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Estrogen and bone: Insights from estrogen-resistant, aromatase-deficient, and normal men

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Abstract

Findings from estrogen-resistant and aromatase-deficient men have provided important insights into the role of estrogen in the male skeleton during growth. Importantly, as reported elsewhere in this issue, these data also suggested dose-response relationships between estrogen and bone turnover. In addition, studies in these unusual patients have stimulated research on defining the role of estrogen in regulating bone metabolism in normal adult and aging men, providing further insights into estrogen regulation of bone metabolism not only in men, but also in women.

1994 represents perhaps a watershed year in our thinking regarding sex steroids and the male skeleton. Prior to that, it was generally assumed that, similar to the critical role of estrogen in regulating bone metabolism in women [1], testosterone was the dominant (and perhaps only) sex steroid governing the maturation and maintenance of the male skeleton. However, a landmark case report published by Smith and colleagues [2] in the fall of 1994 forced a reevaluation of this longstanding dogma. The patient described in that report was a 28 year old male who initially presented to an orthopedic surgeon for evaluation of genu valgum (“knock knees”). As part of his evaluation, he had X-rays performed, which surprisingly showed unfused epiphyses. He was also very tall (6 ft 8 inches) and by history, had continued linear growth into adulthood. Pubertal development was otherwise normal, and through a series of astute studies, the investigators demonstrated elevated estradiol levels and homozygous mutations in his estrogen receptor (ER) α gene, which resulted in a non-functional ER. He also had markedly elevated values for bone turnover (resorption and formation) markers and osteopenia, with a spine bone mineral density (BMD) that was 3.1 SD below the mean for age-matched normal women and more than 2 SD below the mean for 15 year old boys (the patient’s bone age).

This was truly a remarkable patient who focused attention away from testosterone and firmly on estrogen as perhaps critical for the development of the male skeleton. Thus, despite normal testosterone levels, by virtue of his complete resistance to estrogen, this patient had unfused epiphyses, no clear growth spurt but rather slow linear longitudinal growth into his late 20’s, elevated bone turnover, and at least as assessed by dual energy X-ray absorptiometry, osteopenia. The inescapable conclusion was that even in males, estrogen was necessary for epiphyseal fusion, the pubertal growth spurt, and the acquisition of bone mass.

Subsequent to this report, Carani et al. [3] and Bilezikian et al. [4] described two patients with a skeletal phenotype very similar to that of the ER-resistant male. However, in these patients,

while serum testosterone levels were again normal, serum estradiol levels were undetectable, and both men had complete deficiency of the enzyme responsible for the final step in the synthesis of estrogens, aromatase [5]. But, in contrast to the ER-resistant male who had no response to exogenous estrogen treatment, both of the aromatase-deficient males responded to estrogen therapy with epiphyseal fusion and a significant increase in BMD.

It is in this context that the paper by Lanfranco et al. [6] in this issue is of particular interest. These investigators report a new case of aromatase deficiency in a 26 year old male and the long term (5 year) follow up of this patient during transdermal estradiol treatment. The baseline skeletal phenotype of this patient was similar to that of the ER-resistant male [2] and the previously reported cases of aromatase-deficient males [3,4,7,8]. Specifically, this patient also had tall stature, unfused epiphyses, and osteopenia. The novel twist to this report is the fact that the authors took advantage of the non-compliance of the patient to try to develop a dose-response relationship between serum estradiol levels and changes in bone turnover markers; based on their findings, the authors suggest that serum estradiol levels above 73 pmol/L (20 pg/ml) are necessary for closure of the epiphyseal cartilage and normalization of BMD and bone turnover markers in aromatase deficient and, by extension, normal males. These findings are consistent with a study in a different aromatase-deficient male from this same group, where Rochira et al. [7] found that while a transdermal estradiol dose of 25 µg/d (providing serum estradiol levels of 88 pmol/L [24 pg/ml]) increased BMD in that patient, a lower dose of 12.5 µg/d (providing serum estradiol levels of 55 pmol/L [15 pg/ml]) was associated with a decrease in BMD. Collectively, these data suggest that at least during growth in boys, serum estradiol levels of 73 pmol/L (20 pg/ml) or higher are needed for optimal skeletal maturation.

Important as these reports of ER- and aromatase-deficient males are, the question then becomes whether the conclusions regarding the critical role of estrogen in the male skeleton based on findings in these “experiments of nature” are also relevant to normal adult men and either the maintenance of bone mass or the loss of bone with aging? The answer appears to be “yes,” since a number of observational studies have now demonstrated that serum estrogen levels are important determinants of bone mass [9–16] and bone loss [17–19] in men. Moreover, short-term studies in which men are made hypogonadal and selectively replaced either with estrogen or testosterone have also demonstrated the importance of estrogen in regulating both bone formation and bone resorption in adult men [20,21]. Thus, while these findings do not exclude a role for testosterone in regulating bone turnover, it is clear that the lessons learned from the ER and aromatase deficient men are also applicable to normal adult men with mature skeletons, and the overall message is fairly clear: estrogen, even in men, is an important regulator of bone turnover and bone mass.

Is there, then, also a “threshold” for estrogen effects on bone in normal adult males (or females), as suggested by the studies with the aromatase-deficient males? Again, the answer appears to be “yes,” although perhaps a “qualified yes.” Interestingly, it has been easier to tease out dose-response relationships between serum estradiol levels and bone turnover or bone mass in men rather than women, since men span a range of estradiol levels that include this apparent threshold; by contrast, premenopausal women are well above this threshold, whereas postmenopausal women are considerably below it, making it difficult to define the overall relationship between serum estradiol levels and bone metabolism by studying only women [17]. Thus, studies using the selective estrogen receptor modulator (SERM), raloxifene, in men have found that men with low endogenous estradiol levels (< approximately 25 pg/ml) tend to have a decrease in bone resorption markers and men with endogenous estradiol levels above this value have the opposite response following raloxifene treatment – namely, an increase in bone resorption [22,23]. Moreover, rates of bone loss [17,18] and fracture risk [24] seem to be highest in men with estradiol levels below 20–25 pg/ml, and variations in estradiol levels above this range do not appear to be related to bone loss or fracture risk. The qualification to the “yes”

comes from recent studies using quantitative computed tomography (QCT) relating volumetric BMD (vBMD) separately in trabecular and cortical bone to serum estradiol levels [25]. Based on these studies, it appears that there is a clear threshold for this relationship in cortical bone, but perhaps not in trabecular bone; or at least that the relationship between serum estradiol levels and cortical bone plateaus at much lower estradiol levels (Figure 1A) than the relationship between serum estradiol levels and trabecular bone (Figure 1B). These recent findings are, in fact, entirely consistent with earlier data using QCT which found that a 4-fold higher dose of estrogen was required to prevent trabecular as compared to cortical bone loss in women following oophorectomy [26] (Figure 2). Thus, there likely is a threshold below which the male or female skeleton develops estrogen deficiency, but this threshold appears to be much higher for trabecular as compared to cortical bone (i.e., it takes more estrogen to prevent decreases in trabecular bone and less estrogen to prevent decreases in cortical bone).

How might this be explained at a cellular level? The answer is that we don't know, but one can propose plausible hypotheses. To do so, it is important to briefly review what we currently understand regarding estrogen regulation of bone remodeling. Estrogen has three fundamental effects on bone metabolism: (1) It inhibits the activation of bone remodeling and the initiation of new basic multicellular units (BMUs); (2) It inhibits differentiation and promotes apoptosis of osteoclasts, thereby reducing bone resorption; and (3) While estrogen suppresses self-renewal of early mesenchymal progenitors, it promotes the commitment and differentiation and prevents apoptosis of osteoblastic cells, thereby maintaining bone formation at the cellular level. Each of these actions of estrogen are reviewed briefly below.

At the tissue level, estrogen clearly reduces bone turnover, both histologically and as reflected by changes in bone turnover markers [27]. Given the increasing evidence that osteocytes may regulate the activation of bone remodeling via connections with bone lining cells [28], it is likely that the anti-remodeling effects of estrogen are mediated via the osteocyte. Indeed, withdrawal of estrogen is associated with increased apoptosis of osteocytes both in rodents [29] and in humans [30], although the specific molecular mechanisms by which this then leads to increased remodeling on the bone surface remain unclear.

In addition to inhibiting the activation of bone remodeling, estrogen also directly and indirectly suppresses bone resorption. Thus, by increasing OPG [31] and decreasing RANKL [32] production by osteoblastic cells, as well as by suppressive effects on the production of TNF- α [33] and other pro-resorptive cytokines [34], estrogen reduces osteoclastogenesis, at least in part via effects on osteoblastic and perhaps T-cells [35]. In addition, estrogen also modulates RANK signaling in osteoclastic cells [36,37] and induces apoptosis of osteoclasts [38], thereby having direct effects on osteoclastic cells.

Finally, estrogen is clearly important for the maintenance of bone formation. Perhaps the most direct evidence for this comes from human studies showing that acute (3 weeks) estrogen deficiency either in women [39] or in men [20] is associated with a fall in bone formation markers. However, due to the subsequent "coupling" of bone formation with resorption, bone formation increases over time, so that when chronically estrogen deficient women are studied, both bone resorption and bone formation markers are increased [40]. It also appears that the effects of estrogen on progenitor and osteoblastic cells may be stage-specific. Thus, consistent with the overall effects of estrogen on reducing bone remodeling, estrogen does reduce the self-renewal of early mesenchymal progenitors [41]. Perhaps the most consistent effects of estrogen are on inducing commitment of precursor cells to the osteoblast at the expense of the adipocyte lineage [42,43] and on preventing apoptosis of osteoblastic cells [29]. Estrogen has also been shown to enhance osteoblast differentiation [43], although data on effects of estrogen on osteoblastic differentiation are more variable and seem to depend on the model system used.

Given the complex effects of estrogen on bone, then, the challenge is to try to explain why trabecular and cortical bone might have different sensitivities to estrogen? One explanation may come from studies by Bord et al. [44] in developing human bone showing that whereas osteocytes and osteoblasts in cortical bone predominantly expressed ER α , the same cells in trabecular bone expressed not only ER α but also significantly higher levels of ER β than were present in cortical bone. While ER β by itself may have little or no direct role in regulating bone turnover [45], its main role may, in fact, be to modulate the action of ER α , since ER α / β heterodimers appear to be less sensitive to estrogen than ER α homodimers [46]. Thus, if bone cells (osteocytes, osteoblasts, and osteoclasts) in trabecular bone express more ER β than present in these cells in cortical bone, trabecular bone cells would be less sensitive to all of the actions of estrogen on bone noted above. As a consequence, higher levels of estrogen would be needed to preserve trabecular as compared to cortical bone, entirely consistent with the dose-relationship depicted in Figure 1 and the dose-response to estrogen treatment shown in Figure 2. As is also evident from Figure 1, as estrogen levels fall, for example during lactation, the dose-relationship in Figure 1 would predict that relatively more bone would be lost (and calcium mobilized for breast milk) from trabecular bone, while preserving cortical bone, which is critical for locomotion; this is exactly what is observed in lactating women [47]. Thus, the observed differential regulation of trabecular and cortical bone by estrogen makes eminent sense from an evolutionary perspective and the role played by bone as a storage site for calcium that is mobilized during lactation.

It is evident, then, that the ramifications of an unusually tall man with knock knees walking into an orthopedic surgeon's office in 1994 have been profound in terms of our understanding of estrogen regulation of bone metabolism not only in men, but also in women. Together with the subsequent description of the aromatase-deficient men, these human experiments of nature forced us to rethink long held dogmas and to focus our efforts on understanding the dose-relationships between estrogen and bone that were, ironically, easier to delineate in men than in women. It is also clear that despite decades of investigation, there are many unresolved questions about estrogen regulation of bone metabolism that hopefully will continue to provide challenges and intrigue for clinical and basic scientists.

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Figure 1.

Schematic illustration, based on the data of Khosla et al. [25], of the relationship between (A) cortical volumetric BMD (vBMD) and (B) trabecular vBMD and serum estradiol levels in a cohort of 314 men. Note that while cortical vBMD is correlated with estradiol levels at low estradiol levels, no relationship is evident at high estradiol levels, consistent with a “threshold” below which cortical bone becomes estrogen deficient. By contrast, trabecular vBMD remains correlated with estradiol levels at low and high serum estradiol levels, suggesting either the absence of a threshold or a threshold considerably higher than that present for cortical bone. Adapted from Khosla et al. [25], with permission from the American Society for Bone and Mineral Research.

Figure 2.

The estrogen dose-response relationships determined by (A) mean peripheral cortical and (B) vertebral trabecular mineral measurements over 24 months of treatment with the various doses of estrogen indicated. The cross-hatched regions represent no significant change from baseline (i.e., less than twice the coefficient of variation or precision of measurement). Note that while cortical bone loss is prevented at an estrogen dose of 0.15 mg/d (panel A), four times this estrogen dose (0.6 mg/d) is required to prevent trabecular bone loss (panel B). Adapted from Genant et al. [26], with permission.