Sex Steroids, Not FSH, Influence Bone Mass

Hypogonadism, whether caused by the failure of gonadal development or function, frequently results in bone loss. In a research article in the April 21, 2006 issue of *Cell*, Sun et al. investigated the role of follicle-stimulating hormone (FSH) in the bone loss that is characteristic of hypogonadal mice. They report that female mice lacking either FSHβ or its receptor (FSHR) are resistant to bone loss despite hypogonadism. Sun et al. conclude that FSH is directly responsible for bone loss in hypogonadal female mice with unimpaired FSH action (Sun et al., 2006). We challenge the proposal that FSH is required for hypogonadal bone loss. We suggest that the two mouse models used in the Sun et al. study have hormonal features—raised levels of luteinizing hormone (LH) and testosterone as a secondary consequence of FSH loss—that could explain the preservation of bone, without any need to invoke additional bone-specific actions of FSH.

LH stimulates ovarian theca cells to produce testosterone (Kumar, 2005). This effect is especially pronounced in the absence of FSH signaling when LH levels are increased due to overlapping negative feedback pathways in the hypothalamus and pituitary. The increased LH levels in turn boost testosterone production by theca cells. Previous work in mice lacking FSHR showed that blood testosterone levels are increased up to 10-fold in immature and mature female mice (Balla et al., 2003; Danilovich et al., 2000; Abel et al., 2003). Moreover, uterine hypertrophy and other defects in mice lacking either FSHR or FSHβ are likely due to increased testosterone that is of ovarian origin (Abel et al., 2003). We argue that changes in the production of these sex steroids and not the loss of FSH signaling account for the observations by Sun et al. Unfortunately, Sun et al. did not report the concentration of serum LH or testosterone in their two mouse models.

We have shown that in the *hpg* hypogonadal mouse, marked bone loss is present in males (Sims et al., 2005). Sun and colleagues reported similar findings in female *hpg* mice in another recent study (Rajendren et al., 2006). The *hpg* mouse is a naturally occurring model of hypogonadism caused by a mutation in the gene encoding gonadotropin-releasing hormone (*GnRH*) (Cattanach et al., 1977; Mason et al., 1986a). These mice have postnatal deficiencies in FSH, LH, and gonadal sex steroid hormones. As a consequence, the reproductive system fails to mature, rendering *hpg* mice a valuable model of human idiopathic hypogonadotropic hypogonadism. The *hpg* mouse remains sensitive to testosterone or estradiol because hormone replacement reverses the deficits in mature somatic tissues (Singh et al., 1995; Spaliviero et al., 2004). Importantly, the bone deficit in *hpg* mice is rectified by restoration of testosterone in males, or estradiol in females (Rajendren et al., 2006; Sims et al., 2005), regardless of whether FSH/LH secretion is increased or not. These observations demonstrate that FSH is not necessary for the loss of bone in hypogonadal mice, nor does FSH prevent the restoration of bone during androgen or estrogen replacement.

The claim that FSH enhances bone loss implies that hypogonadotropic women, such as those with functional or structural pituitary insufficiency, would have less bone loss than hypergonadotropic women who are deficient in estrogen due to, for example, natural or surgical menopause. Corroboration of this prediction is lacking and appears implausible. We propose that the in vivo observations reported by Sun and colleagues are not attributable to the action of circulating FSH but rather are a reflection of the well-established but overlooked effects of LH-dependent secretion of testosterone on bone metabolism.

Markus J. Seibel,[1,*] Colin R. Dunstan,[1] Hong Zhou,[1] Charles M. Allan,[1] and David J. Handelsman[1,*]
[1]ANZAC Research Institute, Concord Hospital, University of Sydney, Sydney NSW 2139, Australia
*Contact: mjs@med.usyd.edu.au (M.J.S.), djh@anzac.edu.au (D.J.H.)
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