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COMMENTARIES

Dual Mode of Action of Androgens on the Skeleton: Are Androgen Receptor and Estrogen Receptor Activation Equally Important at the Same Time and Place?

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Commentary on: Matsumoto C, Inada M, Toda K, Miyaura C. Estrogen and androgen play distinct roles in bone turnover in male mice before and after reaching sexual maturity. *Bone*. 2005 Oct 5; [Epub ahead of print]

Skeletal actions of androgens may result from direct activation of the androgen receptor (AR), or may alternatively depend on stimulation of the estrogen receptor α (ERα) following aromatization of testicular and/or adrenal androgens into estrogens (1). This concept of "dual mode of action" of androgens is primarily based on replacement studies performed in mice with either a disrupted ERα gene (2) or inactive AR (3). Both receptors are essential for normal skeletal growth and bone mineral acquisition in both mice and humans (4;5).

Although it has been clearly demonstrated that both androgens and estrogens are critically important for male bone homeostasis, the relative impact of AR versus ERα activation for male bone physiology remains unsettled. This raises the question of whether both AR- and ER-mediated androgen actions are equally important at the same 'time' and at the same 'place'. One of the pending issues in this respect is whether trabecular and cortical bone are equally affected by both sex steroids during and after puberty and whether trabecular and cortical bone are equally sensitive to both modes of action.

In a recent article by Matsumoto *et al.* (6), sex steroid deficiency was induced by orchidectomy in wild-type (WT) mice at 3 weeks (start of puberty) and 7 weeks (late puberty) of age, respectively. All animals were sacrificed 4 weeks later and trabecular and cortical bone parameters were compared to sham-operated WT mice. In line with previous observations (7), periosteal bone formation significantly declined between 7 weeks (late puberty) and 11 weeks (maturity) of age in sham-operated WT mice. Sex steroid deficiency, as induced by orchidectomy, further reduced the periosteal bone formation rate, but only when performed at 3 weeks of age, and not at 7 weeks of age. This finding suggests that puberty represents a critical time window during which cortical bone is apparently more responsive to the effects of sex steroid deficiency. However, it remains unclear why periosteal bone cell proliferation is more sensitive to sex steroid deficiency during puberty compared to later stages. Very few studies have measured periosteal bone formation by dynamic histomorphometry in mice, and none have done so at different ages. In rats, on the other hand, earlier studies found a reduction of cortical bone area following orchidectomy even when the procedure was performed after puberty (8;9). Differences in periosteal bone formation rates in orchidectomized rodents may be explained by species differences or by differences in experimental procedure, such as age or duration of sex steroid deficiency. The study by Matsumoto *et al.* (6) clearly indicates that mice may be more responsive to the effects of orchidectomy when performed at the start of puberty rather than during early adulthood. Interestingly, although trabecular bone was not examined in this study, several studies demonstrate that orchidectomy reduces trabecular bone to a similar extent both

during and after puberty. Therefore, in contrast to cortical bone, trabecular bone seems equally sensitive to orchidectomy performed during or after skeletal maturation.

Matsumoto *et al.* (6) also addressed the issue of relative impact of androgen action versus estrogen action on the skeleton. Skeletal changes induced by aromatase deficiency using aromatase knockout mice were compared with changes induced by orchidectomy alone or by orchidectomy in combination with aromatase deficiency. Unfortunately, periosteal bone formation was only studied at maturity (11 weeks of age) and therefore at a time point when periosteal cells, at least according to the experimental procedure of this study, may be less responsive to orchidectomy. The authors imply that aromatase deficiency does not decrease or may even increase periosteal bone formation at this time point. However, an earlier study demonstrated a significantly decreased cortical area in aromatase-deficient male mice (10), which is in line with other studies demonstrating that aromatase deficiency reduces periosteal expansion, at least during puberty in male rodents (11;12). Moreover, aromatase knockout mice in this study have lower areal BMD at the middle part of the femur at 11 weeks of age, suggesting (although not proving) that aromatase deficiency impaired cortical bone size.

Matsumato *et al.* (6) also reported that aromatase deficiency resulted in a significant loss of trabecular bone as a result of an increase in osteoclast number. Interestingly, additional sex steroid deficiency in aromatase-deficient mice further decreased trabecular bone volume and increased osteoclast numbers. In line with these findings, our group previously showed that orchidectomy in combination with the administration of an aromatase inhibitor induced a more severe trabecular bone phenotype than orchidectomy or treatment with aromatase inhibitor alone (11). Therefore, in the absence of testicular tissue, the limited peripheral aromatase activity appears to be able to prevent, to some extent, further bone loss in male rodents. These findings are reminiscent of observations of further bone loss induced by aromatase inhibitors in postmenopausal women and therefore suggest that in both males and females, very low estrogen levels may still affect trabecular bone metabolism.

The authors of this study imply that androstenedione produced by the adrenals undergoes aromatization into estrogens within fat tissue. According to this concept, the additional effect on trabecular bone and osteoclast number in orchidectomized aromatase knockout mice, compared to orchidectomized WT mice, is explained by the absence of aromatization of androstenedione in fat tissue. Peripheral aromatization in rodents, however, is very limited (13), and so no firm conclusions can be drawn about the relevance of this pathway for bone maintenance in rodents. Alternatively, one may hypothesize that reduced aromatase activity affects the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis and thereby lowers IGF-I levels. The relevance of IGF-I for cortical bone metabolism has been previously established (14).

In conclusion, the article by Matsumato *et al.* (6) demonstrates that periosteal bone shows a different sensitivity to the effects of sex steroid deficiency depending on age, with puberty being a critical time period. In addition, the authors show that both androgens and estrogens independently suppress bone resorption and thereby regulate bone turnover and trabecular bone volume. However, questions persist regarding the relative impact of AR and ERα activation on different (trabecular versus cortical) bone compartments.

Conflict of Interest: The authors report that no conflicts of interest exist.

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