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The role of menopausal hormone therapy in the management of osteoporosis

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ABSTRACT

It is now 75 years since Fuller Albright published his observations on the causal relationship between menopausal estrogen deficiency and osteoporosis. He introduced the concept of menopausal hormone therapy (MHT) for the prevention of osteoporosis. Most of his remarkable observations have stood the test of time and scientific scrutiny. Unfortunately, the uptake of MHT for the prevention of osteoporosis and related fractures remains very low. This can be ascribed to several factors. The availability of new drugs, supported by randomized clinical trials, has increased therapeutic options and created the impression that all new drugs are better compared to MHT. Confusion exists as to the benefit/risk profile of menopausal hormone therapy, limitations on the age of initiation of treatment, limitations on the length of treatment, and the need for treatment in the young menopausal woman with low bone density.

INTRODUCTION

Fuller Albright published his observations on postmenopausal osteoporosis in 1941. He observed that, out of a total cohort of 42 osteoporotic patients younger than 65 years, 40 were postmenopausal women (either natural menopause or post oophorectomy). He correctly stated that menopausal osteoporosis was not due to deficient mineralization of bone. He demonstrated that estrogen therapy could minimize vertebral damage and stop height loss. These changes could be prevented by early initiation of estrogen therapy. These principles as coined by Fuller Albright are still valid today. The only conclusion that did not stand the test of time was the hypothesis that estrogen deficiency primarily acts by the inhibition of bone formation. It is accepted today that estrogen primarily acts on bone as an antiresorptive agent by reducing osteoclast numbers and osteoclast function, but estrogen receptors have been demonstrated on both osteoblasts and osteoclasts. Estrogen deficiency, as naturally experienced in the postmenopause or after premature ovarian insufficiency, causes an increase in active osteoclasts with increased bone resorption and loss of bone mineral density (BMD). This effect is mediated via various pathways involving, amongst others, various cytokines and the receptor activator of nuclear factor kappa-B ligand (RANKL) system. It was demonstrated in the 1970s that this process is reversible by the addition of exogenous estrogen in a model of oophorectomized women, using metacarpal bone mineral content as determined by single photon absorptiometry. In 1996, the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial was the first, large, randomized, clinical trial (RCT) utilizing dual X-ray absorptiometry to show that BMD after menopause is conserved at the hip and spine by intervention with estrogen therapy. It was suggested by observational data that menopausal hormone therapy (MHT) prevented fractures, but no RCT with a fracture endpoint had been conducted. In 2002, the preliminary results as well as later final results of the Women’s Health Initiative study (WHI), a large RCT, gave concrete proof of the antifracture efficacy of MHT. This effect was significant for all types of osteoporosis-related fractures, including hip fractures, even in women regarded as being at low risk of fracture.

What then is the reason that, in spite of the aforementioned, MHT is uncommonly used for the primary purpose of fracture prevention? There are several reasons that will be addressed individually.

THE DEVELOPMENT OF NEW BONE-SPECIFIC DRUGS SUPPORTED BY RCT-DERIVED EVIDENCE

A detailed discussion on the registration of new drugs and the impact on MHT has been published. Alendronate made the largest impact at a time when the anti-fracture efficacy of MHT was still unproven. In 1996, a large RCT demonstrated the efficacy of alendronate, a bisphosphonate, in reducing...
vertebral and non-vertebral fractures. This was followed by the regulatory approval of risedronate, raloxifene, calcitonin, teriparatide, strontium ranelate, ibandronate, zoledronic acid and denosumab. It is acceptable to reason that the wider choice of therapeutic options led to lesser interest in a long established modality such as MHT. As important, though, was the perception that the newer drugs were more effective at fracture prevention than MHT. This has never been proven, as there are no head-to-head comparative studies. In the WHI estrogen-and-progestogen arm, reductions in the rates of fractures were reported as hazard ratios: hip fracture 0.66 (95% confidence interval (CI) 0.45–0.98), clinical vertebral fracture 0.66 (95% CI 0.44–0.98) and non-vertebral fracture 0.77 (95% CI 0.69–0.86). In the WHI estrogen-only arm, hazard ratios were: hip fracture 0.61 (95% CI 0.41–0.91), clinical vertebral fracture 0.62 (95% CI 0.42–0.93) and total fractures 0.79 (95% CI 0.63–0.79). These results are remarkable as only clinical fractures were recorded, without routine X-rays to detect morphometric fractures. Furthermore, the population studied was at low risk of fracture. This resulted in the magnitude of anti-fracture efficacy of MHT being understated when compared to RCTs of other bone-specific drugs. It is thus fair to state that the anti-fracture efficacy of MHT is no better or worse than the other agents. As it has proven efficacy against all the major classes of osteoporotic fractures (vertebral and non-vertebral including hip), it has a better profile compared to raloxifene and ibandronate (no primary hip data) and is virtually in a class of its own in offering fracture protection in patients with osteopenia.

**BENEFIT/RISK PROFILE OF MHT AND OTHER DRUGS**

The provisional results of the WHI study in general, but also specific articles on fracture protection, concluded that potential risks outweighed possible benefit. These conclusions should be reconsidered in view of the final adjudicated results published in 2013. The final results, based on the global index as designed by the WHI investigators, still indicated that risk outweighed possible benefit. This method of risk estimation and subsequent conclusion has been questioned. The most significant omission from the final global index is the omission of all fractures except hip fractures. It has been shown that the final global index, when corrected from a bone perspective, indicates a net benefit. It should also be kept in mind that the WHI excluded women suffering from vasomotor symptoms of menopause and did not record improvement in vaginal health. These major advantages of MHT and most common indications for MHT are not considered in the global index.

In contrast to MHT, the other bone-specific drugs were generally considered to be safer than MHT. As experience was gained in clinical practice, it was evident that this was not entirely true. All bisphosphonates and denosumab are causally related to osteonecrosis of the jaw and, when used for periods exceeding 3–5 years, may be associated with atypical fractures of the femur. Bisphosphonates are also associated with an increased risk of atrial fibrillation. Selective estrogen receptor modulators increase the risk of venous thrombotic events (VTEs) to the same extent as oral MHT. Salmon calcitonin has been discontinued because of a possible oncogenic association. Strontium ranelate has been linked to increased cardiovascular risk in susceptible individuals. It is now clear that the benefit/risk profile of any osteoporosis medication needs to be calculated individually. The most important possible risks of MHT are VTEs and stroke. Identifying patients at risk, using transdermal therapy and the lowest effective dose, can manage the risk of these potential unwanted effects. The risk of breast cancer associated with MHT is only present when estrogen is combined with a progestin, as is needed to protect the endometrium from hyperplasia in women with a uterus. This risk can be potentially reduced by using natural micronized progesterone, dydrogesterone or bazedoxifene to oppose the endometrial effect of estrogen.

**THE WINDOW OF OPPORTUNITY**

Whereas the global index included all participants in WHI of all ages, it is now well accepted that, in general, the benefits of MHT will most likely outweigh risks if initiated before the age of 60 or within 10 years of menopause (window of opportunity). This is based on the consideration that the cardioprotective effect of MHT may be attenuated by the degree of atherosclerosis present in coronary arteries and that the cardiovascular risk of MHT is related to the degree of atherosclerosis present in coronary arteries at time of initiation of therapy. Most guidelines thus recommend that MHT only be initiated in this window. This has led to the misconception that MHT will not protect bone if started or continued after age 60. MHT is bone-protective at any age. Initiation after the age of 70 may be associated with cognitive decline, and initiation at ages 60–70 needs careful consideration of underlying risk of coronary arterial disease. Continuation of MHT after the age of 60 is a different question, with the risk of coronary arterial disease and VTE most likely decreasing. The major concern of lengthy treatment with MHT, as is mostly needed in osteoporosis, remains the risk of breast cancer. This has not been assessed in any RCT, but the risk based on observational studies is considered to be low.

**FRACTURE RISK ASSESSMENT IN THE YOUNG MENOPAUSAL WOMAN**

It is widely accepted that individuals with an osteoporosis-associated fracture or DXA-derived T-score less than -2.5 should be treated. Individuals with osteopenia should be evaluated using an integrated risk calculator such as FRAX® to calculate 10-year risk of fracture. If the 10-year risk of fracture
exceeds the threshold for treatment as determined by local guidelines, pharmacological treatment should be instituted regardless of age.

A clinical dilemma arises when it is established that the early menopausal woman has osteopenia but FRAX risk estimation does not reach treatment threshold levels. This leads to anxiety amongst the patient and caregiver as to a further deterioration in BMD and eventual osteoporosis. In the United States of America, MHT and conjugated equine estrogen/bazedoxifene are approved as appropriate agents for the prevention of osteoporosis. In Europe, no medication is approved for the prevention of osteoporosis. The late transitional period and early menopause are characterized by accelerated bone loss secondary to estrogen deprivation. It has been questioned whether the FRAX score accurately reflects future fracture risk in the young menopausal patient. Although BMD gain from MHT during this time will most likely be lost after cessation of therapy, future fracture risk reduction has been demonstrated after estrogen exposure for 2–3 years after menopause.19

THE SITUATION 75 YEARS ON

The accuracy of the observations made by Fuller Albright is remarkable. The application of these principles in the treatment and prevention of osteoporosis and related fractures is unfortunately low in 2015. This is very disappointing as we now have more information on the efficacy and benefit/risk profile in bone medicine than ever before. It is sincerely hoped that this article will inspire more consideration for MHT as a major player in the prevention of osteoporosis-related fracture. We owe that to Fuller Albright and to our patients.

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