SELECTIVE ESTROGEN RECEPTOR MODULATORS: A POSSIBLE NEW TREATMENT OF OSTEOPOROSIS IN MALES

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SUMMARY

More recently, osteoporosis in men has been recognized as an important public health problem. Bone loss begins in mid life and is associated with the decline of the sex steroids production. Although there is no equivalent of the menopause, gonadal function in men is affected in a slow progressive way leading to hypogonadism. Testosterone, the major androgen in men, exerts its effect on bone by local conversion to 5α-dihydrotestosterone or by aromatization to estrogens. Several studies have found that estrogen, rather than testosterone, levels are more closely correlated with BMD in elderly men. Selective estrogen receptor modulator (SERM) raloxifene binds to estrogen receptors and exhibit estrogenic effect in bone, but, contrary to estrogen, without feminizing effect. There are limited numbers of studies investigating the effects of SERMs in males. Animal studies demonstrated that SERMs inhibit bone turnover and prevent bone loss in orchidectomised adult male rats. Raloxifene has been shown to increase bone mineral density of the hip in men receiving androgen deprivation therapy for prostate cancer. Moreover, experimental data demonstrated dramatic increase in cell death in human prostate cancer cell lines after the treatment with raloxifene. All these observations suggest that SERMs may be useful for the prevention and treatment of osteoporosis not only in postmenopausal women but also in elderly men. However, our hypothesis should be tested in a proper designed clinical trial. Several important issues have to be addressed. Does the same drug dose that has been shown to be effective in postmenopausal women should be used in men, too? Does treatment with SERMs reduce the fracture risk in men and is it comparable to that observed in women? Does treatment with SERMs have any beneficial effect on cardiovascular system and prostate cancer? And finally, do men experience adverse events other than women treated with SERMs? Answering to these questions will have great impact in getting the decision of possible SERMs usage in the treatment of osteoporosis in elderly males.

More recently, osteoporosis in men has been recognized as an important public health problem, despite the fact that osteoporosis is more common in women. One-third of all hip fractures occurred in men and mortality after hip fractures is greater in men than women (1). The lifetime risk of hip fracture in men has been estimated to 6% (2).

Bone loss begins in mid life in both women and men and is associated with the decline of the production of sex steroids. Although there is no equivalent of the menopause with its related increase of bone turnover and accelerated bone loss, gonadal function in men is affected in a slow progressive way leading to hypogonadism known as andropause or more appropriately, androgen decline in aging male (ADAM). There is an age-related decline in serum testosterone and increase in sex hormone binding globulin (SHBG) which leads to further marked reduction of bioavailable testosterone. When the diagnosis is based on the measurement of bioavailable testosterone, 70% of men over the age of 60 were found to be hypogonadal (3).

Testosterone, the major androgen in men, exerts its effect on bone by local conversion to 5α-dihydrotestosterone, which has a high affinity for androgen receptors on osteoblasts and osteoclasts. On the other hand, androgens could be aromatized to estrogens, raising the possibility that some of skeletal effects of testosterone may be mediated by aromatisation to estradiol. Indeed, report of osteoporosis in men with aromatase gene (4) or estrogen receptor gene (5) mutations confirm this concept. Moreover, several studies have found that estrogen, rather than testosterone, levels are more closely correlated with BMD in elderly men (6, 7).

Selective estrogen receptor modulators (SERMs) bind to estrogen receptors and produce 3-D conformational changes resulting in differential gene expression. Via binding the ER-α and ER-β receptors which both are expressed in human osteoclasts and osteoblasts, SERMs exhibit estrogenic effect in bone, but, contrary to estrogen, without feminizing effect. SERM raloxifene has been approved for the prevention and treatment of osteoporosis in postmenopausal women.

There are limited numbers of studies investigating the effects of SERMs in males. Animal studies demonstrated that lasofoxifene inhibit bone turnover and prevent bone loss in orchidectomised adult male rats (8). Another SERM, raloxifene, has been shown to increase bone mineral density of the hip in men receiving androgen deprivation therapy for prostate cancer (9). The changes in bone mineral density in these patients were comparable with the increases in bone mineral density in postmenopausal women treated with raloxifene (10).

Moreover, it seems that the mechanism of raloxifene induced changes in bone mineral density is similar in men and women. In addition, experimental data demonstrated dramatic increase in cell death in human prostate cancer cell lines after the treatment with raloxifene (11).

All these observations suggest that SERMs may be useful for the prevention and treatment of osteoporosis not only in postmenopausal women but also in elderly men. However, our hypothesis should be tested in a proper designed clinical trial. Several important issues have to be addressed. Does the same drug dose that has been shown to be effective in postmenopausal women should be used in men, too? Does treatment with SERMs reduce the fracture risk in men and is it comparable to that observed in women? Does treatment with SERMs have any beneficial effect on cardiovascular system and prostate cancer? And finally, do men experience adverse events other than women treated with SERMs? Answering to these questions will have great impact in getting the decision of possible SERMs usage in the treatment of osteoporosis in elderly males.

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