CLINICAL STUDY

Commentary-FSH and bone 2010: evolving evidence

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Abstract

Bone loss due to menopause, natural or artificial, has been attributed solely to low estrogen. However, in a woman's life, the most precipitous bone loss begins 2 years prior to the last menstrual period, during which time estrogen levels are unperturbed whereas FSH is elevated. Our cell-based and mouse genetic studies have shown that FSH stimulates bone resorption by osteoclasts directly in a pituitary–bone axis, independently of the estrogen effect. On the basis of this and evolving clinical and scientific evidence, we propose that elevated FSH contributes to bone loss across the menopausal transition, particularly during late perimenopause. In the current issue of the *European Journal of Endocrinology*, Rendina *et al.* strengthen the view for a primary role of FSH signaling in the regulation of bone mass and bone remodeling in humans by demonstrating that an 'activating' polymorphism AA rs6166 causes low bone mass and high bone turnover.

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Osteoporosis is a devastating and relentless disease, resulting in a fracture in one out of every two individuals over the age of 50. What causes this increased bone fragility and resulting susceptibility to hip, spine, and wrist fractures? In the early 1700s, the British surgeon John Hunter hypothesized that bone undergoes remodeling – i.e. bone is forever changing itself by reorganizing into a newer, stronger configuration to resist ongoing stresses, such as physical activity (1). Bone is lost when the cells degrading old bone, osteoclasts, outpace the cells re-laying new collagen and mineral, the osteoblasts.

What would cause the osteoclasts to degrade bone at a higher rate than the body's ability to re-build bone? During the mid 1900s, Fuller Albright at the Massachusetts General Hospital noted that the most dramatic bone loss occurred after menopause, either naturally or surgically induced (2). Thus, he hypothesized a link between the loss of sex steroids and osteoporosis, a *corpus* of observations that led to estrogen hormone replacement therapy becoming the first successful treatment for osteoporosis.

Within the past decade, hormone replacement therapy has fallen out of favor because of associated cardiovascular risks (3). Fortunately, the plot of bone density loss versus age in both genders has been re-examined, and certain key observations have been made. It was noted that women have a precipitous drop in bone mass during the menopausal transition. Notably, bone loss is profoundly accelerated in the late perimenopause (4, 5). In fact, nearly half of life time bone loss can occur within the first 5 years of menopause; this loss

of bone mass is associated with microstructural degradation ultimately predisposing to fractures (6).

Surprisingly, however, during this phase of rapid, late perimenopausal bone loss, estrogen levels are normal. Thus, a conundrum: could the hypothesis – the loss of estrogen is the *sole* cause of osteoporosis – be wrong? There is clear genetic and pharmacological evidence for a protective role of estrogen on the skeleton (7). *In vitro* studies show that estrogen directly inhibits osteoclast formation (8, 9). Estrogen also acts on osteoblasts to indirectly inhibit osteoclast formation by decreasing the secretion of the pro-osteoclastic cytokine receptor activator of NF- κ B-ligand (RANK-L) and increasing the decoy receptor for RANK-L, osteoprotegerin (10). Indirect effects of estrogen on osteoclast formation also occur through T-lymphocytes, where estrogen inhibits the production of another pro-osteoclastic cytokine tumour necrosis factor- α (TNF- α) (11–13). In addition to its inhibitory effect on osteoclast formation, estrogen has established anabolic actions mediated via osteoblasts (14).

If estrogen protects the skeleton, why then is there striking bone loss occurring in the late perimenopause if estrogen levels during this period are unperturbed? The answer to this question was ultimately inspired by our earlier studies on hyperthyroidism. In 2003, we discovered that the pituitary-derived TSH could bypass its primary endocrine target, the thyroid, and act directly on osteoclasts and osteoblasts to modulate bone turnover (15). The results of those studies had implications for the bone loss associated with subclinical hyperthyroidism in which thyroid hormones are normal and TSH is low. For the first time, we could

explain why bone loss occurred in these patients given their normal thyroid hormone levels – low TSH appeared directly to cause their bone loss (16).

Using a similar line of argument, we hypothesized in 2006 that changes in the circulating levels of the pituitary-derived FSH may contribute to the late perimenopausal bone loss when estrogen levels are unperturbed. This hypothesis was then bolstered by several clinical studies on the menopausal transition, where bone loss was found to correlate with dramatic increases in FSH. The Study of Women's Health Across the Nations (SWAN), a longitudinal, cross-sectional study of 2375 perimenopausal women, found a strong correlation of FSH levels to markers of bone degradation (17), and demonstrated that changes in the levels of FSH over 4 years could predict decreases in bone mass (5). Similarly, Xu *et al.* found a significant association between the incidence of osteoporosis and high serum FSH levels in a group of 689 native Chinese women (18). Likewise, Sowers *et al.* show that spine and femoral neck bone loss accelerates in women between 47.6 and 51 years, i.e. during FSH stage 3 (34–54 mIU/ml), which corresponds to 2 years prior to the final menstrual period (19). These strong correlations can now help to clinically stratify women at a high risk of bone loss using serum FSH (20).

Endowed with the knowledge that FSH levels correlated strongly with bone loss during late perimenopause, we investigated whether FSH could directly stimulate bone degradation by osteoclasts. We found that FSH augmented the formation, function, and survival of both human and mouse osteoclasts (21). By activating the osteoclast FSH receptor (FSHR), FSH triggered several of the signaling pathways used by RANK-L to transduce its pro-resorptive effects (21, 22). Moreover, we and others found that FSH can indirectly stimulate osteoclast formation by enhancing the production of several pro-osteoclastogenic cytokines, TNF α , interleukin-6 (IL-6), and IL-1 β (23, 24). Recently, Pacifici and co-workers have shown that FSH increases CD40 ligand expression on T lymphocytes, thereby triggering increased TNF α production.

Using genetically modified mice, we demonstrated a direct effect of FSH on the skeleton. Notably, mice lacking the β subunit of FSH or the FSHR were protected from bone loss associated with estrogen deficiency, although these mice have a compensatory rise in serum androgens accounting for some of the skeletal phenotype (21). Importantly, however, haploinsufficient FSH β heterozygotes (animals having a 50% reduction in circulating FSH levels, but with normal estrogen levels) displayed increased bone mass (21). This latter finding showed that, even in situations of normal estrogen, FSH was acting independently to decrease skeletal mass (21). We can thus extrapolate that the bone loss occurring in the perimenopausal period partly arises from elevated FSH levels (3).

Three studies take us further towards establishing a cause–effect relationship between FSH and bone loss *in vivo*. Firstly, amenorrheic women with similar estrogen levels having a mean serum FSH of 35 mIU/ml had greater bone loss than those with a level of 8 mIU/ml (25). Second, exogenously administered FSH enhanced ovariectomy-induced alveolar bone loss in rats (26, 27). The bone loss post-ovariectomy, as well as that induced by exogenous FSH, was significantly reduced by an FSH antagonist, providing unequivocal evidence for a direct effect of FSH on bone *in vivo* (26, 27).

While the evidence for causality between high FSH and bone loss continues to expand, several lingering questions remain. Osteoporosis is a multifactorial disorder with genetic variation accounting for up to 80% variation in bone mineral density (28). Rendina *et al.* sought to tie the role of FSH in causing osteoporosis to the genetic variability that exists among the human population (29). To do so, they examined 289 postmenopausal women for FSHR polymorphisms at two sites, rs1394205 and rs6166, and then analyzed the influence these polymorphisms had on bone mass and bone turnover (29).

The results were impressive: the authors found that the single nucleotide polymorphism (SNP) rs6166 of the FSHR gene significantly influenced bone mass in postmenopausal women (29). Prior studies on AA rs6166 have associated this polymorphism with increased stimulation of the ovarian FSHR. Based on knowledge that FSH acts to decrease bone mass, one would anticipate that women bearing an 'activating' FSHR polymorphism will have lower bone density. That was exactly the case: those women with AA rs6166

Figure 1 Polymorphisms in the pituitary–bone axis regulate bone mass and bone turnover. The two anterior pituitary hormones FSH and TSH regulate osteoclastogenesis and bone resorption reciprocally. 'Activating' polymorphisms in the FSH receptor (AA rs6166) and the TSH receptor (Asp727Glu) are therefore associated with low and high bone mass respectively.

showed significantly lower bone density, higher bone resorption markers, and more than twice the fracture incidence compared to women with GG rs6166 (29). The increased risk of osteoporosis in AA rs6166 women was independent of serum estrogen; this observation is clearly consistent with the estrogen-independent actions of FSH during the late perimenopausal period (29) (Fig. 1).

There is thus an ongoing paradigm shift in endocrine physiology, whereby the classic pituitary hormones FSH and TSH act by design on a 'non-endocrine' tissue – bone (30). It is possible that the discovery of polymorphisms in these non-classical pathways, such as the ones described by Rendina *et al.* or TSH receptor polymorphisms (31, 32), may define some of the complex, yet obscure, genetic variation in osteoporosis. As we bridge the gap in our understanding of what else causes osteoporosis, the future appears bright for targeting the pituitary–bone axis to a skeletal advantage.

Declaration of interest

M Zaidi consults for Genentech, Amgen, and Warner Chilcott. M Zaidi is also a named inventor of a pending patent application related to osteoclastic bone resorption filed by the Mount Sinai School of Medicine (MSSM). In the event the pending or issued patent is licensed, he would be entitled to a share of any proceeds MSSM receives from the licensee. J Iqbal and L Sun have nothing to disclose.

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