Reciprocal Regulation of Bone and Energy Metabolism

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Abstract

Background: The primary relationship affecting skeletal tissue involves the association between fat mass and bone mass. However, there is some complexity in this relationship that may be explained by endocrine and neural pathways representing direct, reciprocal signalling between fat and bone tissue. For example, leptin signalling can directly stimulate osteoblastic differentiation and osteoblast proliferation and mineralization, but it also has central signalling actions in that it decreases cancellous bone volume. A novel regulatory loop between bone and adipose tissue suggests uncarboxylated osteocalcin may affect energy homeostasis and afford a pathway by which fat mass can be regulated by bone mass. ***Conclusions:*** The multilayered and complex signals between fat and bone tissue involve both direct and indirect pathways. The endocrinologic nature of these signals highlights an emerging trend in medicine: identification of organ-based endocrine signals.

Relationship of Bone Mass to Fat Mass

One of the most fundamental relationships for skeletal tissue involves a positive association between fat mass and bone mass, as comprehensively reviewed by Reid [1]. This relationship

involves numerous factors associated with indirect results of increased adipose tissue mass (e.g., mechanical loading, falls suppression) and thus it does not represent a true, direct regulatory pathway. However, there are endocrine and neural pathways that do represent direct signalling between fat and bone tissue. In general, the relationship between bone mass and fat mass is positive [1]. However, while reciprocal regulation is not the dominant factor in determining clinical findings, some aspects of the complexity in this relationship that may be explained by the action of these pathways. Indeed, in a recent study, when bone mass was corrected for a number of confounding factors, fat mass was found to be positively associated with fracture [2]. Thus, the clinical picture may not be as simple as first thought. This review examines the pathways between fat and bone cells that may contribute to the complexity evident in some aspects of the relationship between these tissues, with particular focus on recently described endocrine and neural pathways.

Endocrine Signals Between Fat and Bone

Association of Leptin and Bone in Humans

Leptin is an endocrine factor produced by adipocytes and secreted into the blood stream in proportion to prevailing fat mass. Interestingly, this adipocyte hormone has been linked to the regulation of bone tissue. However, studies concerning the role of leptin in bone metabolism in humans have yielded conflicting results. A study in adolescent females by Huang et al., showed no association between serum leptin and total-body BMD [5]. In healthy premenopausal women, Thomas et al. found plasma leptin is positively associated with bone mineral density (BMD) [3], whereas, Jurimae and Jurimae found no direct effect on BMD values after adjustment for body mass index (BMI) [4]. In perimenopausal women, serum leptin levels were negatively correlated

with lumbar spine and total-body BMD [6]. In postmenopausal women, studies reported both no association between leptin and BMD after adjustment for BMI [7] and a positive association [8] with BMD. Findings in men are similarly mixed. Such variations in results may reflect methodological issues, but they may also be influenced by biological variation. One possible source of biological variation is the contribution of the peripheral and central effects of leptin. Because leptin clearly exemplifies the complex nature of signalling between fat and bone, it is examined in some detail.

Direct Effects of Leptin on Osteoblasts

The leptin receptor is expressed in bone cells of both human and murine origin [9, 10], strongly indicating the possibility that it has a direct effect on bone metabolism. Indeed, leptin signaling directly stimulates osteoblastic differentiation [9, 10]. Consistent with this, a dose- and time-dependent increase in markers of osteoblast activity is evident in a human stromal cell line following leptin administration [11]. In addition to leptin's effect on bone cell differentiation, treatment with leptin stimulates human and rat osteoblast proliferation and mineralization in vitro [9]. Such direct responses support the finding that obesity and the concurrent elevation in serum leptin concentration are associated with elevated bone mass and protection from osteoporosis and fracture. The increase in leptin signalling resulting from increased fat mass acts to stimulate bone formation, as evident in the characteristic positive association between fat and bone mass. Such direct endocrine regulation of bone cells by fat cells can be explained by the known pattern of regulation indicated by in vitro studies and is consistent with the prevailing clinical picture of a positive relationship between these two lineages, but it is not a reciprocal relationship. However, leptin also exhibits actions opposing those described above.

Central Effects of Leptin on Bone

It is now well established that bone metabolism is also modulated by centrally mediated pathways involving leptin, indicating a second pathway by which fat tissue regulates bone cell activity. The presence of neurotransmitters and neuropeptides in bone and their receptors on osteoblasts suggests direct signalling between the brain and bone. Indeed, a landmark study identified a central, neural regulatory loop between fat and bone cells. After peripheral adipocytes secrete leptin into the circulation, it crosses the blood-brain barrier and binds to its receptors in the hypothalamus. In contrast to the established relationship outlined above, this central leptin signalling decreases cancellous bone volume after intracerebroventricular (ICV) infusion of leptin [12]. This finding demonstrates leptin has both direct and central signalling actions, and therefore there is a reciprocal relationship between fat and bone mass.

Involvement of the Sympathetic Nervous System

The sympathetic nervous system is an important downstream mediator of the central effects of leptin on bone. β2-adrenergic receptors are found in mouse primary osteoblast cultures [13], and while the β-adrenergic agonist isoproterenol normalises the cancellous bone volume of leptin deficient (*ob/ob*) mice, β-adrenergic antagonism increases cancellous bone mass in wild-type mice and protects *ob/ob* mice from cancellous bone loss by icv leptin [13]. Thus, sympathetic signalling is essential for the antiosteogenic actions of central leptin in cancellous bone. This central, neural regulatory loop highlights the potential for indirect interaction between bone and energy homeostasis and the complexity of the interactions between these two tissues.

Other studies provide further evidence of the truly complex nature of this seemingly simple relationship between fat and bone mass. For example, dichotomous skeletal responses are observed in *ob/ob* mice, with leptin-mediated pathways resulting in increased cancellous but reduced cortical bone [12, 14]. This complexity is also evident in results of a study that targeted overexpression of leptin in the hypothalamus of *ob/ob* mice [15]. As expected, leptin therapy normalised body weight and, consistent with initial studies, femur and vertebral cancellous bone volume decreased to wild-type levels, reinforcing the antiosteogenic action in this skeletal envelope. In contrast, femur length and total femur bone volume also increased to wild-type levels, highlighting the pro-anabolic actions of leptin in cortical bone. Moreover, these differing responses emanate from the same region of the brain. Importantly, these effects occurred even though no leptin was detected in the circulation. Thus, the central hypothalamic regulation of bone by leptin is sufficient without peripheral or local effects. This important study clearly depicts the dichotomous skeletal effects of leptin in the hypothalamus, which may, to some extent, account for the inconsistent findings in studies of leptin and BMD in humans.

Interaction with Neuropeptide Y

The cancellous effect of leptin is consistent with adrenergic signalling. While the mechanism responsible for the opposing cortical effect is less well defined, it may play an important role in the conflicting reports regarding the relationship between fat mass and bone mass. One possible mechanism is the change in neuropeptide Y (NPY) in hypothalamic neurons subsequent to leptin signalling. Leptin-deficient mice show increased hypothalamic NPY expression [16], while leptin binding in the hypothalamus suppresses NPY expression [17]. Increased hypothalamic NPY expression reduces bone mass and bone formation [18], and icv infusion of NPY reduces

cancellous bone volume [3]. Blocking central NPY signalling by deletion of the NPY receptor, Y2, solely from the hypothalamus of adult mice[14] or deletion of NPY itself. Leptin and NPY receptors are co-expressed on NPY neurons in the arcuate nucleus and have been shown to interact in mediating leptin's effects on energy homeostasis [19]. They may also be linked to some extent in bone. A recent series of papers suggest that Y1 receptors on bone cells may represent the link between the hypothalamus and bone, as β2-adrenergic receptors are for leptin [20]. Increased NPY signalling may account for the decrease in cortical bone mass associated with leptin deficiency, while adrenergic signalling is capable of overriding this effect in cancellous bone. Consistent with this hierarchy, because NPY effects are more pronounced in cortical than in cancellous bone, when *ob/ob* and *Y2*$^{-/-}$ mice are crossed, bone formation is greater in the cortical bone of Y2$^{-/-}$*ob/ob* double-mutant mice compared with *ob/ob* mice, but cancellous bone formation is not elevated relative to *ob/ob* [16, 20]. Thus, the skeletal response to leptin may represent the coordination of multiple centrally mediated pathways as well as peripheral signals. Moreover, obesity is associated with central leptin insensitivity and reduced transmission of leptin across the blood-brain barrier. Thus, obesity may preferentially promote peripheral leptin signaling over central signalling, thereby stimulating bone formation in obese individuals. In such a scenario, fat mass may interact with bone regulation on a number of levels, including modulation of the endocrine input to bone from fat cells.

Regulation of Energy Homeostasis by Bone Tissue

Recently, a series of papers has described a novel regulatory loop between bone and adipose tissue, with osteocalcin shown to regulate the production of fat tissue in an endocrine manner. Osteocalcin is the most abundant non-collagenous protein in bone and is incorporated into bone

matrix during osteoid production. However, a small but consistent fraction escapes into the extracellular fluid, and this fraction has been used clinically as a measure of bone formation. Following the observation that osteocalcin knockout mice are obese, investigation revealed marked changes in energy and glucose homeostasis in the absence of osteocalcin signalling [21]. Another study demonstrated that the uncarboxylated form of osteocalcin effects energy homeostasis such that increasing levels of osteocalcin inhibit the production of fat as well as the gain in fat resulting from a high-fat diet [22]. This study is the first to describe a pathway by which fat mass is regulated by bone mass. The mechanism involved suggests the involvement of an adipokine, adiponectin, that controls a number of key transcription factors in the adipocyte. Interestingly, adiponectin may also have effects on bone cells, with some initial reports linking serum adiponectin to BMD [23]. Thus, the level of regulatory connection between bone and fat tissue may be even more complex.

Conclusion

It is clear that direct regulation occurs between adipose and bone tissue cells. The endocrine nature of these signals highlights an emerging trend in medicine: identification of organ-based endocrine signals. Historically, endocrine signalling has been considered a central-based system via hypothalamic signals through the pituitary. However, it is increasingly apparent that a more complex system exists in which organs, formerly viewed only as "targets," also produce endocrine signals. Indeed, these signals act not only as feedback for classic endocrine output, but also act to regulate other tissue systems. As outlined above, the signals acting between fat and bone cells are multilayered and complex, involving both direct and indirect pathways. Our

understanding of this complexity is set to increase in coming years, and this research may offer greater diagnostic and therapeutic clarity.

Disclosure Statement

P.B. declares he has left the building…*thankyou very much*

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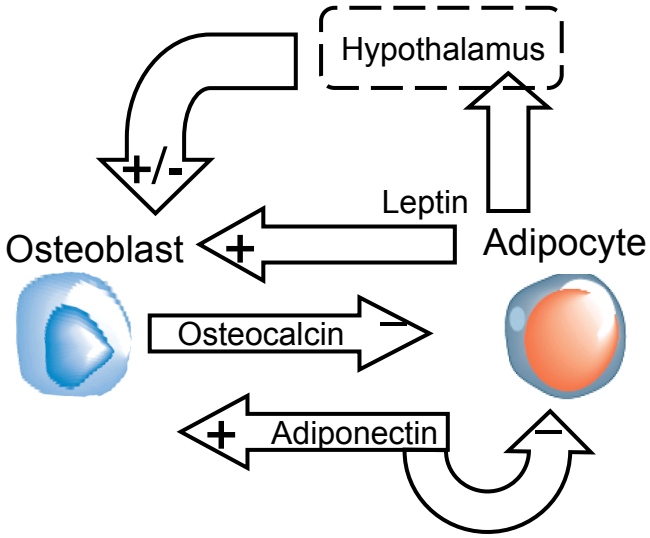

Fig. 1. Endocrine and neural pathways acting between osteoblastic and adipocytic cells.