Obesity and Osteoporosis: Is the Paradigm Changing?

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9.1 Introduction

During the last decades, obesity and osteoporosis have become important global health problems with an increasing prevalence worldwide [1–4], and the belief that obesity is protective against osteoporosis has recently come into question. In fact, the latest epidemiologic and clinical studies have shown that a high level of fat mass might be a risk factor for osteoporosis and fragility fractures [5–8].

Several potential mechanisms have been proposed to explain the complex relationship between the adipose tissue and bone.

For instance, fat has long been viewed as a passive energy reservoir, but since the discovery of leptin and the identification of other adipose tissue-derived hormones and serum mediators [9–11], it has come to be considered as an active endocrine organ involved in the modulation of the energy homeostasis. Adipose tissue, in fact, secretes various inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α) resistin, leptin, and adiponectin, which affect human energy and metabolic homeostasis and are involved in bone metabolism [12–15]. Moreover, fat tissue is one of the major sources of aromatase, an enzyme also expressed in the gonads, which synthesizes estrogens from androgen precursors. As known estrogens are steroid hormones which play a pivotal role in the maintenance of skeletal homeostasis, protecting against osteoporosis by reducing bone resorption and stimulating bone formation, and in obese postmenopausal women, increased

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estrogen synthesis by adipose tissue has been suggested as one of the potential mechanisms for the protective effect of fat mass on the bone. Thus, the pathophysiological role of adipose tissue in skeletal homeostasis lies in the production of several adipokines and hormones which modulate bone remodeling via their effects on either bone formation or resorption.

On the other hand, since the demonstration that bone cells express several specific hormone receptors, the skeleton is considered an endocrine target organ [13–16], and since recent observations have shown that bone-derived factors, such as osteocalcin and osteopontin, affect body weight control and glucose homeostasis [17–19], the bone has come to be considered an endocrine organ itself [20]. These considerations suggest a possible role of the bone as a player of a potential feedback mechanism between the skeleton and the other endocrine organs [20]. Thus, the cross talk between fat and bone likely constitutes a homeostatic feedback system in which adipokines and bone-derived molecules represent the link of an active bone-adipose axis.

Finally, adipocytes and osteoblasts originate from a common progenitor, a pluripotential mesenchymal stem cell (MSC) [21], which has an equal propensity for differentiation into adipocytes or osteoblasts (or other lines) under the influence of several cell-derived transcription factors. This process is complex, suggesting significant plasticity and multifaceted mechanism(s) of regulation within different cell lineages, among which are adipocytes and osteoblasts [22, 23].

9.2 Obesity and Osteoporosis: Fat and Bone Metabolism Interplay

Obesity is recognized as a risk factor for metabolic and cardiovascular diseases [2]. However, it has been considered a protective factor for bone loss and osteoporosis, which is defined as a bone metabolic disease, characterized by a decrease in bone strength leading to an increased risk of developing spontaneous and traumatic fractures. Even though body fat and lean mass are linked with bone mineral density (BMD), with obesity apparently exerting protection against bone loss, especially after menopause, during the last decades numerous evidences have described an opposite event, suggesting an inverse relationship between obesity and osteoporosis. In fact recent studies have shown that an increased abdominal fat tissue might be considered a risk factor for osteoporosis [5, 7, 8].

The mechanisms whereby increased central adiposity leads to metabolic alterations, cardiovascular morbidity, and bone loss have been largely based on the demonstration that adipose tissue secretes a number of cytokines and bioactive compounds, named adipokines.

The adipokines, which include a variety of pro-inflammatory peptides, are involved in many physiological or pathological processes, and their disregulation is a strong determinant of the low-grade inflammatory state of obesity, which promotes a cascade of metabolic alterations leading to cardiovascular complications, insulin resistance or diabetes mellitus, and bone loss [9, 11].

Leptin, the first identified adipose tissue-derived factor, is an anorexigenic hormone secreted by adipocytes in proportion to body fat content. Leptin levels are typically elevated in obesity, which is considered a leptin-resistant state [24]. In obese subjects hyperleptinemia has been widely recognized as an independent cardiovascular risk factor associated with hyperinsulinemia and insulin resistance [25] while its effect on the bone is complex, and both negative and positive actions have been reported on BMD [26, 27]. Leptin-deficient ob/ob mice and leptin receptor-deficient db/db mice are extremely obese, with increased vertebral trabecular bone volume due to increased bone formation [28]. Interestingly, intracerebroventricular infusion of leptin in both ob/ob and wild-type mice was shown to decrease vertebral trabecular bone mass [28]. In vivo studies indicate that the effect of leptin might depend on its site and mode of action [29], and it has been proposed that peripheral administration of leptin could increase bone mass by inhibiting bone resorption and increasing bone formation, while inhibiting bone formation through a central nervous system effect [26]. In vitro studies also found that leptin can act directly on bone marrow-derived mesenchymal stem cells (BMSCs) to enhance their differentiation into osteoblasts and to inhibit their differentiation into adipocytes [30]. Finally, leptin inhibits the expression of neuropeptide Y (NPY), a hypothalamus-derived peptide, essential for the regulation of food consumption, energy homeostasis, and bone remodeling [31]. Specific NPY-knockout mice show a significant decrease in body weight, a significant increase in food intake, and twofold increase in trabecular bone volume compared with wild-type animals [32].

Adiponectin exerts a protective role on cardiovascular system and glucose metabolism, and in contrast with leptin, serum adiponectin levels are reduced in obese and diabetic subjects and increase after weight loss [33]. Low levels of adiponectin are a common feature of obesity and correlate with insulin resistance [34]. Adiponectin levels are inversely related to the circulating levels of C-reactive protein (CRP), TNF-α, and IL-6, which are powerful inhibitors of adiponectin expression and secretion in cultured human adipose cells [35]. Human osteoblasts express adiponectin and its receptors, and in vivo and in vitro studies show that adiponectin increases bone mass by suppressing osteoclastogenesis and activating osteoblastogenesis [36], likely indicating that a rise in adiponectin levels, caused by fat reduction, could have a beneficial effect on BMD.

Resistin is produced by macrophages and visceral adipocytes. It is elevated in obesity and regulates insulin sensitivity in the skeletal muscle and liver, and it is positively associated with insulin resistance and glucose tolerance in both human and animal models [37]. Resistin might also play a role in bone remodeling, increasing osteoblast proliferation, cytokine release, and osteoclast differentiation [38].

TNF-α is a pro-inflammatory cytokine which plays important regulatory effects on lipid metabolism, adipocyte function, insulin signaling, and bone remodeling [39]. Its expression has been shown to correlate with percent body fat and insulin resistance in humans [40], and it was further recognized that inflammatory processes predispose to bone loss, giving rise to speculation that inflammatory cytokines, such as IL-6 and TNF-α, may play critical roles in osteoclast activity [41]. Osteoclasts are the unique cells of the body tasked with resorbing the bone, and in

the late 1990s, the identification of three different molecules built the bases of the modern bone biology: an osteoclastogenic cytokine, the receptor activator of NF-kB ligand (RANKL), its receptor (RANK), and its inhibitor osteoprotegerin (OPG) [42]. It is now clear that RANKL is the key osteoclastogenic cytokine effector, inducing osteoclast formation and promoting osteoclast resorptive activity, while OPG functions as a decoy receptor, preventing association of RANKL with RANK receptor, thus moderating osteoclastogenesis and bone resorption [43]. It has also become clear that TNF-α promotes RANKL production by BMSCs and mature osteoblasts, reduces OPG production, and upregulates the receptor RANK on osteoclast precursors, increasing their sensitivity to prevailing RANKL concentrations [44]. Additionally, TNF-α turns out to have another property that is relatively unique among the inflammatory cytokines; it has potent effects on osteoclastogenesis as it not only promotes RANKL production but synergizes with RANKL to amplify osteoclastogenesis and to intensify osteoclastic resorption by directly modulating RANKL-induced signal transduction pathways [45]. These effects are likely a consequence of the fact that RANKL is a TNF-superfamily member and functions through many of the same pathways induced by TNF-α itself.

IL-6 is a cytokine, which has a wide range of actions; it is secreted by several cell types, including fibroblast, endothelial cells, and adipocytes; and its plasma levels are significantly upregulated in human obesity and insulin resistance [46]. As TNF-α also IL-6 is a well-recognized stimulator of osteoclastogenesis and bone resorption. Several data show that IL-6 mRNA is expressed in preosteoblasts and osteoblasts [47] and that it stimulates osteoblast proliferation and differentiation by controlling the production of local factor [48]. In addition, IL-6 may play a role in bone formation in conditions of high bone turnover [49].

Emerging evidence points to a critical role for the skeleton in several homeostatic processes including energy balance and adipose metabolism, and the connection between fuel utilization and skeletal remodeling seems to begin in the bone marrow with lineage allocation of MSCs into adipocytes or osteoblasts.

Mature bone cells secrete factors that modulate insulin sensitivity and glucose metabolism, such as osteocalcin (OCN), by which the skeleton could function as an endocrine organ itself [50]. OCN is an osteoblast-specific protein and a major noncollagenous protein in the extracellular matrix. Karsenty and colleagues recently demonstrated that uncarboxylated OCN, acting as a prohormone, can increase β-cell proliferation, insulin secretion, insulin sensitivity, and adiponectin expression [51]. Thus, osteoblasts may be able to regulate glucose metabolism by modulating the bioactivity of OCN. In addition, more recent studies showed that OCN bioactivity is modulated by enhanced sympathetic tone driven by leptin, which has been shown to suppress insulin secretion by β-cells [52], and three recent studies have demonstrated an inverse correlation between serum OCN and plasma glucose levels, supporting a role for this pathway in humans [53]. Thus, a novel picture has emerged linking glucose metabolism, adipose stores, and skeletal activity.

Since its first description more than 20 years ago, osteopontin (OPN) has emerged as an active player in many physiological and pathological processes, including biomineralization, tissue remodeling, and inflammation. Modulation of immune

cell response by OPN has been associated with various inflammatory diseases and may play a pivotal role in the development of adipose tissue inflammation, insulin resistance, and diabetes [54]. OPN expression is significantly upregulated by 40- and 80-fold in adipose tissue from diet-induced and genetically obese mice, respectively [55]. Moreover, it has been demonstrated that OPN expression in adipose tissue and circulating OPN levels were substantially elevated in obese, diabetic, and insulin-resistant patients compared with lean subjects and conversely that dietary weight loss significantly decreased OPN concentrations [56, 57].

9.3 Fat Bone Marrow and Osteoporosis: Cause or Consequence?

Adipocytes and osteoblasts originate from a common progenitor, a pluripotential MSC [58], which has an equal propensity for differentiation into adipocytes or osteoblasts or other lines, such as chondrocytes, fibroblast, and endothelial cells, under the influence of several cell-derived transcription factors. This process is complex, suggesting significant plasticity and multifaceted mechanism(s) of regulation within different cell lineages, among which are adipocytes and osteoblasts [24, 59].

Transdifferentiation is the irreversible switching of differentiated cells that sometimes occurs during disease [60], and it interests partially differentiated cells (e.g., preosteoblasts) that switches to another lineage (e.g., adipocytes) [61].

Fat bone marrow is indicative of aging and it is frequently observed in the presence of osteoporosis, especially in postmenopausal women [62]. One possible cause of bone marrow fat deposition is the aberrant commitment of BMMSCs into adipocytes due to their inability to differentiate into other cell lineages, such as osteoblasts. There exists an inverse relationship between bone marrow fat production and bone formation during osteoporosis; in fact an inhibited adipogenesis in patients with a high bone mass has been observed [63].

Recently, a correlation between the osteo-adipogenic transdifferentiation of bone marrow cells and numerous bone metabolism diseases has been established. Human BMMSC-derived osteoblasts, adipocytes, and chondrocytes had the potential to transdifferentiate to each lineage, and these findings provided new insights on the pathogenesis of skeletal diseases such as osteoporosis [64].

Estrogens can regulate several molecular signals within bone metabolism and play an important role in the development of bone marrow fat [65–68]. After menopause an increase in adipogenic switches in bone marrow and a decrease in bone mass have been observed [69, 70]. Several human and animal studies have examined the function of adipocytes in bone marrow. Mesenchymal stem cells isolated from bone marrow in postmenopausal osteoporotic patients express more adipose differentiation markers than those from subjects with normal bone mass [25], and pronounced fatty infiltration in the bone marrow of rats following oophorectomy has been observed, suggesting a pivotal role of estrogen in regulating adipocyte and osteoblast recruitment [26]. More recent studies have shown that estrogens are negative regulators of

adipogenesis, and they are essential for osteogenic commitment; in particular, it seems that estrogens simultaneously induce osteogenesis and inhibits adipogenesis both in vivo and in vitro [71–73], and it has been demonstrated that estrogens suppress osteo-adipogenic transdifferentiation via canonical Wnt signaling, an important system which regulates bone development, adipogenic differentiation, and gene expression in whole process of bone metabolism [63, 74]. Specifically, canonical Wnt/β-catenin signaling is highly expressed in mesenchymal precursor cells and pluripotent cells, especially toward the osteoblast lineage, while it inhibits adipogenic differentiation [75]. Canonical Wnt signaling stabilizes and promotes cellular and nuclear β-catenin levels, which inhibits adipogenesis [75], and the suppression of Wnt signaling is essential for PPARγ induction and preadipocyte differentiation [76].

PPARγ plays a central role in initiating adipogenesis, and mutations of the PPARγ gene are associated with an altered balance between bone and fat formation in the bone marrow [59]. PPARγ insufficiency led to increased osteoblastogenesis in vitro and higher trabecular bone volume in vivo, confirming the key role of mesenchymal stem cell lineage allocation in the skeleton [58]. Interestingly, aged mice exhibit fat infiltration into bone marrow and enhanced expression of PPARγ, along with reduced mRNA expression of bone differentiation factors [77], and mice with premature aging (the SAM-P/6 model) show nearly identical patterns of adipocyte infiltration, with impaired osteoblastogenesis [78], indicating that aging or events that accelerate aging result in significant bone marrow adiposity and a defect in osteoblastogenesis in mice [79].

Conclusions

Body fat and bone interplay through several adipokines and bone-derived molecules, which modulate bone remodeling, adipogenesis, body weight control, and glucose homeostasis.

Thus, the existence of a cross talk between fat and the skeleton suggests a homeostatic feedback system in which adipokines and bone-derived molecules form part of an active bone-adipose axis, which due also its peculiarity to the common origin of osteoblasts and adipocytes from a pluripotent mesenchymal stem cell.

When specific conditions occur, such as aging, menopause, or diseases as osteoporosis, obesity, or metabolic alterations, it has been observed an osteo-adipogenic transdifferentiation and an aberrant commitment of BMMSCs into adipocytes because of their inability to differentiate into other cell lineages, such as osteoblasts.

However, the mechanism(s) by which all these events occur remains unclear, and this molecular control could be crucial to understand the pathogenesis of both obesity and osteoporosis.

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