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Review

Estrogen and bone health in men and women

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ABSTRACT

Estrogen is the key regulator of bone metabolism in both men and women. Menopause and the accompanying loss of ovarian estrogens are associated with declines in bone mineral density (BMD): 10-year cumulative loss was 9.1% at the femoral neck and 10.6%, lumbar spine. Estradiol concentrations also predict fractures. Total estradiol levels, <5 pg/ml were associated with a 2.5-fold increase in hip and vertebral fractures in older women, an association that was independent of age and body weight. Similar associations were found in men. Despite the lower BMD and higher fracture risk in hypogonadal men, there is little association between circulating testosterone, fracture and bone loss. Nevertheless, the combination of any low sex steroid hormone and 25-hydroxyvitamin D was associated with an increased fracture risk. Menopausal hormone therapy has been shown to reduce hip and all fractures in the Women's Health Initiative with little difference between the estrogen-alone and the estrogen plus progestin trials. The risk reductions were attenuated in both trials post intervention; however, a significant hip fracture benefit persisted over 13 years for women assigned to the combination therapy.

Clinical trials of testosterone replacement in older men give tantalizing but inconclusive results. The results suggest that testosterone treatment probably improves BMD, but the results are less conclusive in older versus younger men. The Testosterone Trial is designed to test the hypothesis that testosterone treatment of men with unequivocally low serum testosterone (<275 ng/dL) will increase volumetric BMD (vBMD) of the spine. Results of the Testosterone Trials are expected in 2015.

Contents

1. Introduction

Estrogen is the key regulator of bone metabolism in both women and men. A working model for estrogen regulation of bone turnover via effects on osteocytes, osteoblasts and T-cells has been proposed by Khosla et al. [1], Fig. 1. As depicted in this figure, estrogen has direct effects on osteocytes, osteoblasts and osteoclasts and inhibitory effects blocking the activation of osteoclasts either directly or via osteoblasts and T-cells. The ultimate action of estrogen on the skeleton is to decrease bone remodeling and bone resorption while maintaining bone formation.

The focus of this review is on the clinical relationship between endogenous and exogenous hormones to bone mineral density (BMD) and fracture in both men and women.

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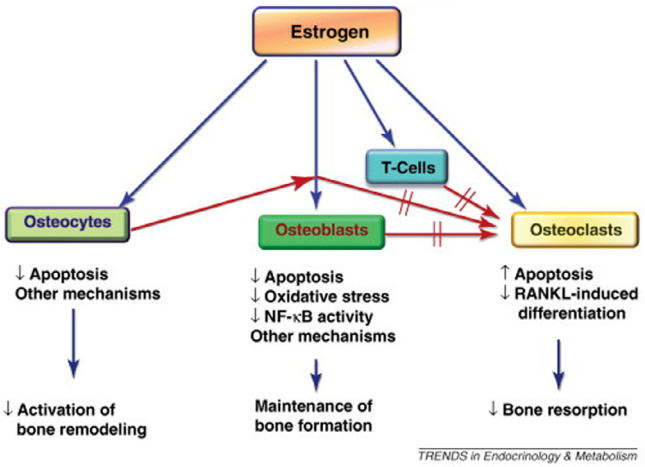

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Fig. 1. Working model for estrogen regulation of bone turnover via effects on osteocytes, osteoblasts, osteoclasts, and T-cells.

1.1. Sex steroid levels and age

Testosterone and estradiol levels, especially, the free or bioavailable fractions decline with increasing age in both men and women. Using sex steroid data from the Mayo Clinic (data chosen since results on men and women derived from same laboratory) [2,3], the mean bioavailable testosterone (*T*) was 138, 103 and 56 ng/dl in men age 20–30, 40–59 and 60+ years, respectively. In contrast, bioavailable *T* levels were 2.3, 2.0 and 2.0 in women age 20–30, 40–59 and 60+ years, respectively. The mean bioavailable estradiol (E2) was 13, 12 and 8 pg/ml in men age 20–30, 40–59 and 60+ years, respectively. Corresponding values in women were 17, 11 and 3 pg/ml in women age 20–30, 40–59 and 60+ years, respectively. Expanding the study in men to include older men, total and free *T* (measured by RIA) declined with age with little difference in the slope of decline in men age 30–40 years compared with 70–80 year olds [4]. The prevalence of hypogonadism (defined in this study as total $T < 325$ ng/dl) increased to about 20% in men over 60, 30% over 70 and 50% over 80 years of age. A higher prevalence was observed if free *T* levels were used. Similar results were observed with *T* measured by the gold standard using liquid chromatography tandem mass spectrometry [5].

1.2. Women

Almost 75 years ago, Fuller-Albright made the fundamental observation that menopause and its accompanying estrogen deficiency was associated with osteoporosis [6]. Early longitudinal studies confirmed this observation. In 1986, Riggs et al. characterized bone loss in 139 women ages 20–80 years. Over the 2-year follow-up, women who remained premenopausal experienced an increase in BMD at the radial shaft by 0.5% but experienced 1.4% loss at the spine. This first longitudinal study suggested that BMD loss begins before menopause, especially at trabecular rich sites [7]. As recently reviewed [8] early studies were limited by small sample sizes, short duration, differential definitions of menopause and use of less precise techniques for measuring BMD.

The Study of Women's Health Across the Nation (SWAN) was designed to overcome the limitations of these earlier studies [9]. The SWAN Bone cohort is a longitudinal study of 2335 women all aged 42–52 years at baseline and reporting at least one menses in the 3 months before enrollment. Menopausal status was initially defined by bleeding patterns: premenopausal, menses within 3 months; early perimenopausal, menses within 3 months but more variability; late perimenopausal, no menses in last 3 months, menses in 4–12 months but more variability; and postmenopausal, no menses in past 12 months. As shown in Fig. 2, after 4 years of follow-up, lumbar spine (LS) BMD loss accelerated markedly in the late perimenopause in each ethnic group [10]. Lumbar spine BMD was most rapid in Japanese and Chinese women, intermediate in Caucasian and slowest in African–American women

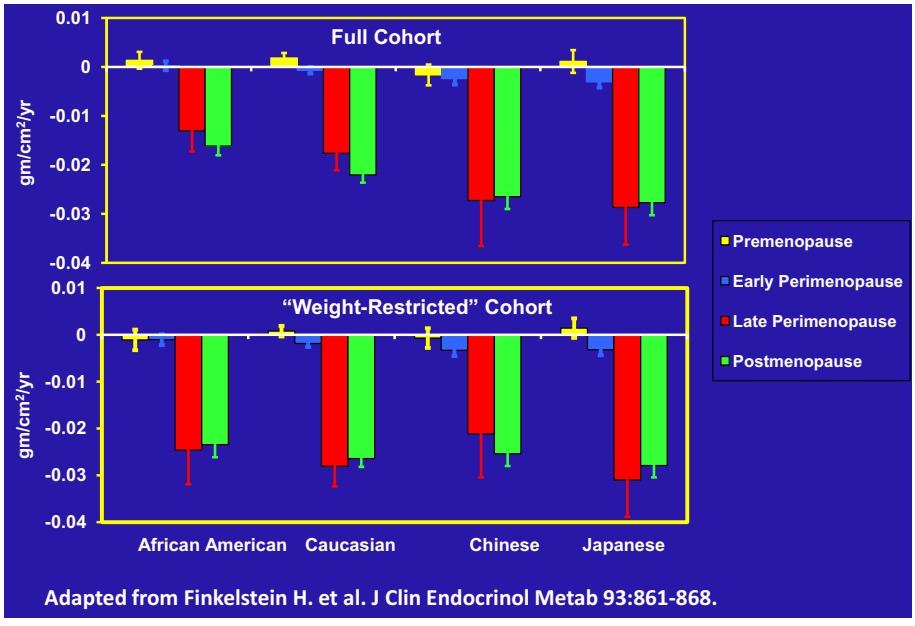

Fig. 2. Annual rate of spine BMD change in premenopausal (red bars), early perimenopausal (blue bars), perimenopausal (yellow bars) and postmenopausal (green bars). African American ($n = 494$), Caucasian ($n = 944$), Chinese ($n = 221$) and Japanese ($n = 243$) women. Error bars represent (95% confidence limits. Top panel: Full cohort; bottom panel: weight restricted cohort (women weighing 50–78 kg). African American, ($n = 198$); Caucasian ($n = 587$), Chinese ($n = 167$) and Japanese ($n = 181$).

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