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COMMENTARIES

Riddle of Estrogen Regulation of IGF-I Action and Periosteal Bone Formation

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Commentary on: Venken K, Schuit F, Van Lommel L, Tsukamoto K, Kopchick JJ, Coschigano K, Ohlsson C, Moverare S, Boonen S, Bouillon R, Vanderschueren D. Growth without growth hormone receptor: estradiol is a major growth hormone-independent regulator of hepatic IGF-I synthesis. *J Bone Miner Res*. 2005 Dec;20(12):2138-49.

The importance of the insulin-like growth factor (IGF)-I axis in the regulation of bone size and bone mineral density (BMD), two important determinants of bone strength, has been well established from clinical studies involving patients with growth hormone (GH) deficiency and IGF-I gene disruption, as well as from transgenic animal studies involving disruption and overexpression of components of the IGF-I axis (1-10). In terms of the mechanisms involved in IGF-I's regulation of bone accretion, it is now widely accepted that GH is the major regulator of IGF-I production, as serum levels of IGF-I are decreased by more than 75% under conditions of GH deficiency (3;5). In addition to GH, a number of osteoregulatory agents, including estrogen, parathyroid hormone (PTH), and bone morphogenic proteins (BMPs), have been shown to regulate IGF-I production in bone cells. Accordingly, comparison of a BMD deficit in mice lacking IGF-I versus GH has shown that both GH-dependent and GH-independent mechanisms contribute to bone accretion (4).

It is also known that puberty is a critical period for bone accretion, as nearly 40% of bone accretion takes place during the period of sexual maturation (4;11). Recent studies using transgenic mouse models lacking GH or IGF-I action have also shown that pubertal growth period-induced increases in bone accretion are severely compromised in the absence of GH/IGF-I action (4), which is consistent with past studies demonstrating that a close interplay between estrogen and GH leads to attainment of peak BMD (12). Although the physiological basis of estrogen and GH interaction is not well understood, estrogen is known to affect GH action on multiple levels, including secretion, receptor expression, and signaling (13). Furthermore, cross talk between IGF-I and estrogen receptor signaling has also been demonstrated (14). In addition to systemic endocrine IGF-I actions, it is now well established that locally produced IGF-I also plays a key role in regulating bone accretion (10). Our limited knowledge of estrogen regulation of production and/or actions of IGF-I at the local tissue level further complicates our understanding of how estrogen regulates GH/IGF-I action in bone and other tissues.

A recent paper published by Venken *et al*. (15) adds further complexity to estrogen's regulation of GH/IGF-I action. In this elegant study, the Leuven group has addressed an important question concerning the extent to which estrogens could regulate skeletal growth independently of GH action by treating orchidectomized (ORX) GH receptor (GHR) knockout or wild type mice with estradiol and evaluating the effects on skeletal growth and IGF-I expression. They found that four weeks of estrogen treatment caused a significant increase in the periosteal bone formation rate, resulting in periosteal expansion in GHR knockout ORX, but not wild type ORX, mice. Furthermore, estrogen treatment increased IGF-I expression in the liver, but not in bone or muscle. Accordingly, serum IGF-I levels

were increased in estrogen-treated ORX mice compared to control groups and these correlated positively with the periosteal bone formation rate. The authors also provide evidence that estrogen's effect on hepatic IGF-I expression in ORX GHR knockout mice may be mediated via activation of STAT5 signaling. These exciting data provide evidence for a novel, GH-independent stimulation of IGF-I synthesis in the liver.

This study also raises a number of questions regarding estrogen regulation of IGF-I actions and periosteal bone formation in mice. First, past studies using mice lacking IGF-I and GH have shown a 40% and 25% reduction in periosteal circumference, respectively (4;6). However, no reduction in periosteal circumference was observed in estrogen receptor (ER)-α and ER-β double knockout female mice (16), while it was reduced by 7% in the double knockout male mice (17). Thus, much of the effect of the GH/IGF-I axis on bone size appears to be independent of ER-α/β in mice, suggesting that estrogen action on periosteal bone formation may be mediated via a mechanism independent of ER-α and/or ER-β. Second, although estrogen treatment increased IGF-I expression in both wild type and GHR knockout ORX mice, serum IGF-I and periosteal bone formation rates were increased only in the GHR knockout mice. Serum IGF-I levels, if any, were lower in the estrogen treated wild type ORX mice compared to controls. Thus, it appears that estrogen regulates serum IGF-I and periosteal bone formation rates only under conditions when hepatic IGF-I expression is low. The molecular basis for this differential effect of estrogen in wild type and GHR knockout ORX mice needs to be determined.

Not withstanding the above unanswered questions, the study by Venken *et al*. (15) provides evidence for a novel mechanism of estrogen control over IGF-I expression in the liver, independently of GH, in GHR knockout ORX mice. While this novel mechanism of action of estrogen is fascinating, its complexity is not surprising given the importance of estrogen and the GH/IGF axis in the regulation of bone growth. Thus, it is likely that further puzzles need to be solved before the riddle of estrogen regulation of IGF-I and periosteal bone formation is completely understood.

Conflict of Interest: The author has declared that no conflict of interest exists.

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