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REVIEW

Assessment and hormonal management of osteoporosis

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ABSTRACT

Postmenopausal osteoporosis is a frequent health issue in women. Because osteoporosis-related fractures cause a significant increase in mortality and morbidity, it is clinically important to identify as soon as possible women at increased risk for future fracture so that preventive measures can be instituted. At the beginning of menopause, evaluation of the subsequent risk of fracture is not so easy. Most screening tools fail to accurately identify those women who will fracture within the next 10 years. A history of a prior fracture and low bone mineral density are the only major consistently found predictors for the risk of fracture. On the other hand, it is no longer a question whether menopause hormone therapy is efficient not only to prevent postmenopausal bone loss but also the incidence of fragility fracture. Over the last years, utility of menopause hormone therapy for the prevention of osteoporosis has been questioned due to safety concerns. In light of the most recent reports on a more favorable benefit/risk balance than was initially claimed in early postmenopausal women, this needs to be reconsidered. Prevention of bone loss in those women with a moderate or slightly high risk of fracture is likely a strategy to reduce fracture risk in older women. Menopause hormone therapy must be considered as a true primary preventive therapy more than an anti-fracture therapy at an age when the risk of fracture is likely much lower than later in life. Only thereafter should other anti-osteoporotic medications be discussed in women still at high risk for fracture.

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Introduction

Postmenopausal osteoporosis is one of the most frequent health issues related to estrogen deficiency. The subsequent decrease in bone mineral density (BMD), along with a greater risk of fracture, is the direct consequence of the increase in bone remodeling and bone loss which occurs from the beginning of menopause. It is estimated that about one out of three women will experience an osteoporosis-related fracture after menopause. Accordingly, at the age of 50 years, the lifetime risk of hip fracture is 15% and of vertebral deformities is about 25%[1]. It is therefore essential for postmenopausal women to receive appropriate guidance for the prevention and management of the risk of fracture. BMD is a widely used tool for diagnosing osteoporosis and for identifying women at increased risk for fracture[2,3]. However, many fractures occur in women with normal or only a slightly reduced BMD value and a given *T*-score translates to very different fracture risk depending on the age of the woman and the presence of additional risk factors[4,5]. Different screening tools have been developed with the objective of providing an estimation of the absolute risk of fracture which could be used to decide whether or not a patient has to be treated. The FRAX® is the most widely used model and has been validated in a large number of osteoporotic cohorts[6,7]. However, several studies have shown that it is of limited value to predict the subsequent 10-year risk of fracture at the time of menopause[8]. In the Danish Osteoporosis Prevention Study (DOPS), FRAX underestimated the absolute risk of fracture at each level of *T*-score in early postmenopausal women[9]. In the MENopause et OS (MENOS) study, it was also shown that the FRAX model had a poor sensitivity for fracture prediction within the first 10 years after menopause, performing no better than a single measurement of hip BMD[10].

There can no longer be any doubt that menopause hormone therapy (MHT) is efficient not only to prevent early postmenopausal bone loss but, more importantly, the incidence of fragility fracture. Moreover, there is epidemiological evidence that early preservation of bone mass results in a decrease in fracture risk. Nevertheless, over the last decade, use of MHT has considerably declined following the publication of the Women's Health Initiative (WHI) results due to safety concerns[11]. MHT is therefore no longer universally recommended as a first-line treatment option in women at risk of fracture[12]. This recommendation needs now to be reconsidered, especially in early postmenopausal women. Subsequent reanalyses and further trials have challenged the initial conclusions of the WHI and it is clear that the individual benefit/risk balance of MHT is very dependent on the type, doses, and duration of MHT as well as the individual risk profile for each woman.

The aim of this short review is to discuss the specificities of the risk of fracture in early postmenopausal women as

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well as the role of MHT for primary prevention in this population.

Bone changes during menopause

Menopause represents a crucial period in the changes in bone mass seen with aging. Estrogen deficiency causes a bone-remodeling imbalance with greater increase in the level of osteoclast-mediated bone resorption than osteoblast-mediated bone formation, leading both to an acceleration of bone loss and alterations in the microarchitecture of bone[13,14], especially at the trabecular level. The Study of Women's Health Across the Nation has highlighted the bone changes that occur throughout menopause[15,16]. Two major conclusions can be drawn from this study. First, the increase in bone resorption activity together with accelerated bone loss can occur before the last menstruation period. Bone resorption begins to increase about 2 years before the last menstruation period, continues to increase for about 2 years after the last menstruation period, and then declines and remains relatively stable from 4 to 6 years after the last menstruation period. Several studies[17–20] had already reported an early acceleration of bone loss at the menopause transition but there was uncertainty surrounding the timing and magnitude of bone loss due to methodological issues or the small size of the studied population. Second, there are large interindividual variations in the time and magnitude of bone remodeling and early bone loss, depending upon the physical characteristics of the women but probably also genetic factors which modulate the bone tissue sensitivity to estrogen deficiency or other factors. For instance, body size is a major determinant of postmenopausal bone loss and numerous studies have shown a greater BMD and lower rate of bone loss after menopause in overweight and obese women as compared to normal weight women[21,22].

Risk of fracture at menopause

All of these considerations need to be taken into account when screening for the risk of fracture at menopause. There are also some specific issues surrounding the risk of fracture in early postmenopausal women (i.e. within the first 10 years of menopause), which need to be kept in mind.

These issues could be summarized as follows:

- The 10-year risk of fracture is generally only moderate in these early postmenopausal women and most fractures occur in osteopenic women[23]. However, this population includes a large number of women and fractures generate considerable costs and loss of quality-adjusted life years in this age group, a consideration that supports screening for early detection of osteoporosis.
- The distribution of fracture is different amongst younger compared to older women[24]. Several cohort studies have reported a greater incidence of peripheral fractures, and especially wrist fractures, compared to that of vertebral or hip fractures within the first 10 years of menopause. In a sample of 3078 randomly selected women aged between 47 and 56 years residing in Kuopio, Finland, 295 fractures were recorded over a mean follow-up period of 3.6 years. Wrist, ankle (malleolar), and rib fractures were the more frequent fractures, representing more than 55% of all observed fractures[25]. In the MENOS study which included 2650 early postmenopausal women aged on average 53 years at baseline, wrist, ankle, and rib fractures represented more than 65% of the first incident fractures which were observed over a 10-year follow-up period[10]. In the National Osteoporosis Risk Assessment survey that evaluated the risk of osteoporotic fracture in over 200,000 women, the incidence of wrist/forearm fractures among women aged 50–59 years was seven-fold higher than that of hip fracture and represented about 50% of all fractures in this age group[23]. Nevertheless, it was shown that the magnitude of increase in both absolute and relative risks for future fractures was similar for younger and older postmenopausal women who had experienced a wrist fracture after menopause.
- Several studies have shown the quite poor sensitivity of clinical risk factors to predict low bone mass in early menopause that highlights the predominant impact of genetic factors on the BMD variance. Accordingly, about 50% of the women who begin menopause with an already low BMD have no clinical risk factor[26–28]. Some of them cannot be identified at the time of menopause. Family history is often non-contributory (due to the relatively young age of parents) and the risk of falling is negligible in younger healthy postmenopausal women compared to older women.

Validity of screening tools

Altogether, this raises the question of the validity of screening tools such as FRAX or the Garvan fracture risk calculator that have been developed and validated in older population cohorts and, mainly, for the prediction of hip fracture. Very few studies were performed for the purpose of identifying the best strategy to predict the risk of fracture in early postmenopausal women. The National Osteoporosis Risk Assessment survey evaluated 18 potential risk factors in 91,562 postmenopausal women between the ages of 50 and 64 years to predict the risk of osteoporotic fracture over 3 years[29]. Prior fracture, a low peripheral BMD *T*-score, and self-reported fair/poor health status were the most important determinants for short-term fracture within 3 years. The DOPS is a prospective, multicenter trial whose original objective was to investigate the effect of MHT on prevention of osteoporotic fractures. A total of 2006 healthy early postmenopausal women aged on average 50.5 years at baseline were included. The MHT arms were stopped as a consequence of the results from the WHI study; 872 women who were enrolled in the non-MHT arm of the study were followed over a 10-year follow-up period. Whereas fracture risk in this age group remains relatively low with an incidence of any first fracture of 9% over 10 years, it was 76% higher than that expected from the FRAX model[9]. In the MENOS study, a large cohort of 2650 early postmenopausal women was

followed for an average 13-year period of time. Similarly to the DOPS, the incidence of fracture was about 8% over 10 years. A low vertebral and/or hip BMD and a history of a prior fragility fracture were the only significant and independent factors associated with the risk of fracture. There was no significant improvement in fracture prediction with the FRAX model over the discriminative value of the single hip BMD measurement[10]. In an analysis of the WHI data from women aged 50–64 years not taking medications likely to influence BMD, it was shown that the US Preventative Services Task Force strategy, which is based on a FRAX threshold of at least 9.3%, had a poor sensitivity for discriminating women who did and did not subsequently experience fracture[30]. No alternative FRAX threshold was found associated with a better predictive value. Thus, none of the screening strategies based on the identification of clinical risk factors evaluated in this population was substantially better than chance alone in predicting the risk of fracture.

Clinical predictors of risk of fracture

Overall, at the time of menopause, there are only a few clinical predictors of the 10-year risk of fracture. A history of a prior fracture is consistently found as the major predictor of the risk of fracture. A low BMD is also no longer discussed as a strong risk indicator for fracture risk. Interestingly, it is between the age of 50 and 60 years that the gradient of risk for hip fracture is the highest as compared to that in older women[31,32]. This might be due to the increased influence of extra-skeletal risk factors with aging, such as liability to falls. Therefore, greater reliance has to be placed on BMD in younger women, whereas, in the elderly, risk will be better assessed by clinical risk factors, many of which increase in frequency with age. Finally, several prospective studies have shown that markers of bone turnover are able to predict osteoporotic fracture risk[33–35]. This might be of particular value at the beginning of menopause where the bone remodeling activity level is at its highest. Modulating the magnitude of bone loss as well as the deterioration of trabecular architecture may ultimately contribute to the subsequent risk of fracture. In the Os des FEmmes de LYon (OFELY) study, the combination of a low BMD with a prior fracture and increased bone turnover markers allows one to identify the majority of women who will have an incident fracture over a follow-up period of 4 years[36,37]. At baseline, about 50% of the women who sustained a fracture had a BMD within the osteopenic range. It was shown that the risk of fracture in those women with one or more of the three risk factors (a *T*-score value between –2 and –2.5, a prior fracture, or a bone turnover marker in the highest quartile) was almost as high as that in osteoporotic women, irrespective of their risk factor profile. In contrast, the risk of fracture in osteopenic women without any of these three risk factors was close to that in normal women. This pattern was even more apparent in women younger than 65 years of age.

Prevention of fractures

Although fractures mainly occur among elderly women, it is clinically important to identify women at increased risk for future fracture so that preventive measures can be instituted. Prevention not only of bone loss but also of deterioration of the bone microarchitecture[14] in younger postmenopausal women, when rates of bone loss are the highest, is likely an effective way to prevent or delay fractures in postmenopausal women as they age. There are currently no specific clinical guidelines for the management of bone loss in early postmenopausal women. MHT has been shown to reduce bone turnover, prevent postmenopausal bone loss, and decrease fracture risks. In the WHI, MHT use was associated with a significant lower rate of fracture which resulted in a saving of five hip fractures per 10,000 women per year but also, and more importantly, of 18 wrist fractures and a total of 47 fragility fractures per 10,000 women per year[38,39]. A systematic review and meta-analysis demonstrated a significant decrease of fracture risks with MHT use, particularly in women younger than 60 years of age (relative risk 0.55; 95% confidence interval [CI] 0.44–0.68)[40]. Furthermore, this is the only anti-osteoporotic therapy that has proven its efficacy whatever the location of fracture, the age of the woman, or the underlying level of bone mass, even in women at low risk for fracture[38,39].

However, MHT utility for the prevention of osteoporosis has been questioned due to safety concerns. Following the release of the WHI data, many societies and health organizations claimed that MHT was dangerous and recommended the use of hormones only when vasomotor symptoms are severe and cannot be controlled by alternative therapies. Since then, much has been written about the WHI. Several reanalyses and new prospective studies have provided reassurance that the reported MHT-associated adverse events occurred largely in older women. Also, use of transdermal preparations has been shown to be less likely to increase the risk of venous thromboembolism, stroke, and coronary heart disease than oral preparations[41–44]. The harmful effect of MHT on the breast was also found to be influenced by the type of MHT and duration of treatment. Among women with no prior use of MHT before entering the WHI, there was no difference in breast cancer rates over time between the women assigned to placebo or conjugated equine estrogens (CEE) + medroxyprogesterone acetate. In addition, there was a striking contrast between the results with CEE alone as compared to CEE + medroxyprogesterone acetate[45]. Even though the initial paper reported only a trend toward reduced breast cancer with a hazard ratio (HR) of 0.77 (95% CI 0.59–1.0), further analyses and extended follow-up confirmed that use of CEE alone was associated with decreased breast cancer incidence (HR 0.77; 95% CI 0.62–0.95; $p = 0.02$) but also breast cancer mortality (HR 0.55; 95% CI 0.33–0.92) over a median 11.8 years of follow-up[46]. Several observational studies have also reported a lower risk of breast cancer in women treated with estrogen alone as compared to combined MHT. Moreover, three European studies[47–49] suggested that micronized progesterone or dydrogesterone in

association with estradiol might be associated with a lower risk of breast cancer than synthetic progestins.

Even more importantly, the all-cause mortality in women aged 50–59 years from the pooled cohort of the two WHI randomized trials during the intervention phase was significantly reduced (HR 0.61; 95% CI 0.43–0.87)[50]. This reduction in mortality was still present at 18 years even though it failed to meet statistical significance (HR 0.87; 95% CI 0.76–1.00).

This observation has led the International Menopause Society, together with several international menopause societies, to launch consensus statements that highlight the fact that benefits are more likely to outweigh risks if MHT is initiated before the age of 60 years or within 10 years after menopause[51]. It also emphasizes that MHT is the only therapy available with randomized controlled trial-proven efficacy of fracture reduction in postmenopausal women with *T*-score values in the normal to osteopenic range.

Conclusions

It is thus time to reconsider the use of MHT for primary prevention and treatment of osteoporosis in early postmenopausal women. Moreover, it should be recalled that, to date, osteoporosis is a chronic disease that cannot be cured. Long-term preventive strategies tailored to younger postmenopausal women at increased risk for fracture are needed. One strategy to reduce fracture risk in older women would be to prevent bone loss in women who begin menopause with a moderate or slightly higher risk of fracture due to low bone mass and/or clinical risk factors for fracture. Because the choice of the first treatment option should be made in consideration of a more global long-term strategy, MHT should be the preferred option whenever possible in the absence of contraindication. It must be considered as a true primary preventive therapy to maintain bone mass and the quality of bone, more than an anti-fracture therapy at an age where the risk of fracture is likely much lower than that later in life. When MHT cannot be used, raloxifene might be a valuable alternative option in asymptomatic women at risk of spine fracture, especially if there are concerns about breast cancer risk[52]. It is only in women with a true contraindication to estrogens and a very high risk of fracture that other anti-osteoporotic drugs (bisphosphonates, denosumab, teriparatide) should be discussed in early postmenopausal women. Thereafter, their use could be considered when the individual benefit/risk balance of MHT (or raloxifene) might not be considered as favorable as at the beginning of menopause in the women who are still at high risk for fracture. Moreover, it is in older women at high risk of fracture, especially of hip fracture, that their efficacy has mainly been demonstrated.

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