Testosterone: More Is Not Always Better

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Having conducted population-based studies on the relationship of sex steroid levels to bone mass in Rochester, Minnesota for many years, I have been struck by just how often male members of the medical staff at our institution who participate in these studies inquire about their testosterone level. Discovering that they happen to be in the top 10th percentile is often a cause for celebration; conversely, being told that they happen to be "average" or, most distressingly, "below average," generally leads to at least temporary anguish. Not surprisingly, despite the numerous publications from our group and others regarding the key role for estrogen in bone metabolism in men (summarized in Ref. 1), none of my colleagues inquire or seem to care one way or another about their estradiol level. At least based on this anecdotal experience, it seems that even in the minds of well-informed male medical professionals, more testosterone is clearly "better," whereas estrogen is largely irrelevant.

It is in this context that men with modest testosterone levels should perhaps have their chance to celebrate based on the results of the study by Burnett-Bowie *et al.* (2) published in this issue of *JCEM*. This carefully conducted clinical trial clearly demonstrates that at least for bone, more testosterone is not necessarily better, especially if it comes at the price of lower estrogen production.

The trial is based on the premise that because male aging is associated with declining testosterone levels and with increased body fat, decreased muscle mass, strength, and bone mineral density (BMD) (1), replacing testosterone in elderly men should be beneficial. However, rather than administering exogenous testosterone, which requires topical or parenteral dosing and significantly increases estrogen levels (via peripheral aromatization) and which may, in turn, result in side effects such as gynecomastia, the authors chose to test the effects of increasing endogenous testosterone production by blocking aromatization of testosterone to estradiol using a potent orally administered aromatase inhibitor, anastrozole (2). By removing negative feedback signals, the anastrozole-induced decrease in estradiol increases GnRH and gonadotropin production at the hypothalamus and pituitary, respectively, thereby increasing testosterone production (3).

The Burnett-Bowie *et al.* (2) paper reports on 69 men, aged 60 and older, who completed the 1-yr, double-blind, randomized, placebo-controlled trial. Anastrozole had the desired effects on serum testosterone levels, with mean values increasing from 319 ng/dl (the lower end of the normal range) at baseline to 524 ng/dl at 3 months and a slight decline to 474 ng/dl at 1 yr, an overall increase of approximately 50%. As expected, estradiol levels decreased (by 20%), from 15 to 12 pg/ml at 3 months, and remained stable at this level thereafter. However, despite the substantial increase in serum testosterone levels, posterior-anterior (PA) spine BMD decreased by 1.7% in the anastrozole group while increasing by 0.8% in the placebo group ($P = 0.0014$ for the difference between groups), with similar trends for differences between the groups for femoral neck, total hip, and total body BMD. The inescapable conclusion from these data is that the 50% increase in testosterone levels was trumped by the much more modest 20% reduction in estradiol levels, leading to negative skeletal effects of anastrozole therapy in aging men.

To some extent, these findings are not surprising and are perhaps predictable, based on the now extensive body of evidence for a critical role for estrogen in regulating the male skeleton (1). Although previous studies in men had shown that serum estradiol levels were related to bone density (4) and that estrogen regulated bone turnover (5,

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Abbreviations: BMD, Bone mineral density; SARM, selective androgen receptor modulator.

6) and bone loss (7) in elderly men, more recent studies have now also demonstrated that serum estradiol, and not serum testosterone, levels are the most robust hormonal predictors of fracture risk in aging men (8–10). What is perhaps somewhat surprising from the study of Burnett-Bowie *et al.* (2) is that relatively small reductions in estradiol levels appear to significantly modulate rates of bone loss. Although this may reflect just how heavily leveraged the male skeleton is on circulating estrogen levels, an alternate explanation for this finding is that changes in serum estradiol levels may not fully reflect reductions in local estrogen production in osteoblastic cells (11), and the extent of skeletal estrogen deficiency induced by anastrozole may therefore be underestimated by serum estradiol measurements.

It is also perhaps somewhat surprising that despite a fairly consistent pattern of changes in BMD at various sites, anastrozole treatment did not alter markers of bone formation or resorption (2). Because other studies have shown that estrogen clearly suppresses bone resorption in men and is also critical for the maintenance of bone formation (5), the lack of change in bone turnover markers may reflect the relative insensitivity of these markers to a subtle imbalance between bone resorption and bone formation induced by aromatase inhibition, which nonetheless resulted in measurable bone loss even over just 1 yr.

The findings of Burnett-Bowie *et al.* (2) also need to be placed in the context of previous trials of testosterone replacement in older men. Thus, Amory *et al.* (12) found that 200 mg of im testosterone every 2 wk increased spine BMD by 10% and total hip BMD by 3%. By contrast, effects of transdermal testosterone on bone density have been marginal (13), suggesting that the higher testosterone levels associated with im treatment may be necessary for achieving beneficial skeletal effects. Based on the evidence provided by Burnett-Bowie *et al.* (2), it is probable that it is the higher estradiol levels associated with the higher testosterone levels (rather than the testosterone levels themselves) that are necessary for optimal skeletal benefits.

In the same study of im testosterone noted above, Page *et al.* (14) also found that testosterone therapy was associated with beneficial changes in body composition, including an increase in lean mass and a decrease in fat mass. Interestingly, a previous report by Burnett-Bowie *et al.* (3) using body composition data from the same anastrozole trial found no effect of anastrozole on either lean or fat mass. This finding raises the question of whether the body composition changes associated with testosterone therapy may also be mediated, at least in part, via aromatization to estradiol. As noted by the authors in their previous publication (3), there is evidence from rodent and human studies supporting a role for estrogen in regulating body composition. Thus, male mice with inactivation of either estrogen receptor α or the aromatase genes have increased fat mass (15, 16). Moreover, Vandenput *et al.* (17) found that in orchidectomized rats, estradiol not only prevented bone loss but also increased lean body mass and inhibited the orchiectomy-associated increase in fat mass. Studies in men with prostate cancer have found that treatment with bicalutamide (an androgen receptor blocker that increases estradiol levels) results in smaller increases in fat mass compared with treatment with a GnRH agonist (which reduces both testosterone and estradiol production) (18). Combined with the data from the anastrozole study (3), these findings indicate that aromatization of testosterone to estradiol may be critical not only for skeletal preservation but also for beneficial effects on body composition.

The anastrozole data also have potential implications for the development of selective androgen receptor modulators (SARMs), which are generally not aromatized to estrogens. There is considerable pharmaceutical interest in small molecule SARMs, which activate the androgen receptor in certain tissues, such as muscle and bone, but not in other tissues, such as the prostate. While rodent studies with such compounds have shown promise (19), a caveat to be kept in mind is that whereas there is widespread expression of the aromatase enzyme in primates and in humans (*e.g.* in adipose tissues and bone), expression of aromatase is much more limited in rodents, with the major sites of expression being the gonads and the brain (20). This is reflected by the much lower serum estradiol levels in male mice (~5 pg/ml or less) (21) compared with adult men (~30 pg/ml) (7). Moreover, administration of even physiological doses of testosterone to men results in clear increases in serum estradiol levels due to peripheral aromatization of testosterone to estradiol (12); by contrast, administration of even highly pharmacological doses of testosterone fails to increase serum estradiol levels in male mice (22), due to the relatively poor peripheral aromatization of testosterone to estradiol in rodents. As such, the male rodent skeleton may have intrinsically different responses to estradiol *vs.* testosterone than the human skeleton, and findings in rodents regarding the efficacy of nonaromatizable SARMs in preventing bone loss (and perhaps in improving body composition) may not be relevant to humans. Ongoing clinical trials with these compounds should provide an answer to this important question.

In summary, whereas the concept of using an aromatase blocker to enhance endogenous testosterone production was an attractive one, it does not appear to be a viable approach for preventing age-related declines in bone mass or in improving parameters of body composi-

tion in men. These findings also suggest that as males, we should perhaps be just as interested in our estradiol levels as we seem to be in our testosterone levels, if not more so. For many reasons, however, such a dramatic change in focus seems unlikely.

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