis treatment, hormone therapy, DXA-scan

Abstract
The concerns raised by the findings of the Women’s Health Initiative study resulted in many practitioners no longer considering the use of menopausal hormone therapy for the treatment of osteoporosis. Subsequent re-analyses of this study, recent publications on the use of lower doses and different modes of delivery of hormone therapy, and data suggesting that certain women will receive longer-term fracture prevention even with short-term use have resulted in a reappraisal of the use of oestrogen and oestrogen plus progestin therapy for the prevention and treatment of osteoporosis. These issues are discussed, and based on these more recent analyses it is suggested that menopausal hormone therapy could still be considered a first-line option for osteoporosis prevention and treatment in certain patients.

Peer reviewed (Submitted: 2009-11-11, Accepted: 2010-03-12) JEMDSA 2010;15(1):49-51

Introduction
The use of menopausal hormone therapy (HT) to prevent bone loss has long been considered one of the major indications for its use. Following the publication of the Women’s Health Initiative (WHI) study in 2003 the role of HT in the prevention of chronic diseases such as osteoporosis and cardiovascular disease has been questioned. Subsequently the majority of guidelines emanating from menopause societies recommended that the primary role of HT, be it oestrogen only (E) or oestrogen with progesterin (E/P), should be the alleviation of the symptoms of early menopause and that it should be used in the lowest effective dose for the shortest possible time. In the years since the publication of the WHI results there have been publications from sub-studies and re-analyses of the WHI as well as publications on the use of different products and different modes of delivery of oestrogen and progestin. The current status of HT therefore needs to be re-evaluated in the light of these more recent publications.

Hormone therapy and bone density
Oestrogen administration, both with and without a progestin, results in an increase of bone mineral density (BMD). In the Postmenopausal Oestrogen/Progesterin Intervention (PEPI) trial,” a double-blind placebo-controlled study, women were randomised to receive placebo, conjugated equine oestrogen (CEE) or a combination of CEE and medroxyprogesterone acetate (MPA). By 36 months those patients on placebo had lost an average of 2.8% of spinal BMD and 2.2% of hip BMD. Those compliant with any active regimen gained approximately 5.1% BMD in the spine and 2.3% in the hip.

Hormone therapy and prevention of fractures
The WHI study was the definitive study demonstrating the anti-fracture efficacy of HT. There was a reduction in both vertebral and hip fractures: the relative risks (RR) for fracture in patients on E/P compared to placebo was 0.65 (CI 0.46-0.92) and 0.67 (CI 0.47-0.96) for spine and hip respectively. It is important to realise that the patients in the WHI study were not necessarily osteoporotic or considered at high risk for fracture, adding more weight to the significant reduction of fractures, particularly in the hip, where many studies using other osteoporotic agents had been unable to show such a reduction.

However, the prevention of fractures was not a primary endpoint of the WHI study. The primary endpoints were myocardial infarction and coronary death, and the initial publication reported a significant increase in these events. In a later publication, after adjudication of events, the increase in coronary events did not reach statistical significance. The results of the WHI study also showed an increase in thrombotic strokes, venous thromboembolism and breast cancer (not significant), as well as a reduction in colorectal cancer. The authors of the publication on osteoporosis concluded, however, that despite the significant reduction in fractures there is no place for the use of HT in the treatment of osteoporosis in asymptomatic patients. This conclusion was based on the use of an index the authors termed the global index of health risk, which was purported to estimate the balance of health versus risk. The authors concluded that the overall health risk was greater with the use of HT in patients at low, moderate and high risk for fracture.
A further problem with the use of HT for the prevention or treatment of osteoporosis is that long-term use would be necessary if the population at most risk for fracture, namely elderly patients, is to be protected against fracture. The need to continue with HT on a long-term basis is supported by the findings of numerous studies that suggest that the bone protective effects of HT are lost soon after discontinuation. The most compelling data comes from an analysis of the National Osteoporosis Risk Assessment (NORA) study. This study investigated bone mineral density and one-year fracture risk in relation to duration of hormone therapy (HT) use and time since discontinuation in 170,852 women. As regards density, current users had the highest T-scores. Women who had stopped HRT more than five years previously, regardless of duration of use, had T-scores similar to those who have never used HRT. Current users of HT had a 21 to 29% lower risk for fracture over one year than non-users. This protection was lost within five years of discontinuation. Increased duration of therapy did not appear to confer any greater protection. Studies published by Lindsay and Ascott-Evans have supported the finding of rapid loss of the density gained whilst on HT when the therapy is discontinued.

**A re-appraisal of hormone therapy use**

There remain many proponents of the use of HT for osteoporosis. The International Menopause Society (IMS) supports a re-evaluation of HT for the prevention and treatment of osteoporosis and state that HT can be considered a first-line therapy in women under 60 years. The global index of health risk as used in the WHI study is not a validated health risk assessment tool. In addition, the overall health risks in the WHI study apply to a specific population of women whose average age was 63 years. These risks may therefore not be applicable to a younger population of women. A re-analysis of the combined results of the E only arm and the E/P arm of the WHI study investigated cardiac risk in patients aged 50 to 59 years at initiation of HT and also considered the effects on cardiac events with early intervention as opposed to late intervention with HT. This re-analysis indicated a trend towards a lower risk with early intervention, but this did not reach statistical significance. What did reach statistical significance, however, was a 30% lower overall mortality compared to placebo in the group of women starting HT within 10 years of the onset of menopause. The cardioprotective effect of HT with early intervention has also been shown in a re-analysis of the Nurses’ Health Study.

The issue of rapid bone loss after cessation of therapy is not yet fully resolved as not all studies have shown accelerated loss of density after discontinuation of therapy. In the PEPI study, 495 women had bone density measured for the three years of the study and then annually for four years thereafter. The mean annual loss after stopping HT was 1.01% in the spine and 1.04% in the hip. There was no significant difference as to annual loss when comparing the women who had been on HT and those who had not. Christiansen, in a three-year study of 94 women, showed a 3.7% increase in bone mineral content (BMC) in the forearm in patients taking HT compared to a loss of 5.7% in those on placebo. After completion of the study the annual loss was similar in both groups. Similar long-term protection was found in a study of 347 women who had participated in four placebo-controlled HT trials. Follow-up DXA examinations were performed at five, 10 and 15 years after the end of the studies. BMD remained 5% higher in previous users of HT and the RR for fracture in this group was 0.48 (CI 0.26-0.88). An interesting finding in this study was that there were fast bone losers in both the placebo group and the group who had been on HT and that the rate of bone loss affected fracture risk. The fast bone losers in the placebo group had the highest risk of fracture. The fast bone losers in the group who had been on HT had a risk equal to the slow bone losers who had been on placebo. The group with the lowest risk of fracture was the HT group who remained slow bone losers after completion of HT.

The risk profile of HT may also be less with lower doses and different modes of delivery. The findings of the WHI study and other prospective studies on HT, such as the HERS studies, resulted in a reassessment of dose, type of hormone use and mode of delivery. Risk for thrombosis appears to be low or not increased at all with the use of transdermal oestrogen. Transdermal therapy has advantages over oral therapy as regards its effect on surrogate markers of cardiovascular risk. Given the necessary size and duration of a prospective study that would compare oral and transdermal delivery systems on cardiac events, it is highly unlikely that such a study will take place. However, the Kronos Early Oestrogen Prevention Study (KEEPS), a five-year prospective study, will allow comparison of oral and transdermal HT on carotid intima-media thickness and coronary artery calcium. Recruitment started in 2005 and will close out in 2010. Protection against bone loss occurs with the use of lower doses of oestrogen than those used in the WHI study. Even ultra-low dose transdermal oestrogen in the form of a 14 µg patch has been shown to protect against bone loss in the majority of patients. The use of less androgenic progestins may have a more beneficial cardiovascular profile. Prospective fracture prevention studies using lower doses of oestrogen, comparing different modes of delivery and using different progestins would allow a more conclusive comparison of the risk versus benefit profile of HT compared to other drugs used to treat osteoporosis. Given the results of the studies discussed above that suggested that after cessation of HT the rate of bone loss differs from person to person, further studies are needed on the use of markers of bone resorption to identify fast bone losers. This may allow for patients who have been treated with HT in early menopause to be switched to alternative treatment modalities which will result in ongoing protection against bone loss and fracture.

**Tibolone and osteoporosis**

No discussion of the place of hormone therapy in the treatment of osteoporosis is complete without considering the place of tibolone. Tibolone is a selective tissue oestrogenic activity regulator (STEAR) which exerts its effect on bone via its 3α- and 3β-metabolites that
stimulate the oestrogen receptor. The Long-Term Intervention on Fractures with Tibolone (LIFT) study, 23 a placebo-controlled randomised controlled study on women between the ages of 60 and 85, showed a significant reduction in vertebral (RR 0.55, CI 0.41-0.74) and non-vertebral (RR 0.74, CI 0.58-0.93) fractures. The study was terminated prematurely due to an increase in stroke risk in the tibolone group (RR 2.19, CI 1.14-4.23). The authors concluded that tibolone was effective in preventing vertebral fractures in postmenopausal women but that due to the risk of stroke it should not be used in elderly women and women with risk factors for stroke.

Conclusions

Based on the data from the more recent WHI re-analyses, HT is safe when used in early menopause. Therefore, in the younger symptomatic patient, where the primary indication is the alleviation of the symptoms of menopause, HT will prevent bone loss and decrease the risk of fractures and should therefore be considered as one of the first-line therapies in these patients. As the primary indication for the use of HT in these patients is symptom relief the therapy would be used for as long as needed for this indication. When used correctly soon after the onset of menopause, the risks are minimal. In the asymptomatic patient, the issue is not as clear. However, HT can be considered along with drugs such as strontium ranelate, the bisphosphonates and raloxifene in the younger asymptomatic patient considered to be at high risk for fracture. The side effect and risk profile of each drug would need to be considered and discussed with each patient to allow for individualised therapy. Where HT is used, be it in the symptomatic or asymptomatic patient, when the therapy is terminated alternative therapies need to be initiated in patients still considered to be at high risk for fracture. The duration of use will be determined by a regular reassessment of the balance of benefit and risk. Those patients who do not need alternative treatments should have follow-up bone density assessments so that fast bone losers can be identified and treated appropriately.

Conflict of interest

Dr Davey has received honoraria and/or travel grants from the following companies:

Adcock Ingram, Lilly, MSD, Novartis, Novo-Nordisk, Servier, Sonofi-Aventis, Wyeth.

References