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EDITORIAL

Further evidence that FSH causes bone loss independently of low estrogen

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Introduction

The premise that menopause causes osteoporosis was first proposed by Fuller Albright at the Massachusetts General Hospital [1]. His hypothesis linking the loss of sex steroids to bone loss led to estrogen hormone replacement therapy (HRT) becoming the first successful treatment for osteoporosis [2]. More recently, however, a finer re-examination of menopausal bone loss has revealed that nearly half of lifetime loss occurs within the first 5 years [3, 4]. Bone loss accelerates dramatically during the late peri-menopause, and can, in fact, be most rapid up to 3 years before the last menstrual period [3–5] (Fig. 1a). During this early phase up to 5 years before the last menstrual period, estrogen levels are relatively unperturbed, whereas follicle-stimulating hormone (FSH) levels are rising to compensate for failing ovaries [6, 7] (Fig. 1b). These most rapid rates of bone loss cannot conceivably be explained by low estrogen; other pathophysiological mechanisms must play a dominant role.

In the early 2000s, we showed that pituitary hormones can directly affect the skeleton by bypassing their usual endocrine targets. Thyroid-stimulating hormone (TSH) was first documented to regulate bone remodeling directly by acting on both osteoclasts and osteoblasts [8]. Not only did this study attribute the osteoporosis of hyperthyroidism, in part, to low TSH levels, it set forth a new paradigm for the existence of a pituitary-bone axis (Fig. 2). As part of this paradigm shift, we later discovered that FSH directly stimulates bone resorption [9]; thus the idea that rising FSH levels during the late peri-menopause could potentially contribute to the bone loss traditionally attributed solely to low estrogen [10]. We are by no means limiting the proven importance of low estrogen in causing bone loss. Instead, we suggest circumstances, such as the late peri-menopause, where FSH may play a dominant role.

Several studies have confirmed direct effects of FSH on bone. Amenorrheic women with a higher mean serum FSH (~35 IU/L) have greater bone loss than those with lower levels (~8 IU/L) in the face of near-equal estrogen levels [11]. Likewise, in a recent study, patients with functional hypothalamic amenorrhea, in whom both FSH and estrogen were low, showed slight to moderate skeletal defects [12]. Furthermore, women harboring an activating FSH receptor (FSHR) polymorphism, rs6166, have lower bone mass and higher resorption markers [13]; this attests to a role for FSHRs in human physiology, and perhaps, even human pathophysiology. Consistent with these human studies, exogenously administration of FSH to rats augmented ovariectomy-induced bone loss [14, 15]. Moreover, an FSH antagonist reduced bone loss post-ovariectomy, as well as that induced by exogenous FSH [14, 15].

Clinical correlations between bone loss and serum FSH levels have been documented extensively. Most impressive is the Study of Women's Health across the Nations (SWAN), a longitudinal cohort of 2,375 peri-menopausal women. Not only was there a strong correlation between serum FSH levels and markers of bone resorption, a change in FSH levels over 4 years predicted decrements in bone

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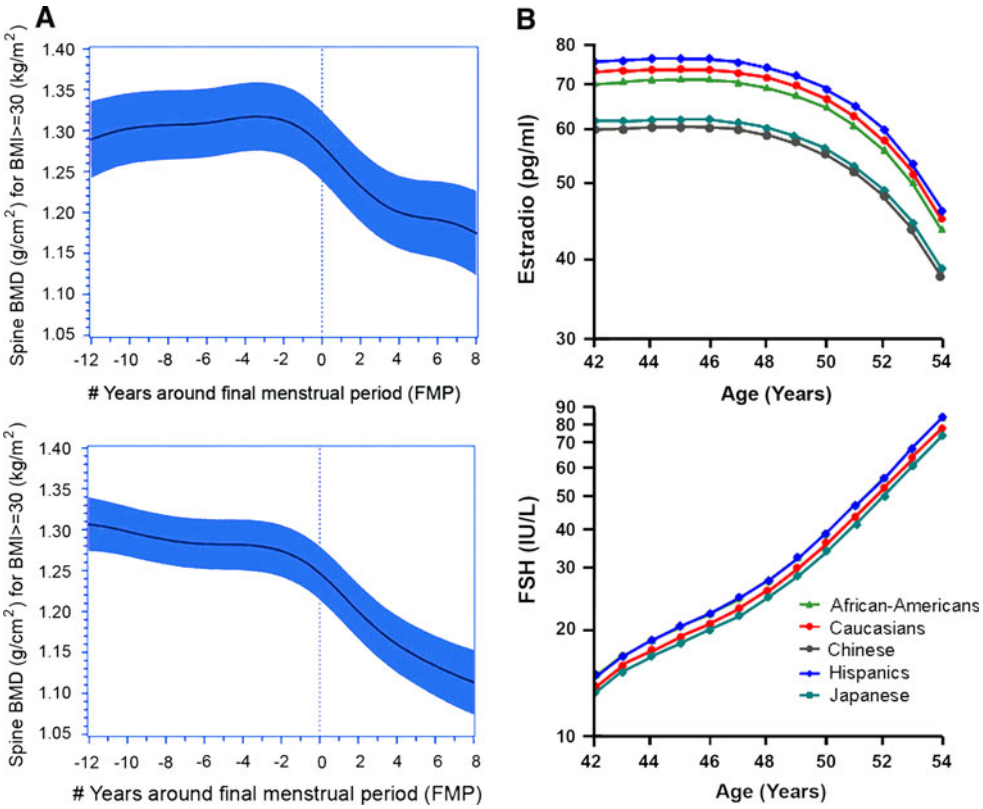

Fig. 1 Bone loss at the most rapid rate in obese (*top panel*) or non-obese (*bottom panel*) begins 2–3 years before the last menstrual period (**a**), during which time serum estrogen levels are stable while serum FSH is rising (**b**). Adapted, with permission, from refs [3] and [6]

mass [16]. Analyses of data from Chinese women showed similar trends: a significant association between bone loss and high serum FSH [17, 18]. In a group of southern Chinese women aged between 45 and 55 years, those in the highest quartile of serum FSH lost bone at a 1.3- to 2.3-fold higher rate than those in the lowest quartile [19]. Likewise, a further detailed examination of the Third National Health Examination and Nutrition Survey (NHANES III) cohort of women between the ages of 42 and 60 years showed a strong correlation between serum FSH and femoral neck bone mineral density (BMD) [20]. A recent cross-sectional analysis of 92 postmenopausal women found that serum osteocalcin and C-terminal telopeptide of type I collagen (CTX) were both positively correlated with FSH, but not with estradiol [21]. Serum CTX was highest in the highest quartile of FSH [21]. Finally, the BONTURNO study group showed that women considered peri-menopausal based on their serum FSH levels of >30 IU/mL had significantly higher bone turnover markers than age-matched women, despite having normal menses [22]. Together, these compelling studies prompt the use of FSH at least as a critical serum marker for identifying "fast bone losers" during the early phases of the menopausal transition [23].

In contrast, Gourlay et al. [24] fail to show a strong relationship between bone mass and FSH or indeed estrogen. This is surprising; such differences are likely related to distinct patient cohorts and statistical designs. Interestingly, the same authors show an independent correlation between FSH and lean mass [25]. This association makes biological sense inasmuch as FSHRs are present on mesenchymal stem cells [9], which are known to have the propensity for adipocytic differentiation. However, studies have yet to determine whether FSH inhibits adipogenesis.

Mechanistically, others and we have shown that FSH increases osteoclast formation, function, and survival through a distinct FSHR isoform [9, 26–28]. Wu et al. [28] further showed that the osteoclastogenic response to FSH was abolished in mice lacking ITAM adapter signaling molecules. This suggested an interaction between FSH and immune receptor complexes, although the significance of this finding remains unclear. In a separate study, FSHR activation was shown also to enhance expression of receptor activator for NF-κB (RANK) [29].

In addition to having direct effects on the osteoclast, FSH also indirectly stimulates osteoclast formation by releasing osteoclastogenic cytokines [30, 31]. It induces pre-osteoclasts to secrete IL-1β, TNF-α, and IL-6 in proportion to the surface expression of FSHRs [31]. In a study of 36 women between the ages of 20 and 50, serum FSH concentrations correlated with circulating cytokine concentrations [31, 32].

Two groups have, however, failed to identify FSHRs on osteoclasts, having likely used primers designed to detect the ovarian isoform [33, 34]. We suggest that they look

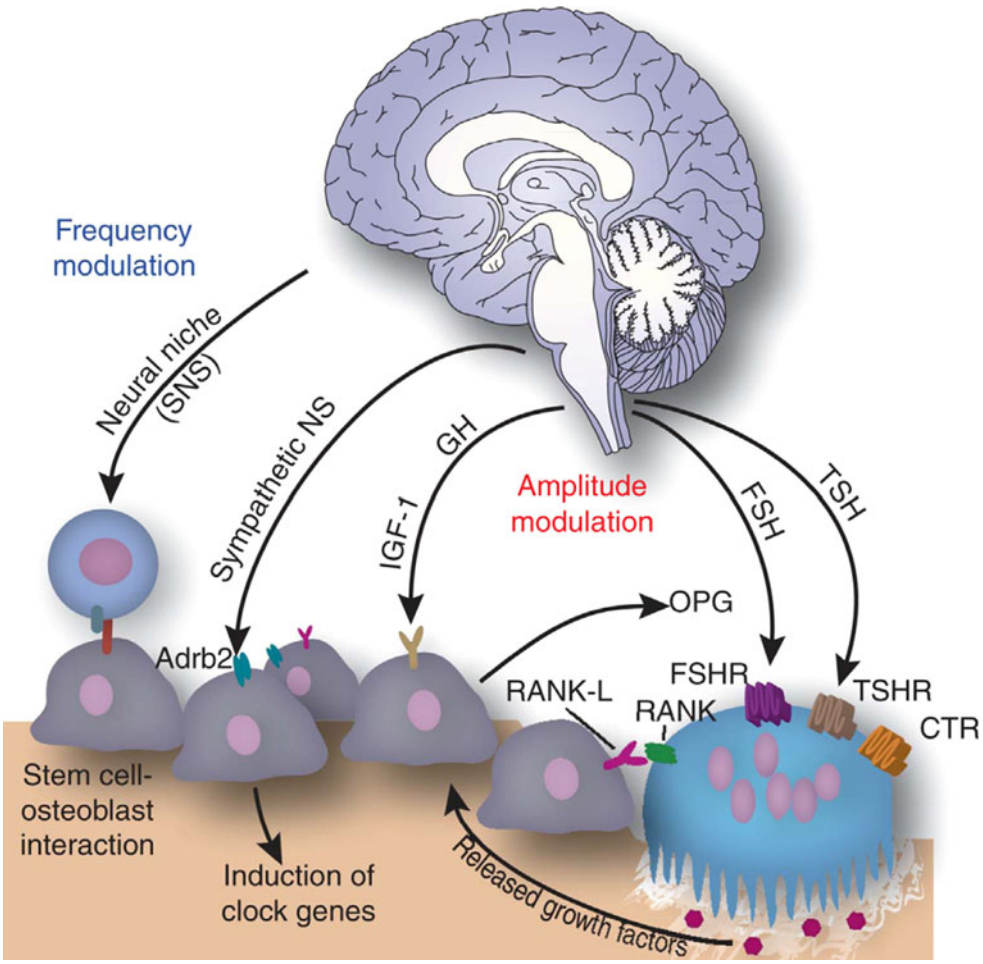

Fig. 2 Follicle-stimulating hormone contributes to skeletal regulation. Bone remodeling is under extensive and varied control mechanisms allowing integration and adaptation to a variety of stimuli. Rapid neural signals from the brain regulate osteoblastic control of the hematopoietic stem cell niche (labeled frequency modulation) as well as bone formation. Broad and relatively slower shifts in bone turnover are controlled by the pituitary hormones follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) largely targeting osteoclasts, and by members of the growth hormone (GH) pathway targeting osteoblasts [38]

more closely using appropriate primers [26]. Furthermore, injection of FSH into mice with intact ovaries [34], or its transgenic overexpression [33], even in *hpg* mice, is unlikely to reveal pro-resorptive actions of FSH. This is because direct effects of FSH on the osteoclast will invariably be masked by the anti-resorptive and anabolic actions of the ovarian estrogen so released in response to FSH. It is admittedly difficult, therefore, to tease out the action of FSH from that of estrogen in vivo as FSH releases estrogen and their actions on the osteoclast are opposed. These negative studies therefore do not rule out direct receptor-mediated actions of FSH on the skeleton and skeletal cells demonstrated in both rodents and humans.

Whether lowering FSH in a hypogonadal state to prevent bone loss can be leveraged therapeutically remains to be determined. There is evidence that women with low FSH levels undergo less bone loss [11], and that the effectiveness of estrogen therapy is related to the degree of FSH suppression [35]. With that said, patients with pituitary hypogonadism can, in circumstances, lose bone. This was in fact elegantly demonstrated in an intervention study, wherein luperide treatment, and hence the lowering of FSH, did not prevent hypogonadal bone loss [36]. While this study proved that low estrogen is a cause of acute hypogonadal bone loss, this did not exclude a role for FSH in human skeletal homeostasis [36]. Specifically, the study did not examine the confounding effects of perturbations in GnRH, LH or indeed, inhibin; the latter stimulates bone formation [37]. We believe that rather than blocking FSH in acute hypogonadism, where the effect of low estrogen is likely to be overwhelming, FSH inhibition during the late peri-menopause, particularly when estrogen levels are normal and FSH is high, could potentially be of therapeutic significance. A highly selective approach, such as the use of a blocking antibody, is thus envisaged.

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