Gonadal hormones and their influence on skeletal health in men

Keywords

Osteoporosis in men

Testosterone

Estradiol

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Abstract

Osteoporosis in men has only recently begun to receive more attention despite it being estimated that about one third of all osteoporotic fractures occur in men and that the residual lifetime fracture risk in a man aged 60 years may be as high as 30%. Accrual of bone mass and age-related bone loss in aging healthy men are multifactorial processes involving hormonal, environmental, and genetic factors. This review will summarise the effects of gonadal steroids on bone turnover and bone mass in men.

Introduction

Osteoporosis in men has only recently received more attention with studies being performed to elucidate the pathogenesis of age-related bone loss in men. It is estimated that about one third of all osteoporotic fractures occur in men [1,2], and that the residual lifetime fracture risk in a man aged 60 years may be as high as 30% [3]. These fractures result in significant morbidity, mortality, and healthcare costs to the community [4,5], particularly since the mortality and morbidity of bone fractures in older men exceed those of women.

Accrual of bone mass and age-related bone loss in aging healthy men are multifactorial processes with hormonal, environmental, and genetic factors all being important. At puberty, a dramatic increase in bone mineral content and bone mass occurs, which is associated with a sharp increase in gonadal hormones. After peak bone mass has been achieved, bone mineral density (BMD) decreases gradually, but to a much lesser extent than in women. This age-related bone loss in men is accompanied by a slow decrease in circulating androgen levels. However, whether a causal relationship exists between the age-related decreases in androgen levels and bone health remains unclear. This review will summarise the effects of gonadal steroids on bone turnover and bone mass in men.

Sex hormone metabolism and action

Androgens are synthesized from cholesterol through several enzymatic pathways in which the side chain of cholesterol is shortened through oxidation from 27 carbons to 19 carbons [6]. In men, androgens are secreted almost exclusively from the testes as testosterone. The adrenal glands also secrete dehydroepiandrosterone (DHEA), which is a minor androgen that also serves as a substrate for peripheral aromatisation to estradiol (E2). Testosterone is either converted by 5α-reductase to dihydrotestosterone (DHT), or metabolized to E2 by aromatase, a widely distributed microsomal cytochrome P450 enzyme. The former pathway amplifies androgen action locally while the latter pathway diversifies androgen action [6]. Hence, enzymatic androgen activation leads to testosterone acting directly or via its more potent metabolite DHT through the androgen receptor (AR), or indirectly via aromatization to E2 through the estrogen receptors (ERs). Thus, testosterone functions as a precursor for peripheral conversion into biologically highly active hormones. Estradiol,

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Online 31 May 2007

which is thought to play a major role in bone metabolism in men, is largely synthesized by extratesticular aromatization of circulating testosterone with only a small proportion of E2 (approximately 15–20%) being directly secreted by the testes [7]. Depending on the relative activity of aromatase, 5α-reductase, and dehydrogenases, and the relative distribution of ARs and ERs in peripheral target tissues, testosterone and its metabolites may predominantly activate either the AR or the ER. In bone tissue, the expression of aromatase [8–14], 5α-reductase [15–18], 17beta-hydroxysteroid dehydrogenase (17β-HSD: [9–11,15,19]), and 3β-HSD [9,20] has been documented, supporting the concept of tissue-specific peripheral activation of gonadal hormones.

The AR has been identified in most bone cells, including osteoblasts [21], osteocytes [22], and osteoclasts [23,24]. Estrogen action on bone, in men and women, is mediated via ERs. These nuclear hormone receptors are also expressed in osteoblasts, osteoclasts, and osteocytes [25,26]. Two ERs have been identified: ERα is predominantly expressed in cells resident in cortical bone, whereas ERβ shows higher levels of expression in cells found in cancellous bone [26–28]. Alternate, non-genomic pathways have also been described in which ARs and ERs modulate transcription indirectly, via protein–protein interactions.

Age-related changes in gonadal hormones in men

Male aging is associated with a gradual, progressive decrease in circulating testosterone [29,30]. Longitudinal population-based studies show that serum total testosterone concentrations decline by approximately 1% per year in men, but the importance of such a decline remains unclear. A variety of derived testosterone measures (''free'', ''bioavailable''), which putatively reflect various binding and tissue availabilities of testosterone to carrier proteins, have been postulated to reflect androgen action more closely, however, the underlying free hormone hypothesis lacks adequate empirical verification [31]. For example, while ''free'' testosterone (i.e. the fraction of total testosterone that is unbound, particularly to albumin or sex hormone-binding globulin (SHBG)) is reported to fall more rapidly due to a concomitant twofold rise in SHBG binding capacity [32–34], it is unclear whether this represents more or less net androgen action at a tissue level, since the unbound hormone fraction is more accessible to both sites of hormone action as well as to degradation [35].

Although an age-related fall in blood estrone level has been observed in men [34], similar reductions in E2 have not been well documented. This may be due to increased aromatase activity with age, which in turn is attributed to the age-associated increase in fat mass [36]. By analogy with testosterone, non-SHBG bound E2 levels decrease with age (by about 50% over 6 decades) as a consequence of increasing SHBG concentrations [37]. However, the biological validity of this derived E2 measure remains to be established, since binding to SHBG is competitive with testosterone, which is present in 100-fold higher molar concentrations. While the available evidence indicates that E2 has significance for the male skeleton, the circulating blood E2 concentration in men is comparable with estrogen-deficient post-menopausal women, raising the paradoxical issue of why male bone does not acquire the osteoporotic state of post-menopausal women.

Gender-specific effects of sex hormones on bone geometry

There is little difference in bone size and volumetric bone mineral density (vBMD) between girls and boys until puberty, when sexual dimorphism begins. During puberty, skeletal mass doubles. The increase in statural height is greatest in early puberty and then declines in both sexes, whereas the maximal increases in vBMD occur at the menarche in girls and in late puberty in boys. The pattern of growth differs in boys from that of girls. In boys, puberty occurs approximately 2 years later than in girls and thus boys have 2 extra years of prepubertal growth. Furthermore, the pubertal growth spurt lasts for 4 years in boys compared to 3 years in girls [38,39]. These differences account for the 10% greater height and the 25% greater peak bone mass achieved by boys. The greater bone mass in boys is, for the most part, due to their greater bone size. Peak vBMD is no different in young men and women.

The endosteal and periosteal bone compartments change differentially during bone