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Perspective

Nutrition-Related Peptides and Bone Homeostasis

Ian R Reid,[1] Jillian Cornish,[1] and Paul A Baldock[2]

INTRODUCTION

The skeleton serves two main functions. First, it has a structural role, to support, protect, and facilitate the function of the soft tissues. Second, it is a mineral reservoir, which can be drawn on when dietary intake is inadequate to meet the body's needs. Optimal function in each of these roles requires regulation of skeletal mass and function in relation to the demands being placed on it. From the structural perspective, the size and strength of the skeleton should be proportional to the mass of soft tissue that it supports, so that the skeleton is structurally adequate without being larger or heavier than necessary. To function as an effective mineral reservoir, there must be a mechanism by which mineral release from the skeleton can occur during times of privation and its replacement be affected when there is dietary abundance. Both the structural and reservoir roles of the skeleton suggest that skeletal homeostasis should be regulated by factors that reflect soft tissue mass on the one hand and nutritional status on the other. Because soft tissue mass and nutrition are themselves linked, there is the possibility of a complex interaction of regulatory factors that act across these two dimensions. Recent research indicates that this is the case, and this Perspective will review our current understanding of this relatively new area of bone science.

SOFT TISSUES, BMD, AND FRACTURE RISK

Soft tissue mass is, to some extent, a reflection of nutritional status, and there is now abundant evidence that soft tissue mass is related to both BMD and fracture risk.[1] For instance, the correlation of areal BMD with weight is 0.4–0.5. Vertebral fracture prevalence was closely related to mean body mass index across the countries involved in the European Vertebral Osteoporosis Study (EVOS) study ($r = -0.66$),[2] and body weight is also a key determinant of the risk of hip fractures.[3] The cross-sectional relationship between BMD and soft tissue mass can also be seen prospectively, in that changes in body weight correlate with changes in bone mass.[4]

NUTRITION AND BONE TURNOVER

Nutritional status also impacts on bone, and protein consumption is an important predictor of lower limb bone mass in elderly women.[5] Nutritional supplementation (12–24 g protein, 12–24 g fat, and 37–74 g carbohydrate together with vitamins, minerals, and trace elements daily) in elderly women over a period of 1 year reduced serum osteoprotegerin and serum C-terminal telopeptide of type I collagen by ~30% and increased bone alkaline phosphatase and osteocalcin.[6] Similarly, the infusion of an intravenous nutrition preparation (glucose, lipid, and amino acids in ratios of 55:30:15 by energy) increased protein turnover in bone by 66% in the following 4 h.[7] Congruent findings have come from studies in starvation. Grinspoon et al.[8] studied normal young women during a 4-day fast and found a halving of bone formation markers. Ihle and Loucks[9] provided young women with energy-restricted diets for 5 days and showed a reduction in bone formation that was related to the degree of energy restriction. Bone resorption is inversely related to BMI in normal postmenopausal women ($r = -0.57$).[10] This is a dynamic relationship: 25% weight loss increasing hydroxyproline excretion by 50%[11] and 10% weight loss producing comparable changes in deoxypyridinoline excretion.[12] These important relationships pose the question of what mechanisms underlie them. Factors related to either soft tissue mass or to the ingestion of nutrients are prime candidates to account for these effects.

PEPTIDE RESPONSIVE TO ADIPOSITY

Adipocyte factors

Leptin: Leptin is the most widely recognized hormonal product of the adipocyte. It regulates appetite and reproductive function through its hypothalamic receptors, and it is now clear that it also has direct and indirect actions on bone.[13,14] The signaling form of the leptin receptor is expressed in osteoblasts and chondrocytes,[15,16] and leptin promotes proliferation and differentiation in a variety of osteoblast models in vitro.[16–18] It has similar stimulatory effects on chondrocytes both in vitro and in vivo.[16,19] Leptin also directly regulates osteoclast development, reducing production of RANK and RANKL and increasing osteoprotegerin,[20,21] with a resultant inhibition of osteoclastogenesis.[16] Leptin deficiency is associated with profound obesity, reduced linear growth, reduced cortical bone mass, and increased trabecular bone in the spine but reduced trabecular bone in the femora, where huge adipocytes occupy much of the marrow space.[22] Leptin replacement

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[1]Department of Medicine, University of Auckland, Auckland, New Zealand; [2]Garvan Institute of Medical Research, Sydney, Australia.

reverses the adipocyte phenotype and increases BMC by >30%.[23] However, leptin action in the central nervous system also impacts on bone. Intracerebroventricular infusion of leptin causes bone loss in leptin-deficient and wild-type mice through inhibition of bone formation[14] and possibly stimulation of bone resorption.[24] Studies using blockade of the sympathetic nervous system indicate that this neural pathway mediates leptin's effect on bone, acting through the β-adrenoreceptor on the osteoblast.[25] Partitioning of leptin effects into central and peripheral mechanisms is complicated by interactions between hypothalamic leptin levels and peripheral adipose mass. Central administration of leptin causes rapid loss of adipocytes from peripheral stores, thereby reducing serum leptin levels.[26,27] Thus, some of the effects of central administration of this peptide may be mediated by its reduced peripheral secretion.

The integration of leptin's direct and indirect effects on the skeleton can be assessed by administering it systemically. In animals, such studies consistently show an improvement in bone formation, skeletal mass, or strength,[15,16,21,28] although the opposite was seen when leptin was overexpressed in the murine liver.[29] Thus, in most circumstances, the peripheral actions of leptin are dominant, and those of endogenous leptin are likely to be even more so because leptin is produced in bone marrow adipocytes and other bone cells,[30] thus exposing bone to relatively higher concentrations of leptin than occurs with systemic administration. This differential is even more marked in obesity, which is associated with reduced transfer of leptin across the blood–brain barrier.[31] Ultimately, this dominance is attested to by the consistent positive relationship between fat mass and BMD—if the central effects of leptin were dominant, there would be an inverse relationship.[1] Possibly the central effect of leptin has a role in skeletal protection during periods of privation, when falling leptin concentrations might increase bone formation.[32]

Descriptions of the bone effects of leptin in humans are limited. Farooqi et al.[33] provided leptin replacement to a 9-year-old girl and observed weight loss accompanied by bone gain. Recently, eight women with hypothalamic amenorrhea received leptin treatment for up to 3 months.[34] Leptin significantly increased levels of estradiol, free triiodothyronine, free thyroxine, IGF-I, IGF-binding protein 3, bone alkaline phosphatase, and osteocalcin, showing the many indirect mechanisms by which this hormone can impact on the skeleton. Circulating leptin concentrations are inversely related to bone resorption in postmenopausal women, after adjustment for fat mass.[35] These results, again, suggest that the final integration of leptin actions on the skeleton is positive.

Adiponectin: In 1995, another adipocyte-specific secreted peptide was identified, now usually referred to as adiponectin. Adiponectin increases insulin sensitivity, and its circulating levels are reduced in obesity and diabetes.[36,37] It may act directly on bone, because adiponectin receptors are found on osteoblasts,[38] and these cells also secrete adiponectin, so autocrine regulation is a possibility. In endothelial cells, adiponectin inhibits NF-κB signaling,[39] the pathway regulating osteoclastogenesis in pre-osteoclasts. Inhibition of osteoclastogenesis, osteoclast activity, and in vivo bone resorption have now been shown, together with positive effects on osteoblast differentiation in vitro and increases in bone mass in mice in vivo.[40] However, adiponectin is able to bind a variety of growth factors,[41] which would tend to oppose these anabolic effects. Because of its profound effects on insulin resistance, there will be an interplay of actions, the final outcome of which is not predictable at this time.

The associations of adiponectin with BMD have now been studied by several groups. Huang et al.[42] found an inverse association ($r = -0.52$) between adiponectin and total body BMD in adolescent women, which was no longer apparent after adjustment for fat mass and Tanner stage. Lenchik et al.[43] found a similar association in adult men and women, which remained significant after adjustment for fat mass. As with leptin, these cross-sectional analyses have only a limited capacity to dissect out the effects of these highly intercorrelated variables.

Resistin: Resistin is also a product of the adipocyte. This peptide was discovered as a result of a search for genes that are downregulated by thiazolidinedione antidiabetic drugs.[44] We have shown that resistin modestly increases the proliferation of osteoblasts in both cell and organ culture systems (J Cornish, unpublished observations, 2005). It also increases the formation of osteoclasts in bone marrow culture and their activity in organ culture. Whether these counterbalancing effects lead to any change in bone mass is not known at present.

Pancreatic hormones

Hyperinsulinemia occurs in obesity because of resistance in the liver and skeletal muscle to the hypoglycemic effects of insulin. Amylin and preptin are cosecreted with insulin from the β cells of the pancreatic islets, so these three hormones could act in concert to produce bone anabolism.

Insulin: Insulin is mitogenic to osteoblasts in vitro and increases bone formation in vivo when administered locally.[45] These effects are mediated by insulin receptors in osteoblasts and possibly by IGF-I receptors also. BMD is directly related to circulating insulin concentrations[46,47] and is inversely related to insulin sensitivity.[48] Hyperinsulinemia can also impact on bone indirectly, because it results in androgen and estrogen overproduction in the ovary and reduced production of sex hormone binding globulin in the liver, resulting in increased free concentrations of sex hormones. As a result, high BMD is a consistent finding across a wide range of hyperinsulinemic states, including type 2 diabetes, polycystic ovary syndrome, and congenital generalized lipodystrophy. In contrast, BMD tends to be reduced in insulin deficiency (i.e., type 1 diabetes).

Amylin: Amylin is a 37 amino acid peptide that belongs to the calcitonin family. It has evolutionary links with insulin and is cosecreted with it. Amylin directly stimulates osteoblast proliferation in vitro[49] and acts like calcitonin to reduce osteoclast development and activity, and thus, bone resorption.[50] Systemic administration of amylin has positive effects on bone mass in both mice[51] and rats.[52,53] The related peptide, adrenomedullin, is also anabolic to the

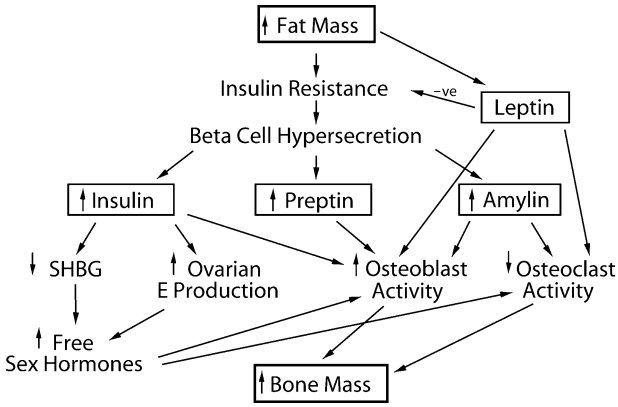

FIG. 1. Possible mechanisms by which fat mass may influence bone cell function, and thus, bone mass, independent of the effects of feeding. SHBG, sex hormone binding globulin. Reprinted with permission from IR Reid.

osteoblast[54] and secreted from the pancreatic islets,[55] although its secretion has not been shown to be related to adiposity. Recently, we have shown that the proliferative effects of adrenomedullin and amylin are dependent on the presence of the IGF-I receptor,[56] implying a common mechanism of action for several of the factors discussed in this review.

Preptin: Preptin, a 34 amino acid peptide hormone that increases glucose-mediated insulin secretion, has recently been isolated from the same secretory vesicles that contain insulin and amylin.[57] Preptin corresponds to Asp^{69}-Leu^{102} of pro-IGF-2 (pro-IGF2). It is anabolic to osteoblasts in cell and organ culture but does not influence osteoclast activity. In vivo, its local administration increases bone formation and bone area in adult male mice.[58] The anabolic activity of preptin on bone is likely to contribute to the development of osteosclerosis in some patients with hepatitis C, because immuno-activity of pro-IGF2-(89–101) is increased in this condition.[59] In contrast, excess of other forms of pro-IGF2 that do not contain the preptin sequence are not associated with increased bone mass.[59]

The possible interaction of these factors is shown in Fig. 1.

PEPTIDES RESPONSIVE TO FEEDING

It has been known for many years that oral glucose loading is followed by a transient suppression in serum calcium. Our own unpublished data showed that this is partially a result of decreases in serum albumin, presumably representing hemodilution related to the osmotic changes that accompany the absorption of a glucose load. However, ionized calcium also decreases, and there is an increase in urinary calcium excretion.[60] These changes are likely to be contributed to by reduced PTH secretion,[60,61] increased circulating concentrations of amylin (which has a calciuric action through the renal calcitonin receptor[62,63]), and increased calcitonin secretion.[64] There is also evidence of reduced bone resorption after feeding of fat, protein, or glucose in humans.[65–67] This could also be mediated by changes in PTH, amylin, and calcitonin, but there are other potential players. These nutrients stimulate secretion of the incretin hormones, glucagon-like peptides (GLP) 1 and 2 and glucose-dependent insulinotropic polypeptide (GIP), which act to enhance postprandial insulin secretion. Parenteral administration of GLP-2 produces a dose-dependent reduction in serum C-terminal telopeptide of type I collagen,[66] and GLP-2 administration over a 5-week period decreased bone resorption and increased BMD in a small uncontrolled study.[68] GLP-1 and GIP do not acutely influence bone resorption,[66] but GIP stimulates osteoblast proliferation and can attenuate postovarectomy bone loss.[69,70]

In addition to these mixed-meal effects, it is well established that ingestion of calcium has acute and chronic effects on bone metabolism, acutely stimulating calcitonin secretion, reducing PTH secretion, and reducing bone resorption.[71–73]

IGF-I is an important regulator of bone growth. Its secretion is reduced in states of poor nutrition, possibly because of resistance to the actions of growth hormone. Long-term feeding of protein supplements has been shown to increase circulating IGF-I in a randomized, controlled trial in patients with recent hip fractures, in whom there was a 2.4% increase in hip BMD over 1 year.[74] A milk supplementation study in normal young women also found increases in IGF-I.[75] IGF-I (and insulin) are also likely to be anabolic to muscle, contributing to the relationship between lean mass and bone density.

Ghrelin is a recently discovered hormone of nutrition, synthesized in the stomach and released in response to fasting. Thus, circulating levels are maximal before meals, and ghrelin is an appetite stimulant. Its receptor is expressed in osteoblastic cells, and ghrelin stimulates osteoblast proliferation and differentiation, as well as osteoclastogenesis and the bone-resorbing activity of mature osteoclasts[76] (J Cornish, unpublished observations, 2005). The latter data suggest that ghrelin may contribute to the increased bone resorption that accompanies fasting. However, its anabolic effects seem to predominate, because it increases BMD in rats.[76]

A schema of how these hormonal influences may act in concert is shown in Fig. 2.

INCREASED NUTRITION AS A CAUSE OF FRACTURE?

Whereas the discussion above has focused on the effects of nutrition-related factors on bone, it is important to remember that many of these effects are also seen in chondrocytes, and factors such as leptin and amylin directly increase growth plate thickness and stimulate linear growth of long bones.[15,16,51] These effects might mediate the steady increase in the height of young adults over the last 150 years, which continues at a rate of about 1 cm/decade.[77] There is also evidence of a parallel increase in hip axis length.[78,79] Both height and hip axis length are important risk factors for hip fracture. Thus, increases in skeletal growth may underlie the increases in hip fracture incidence that have been observed in many countries and are a par-

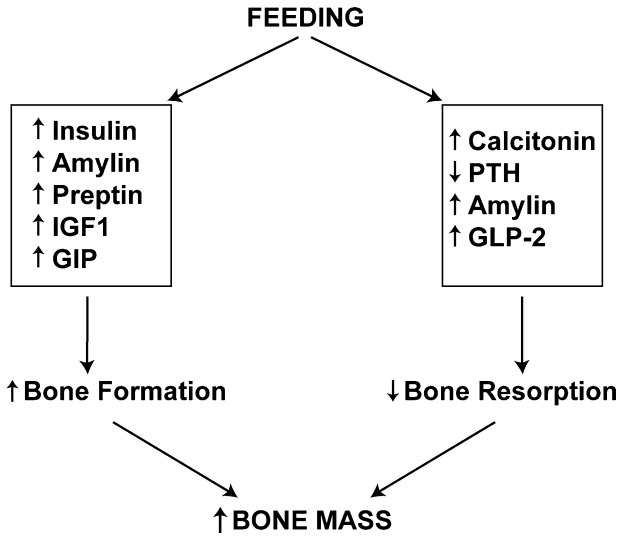

FIG. 2. Possible mechanisms by which feeding may influence bone cell function, and thus, bone mass. Reprinted with permission from IR Reid.

ticular issue at present in the rapidly urbanizing regions of Asia.[80] Increased size will also increase the forces on bone after a fall, and increasing obesity is likely to be associated with an increased risk of falling.

CONCLUSIONS

There is now clear evidence of many interconnections between nutrition and bone metabolism, as would be predicted. These are immediately relevant to clinical assessments of bone turnover, which are substantially different in the fed and fasted states. The regulatory pathways identified will generally result in denser bones as nutritional status becomes more positive, which would be expected to result in greater skeletal strength. However, greater body weight increases the load that the skeleton carries, and lengthening of bones may carry with it mechanical disadvantages, so the impact of changing nutrition on fracture rates may not always be easily predictable. Thus, nutritional influences may underlie the changing epidemiology of fractures, but the bone-active factors that mediate the effects of nutrition on bone may also provide novel therapeutic strategies for osteoporosis management.

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Address reprint requests to:
IR Reid, MD
Department of Medicine
University of Auckland
Private Bag 92019
Auckland, New Zealand
E-mail: i.reid@auckland.ac.nz

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