Obesity and osteoporosis

I.R. Reid
Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand.

Reprint request: I.R. Reid, address above.

The advent of dual-energy x-ray absorptiometry (DXA) in the late 1980s led to the realization that BMD is closely related to body weight [17, 37, 38, 49, 50]. Typically such correlations are of the order of 0.3-0.6, they are seen in both sexes, across the entire adult age range, with a variety of bone assessment methodologies (eg, QCT, radiogrammetry and ultrasound [55]), and throughout the skeleton [17, 50, 51]. There are now a number of prospective studies of the change in bone density over time, showing a similar dependence on body weight [25, 41, 49, 53, 59, 67]. These clinical studies are complemented by those in animals which show that weight loss is accompanied by reductions in bone density, strength and calcium content [69]. Epidemiological studies confirm that body weight is also an important risk fracture for fracture [3, 14, 15, 24, 28, 31, 33, 35, 40, 44, 62, 68, 73]. Corroboration of the relationship between bone and soft tissue is provided by the finding that biochemical markers of bone turnover are also related to soft tissue mass [24, 29, 49, 57, 58]. Thus, body weight is an important risk factor for osteoporosis, in many studies having a greater impact than age. The theoretical implication of these observations is that an understanding of the mechanism by which body weight is related to bone density may provide understanding of the pathogenesis of osteoporosis, and suggest novel targets for pharmaceutical development in this area.

The knowledge that body weight influences bone metabolism raises the question of the relative contributions of the fat and lean components of soft tissue to this relationship. Our group carried out a series of studies in pre- and postmenopausal women, to determine the relative importance of fat mass and lean mass to bone density. In postmenopausal women we found a correlation between lean mass and bone density throughout the skeleton (0.18<r<0.20), but found this to be somewhat less than the fat mass-bone mass correlation (0.34<r<0.55). As a result, when both fat and lean masses were entered as independent variables into a multiple regression analysis, only fat mass was found to be related to bone density [50]. When direct measurement of vertebral volumetric density was performed, the dependence of bone density on fat mass remained significant, whereas the relationship to lean mass was lost entirely [54]. This suggested that the apparent relationship of lean mass to bone density was substantially attributable to the mutual dependence of lean mass and areal bone density on skeletal size. Prospective studies [53], studies in premenopausal women [51], and those by other groups [32, 47, 49, 65, 75] have produced essentially similar results, though in some studies lean mass also was significant.

There is now data relating fracture incidence to fat and lean masses. In the Study of Osteoporotic Fractures, both fat and lean tissue mass (assessed using electrical bioimpedance) were found to predict fracture risk [14]. In contrast, Lau’s study of vertebral fractures in Chinese men showed that the lowest quartile for lean mass had a relative risk of fracture of 2.2 (NS) whereas for fat mass, the relative risk was 7.0 [35]. Hassager has shown reductions in fat mass and bone mass, but not lean mass, in women with fractures [24]. In the EPIDOS study (using DXA) the relative risk of hip fracture per standard deviation of lean mass was 1.0, whereas that for fat mass was 1.4 (P<0.05).

MECHANISMS OF FAT-BONE RELATIONSHIP

Both fat and lean masses contribute to the skeletal load and this simple mechanical effect may contribute to the fat-bone relationship to some extent. The finding that the effects of fat mass are substantially greater than those of lean mass in some studies, suggests that fat also impacts on bone in other ways. A number of hormones may link the two tissues.

Nutrition-related hormones

These factors are prime candidates to contribute to this relationship. There is biochemical evidence that both food intake and weight change can impact on bone turnover. Thus, fasting for three days significantly reduces indices of osteoblast activity, and this is not accounted for by coexistent acidosis [21]. There is a large number of
hormones regulated in response to feeding, and these could account for the effects of acute fasting on bone formation. These include glucose-dependent insulinotropic peptide, a gut-derived hormone which is anabolic to bone [6], and glucagon-like peptide-2 which increases bone density in patients with bowel resections [22]. Ghrelin is a 28-amino acid growth hormone secretagogue produced in the stomach and released into the circulation. It is increased by fasting. Its receptor is expressed in osteoblastic cells, and ghrelin stimulates osteoblast proliferation and differentiation, as well as osteclastogenesis and the bone-resorbing activity of mature osteoclasts [18] (Cornish et al., unpublished observations). The latter data suggest that ghrelin may contribute to the increased bone resorption that accompanies fasting. However, its anabolic effects appear to predominate, since it increases BMD in rats [18]. It is, therefore, a candidate factor linking food intake to the regulation of bone cell activity. There are other hormones whose secretion is related to nutrition which are already known to have an anabolic action on bone — these include IGF-1 and IGF-2.

**Beta cell hormones**

Insulin is a potential regulator of bone growth, since osteoblasts have insulin receptors [48] as well as IGF-1 receptors, which can also mediate the effects of insulin. Insulin stimulates proliferation of osteoblasts in vitro [26] and increases indices of bone formation when administered locally over bone in vivo [9]. In normal postmenopausal women, we found that insulin levels and bone density are related [52]. Similar effects have been demonstrated in the Rotterdam study [63], San Antonio Heart Study [23] and by Abrahamsen et al. [1]. The resistance to insulin in obesity and other states is specific to its hypoglycaemic effects, and the other actions of the hormone appear to be intact. Thus, hyperinsulinaemic patients develop a cluster of abnormalities, including androgen and oestrogen over-production in the ovary, and reduced production of sex hormone binding globulin in the liver. These phenomena result in increased free concentrations of sex hormones, resulting in reduced osteoclast activity and possibly increased osteoblast activity, leading to increased bone mass. These indirect mechanisms will complement the direct effects of insulin on the osteoblast. The potential interaction of these mechanisms to increase bone mass is set out in the **figure 1**. As a result, high bone density is a very consistent finding across a wide range of hyperinsulinaemic states, including obesity, type 2 diabetes [36], polycystic ovary syndrome [13, 20, 76] and congenital generalized lipodystrophy [71]. The latter is particularly significant because it represents a dissociation of fat mass and insulin levels. In contrast, bone density tends to be reduced in insulin deficiency eg, type 1 diabetes [36].

Insulin is co-secreted with amylin, which directly stimulates osteoblast proliferation in vitro and in vivo [8], inhibits osteoclast activity [2], and substantially increases bone volume when administered to adult mice [10]. The recently discovered beta cell hormone, preptin [7], also has anabolic effects on bone (Cornish et al., submitted) which will augment the effects of amylin and insulin, as shown in the **figure 1**.

**Adipocyte hormones**

The adipocyte has long been recognized as an oestrogen-producing cell, particularly in postmenopausal women. Thus, early postmenopausal women who lose bone rapidly have lower levels of both oestrone and oestradiol than “slow losers”, and this may be accounted for by their lower fat mass [59]. Our own work has confirmed a relationship between circulating oestrone levels and bone density, but has shown this to be both independent of the effects of fat mass and substantially weaker [50]. This implies that oestrogen is not the only pathway by which fat influences bone density, a suggestion supported by the finding of a fat-bone relationship in premenopausal women, in whom the adipocyte is a relatively minor source of oestrogens.

The discovery of leptin provides another possible link between these two tissues. As well as being produced in adipose tissue, leptin is produced in bone marrow ad-
ipocytes [34], its receptor is found on osteoblasts [11, 61, 64, 66], and it stimulates osteoblast proliferation [11, 56, 66]. In addition, leptin regulates osteoclast development and bone resorption [11, 27], and systemic administration of leptin increases skeletal mass [11, 16, 61]. Circulating leptin concentrations are related to bone density [19, 45, 74] and leptin levels are reduced in women with vertebral fractures [74]. Leptin also acts indirectly on bone, in that infusion of leptin into the third ventricle is associated with bone loss. One possible mechanism for this effect, is via leptin’s potent effects on insulin secretion — the central or systemic administration of leptin reduces circulating insulin concentrations by up to 85% [30, 46]. This is mediated, in part, through the sympathetic nervous system [39]. Reduced insulin levels, acting through the mechanisms discussed above, will contribute to the bone loss observed in these experiments. In addition, leptin also influences a number of other neuropeptides, which could themselves act directly or indirectly to produce bone loss. For instance, alpha-MSH which is secreted from the pituitary in response to leptin, causes profound bone loss when administered systemically to normal mice [12]. However, the experiments with systemic leptin administration clearly demonstrate that the net effect of leptin is to cause bone gain. Since leptin originates in the systemic circulation not centrally, these findings are most relevant to determining its physiological role in bone.

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 [4, 72]. It may act directly on bone, since adiponectin receptors are found on osteoblasts [5], and these cells also secrete adiponectin, so autocrine regulation is a possibility. In endothelial cells, adiponectin inhibits NF-κB signaling [43], the pathway regulating osteoclastogenesis in pre-osteoclasts. Inhibition of osteoclastogenesis, osteoclast activity and in vitro bone resorption have now been demonstrated, together with positive effects on osteoblast differentiation in vitro, and increases in bone mass in mice in vivo [42]. However, adiponectin is able to bind a variety of growth factors [70], 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.

Resistin is also a product of the adipocyte. This peptide was discovered as a result of a search for genes which are down-regulated by the thiazolidinedione anti-diabetic drugs [62]. We have demonstrated that resistin modestly increases the proliferation of osteoblasts in both cell and organ culture systems (Cornish, unpublished observations). It also increases the formation of osteoclasts in bone marrow culture, and their activity in organ culture. Whether these counter-balancing effects lead to any change in bone mass is not known at present.

**CONCLUSIONS**

There are many possible factors contributing to the dependence of bone mass on fat mass. While a number of regulators of bone cell activity have emerged from this area of enquiry, there is no single factor which, at present, seems to predominate. Recent discoveries in adipocyte biology have provided novel factors that may contribute to the fat-bone relationship. Furthermore, a diversity of clinical data suggests an association between insulin resistance and bone density, but these observational studies cannot establish cause and effect. In the clinical context, the important message is that obese subjects have a low risk of fracture, and this is likely to remain so even in those who successfully participate in weight loss programmes.

**REFERENCES**


