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Review

# Skeletal integration of energy homeostasis: Translational implications☆

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ABSTRACT

New evidence has recently emerged defining a close relationship between fat and bone metabolism. Adipose tissue is one of the largest organs in the body but its functions vary by location and origin. Adipocytes can act in an autocrine manner to regulate energy balance by sequestering triglycerides and then, depending on demand, releasing fatty acids through lipolysis for energy utilization, and in some cases through uncoupling protein 1 for generating heat. Adipose tissue can also act in an endocrine or paracrine manner by releasing adipokines that modulate the function of other organs. Bone is one of those target tissues, although recent evidence has emerged that the skeleton reciprocates by releasing its own factors that modulate adipose tissue and beta cells in the pancreas. Therefore, it is not surprising that these energy-modulating tissues are controlled by a central regulatory mechanism, primarily the sympathetic nervous system. Disruption in this complex regulatory circuit and its downstream tissues is manifested in a wide range of metabolic disorders, for which the most prevalent is type 2 diabetes mellitus. The aim of this review is to summarize our knowledge of common determinants in the bone and adipose function and the translational implications of recent work in this emerging field.



**Contents**



## 1. Introduction

The markedly increased fracture rate in patients with Type 1 (T1D) and Type 2 (T2D) diabetes mellitus, despite in most cases, normal bone mineral density, has led to substantial efforts to explain the pathophysiologic basis for the development of this unique but important diabetic complication [1]. On the other hand, this manifestation also has provided investigators with evidence of a close link between bone and energy metabolism. Diabetes is a complex disease defined by intracellular glucose starvation of muscle and fat cells. Besides impairment in cellular mechanisms for glucose utilization due to either insulin resistance (T2D) or insulin deficiency (T1D), this disease is accompanied by profound systemic changes that affect every organ system. These changes include, but are not restricted to hyperinsulinemia, hyperlipidemia, hyperglycemia, changes in hypothalamic determinants of energy metabolism, and enhanced reactive oxygen species and advanced glycation end products (AGEs) in many tissues.

Adipose tissue dysfunction is a major pathophysiologic component of T2D, but is also impacted by a cascade of diabetic pathologies including those that are bone-associated. In this review, we analyze bone and adipose relationships at the functional level with a premise that better

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understanding of these relationships will provide the basis for the development of therapies that improve the function of both organs and ultimately support maintenance of normal glucose levels and utilization.

## 2. Distinct adipocytes and their depots

The last two decades of research provided substantial evidence that adipose tissue consists of distinct morphological characteristics defined by local, systemic, and environmental signals. The major building blocks of adipose tissue are adipocytes, highly specialized cells that control fuel management through a continuous process of lipogenesis, lipid storage, and lipolysis. Adipose tissue also consists of other cell types, with macrophages playing an important role in managing the inflammatory environment that impacts adipocyte development, function, and insulin sensitivity. A unique feature of the adipose organ is that its distribution is directly associated with its function [2]. Thus, subcutaneous fat provides insulation for internal organs and is more insulin sensitive, while adipose tissue surrounding the heart has thermogenic characteristics, and visceral fat is more pro-inflammatory and insulin resistant. Adipose tissue is also present in the bone marrow and our understanding of its function is just emerging. In that context, we juxtaposed bone and fat because the regulation of mesenchymal stem cell (MSC) differentiation toward adipocytes vs. osteoblasts was considered as mutually exclusive, and because of the clinical finding of an inverse correlation between bone mass and marrow fat content. However, there is emerging evidence that bone marrow adipose tissue (MAT) is characterized by a high degree of plasticity. The regulation of MAT is still being explored but in some circumstances, marrow adiposity is influenced by the same modulators (e.g. sympathetic tone) as extramedullary adipose tissue, while in other circumstances, MAT is independent of peripheral adipose tissue regulators (e.g. anorexia nervosa) [3,4].

There are two types of adipocytes categorized by their morphology and metabolic function, white and brown. Most recently, a third type has emerged, 'beige' adipocytes, cells that can be recruited from white progenitors in response to cold or β-adrenergic stimuli [5]. White adipose tissue (WAT) consists of adipocytes that expand in response to nutrient availability by incorporating fatty acids to store as triglycerides for later use. Classically, visceral adipocytes, particularly during expansion, have been associated with the elaboration of inflammatory cytokines such as TNFα, IL-1, IL-6, and resistin, as well as several adipokines [6–10]. These peptides may have variable effects on the skeleton depending on time, site, and relative concentration. Although somewhat controversial, generation of new genetic models supports the precept that during high fat feeding, most of the increase in adipose volume is due to hypertrophy (i.e. expansion of existing adipocytes) rather than proliferation, particularly in the visceral compartment [11]. Once cellular expansion of the fat cell exceeds healthy boundaries (e.g. in obesity), adipocyte death, fibrosis and inflammation can occur, and storage of triglycerides begins in other tissues, particularly in the liver, muscle, and bone marrow; this ultimately leads to the development of insulin resistance.

Brown adipocytes are present in inter-scapular adipose tissue and regulate body temperature and glucose metabolism. These cells are innervated by the sympathetic nervous system (SNS) and are the major regulators of non-shivering thermogenesis in virtually all neonates [12]. Until recently, preformed brown adipose tissue (BAT) was thought to be present only in neonates; however with the advent of positron emission tomography using (18)F-fluorodeoxyglucose ((18)FDG-PET), metabolically active BAT has been detected in adults as discrete loci located in the neck and supraclavicular region [13,14]. Brown adipocytes are derived from a Myf-5-positive muscle-like cellular lineage and have a specific metabolic program [15]. They contain very high numbers of mitochondria as well as uncoupling protein 1 (UCP1) and Pgc1α (ppar gamma co-activator 1 alpha) that are necessary for fatty acid oxidation and uncoupled heat generation [16,17]. That metabolic machinery also makes brown adipose tissue a target for insulin-mediated glucose uptake. Recent work suggests that the volume of BAT in adults may be positively related to BMD [18–20]. This may in part be due to endocrine secretory factors or confounding from the strong positive relationship of brown fat to muscle mass, likely from the shared transcriptional determinant, Myf5 [15]. Impairment in BAT function or ablation of beige fat in mice leads to development of insulin resistance and low bone mass [21–23]. In humans, the activity of BAT is attenuated in diabetes and during aging, both conditions associated with increased fractures [24].

The existence of beige adipocytes is an emerging concept; their contribution to regulation of energy metabolism in mammals is debatable. In rodents, beige adipocytes are present predominantly in the inguinal fat depots [25]. In humans, they are identified in the classical BAT depots but they may also develop as discrete loci in subcutaneous fat in response to distinct hormonal and environmental stimuli [5]. These include chronic cold exposure, adrenergic signaling, and pharmacologic and nutritional factors which increase mitochondrial number and enhance expression of brown-adipose specific proteins to uncouple respiration [26]. It remains controversial as to whether white adipocytes can trans-differentiate into beige cells or whether their progenitor is distinct [25]. Nevertheless, beige cells are controlled by specific transcription factors (Prdm16, Tbx15, FoxC2, others) and perhaps SNS tone, yet they can be distinguished from brown and white adipocytes by expression of unique sets of gene biomarkers [25,27,28]. The involvement of the SNS in beige fat development and bone remodeling is complex. In states in which SNS tone is high (e.g. cold exposure or FGF-21 excess), beige cells are found in the subcutaneous or inguinal depot [29]. On the other hand, bone mass is significantly reduced during high SNS tone, principally due to activation of the β2 receptor on osteoblasts. Activation of this receptor suppresses the key transcription factor, ATF4, and enhances RANKL production [30–35].

Besides their role in fatty acid oxidation and increased respiration, beige adipocytes secrete factors that may have anabolic effects on bone. Mice with adipocyte-specific expression of the FoxC2 transcription factor, which increases mitochondrial biogenesis and promotes "browning" of white adipocytes, have high bone mass [36]. A secretome of beige adipocytes isolated from an epididymal fat depot or from the bone marrow of these mice includes Wnt10b and IGFBP2 proteins, which increase osteoblast differentiation and function [36].

Although identified in humans, the volume of beige fat and its thermogenic function are still unclear. Moreover, it is not known whether the recruitment of human beige adipocytes by environmental or hormonal factors can enhance their thermogenic capacity. Recent efforts toward characterization of beige adipocytes led to the identification of specific biomarkers, which will undoubtedly constitute a very promising step toward determining their contribution to energy homeostasis and provide a basis for the development of new therapies to treat metabolic diseases and perhaps osteoporosis [37].

Marrow adipose tissue (MAT) represents a unique fat depot. It is an obvious candidate for a regulatory effect on the bone due to its proximity and juxtaposition to skeletal surfaces. Indeed, MAT likely modulates hematopoietic and skeletal turnover in several different ways [38,39]. In adult humans, MAT may constitute up to 1 kg of tissue, and its volume may increase in conditions of impaired energy metabolism including obesity, diabetes, aging, lipodystrophy and anorexia nervosa (reviewed in [36]). However, unlike in WAT, this increase is due to de novo differentiation rather than an increase in volume of existing adipocytes [40]. In some circumstances (e.g. aging and diabetes), particularly in humans, increased total adipocyte volume per marrow volume correlates with a decrease in bone mass/quality and increase in fractures (reviewed in [41]). But because the origin and function of marrow adipocytes are not known, our understanding of bone–fat interactions, particularly in the niche is lacking. It has been hypothesized that some marrow adipocytes develop from progenitors delivered during the process of vascularization of developing bone [42]. However, and unlike other marrow components, either mesenchymal or hematopoietic, these progenitors