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COMMENTARIES

Low Free 17β-estradiol Level in Men with Idiopathic Osteoporosis and Their Sons with Low Bone Mineral Density

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Men with idiopathic osteoporosis have decreased areal bone mineral density (aBMD), with a deficit in aBMD that is more severe at the lumbar spine than the hip or distal forearm (1-4). Volumetric BMD (vBMD) is decreased at the spine and femoral neck. Moreover, the volume of the third lumbar vertebra (L3) body is lower (1;5). Levels of biochemical markers of bone turnover are similar in patients and controls (1-2 ;4 ;6).

Genetic analysis indicates a hereditary component in the pathogenesis of idiopathic osteoporosis (7-9). First-degree relatives of patients with idiopathic osteoporosis have decreased aBMD (1 ;3 ;9). Their sons have lower vBMD at the lumbar spine and femoral neck, as well as a smaller L3 vertebral body (1). Thus, idiopathic osteoporosis in men may be principally caused by impaired bone growth and mineral acquisition, rather than accelerated bone loss. This deficit might develop during late puberty, the period of accelerated spine growth, whereas the limbs are in the period of calcification of growth plate cartilage and consolidation (10).

Hormonal mechanisms underlying idiopathic osteoporosis in men are only partly elucidated. Decreased circulating 17β-estradiol, mainly of its free and bioavailable fractions, is reported in most (2 ;6 ;11-12), but not all (5 ;13) studies. Pottelbergh *et al.* (14) reported a lower level of free 17β-estradiol in 64 patients with idiopathic osteoporosis (probands) and their 21 sons, compared with their respective age-matched controls. Sons in the lowest tertile of lumbar spine aBMD had decreased levels of free 17β-estradiol and free testosterone.

The concentration of sex hormone-binding globulin (SHBG) was elevated in probands, not sons (14). However, the absolute difference in SHBG level, relative to corresponding controls, was similar in both groups, but the number of sons was smaller. This finding suggests that the difference in SHBG level in sons was not significant because of the insufficient statistical power, not necessarily because of the biological difference between the SHBG synthesis and secretion in fathers and sons. In multiple regression analysis, body mass index was the only independent determinant of low BMD in probands. Aromatase allelic frequency distribution was similar in probands and their controls.

Van Pottelbergh *et al.* have addressed a new topic: the role of sex steroids in the familial occurrence of idiopathic osteoporosis in men. A familial (hereditary?) deficit in free 17β-estradiol level may be a determinant of impairment of bone mineral acquisition that results in lower aBMD. Limbs grow mainly in early puberty, a time when the concentration of sex steroids starts to increase, but still remains relatively low. The spine grows mainly in late puberty, a time when the concentration of sex steroids approaches the values observed in adult men. Thus, familial deficit in sex steroids may negatively influence growth and mineral acquisition more at the spine than the long bones (*e.g.*, the femur).

This finding is an important contribution to the understanding of the role of 17β-estradiol in the pathogenesis of idiopathic osteoporosis in men. Several questions remain unanswered. Is low free 17β-estradiol the result of decreased androgen synthesis, impaired aromatase activity, or higher SHBG? Does low free 17β-estradiol result in impaired bone mineral acquisition in idiopathic osteoporosis or reflect difference in body composition? If the former, what mechanism mediates the effect of 17β-estradiol deficit: a direct effect, interaction with somatotropic axis (4 ;15), or a joint effect with decreased expression of estrogen receptor α in bone cells (16)?

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