Relationships Between Body Fat and Bone Mass

7

Ian R. Reid

Abstract

Body weight impacts on both bone turnover and bone density and is therefore an important risk factor for vertebral and hip fractures, ranking in importance alongside that of age. The effect of body weight is probably contributed to by both fat mass and lean mass, though in postmenopausal women, fat mass has been more consistently demonstrated to be important. A number of mechanisms for the fat-bone relationship exist and include the effect of soft tissue mass on skeletal loading and the association of fat mass with the secretion of bone-active hormones from the pancreatic beta cell (including insulin, amylin, and preptin). Insulin circulates in increased concentrations in obesity and exerts anabolic effects on bone. The adipocyte is also an important source of factors that act as circulating regulators of bone metabolism. These include estrogens and the adipokines, leptin, and adiponectin. Leptin acts directly on bone cells, and in some experimental models, these effects are modified by its actions on the central nervous system, which impact on appetite, body weight, and insulin sensitivity. Adipokine levels correlate with bone turnover, suggesting that they dynamically influence bone metabolism. In postmenopausal women they may be among the principal regulators of bone turnover, accounting for their increasing importance as determinants of bone density with age. Of the adipokines, adiponectin appears to have the strongest relationships with bone parameters in postmenopausal women.

This area of research has provided important insights in bone biology. Its greatest importance, however, is to emphasize the critical role that weight maintenance plays in osteoporosis prevention.

I.R. Reid, MD
Department of Medicine, University of Auckland,
Private Bag 92019, Auckland, 1142, New Zealand
e-mail: i.reid@auckland.ac.nz

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Introduction

Osteoporosis has long been characterized as a problem afflicting small, thin, elderly women. The advent of axial bone densitometry in the 1980s allowed the relationship between body weight and bone density to be quantified, and the expected positive relationship was found. This has now resulted in a substantial literature in which a wide variety of measures of skeletal health have been assessed in relation to a similar diversity of soft tissue assessments. This explosion of the clinical literature has been mirrored in a large number of laboratory studies seeking to understand the pathways which link soft tissue mass to skeletal health. As the diversity of investigations has increased, this has sometimes obscured, rather than clarified, the key observation, which is that thin people have low bone density and more fractures.

Soft Tissue Mass Is Positively Related to Bone Density

Many investigators have consistently shown a positive relationship between bone density throughout the skeleton and either body weight or body mass index (BMI) (Fig. 7.1) [2–5]. With advances in dual-energy X-ray absorptiometry (DXA), it has become straightforward to assess fat mass and lean mass separately, and typical results for such analyses in postmenopausal women are shown in Fig. 7.2. As is demonstrated here, both fat mass and lean mass are positively related to bone density. These cross-sectional relationships are mirrored in the findings of longitudinal studies, in which changes in bone density over a decade in postmenopausal women are found to be impacted on by baseline fat mass and by changes in fat mass [6]. Thus, women with higher fat mass at baseline and who have gained in fat mass over time have slower rates of bone loss.

The relationship between fat mass and bone density tends to be most marked in postmenopausal women [7]. We have found it also to be detectable in premenopausal women [8] but to be further attenuated in premenopausal women who exercise regularly [9]. In men, the effect is less obvious, and once correction has been made for skeletal size (which impacts on DXA measurements of bone mineral density [BMD] and on lean mass), the effect of fat may be lost altogether [8]. These gender differences are not surprising since sex hormones have a profound impact on soft tissue composition as well as on skeletal mass. Thus, if fat mass positively impacts on bone mass in the absence of sex hormones, the introduction of testosterone will tend to reduce this association through its anabolic effects on bone, while its effects on fat mass are quite the opposite. Thus, any underlying relationship will be obscured. The introduction of estrogen will also have positive effects on bone mass without directly reducing fat mass, so a fat/bone relationship is still present in premenopausal women, though attenuated. The introduction of regular exercise is somewhat similar to the effects of androgen, in that it increases bone mass and leads to a reduction in fat mass. These biological considerations account for some of the diversity of findings in the literature.

This diversity is probably also contributed to by the use of different techniques for the assessment of bone and soft tissue. For instance, DXA measures areal bone density, which is inherently positively associated with skeletal size. Measurements of true volumetric BMD by quantitative CT scanning do not have this problem of colinearity. Different DXA softwares may have subtle differences in the separation of lean and fat masses, which may contribute to diversity of outcomes in clinical studies. Other techniques, such as bioimpedance analysis may separate fat and lean tissues quite differently from DXA, and thus result in the finding of different relationships. Some investigators have used cross-sectional measurements of fat area rather than

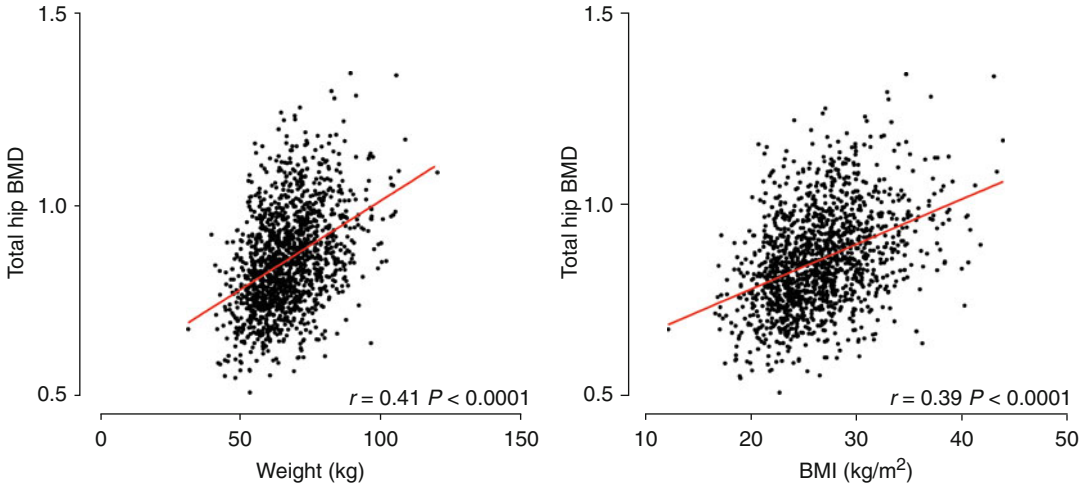

Fig. 7.1 Dependence of total hip bone mineral density (in g/cm^2) on weight and BMI in 1,462 normal postmenopausal women from the Auckland Calcium Study [1]. "*r*" is the Pearson correlation coefficient (Copyright I.R. Reid, used with permission)

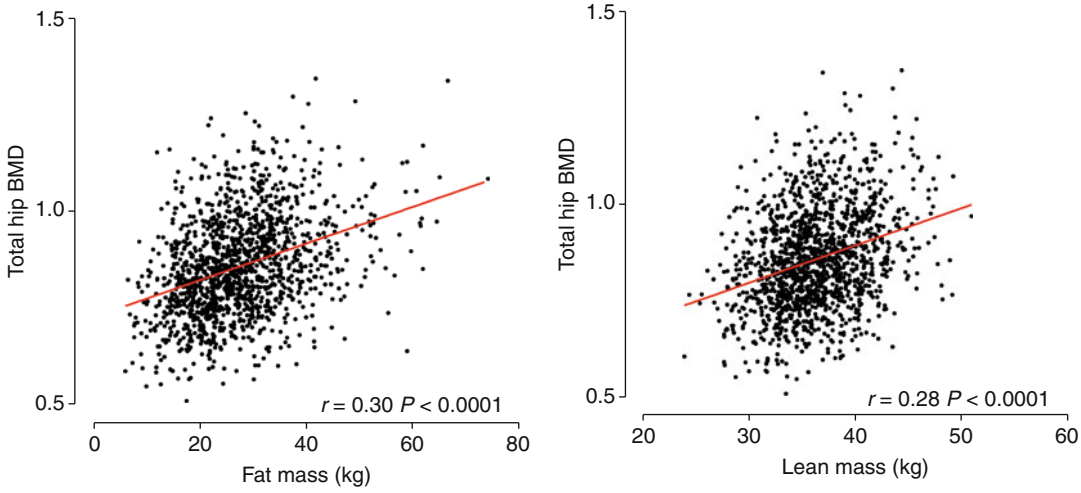

Fig. 7.2 Dependence of total hip bone mineral density (in g/cm^2) on fat mass and lean mass (all determined with dual-energy X-ray absorptiometry, in the same cohort as that in Fig. 7.1. "*r*" is the Pearson correlation coefficient (Copyright I.R. Reid, used with permission)

inferring the actual mass of adipose tissue from DXA scans, and again it would not be surprising if different relationships emerged from these analyses.

Soft Tissue Mass and Fractures

Numerous epidemiological studies have shown low body weight to be a risk factor for fractures. A number of these studies were meta-analyzed by de Laet, who demonstrated that each unit of increase in BMI diminished total fracture risk by 2–3 %, with similar effects being found in men and women [10]. For hip fractures, the dependence on BMI was more dramatic, with fracture risk declining 7 % for each unit increase in BMI. When these analyses were adjusted for individuals' BMD, the protective effect of BMI on total fracture risk was eliminated, implying that BMI prevented fractures by increasing BMD. However, for hip fractures, there was

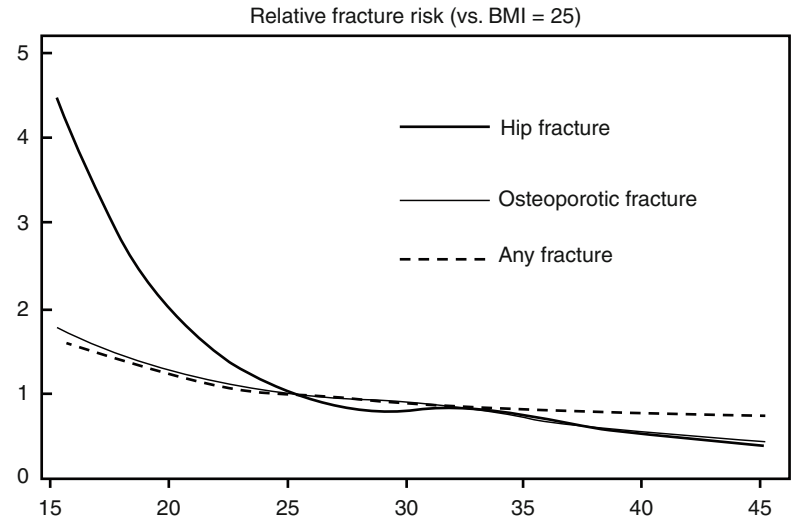

Fig. 7.3 Relative risk of fracture in relation to BMI (kg/m^2) for almost 60,000 men and women from 12 prospective population-based cohort studies. Data are adjusted for age and duration of follow-up (Reprinted from De Laet et al. [10]. With permission from Springer Science + Business Media)

still a residual, though attenuated, protective effect of BMI, implying a non-BMD-mediated mechanism. The direct shock-absorbing capacity of subcutaneous fat overlying the greater trochanter is likely to be at least part of this effect, though the independent effect of height as a risk factor for hip fracture may also be involved in the persistence of a BMI effect after adjustment for BMD. This marked dependence of hip fracture risk on body weight may account for the falling hip fracture rates observed in many Western countries over the last decade. A study of Chinese men has attempted to dissect out the independent effects of fat mass and lean mass on the risk of vertebral fracture and found a more marked protective effect from high fat mass compared with lean mass [11].

This body of data has led to the assumption that fractures are a low health priority in the overweight and elderly. However, with the steadily climbing incidence of obesity combined with similar trends in longevity, there are now substantial numbers of fractures occurring in individuals with high BMI. Thus, Compston et al. [12] have recently demonstrated, in a practice-based study, that a quarter of postmenopausal women with fractures were obese. Their analysis further showed that obesity may impact differently on various types of fractures. In particular, they observed that obesity is a risk factor for ankle fractures, implying that increased propensity to fall or altered fall mechanics in the obese may be contributing to this effect. These findings justify a closer look at the relationships between BMI and fracture risk in the de Laet, population-based analyses. While their findings have typically been interpreted as showing a linear relationship between fracture risk and BMI, in fact, the original publication demonstrates only a weak relationship between fracture risk and BMI in the overweight and obese, in contrast to a dramatic rise in fracture risk when the BMI is less than 25 (Fig. 7.3). Thus, the general conclusion that obesity is protective against fracture should be recast as a statement that "fracture risk rises steeply as BMI decreases below 25."

Methodological Considerations in Separating Fat and Lean Effects

The finding of a positive relationship of bone density with both fat mass and lean mass, together with the knowledge that these two entities are correlated with one another, has led to the use of multiple regression analysis to determine whether fat and lean masses have independent effects on bone density. The correlation between fat mass and lean mass is usually between 0.3 and 0.4, which should not violate the assumption regarding the independence of variables entered into a multiple regression analysis, so we have used this technique in a number of our previous studies. This has demonstrated that, in postmenopausal

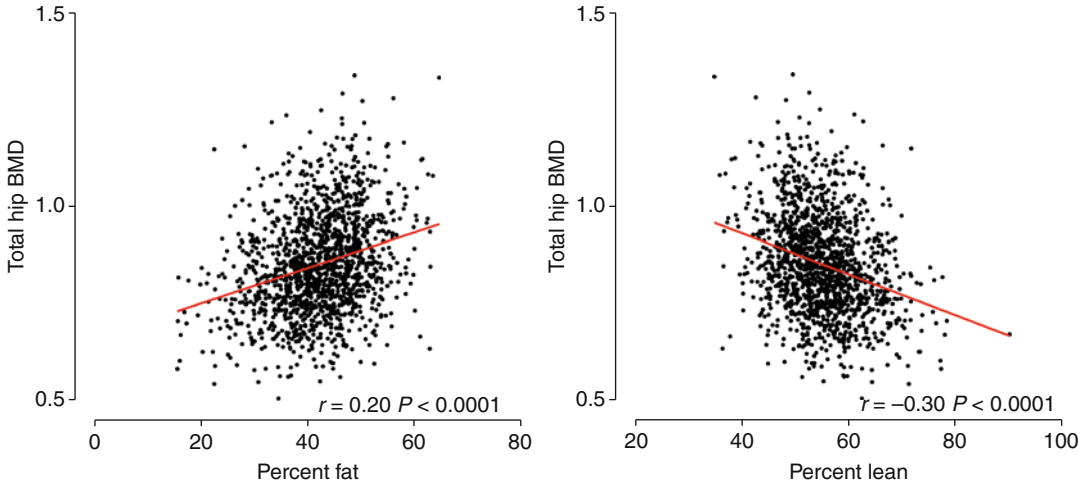

Fig. 7.4 Relationships between total hip bone mineral density (in g/cm^2) and fat mass and lean mass, each expressed as a percentage of body weight, in the cohort of postmenopausal women presented in Fig. 7.1 (Copyright I.R. Reid, used with permission)

women, the relationship between body weight and bone density is substantially driven by fat rather than lean mass, with attenuation of the fat effect in premenopausal women and, to an even greater degree, in men [7, 8]. However, some investigators have chosen to enter both fat mass and body weight or fat mass and BMI into the same multiple regression analysis. The correlations between fat mass and these other variables are greater than 0.9 indicating that there will be a substantial problem of colinearity between the supposedly "independent" variables [13]. This violates the assumptions that underpin multiple regression analysis and will lead to completely misleading findings. This can be demonstrated using the data presented in Figs. 7.1 and 7.2. If we pose the question as to how fat mass and lean mass impact on bone density, independent of weight, and enter all three of these variables into the multiple regression analysis, we find that total hip BMD is directly related to weight, but inversely related to both fat mass and lean mass [13]. Interpreted in a clinical context, this would indicate that we should be encouraging our patients to maximize their weight while minimizing their fat mass and lean mass. This is obviously impossible and the ridiculousness of this finding simply illustrates that if we perform analyses that ignore the mathematical rules on which multiple regression analysis is founded, nonsense will result. However, many investigators have committed this error and have wrongfully concluded that fat mass is inversely related to bone density, because they have adjusted their analyses for either body weight or BMI. All such analyses are flawed and lead to the generation of completely inappropriate advice to patients.

Another way of carrying out these analyses which does not depend on the complicated technique of multiple regression analysis is simply to express either fat or lean mass as a percentage of total body weight. When these analyses are carried out in the same cohort of postmenopausal women, we find that percent fat is *positively* related to hip bone density, whereas percent lean is inversely related to hip bone density (Fig. 7.4) [13]. This is giving essentially the same information as the multiple regression analysis but without the same mathematical assumptions and demonstrates the importance of adequate fat mass to optimal skeletal health in postmenopausal women.

Central Versus Peripheral Fat

In recent years it has become possible to assess both abdominal and visceral fat masses and to contrast their metabolic effects and associations

with either appendicular or subcutaneous fat. A number of investigators have demonstrated that both visceral and subcutaneous fat are positively correlated with bone density [14], though in some studies the relationship between bone mass and visceral fat was weaker, not reaching significance [15]. However, many investigators have adjusted these analyses for either subcutaneous fat mass or for total body fat. The correlation between subcutaneous fat and visceral fat is of the order of 0.7 [15], again raising the major problem of colinearity in these analyses, which invalidates the conclusions drawn. It is a major experimental challenge to dissociate the effects of subcutaneous and visceral fat on bone density, and at the present time, there are no data which satisfactorily do this. At present it can be stated that visceral fat is positively related to bone density, though in some studies more weakly so than the effects seen with total body fat. Yamaguchi has demonstrated that men without vertebral fractures have higher visceral adipose fat mass than those with fractures [14], suggesting that the relationships are similar to what has been observed for total fat mass.

Mechanisms of the Fat-Bone Connection

When the association between fat mass and bone mass was first observed, its mechanism was quite unclear since adipose tissue was widely regarded as an inert depot for energy storage. As a result, fat mass was thought to influence the skeleton simply by increasing skeletal load. While this is no doubt a contributor, the clinical studies reviewed above show similar correlations of weight-bearing and non-weight-bearing bones with indices of adiposity. Therefore, other explanations are required, and endocrine connections between adipose tissue and bone have received the most attention. It is now clear that the adipocyte directly secretes cytokines and hormones and indirectly affects the function of a number of other endocrine glands. Thus, we have moved from a dearth of explanations to a plethora, and the challenge at present is to discern which of the potential mechanisms are the most important.

Adipocyte Hormones

The adipocyte has long been recognized as a site of estrogen production from adrenal androgen precursors. This is probably most important in postmenopausal women and may be one of the reasons why fat and bone are most consistently associated in this group. The adipocyte is also a site of production of interleukin-6, which is known to be bone active, and it produces a number of putative hormones, the function of which is unclear (e.g., resistin). However, the two most investigated hormonal products of the adipocyte are leptin and adiponectin.

The *leptin*-bone literature is effectively divided into two. There are a number of studies which have assessed the action of leptin directly on bone. These studies have established that the leptin receptor is present on osteoblasts [16, 17], that leptin directly stimulates osteoblast proliferation and inhibits osteoclastogenesis [17–20], and that systemic administration of leptin to animals and humans increases bone mass [16, 17, 21–25]. Set against this is a suite of studies, many from the Karsenty laboratory, which have assessed the effects of leptin administered into the third ventricle of mice. Centrally administered leptin results in bone loss, and considerable effort has been invested into delineating the mechanisms that underpin this [26, 27]. However, it is often overlooked that central administration of leptin results in a profound loss in body weight as a result of diminished appetite, and this loss in body weight in turn results in reduced peripheral leptin levels and reduced circulating insulin levels, both of which decrease anabolic effects on bone [28–30]. Indeed, it has been shown that caloric restriction alone results in significant reductions in bone density [31, 32]. Thus, these two sets of experiments (central versus peripheral administration) are not necessarily contradictory. It should be remembered, however, that in normal human physiology, leptin is produced systemically in

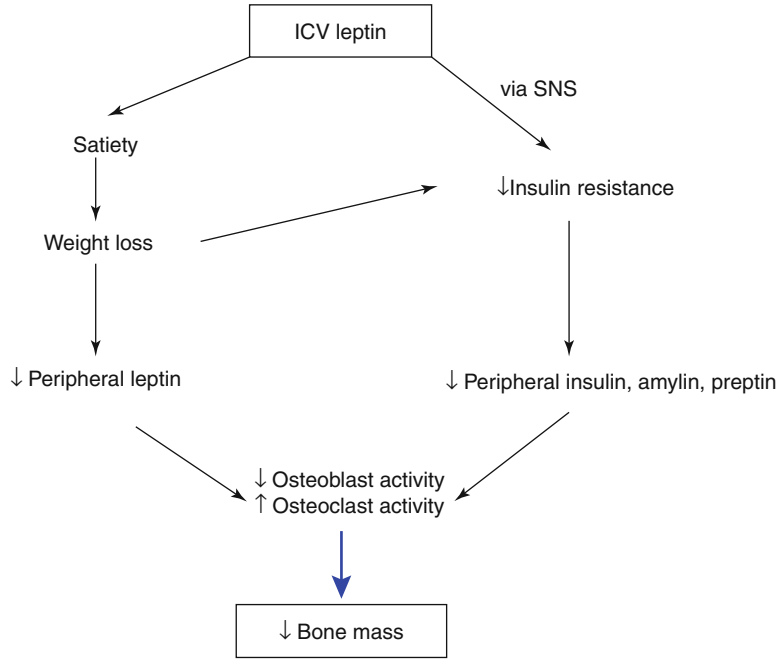

Fig. 7.5 Possible mechanisms for central leptin effects on bone, via reduced peripheral insulin and leptin levels. *SNS* sympathetic nervous system (Copyright I.R. Reid, used with permission)

adipocytes, including the adipocytes in bone marrow, so it will have direct access to bone cells. The fact that most studies of systemic administration result in *increases* in bone mass in both animals and humans indicates that the direct anabolic effects of leptin usually outweigh its negative indirect effects on bone mass, mediated through its central nervous system receptors. These relationships are set out in Fig. 7.5.

Adiponectin is a 28-kDa protein secreted from the adipocyte, whose circulating levels are inversely related to fat mass. Its actions on bone cells have been studied, producing conflicting results (reviewed in Williams et al. [33]). There is evidence that it inhibits osteoclastogenesis. However, it stimulates osteoblast differentiation; binds some growth factors, which might reduce bone formation; and is an insulin sensitizer, so it reduces circulating insulin levels. Further, adiponectin circulates in a number of different molecular forms, which have differing biological properties, so this might contribute to some of the diversity of results that has been found. However, it is now clear that in the adiponectin knockout mouse, bone mass is increased [33], suggesting that the net effect of this hormone is to reduce bone mass. This is consistent with clinical studies which show bone mass to be inversely related to circulating adiponectin levels [34, 35].

Pancreatic β-Cell Hormones

Obesity is associated with hyperinsulinemia, and insulin has been shown to directly stimulate proliferation of osteoblasts in vitro [36] and bone formation in vivo [37]. In vivo, insulin has other actions relevant to bone physiology, through reducing hepatic production of sex hormone-binding globulin (thus increasing free sex hormones) and through directly stimulating ovarian estrogen production in premenopausal women.

The pancreatic β-cell also produces amylin, a peptide related to calcitonin gene-related peptide, which has calcitonin-like effects on bone resorption [38], and also is anabolic to osteoblasts [39]. A further product of the pancreatic β-cell is preptin, a fragment of the IGF2 precursor, which itself is anabolic to osteoblasts [40]. Thus, the pancreatic β-cell produces a trio of bone-active peptides

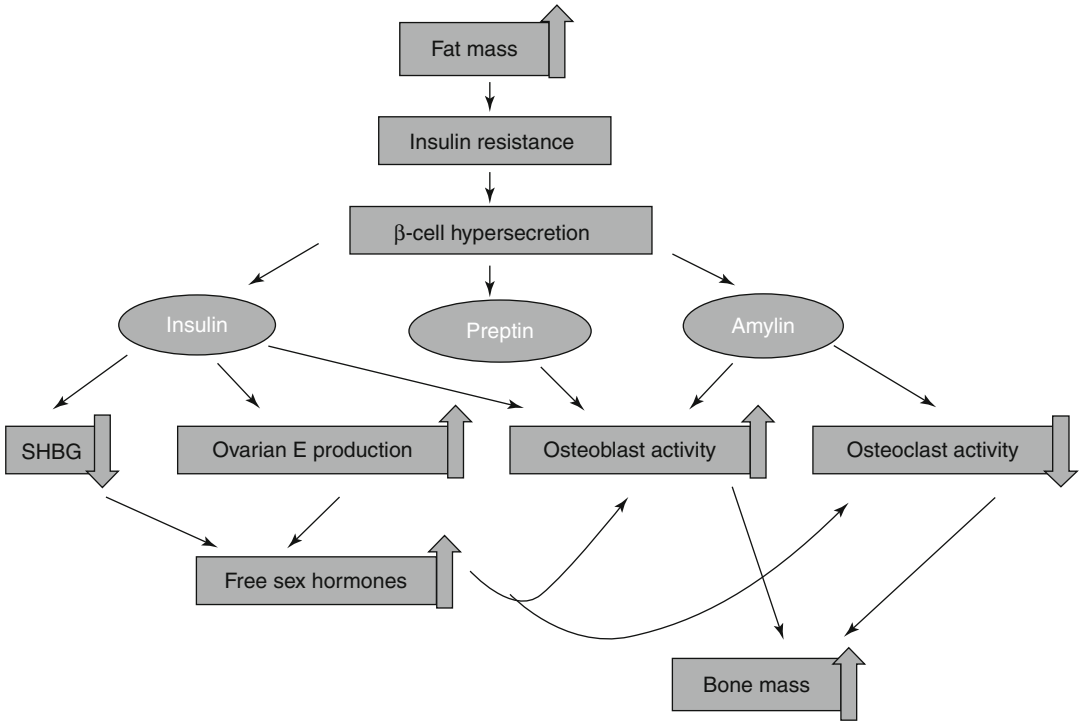

Fig. 7.6 Summary of the principal mechanisms by which the hyperinsulinemia associated with obesity contributes to increased bone mass (Copyright I.R. Reid, used with permission)

which collectively stimulate bone formation and reduce bone resorption, thus tending to increase bone mass (Fig. 7.6).

Integrated Relationships Between Soft Tissue, Adipokines, and Bone

In an attempt to determine which of these factors were the principal drivers of bone density in normal women, we have analyzed hormonal and bone density data from 453 premenopausal women and 215 postmenopausal women [41]. Leptin was positively related to bone density ($r \approx 0.75$) in both groups, weakly positively related to insulin ($r = 0.04$–0.22), and inversely related to adiponectin ($r = -0.13$ to -0.27). In the premenopausal women, multiple regression analyses at the different skeletal sites showed a consistent positive relationship to lean mass and to one or other of the fat-related variables – which one varied from site to site. Bone turnover in the premenopausal women was inversely related to the fat-related variables. In postmenopausal women, however, while the positive relationships with lean mass persisted, adiponectin was inversely related to bone density at all sites, a much more consistent effect than any of the other fat-related variables. Again, turnover was related to fat-related variables. Thus, turnover throughout adult life is influenced by fat mass, which might account for the growing influence of fat mass on BMD in older women. It is not clear why adiponectin is so much more consistently related to BMD in postmenopausal women than are other fat-related variables, since it is less closely linked to fat mass itself than is leptin. This suggests that adiponectin best reflects the metabolic influences that ultimately act to determine bone mass in postmenopausal women. It is clearly important to unravel the mechanisms that underpin this.

Feeding Effects on Bone

With the development of bone turnover markers, it has become clear that feeding results in an acute inhibition of bone resorption, observable

within an hour of meal ingestion [42]. Further, caloric restriction over a period of 5 days has been shown to impact not only on resorption but also on bone formation [43]. Feeding results in increased circulating levels of insulin, amylin, preptin, IGF1, and glucose-dependent insulinotropic polypeptide, all of which tend to promote bone formation. The suppression of bone resorption is probably mediated by increased secretion of calcitonin, amylin, and glucagon-like peptide-2, together with an inhibition of parathyroid hormone (reviewed in Reid [13]). Collectively, these effects cause feeding to have positive effects on bone mass.

Conclusions

As noted above, the relationships between fat and bone have become increasingly complex over the last two decades, but the key conclusions for clinicians are that thin people have an increased fracture risk as a result of low BMD and that both fat and lean masses appear to contribute to this effect. There is an important public health message, particularly targeted at young women, that having a low BMI is likely to increase future risk of osteoporotic fractures, though it is now becoming clear that the converse is not necessarily true – that is, obese individuals are not immune from frailty-related fractures in old age. Continued study of this area is important since it will increase our understanding of bone physiology and may throw up new possibilities for the development of anti-osteoporotic drugs.

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