Role of sex steroids in the regulation of bone metabolism in the adult skeleton

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SEX STEROIDS AND SKELETAL MATURATION

Pubertal exposure to rising blood concentrations of sex steroids, partly in concert with transiently increased activity of the somatotropic axis, is instrumental in a pubertal acceleration of bone growth and acquisition of bone mass, followed by growth inhibition and closure of the epiphyseal cartilages in the late pubertal stages. Skeletal changes during pubertal maturation result in a degree of gender dimorphism, with peak bone mass in men being about 25% greater than in women. The latter difference corresponds essentially to achievement of larger bone sizes and slightly thicker cortices in men, which is in turn explained by later timing of puberty with longer growth of the long bones and by greater periosteal bone apposition in boys in response to pubertal sex steroid exposure. In adulthood and during aging gender differences are maintained and deepened because the continued periosteal bone apposition throughout life occurs at a greater rate in men as compared to women, with resulting lesser net loss of cortical bone and greater gain of sectional bone area. This gender dimorphism procures and advantage to men in terms of biomechanics, which translates in a substantially lower fracture incidence in elderly men compare to their female counterparts [33-35].

Estrogens are essential for skeletal maturation with closure of epiphyseal cartilages and for adequate acquisition of bone mass in both women and men. This is illustrated by observations of a low bone mass and failure of growth plate fusion in men with lack of functional estrogen-receptor alpha (ERα) or with aromatase deficiency, which in the latter cases can be reversed by estrogen treatment [4, 6, 37]. The gender-dimorphism in skeletal maturation with greater periosteal expansion and radial bone growth in men has traditionally been attributed to opposite actions of sex steroids on periosteal bone apposition with androgen-driven stimulation in males and estrogen-mediated inhibition in females. However, evidence from animal studies [29, 49] and observations in the human [5] indicate that estrogens play an important role in the stimulation of periosteal apposition and radial bone growth. The action of estrogen on periosteal apposition might in fact be biphasic and dose-dependent with stimulation of periosteal expansion at lower concentrations in early puberty in girls and throughout puberty in boys and in adult men, whereas higher estrogen concentrations in late puberty in girls and in adult women may rather exert an inhibitory action [5]. The greater periosteal expansion in men may then result from combined effects of androgens (testosterone and its 5α-reduced active metabolite dihydrotestosterone) mediated by the androgen receptor (AR) and of estradiol (E2), the main aromatisation product of testosterone (T), mediated by ERα, whereas inhibitory actions of E2 in women might possibly be mediated by ERβ [46]. The biphasic estrogen actions might be mediated in part by changes in growth hormone and/or IGF-1 levels and through modulation of the sensitivity of periosteal bone to mechanical stimuli, with sensitization of bone to mechanical loading at low estrogen concentration acting to reinforce the effects of increased mechanical loading as a consequence of increased muscle mass and strength in response to the anabolic action of T [47]. It should be pointed out that there have been divergent views on the role of estrogens on the regulation of periosteal bone formation in the literature [17] and it should also be noted that there has been data suggesting that estradiol can also inhibit radial bone growth in pubertal boys [24].

SEX STEROIDS AND SKELETAL CONSERVATION

Estrogen deprivation in adult women following ovariectomy or other acquired causes of hypogonadism before menopause, results in transient marked acceleration of bone turnover with accelerated bone loss, which slows down exponentially over several years towards a continuous slower age-related bone loss; the pattern of changes following reduced estrogen expo-
sure after natural menopause is similar with usually a more mitigated course. This illustrates a major role of estrogens for conservation of bone mass at the tissue level [33]. The high bone turnover state with accelerated bone loss typical of recent estrogen deficiency is the result of a high activation frequency with substantially increased number of active basic remodelling units, on the one hand, and, on the other hand, of remodelling imbalance with increased bone resorption incompletely matched by bone formation at the level of the basic remodelling units.

Indeed, estrogens tonically suppress bone turnover and help to maintain a balance between the rates of bone resorption and formation. Estrogens reduce formation rate, activity and lifespan of osteoclasts. Although data for estrogen action on osteoblasts have been less consistent, there is evidence indicating that estrogens can increase recruitment, proliferation, differentiation and lifespan of osteoblasts [8, 25, 33]. Most of these estrogen actions on bone cells are mediated by activation of ERα, although some ERα-mediated estrogen actions on bone may be antagonized by activation of ERβ and it has been suggested that ERβ may play a permissive role for age-related bone loss in females [33, 50]. Osteoblast-derived nuclear factor-κB ligand (RANK-ligand) is responsible for recruitment of osteoclasts, requiring permissive concentrations of M-CSF, stimulates osteoclast function and decreases apoptosis. Estrogens increase the osteoblastic production of osteoprotegerin (OPG), a decoy soluble receptor that neutralizes RANK-ligand, and decreases both M-CSF and RANK. Estrogen effects on this important RANK — RANK-ligand — OPG system are probably in part indirect through modulation of intermediary cytokines and other signalling compounds [33, 40, 41].

In men as in women, acquired profound hypogonadism results in a state of high bone turnover with accelerated bone loss [28, 38, 39]. Although AR-mediated androgen effects in the adult male skeleton help preventing osteoporosis by preservation of cancellous bone and stimulation of periosteal cortical bone apposition, there is ample direct and indirect evidence in experimental animals and humans indicating a major role of aromatisation of T to E2 in the regulation of bone homeostasis in men. Estrogen derived from aromatisation of T is required for restraining of bone turnover and it has been suggested that threshold concentrations of bioavailable E2 may be required to limit age-related bone loss [12, 22].

**SEX STEROIDS AND SENILE BONE HOMEOSTASIS**

In women and men age-related bone loss persists throughout life with a tendency to accelerate in the elderly, the latter being commonly considered as a consequence of relative secondary hyperparathyroidism.

Whereas the first years following menopause the ovary may still secrete substantial amounts of sex steroids, in elderly menopausal women adrenal androgen become the major, albeit declining, source of circulating androgens and their aromatisation products, estron and E2. There is evidence that also in postmenopausal elderly women differences in circulating estrogen concentrations may be relevant to the determination of bone loss and skeletal status [16, 20], although data on the consequences of late bilateral oophorectomy as to fracture risk have not been univocal [2, 27]. Interestingly, the extraskeletal consequences of estrogen deficiency, such as on vitamin D action and renal calcium handling may contribute to the occurrence of secondary hyperparathyroidism. There is presently little data on the contribution of AR-mediated androgen effects in the regulation of bone homeostasis in elderly women, besides the role of androgens as estrogen precursors.

Aging in men is accompanied by a progressive decline of T production with moderate decrease of serum total T levels. A marked age-related increase of sex hormone binding globulin (SHBG) results in a more substantial decrease of the non-SHBG bound fractions that are readily available for biological action. Notwithstanding the decreased T precursor levels, serum concentration of total E2 is maintained with aging as result of a relative increase in fat mass and aromatisation capacity. Nevertheless, the increase of SHBG levels results in a moderate age-related decrease of non-SHBG bound fractions of serum E2 [18]. These age-related hormonal changes raise the question of their potential relevancy as to senile bone loss and osteoporosis in men.

Cross-sectional studies, in which age and body mass index or weight are major confounders, have yielded inconsistent results as to the association of serum T levels and prevalent BMD in elderly men, with no independent association found in some studies [9, 10, 26] and weak but significant associations in others [15, 19, 20, 30, 45]. In any case, multivariate analysis of cross-sectional studies consistently indicated that free or bioavailable E2 is a better predictor of prevalent BMD in elderly men than free or bioavailable T [1, 7, 15, 20, 31, 36, 42, 45, 48]. Serum E2 has also been associated with volumetric BMD and geometric variables of bone as assessed by quantitative computerized tomography [23]. Furthermore, high values for markers of bone resorption are more consistently associated with serum E2 than with serum T levels [14, 23, 43, 44]. Osteoprotegerin levels have been reported to be positively associated with E2 levels and negatively correlated to markers of bone resorption [21, 43]. A role for aromatisation of T to E2 in the regulation of bone turnover in elderly men
has also been demonstrated during short-term controlled manipulation of sex steroid levels [11].

There is presently limited data linking serum E2 to fracture risk in men. In the Rancho Bernardo study serum concentrations of E2, but not of T were associated with prevalent vertebral fractures in elderly men [3]. In a case-control study in elderly men participating in the Rotterdam Study there was no association of vertebral fracture risk with either bioavailable T or E2 [13]. On the other hand, in the Mr. Os study incident non-vertebral fracture has been found to be associated with bioavailable serum concentrations of T and E2 [32]. The whole of the data thus indicates that aromatisation of T to E2 plays an important role in the regulation of bone homeostasis in elderly men and that relative estrogen deficiency can contribute to the pathogenesis of senile bone loss and osteoporosis.

There is no convincing evidence that the drastic decline of the adrenal androgens dehydroepiandosterone (DHEA) and DHEA-sulfate in aging men contributes to the pathogenesis of senile bone loss and osteoporosis [18].

Both in elderly men and women there are undoubtedly relevant functional links with regard to regulation of bone homeostasis between the sex steroids and the somatotropic axis, but at present information on this important area for research are rather limited [18, 33].

REFERENCES


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