

Changes in Bone Structure During Growth and Aging

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Using both conventional and high resolution quantitative computed tomography (QCT) imaging as well as mouse studies, our group has focused on better defining bone structural changes during growth and with aging. In adolescence, the most common site of fracture is the distal forearm, with peak incidence at the pubertal growth spurt (1). Our previous study in Rochester, MN revealed that the incidence of forearm fractures increased by 32% in boys and 56% in girls over the past 30 years (2). Since 25-50% of adult bone mass is accumulated during the pubertal growth spurt, adolescents today may be at increased risk of osteoporotic fracture later in life.

While previous studies have used DXA to assess changes in bone mass during growth, DXA measurements are confounded by bone size and are unable to differentiate cortical from trabecular bone. Moreover, standard peripheral QCT (pQCT) has an in vivo resolution of ~400 μm and thus cannot assess bone microarchitecture or evaluate bone strength. Thus, we studied healthy 6 to 21 year-old girls ($n = 66$) and boys ($n = 61$) using high-resolution pQCT (HRpQCT, voxel size, 82 micrometers) at the distal radius (3). Subjects were classified into 5 groups by bone-age: Group I (pre-puberty, 6-8 yrs), Group II (early puberty, 9-11 yrs), Group III (mid-puberty, 12-14 yrs), Group IV (late puberty, 15-17 yrs) and Group V (post-puberty, 18-21 yrs). Compared to Group I, trabecular parameters (bone volume fraction, trabecular number and thickness) did not change in girls, but increased in boys from late puberty onwards. Cortical thickness and density decreased from pre- to mid-puberty in girls, but were unchanged in boys, before rising to higher levels at the end of puberty in both sexes. Total bone strength, assessed using micro-finite element models, increased linearly across bone age groups in both sexes, with boys showing greater bone strength than girls after mid-puberty. The proportion of load borne by cortical bone, and the ratio of cortical to trabecular bone volume, decreased transiently during mid- to late-puberty in both sexes, with apparent cortical porosity peaking during this time. This mirrors the incidence of distal forearm fractures in prior studies. These findings thus demonstrated that regional deficits in cortical bone may underlie the adolescent peak in forearm fractures. Whether these deficits are more severe in children who sustain forearm fractures or persist into later life warrants further investigation.

In parallel studies, we used HRpQCT imaging to define, in a relatively large ($n = 602$) population-based sample of women and men spanning a broad age range (21 to 97 years), sex and age effects on bone microarchitecture at the wrist (4). We found that relative to young women (age 20-29 years), youngmen had greater trabecular bone volume/tissue volume (BV/TV, by 26%, $P = 0.001$) and trabecular thickness (TbTh, by 28%, $P < 0.001$) but similar values for trabecular number (TbN) and trabecular separation (TbSp). Between ages 20 and 90 years, cross-sectional decreases in BV/TV were similar in women (-27%) and in men (-26%), but whereas women had significant decreases in TbN (-13%) and increases in TbSp (+24%), these parameters had little net change over life in men (+7% and -2% for TbN and TbSp, respectively, $P < 0.001$ vs. women). However, TbTh decreased to a greater extent in men (-24%) than in women (-18%, $P = 0.010$ vs. men). These findings demonstrated that while decreases with age in trabecular BV/TV are similar in men and women, the structural basis for the decrease in trabecular volume is quite different between the sexes. Thus, over life, women undergo loss of trabeculae with an increase in TbSp, whereas men begin young adult life with thicker trabeculae and primarily sustain trabecular thinning with no net change in TbN or TbSp. Since decreases in TbN have been shown to have a much greater impact on bone strength as compared to decreases in TbTh, these findings may help explain the lower life-long risk of

fractures in men, and specifically, their virtual immunity to age-related increases in distal forearm fractures.

In cross-sectional (5) and longitudinal (6) studies using QCT at multiple sites (spine, hip, wrist, tibia), we further demonstrated that cortical bone loss begins in middle life in women and around age 70 years in men, concomitantly with, and probably due to, the previously documented menopausal and late-life decreases in sex steroids in each sex, respectively. However, in both cross-sectional and longitudinal studies, we found that trabecular bone loss at multiple sites begins in both sexes in the 3rd decade, during sex steroid sufficiency. Thus, while trabecular bone loss is accelerated by sex steroid deficiency (e.g., menopause in women), a substantial proportion of trabecular bone loss over life is independent of changes in sex steroids.

In recent mouse studies (7), we have attempted to better define the role of estrogen deficiency in age-related trabecular versus cortical bone loss. While female mice do not have the equivalent of a menopause, they do undergo reproductive senescence. Thus, to dissociate effects of aging versus estrogen deficiency on age-related bone loss, we sham operated, ovariectomized, or ovariectomized and estrogen replaced female C57/BL6 mice at 6 months of age and followed them to age 18-22 months. Lumbar spines and femurs were excised for analysis. Six month old intact control mice were sacrificed to define baseline parameters. Compared to young mice, aged/sham mice had a 42% reduction in lumbar spine bone volume/total volume (BV/TV), and maintaining constant estrogen levels over life in ovariectomized/estrogen-treated mice did not prevent age-related trabecular bone loss at this site. By contrast, life-long estrogen treatment of ovariectomized mice completely prevented the age-related reduction in cortical volumetric BMD and thickness at the tibial diaphysis present in the aged/sham mice. These data thus demonstrate that, in mice (as in humans), age-related loss of cortical bone in the appendicular skeleton is potentially related to estrogen deficiency, whereas trabecular bone loss, while accentuated by estrogen deficiency, is largely independent of estrogen. Further studies in rodents and in humans are needed to define the cause(s) of trabecular bone loss over life independent of changes in sex steroid levels.

References:

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