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EDITORIAL

Estrogens, the be-all and end-all of male hypogonadal bone loss?

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Gender is one of the strongest predictors of osteoporotic fracture risk, second only to ageing. A recent systematic review of worldwide epidemiology revealed that hip fracture incidence is about twofold lower in men compared to women, despite greater than tenfold variation between geographic regions [1]. This lower fracture incidence occurs despite persisting underdiagnosis and undertreatment of osteoporosis in men, which probably explains why hip fracture incidence may be decreasing in women but not men [2–5]. It is well known that men generally have a more robust body composition; even after correction for an average 10 % greater height and bone length, men at the age of peak bone mass have 25 % greater bone mineral content [6], almost 50 % greater muscle mass and power and half the fat mass of women [7]. Conversely, late-onset male hypogonadism increases the risk of bone loss, muscle atrophy and fat accumulation [3, 8]. Understanding the underlying mechanisms involved in this gender dimorphism in body composition may thus identify additional therapeutic targets not only for osteoporosis, but also for sarcopenia and obesity.

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Female sex steroids on a male genetic background

Embryonically, we are all destined for female development, unless SRY (sex-determining region on the Y chromosome) and other transcription factors turn the bipotential gonads into testes capable of testosterone (T) production. Studies on bone health in sexual medicine provide unique opportunities to examine whether sexual dimorphism is ultimately determined by sex chromosomes (genetic determinism) or sex steroids (endocrine regulation).

Van Caenegem et al. [9] are the first to study changes in areal and volumetric bone mineral density (aBMD, vBMD) and bone geometry in a representative, sizeable cohort (compared to the small number of subjects treated for gender dysphoria) of 49 male-to-female transsexual persons. The strength of this research paradigm is evident to anyone closely familiar with the spectacular bodily transformations experienced by subjects under cross-gender hormonal therapy. In a previous cross-sectional study by Van Caenegem et al., female-to-male transsexual persons had normal female body composition at baseline, but those on long-term T therapy exhibited increased lean body mass and grip strength, decreased fat mass with android distribution and increased radial cortical bone size with lower cortical vBMD [10]. The prospective design of their current study is however important because, compared to male controls, these male-to-female transsexual persons had baseline low aBMD due to somewhat lower periosteal circumference and lower trabecular vBMD, lower lean body mass, lower grip strength and muscle cross-sectional area. This was probably related to lifestyle differences, as evidenced by less sports activities and lower serum 25-OH-vitamine D levels.

The main finding of this study was that vBMD and cortical bone size remained stable (although trabecular vBMD slightly decreased) after 1 to 2 years of estrogen therapy with or without the anti-androgen cyproterone acetate (which brought T and estradiol (E2) levels within the normal female range). Bone turnover markers decreased, muscle mass and strength further decreased and fat mass increased. Another strength of this study is the use of peripheral quantitative computed tomography (pQCT) to avoid the limitations due to the projectional nature of conventional dual energy X-ray absorptiometry; aBMD apparently increased, but the pQCT data and lack of a prospective control group cast doubt on whether this is a true finding. Although this study has some additional limitations including short follow-up and use of lenient statistics, it offers reassurance about bone loss during cross-sex hormonal therapy in transgender subjects. But what are the broader implications of these results, if we look at the state of the science on how sex steroids regulate musculoskeletal maintenance?

Van Caenegem et al. rightly conclude that despite substantial muscle loss with androgen suppression, the prevention of bone loss in these male-to-female transsexual person is yet another attestation to the major role for estrogens in the male skeleton. Indeed, older men have higher E2 levels than postmenopausal women [6] because T levels (the substrate for E2 via aromatization) are well maintained in most elderly men. In our opinion however, two important questions remain: Is there an independent role for androgens in bone loss in older men? And secondly, are there other factors beyond androgens and estrogens responsible for skeletal sexual dimorphism and hypogonadal bone loss?

Male bone maintenance: is there an independent role for androgens?

Preclinical studies

Critics about direct androgen actions in bone could say that their effects may rely entirely on their myotrophic actions. Because it is quite difficult to study effects of androgens on bone independent of muscle-bone interactions in humans [10], preclinical models provide useful mechanistic insights. Earlier studies in androgen-resistant, AR/ERα knockout and overexpressing rodent models and in vitro studies suggest a dual mode of action by which both AR and ERα play a direct role in restraining male bone turnover and stimulating periosteal bone formation; there is even some animal evidence for a similar effect of both AR and ERα in muscle and fat [3, 11, 12]. However, these conclusions were reached in ubiquitous AR/ERα knockout models. In more recent conditional, cell-specific knockdown mouse models, male cortical and trabecular bone is directly regulated by ERα in osteoprogenitor cells, osteoblasts and osteocytes [11], while AR in these bone cells has only a mild effect which is limited to trabecular bone. Nevertheless, AR overexpression in osteoblasts stimulates periosteal bone in the calvaria [13], which is unlikely to be explained by bone-muscle interactions. Conditional AR ablation in muscle [14, 15] and adipose tissue [16] also confirms a direct but humble role for androgens in these tissues. Thus, these conditional knockdown models do not fully reproduce the cortical bone deficits, sarcopenia and metabolic adversities observed in hypogonadal men or global ARKO male mice (both of which may have not only low T but also E2 levels) [11]. Non-aromatizable androgens clearly stimulate periosteal bone formation via AR in preclinical studies [17]; conditional genetic knockdown models may have been unable to confirm this role for AR in cortical bone because of the limitations of Cre-LoxP technology, or because the right target cells remain to be identified.

Epidemiological studies

Regarding the first question of independent effects of androgens and estrogens on ageing men's bone loss, we already have multiple lines of evidence already supporting the role of estrogens in male skeletal conservation. Firstly, dozens of observational and genetic studies in ageing men show an independent association between male bone mass, microarchitecture or fracture risk and circulating E2 levels or polymorphisms in the estrogen receptor alpha (ERα) or aromatase gene. The same associations with T levels or AR polymorphisms were however weak or disappeared after correction for estrogen effects in most studies [3, 11]. Nonetheless, some studies have shown an independent association of T with BMD at cortical sites or bone area [18, 19], muscle mass and strength, reduced fat mass [20, 21] and even decreased fracture risk, albeit mostly independent of aBMD [22, 23]. In two MrOS studies, low T was independently associated with bone loss and fractures but only in men with low E2 levels [24, 25]. Based on these results, Khosla proposed a model in which estrogens hold the dominant effect on male bone loss and fracture risk, whereas androgens further modulate this risk mainly via extraskeletal fracture determinants like muscle mass (which also determines cortical bone development) and risk of falls [26]. However, nearly all of these observational studies are limited by the small numbers of endpoints, variation of T and E2 levels within the normal range instead of more narrowly defined male hypogonadism [8], as well as inherent covariation between androgens, estrogens and sex hormone-binding globulin. Furthermore, there is growing evidence that calculated free or bioavailable serum sex steroid concentrations have serious limitations [27]. Studies with high-resolution pQCT have emerged, but we still need more prospective instead of cross-sectional studies. But in the end, observational studies cannot prove causality; both

sex steroid concentrations and bone loss could be determined by other reproductive or hypothalamic signals (see next section on reproductive signals).

Interventional studies

A higher level of evidence is offered by placebo-controlled, randomized trials. In men with prostate cancer treated with androgen deprivation therapy (which is also brings estrogens in the postmenopausal range), selective estrogen receptor modulators (SERMs) have been shown to maintain aBMD and prevent vertebral fractures [28, 29]. In healthy adult male volunteers, aromatase inhibition [30] or treatment with non-aromatizable dihydrotestosterone [31], both of which increase androgen bioactivity but suppress estrogens, invoke bone loss. Although studies with gonadotropin-release hormone agonists and T or E2 replacement suggested that androgens maintained bone formation markers and estrogens suppressed bone resorption markers in men [32, 33], another study contradicted this [34]. Recently, Finkelstein et al. conducted a similar, larger study with chemical castration and graded T replacement with or without aromatase inhibition [35]. They concluded that loss of androgens causes muscle loss whereas loss of estrogens increases adiposity in men with low T. Bone microarchitectural outcomes have been published in abstract [36], showing again a dominant role for estrogens and not androgens. Yet, we should not ignore the fact that most of these interventions were acute and short-term, whereas transgender studies allow characterization of long-term effects. Importantly, the effect of physiological (or anabolic) T replacement doses in the context of normal E2 levels remains unclear (Table 1). Although it is important to realize that androgens cannot prevent bone loss due to near-total E2 deficiency, it may be more important to resolve the controversy surrounding the skeletal efficacy [37] as well as the cardiovascular safety of T replacement in frail older men at risk of osteoporosis [38]. The Testosterone Trials (NCT00799617) and especially the bone substudy will hopefully shed light on this matter. Hopefully thereafter, we can start thinking about studies to examine whether androgens offer selective benefits beyond their role in maintaining estrogen levels.

In summary, we believe the pendulum shouldn't swing too far. Even in the face of an overwhelming amount of data pointing towards the importance of aromatization and estrogens in the male skeleton, we need to distinguish between what we know, what we think we know, and what we still don't know. Although the obligation lies with andrology researchers to provide much needed evidence in humans, we would like to remind readers that lack of evidence for an effect—as for bone preservation despite loss of androgens in the controlled study by Van Caenegem et al.—should not be taken as evidence for a lack of effect.

Beyond sex steroids: bone's ties with reproduction

A growing body of evidence supports an intimate relation between bone and gonadal factors beyond sex steroids. We refer the reader to a recent review for a more comprehensive discussion on this topic [39], and limit ourselves to a few examples. Direct bone cell regulation by gonadotropins has attracted considerable attention, but the presence of follicle-stimulating hormone receptors in bone cells or a direct role independent of sex steroids remains controversial in both rodent and human studies [11, 40, 41]. Inhibin A however is a credible positive regulator of bone mass and turnover [40, 42, 43]. In the testis, Leydig cells have been suggested to express CYP2R1 which has been implicated in vitamin D 25-hydroxylation [44], although definitive support for this mechanism remains lacking [39]. The increase in vitamin D despite gonadotropin suppression in the study by Van Caenegem et al.

Table 1 Evidence synopsis regarding the influence of androgens and estrogens on bone health in adult and elderly men

		aBMD	vBMD and structure	Bone turnover	Fractures	Muscle mass
Effect of deficiency (population setting)	Low E2, normal or high T	↓ [A,B]	↓ [A,B]	↑ [A,B]	↑ [B]	= [A,B]
	Low T, low E2	↓ [A,B]	↓ [A,B]	↑ [A,B] (↓ formation [A])	↑↑ [B]	↓ [A,B]
	Low T, normal E2	= [B]	?	(↓ formation [A])	↑ [B]	↓ [A,B]
Effect of replacement (clinical setting)	SERMs (ADT)	↑ [A,B]	?	↓ [A]	↓ [A]	=
	E2 (trans women)	↑ [B]	= [B]	↓ [B]	?	↓ [B]
	T (trans men)	↑ [B]	↑ [B]	↑ [B]	?	↑ [B]
	T (and E2) (elderly men)	(↑) [A,B]	?	↓ [A,B]	?	↑ [A,B]
	SARMs/DHT with normal E2	?	?	?	?	?

↓ decrease; ↑ increase; = no change; () equivocal evidence; ? no conclusive evidence available; [A] evidence from randomized controlled trials; [B] evidence from controlled intervention studies or large, population-based epidemiological studies in older men

SERMs selective estrogen receptor modulators, *ADT* androgen deprivation therapy for prostate cancer

[9] apparently contradicts a major role for gonadal vitamin D 25-hydroxylation, although this finding is probably confounded by vitamin D supplement prescription and lifestyle changes during clinical follow-up in these transgenders. Leydig cells also produce insulin-like peptide 3 which modulates osteoblast activity [39]. Critical transcription factors acting downstream of SRY to induce male sexual differentiation like SRY-box 9 (SOX-9) and the desert hedgehog gene have been associated with BMD in genome-wide meta-analysis [45]. SOX-9 in turn is essential for COL2A1 expression and chrondrogenesis. Finally, gonadal factors may not only improve bone health, but the causality may also lie in the opposite direction. The group of Karsenty recently showed that osteocalcin promotes testosterone biosynthesis in Leydig cells, and that heterozygous missense mutations in the osteocalcin receptor GPRC6A are a cause of primary testicular failure [46]. However, these findings remain to be viewed cautiously because of difficulties in translating these findings in other mouse models or in humans [47, 48].

We can conclude that bone has intricate and complex ties with gonadal and reproductive functions which include androgens, estrogens, transcription factors involved in sexual differentiation and possibly other gonadal endocrine factors, which however require further confirmation in further studies on male osteoporosis. Sexual and reproductive medicine may offer fertile grounds for further translational bone research.

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