



Published in final edited form as:

Lancet Diabetes Endocrinol. 2015 February ; 3(2): 141–147. doi:10.1016/S2213-8587(14)70007-5.

The Bone Fat Interface: Basic and Clinical Implications of Marrow Adiposity

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Abstract

Obesity and osteoporosis are two of the most common chronic disorders of the 21st century. Both are accompanied by significant morbidity. The only place in the mammalian organism where bone and fat lie adjacent to each other is in the bone marrow. Marrow adipose tissue is a dynamic depot that likely exists as both constitutive and regulated compartments. Adipocytes secrete cytokines and adipokines that either stimulate or inhibit adjacent osteoblasts. The relationship of marrow adipose to other fat depots is complex and may play very distinct roles in modulating metabolic homeostasis, hematopoiesis and osteogenesis. Understanding the relationship between bone and fat cells that arise from the same progenitor within the ‘niche’ provides insight into the pathophysiology of age-related osteoporosis, diabetes mellitus and obesity.

Introduction

Obesity and osteoporosis are chronic disorders with extremely high prevalence rates and secondary disorders that lead to significant morbidity and mortality. Once thought to be mutually exclusive diseases, it is now clear that both frequently coexist and may have a causal relationship. Indeed, in the Osteoporotic Fractures in Men (MrOS) Study, a prospective cohort study of the determinants of fracture in older men, obesity is a major risk factor for osteoporotic fractures.(1) In addition, Type II diabetes mellitus that is characterized by obesity and insulin resistance is associated with normal or high bone mass but a greater risk of fractures.(2) And in Type I diabetes mellitus, fractures are a major comorbidity, and often associated with marrow adiposity.(3) The pathophysiology of these disorders has provided us with critical links between adipocyte dysfunction and osteoblastic differentiation. A closer examination of their origins also reveals shared pathophysiologic pathways within the bone marrow microenvironment.

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Conflicts of Interest: We declare that we have no conflicts of interest.

Contributions: MD and CR designed the search criteria, performed the literature search, and wrote the manuscript. CR created the figures.

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A common mesenchymal progenitor found in the marrow, in the stromal vascular fraction of adipose depots and adjacent to vascular structures in other tissues, can give rise to osteoblasts, adipocytes, and myocytes.(4, 5) There is widespread support for the hypothesis that these mesenchymal stromal cells enter only one lineage in a mutually exclusive manner and that this 'choice' is determined by an orderly array of transcription factors and hormones.(6) However, with newer technologies for lineage tracing and dynamic imaging, this tenet is probably too simple and does not consider the potential plasticity of progenitors that are already presumed to be committed to one lineage (see Figure 1). Furthermore, there are now animal models demonstrating the positive 'coexistence' of marrow adipocytes and osteoblasts in mice with a high bone mass phenotype.(7) Notwithstanding the complexities of numerous differentiation factors and the variable phenotypes of genetic models, the bone marrow still provides our best window into the process of mesenchymal differentiation and ultimately lineage allocation. As such, it is also likely that therapeutic interventions for both disorders will ultimately be directed at this bone-marrow interface.

Overview and Fundamental Questions

Adipocytes in bone marrow have been noted since the 19th century,(8) but these cells were thought to be quiescent and metabolically inert. Recent studies have revealed that marrow adipose tissue (MAT) has, in some instances, high metabolic activity (whereas in others, low), is responsive to physiological stimuli such as calorie restriction and cold temperature, and actively interacts with osteoblasts to mediate skeletal homeostasis.(7, 9-12)Endosteal adipocytes are rare in neonates, accumulating steadily thereafter throughout the lifespan,(13) and comprising a greater proportion of the marrow cavity of long bones in aging, osteoporosis, anorexia nervosa, diabetes, and skeletal unloading (Table 1). (14-20)

In the axial skeleton of most mammals, marrow adiposity is only evident with advanced age. The increase in MAT in metabolic disorders of low bone mass and the observation that osteoblasts and adipocytes derive from a common pool of mesenchymal progenitors suggested a simple tradeoff between bone and fat mass, with the greater formation of adipocytes at the expense of osteoblasts thereby leading to lower bone mass. However, despite over a decade of active investigations into marrow adipose tissue, fundamental questions remain about how bone-fat interactions influence skeletal homeostasis and vice versa.

First, the function(s) of MAT is unclear, and may indeed be context specific. Marrow adipocytes are found in the long bones of healthy individuals, and increase most rapidly around peak skeletal acquisition,(13, 21) suggesting these cells could be normal residents of the endosteal niche. Moreover, MAT is found across virtually all skeletal sites in humans (i.e. particularly in the appendicular skeleton post puberty) and is thought to comprise up to 15% of total fat stores in adults. (personal communication, Will Cawthorn) Yet there is clear evidence that marrow adiposity is also negatively associated with hematopoiesis, both in normal states and in blood disorders such as aplastic anemia and multiple myeloma.(30) These observations have raised the question of whether marrow adipocytes prolong the status of hematopoietic stem cells and inhibit their differentiation. As such, adipocytes could act as 'place holders' to maintain stemness until other factors override the secretory factors

that may regulate hematopoietic differentiation. In support of that hypothesis, it is well recognized that after radiation +/- chemotherapy for bone marrow transplantation, marrow adipogenesis is florid and only subsides at the appearance of hematopoietic precursors.(30) On the other hand, the negative association of high marrow adiposity and low bone mass is more heterogeneous, and is found in a diverse set of metabolic diseases. Based on those observations, marrow adipose tissue has been considered deleterious to the skeleton. Yet we know that during puberty the appendicular skeleton converts from red to yellow marrow even as bone formation is at its peak.(13, 21) Moreover, several animal models have high bone mass and increased marrow adipose tissue.(9, 31) So, an essential question is whether the MAT of healthy individuals differs from the fat that accumulates in disease.(32) This might suggest there are two types of marrow adipose, one that is present throughout life (i.e. constitutive), and one that is regulated by local and systemic factors.(7, 10)

Second, the relationships between the bone marrow adipose tissue and white adipose depots are complex. High body mass has been thought to maintain bone mass via greater mechanical loading, but white fat may contribute to osteoporosis by disrupting bone maintenance through the release of inflammatory cytokines such as IL6 and TNF.(33) Bone marrow adipocytes tend to accumulate when white fat depots are depleted, but the precise effects of white fat vs. marrow adipose on bone remain a subject of active investigation.(14, 16, 34) In contrast, feeding high fat diets to rodents leads to marked increases in visceral fat depots, but only marginal increases in marrow adipose tissue.(35) (Figure 2)

Third, the origin of marrow adipocytes remains unknown. Although an essential part of the marrow 'niche', it is uncertain how these cells arise, particularly over extended periods such as aging, and how these cells relate to osteoblasts and hematopoietic elements. There is some support for the tenet that marrow adipocytes may have unique properties that distinguish them from brown or white adipocytes.(32) For example, after irradiation, even distant from the direct exposure site, or chemotherapy, marrow adiposity is observed and can persist for months or years.(35) Injury of any kind to the marrow provides the stimulus for infiltration of adipocytes, but are these cells derived from bone lining cells, hematopoietic-like precursors, stromal elements such as reticulo-endothelial cells, or a unique adipocyte progenitor that arises de novo? Once again, animal and human models have provided some insights but questions remain.

Fourth, the mechanical implications of extensive marrow adiposity have not been well delineated. Does the presence of fat in the marrow confer an increased risk of fracture by changing the skeletal response to particular stresses? During the aging process and with diabetes mellitus, cortical porosity is a prominent feature whereby the cortical bone surrounds elements of the marrow cavity.(36, 37) Does the presence of MAT in these "pores" lead to weaker bones, particularly in response to stress on the periosteum?

The goal of this review is to describe recent progress in understanding bone-fat interactions both inside and outside the marrow compartment, and to highlight areas for further investigation. Specifically, we focus on whether there is evidence for a final common pathway leading to marrow adipocyte formation in physiologic states, and whether there are disease-specific pathways to greater marrow adiposity. More importantly, we raise some

important clinical examples from the study of this important component of the marrow niche, to underlie the relative translational significance of marrow adipose tissue.

Although it is well known that bone marrow adipocytes accumulate with time in normal, healthy individuals,(24) it is less clear whether more marrow adipose always means less bone. MAT accumulation peaks at puberty in the appendicular skeleton, coinciding with peak bone mass acquisition,(13, 21) implying that simultaneous rapid accumulation of bone mass and MAT is possible. In support of this notion, a recent study of girls in early puberty found that bone mineral content is positively related to bone marrow adipose, although this association may be mediated via a positive association of both factors with total body fat. (38) However, other recent studies have found that bone mineral density (BMD) and bone marrow adiposity are inversely correlated even in young, healthy individuals.(39-42) While it remains to be determined whether there are tradeoffs between MAT and bone mass in young, healthy individuals, such tradeoffs are more evident in metabolic disease, including anorexia nervosa, diabetes, obesity, osteoporosis, and mechanical unloading.

Anorexia nervosa

Increased marrow adiposity at both axial and appendicular sites is widely seen in anorexia nervosa, along with depletion of visceral and subcutaneous adipose depots, hypoleptinemia, and suppressed bone acquisition.(14, 16, 22) Recent studies demonstrated that accumulation of MAT in anorexia is associated with circulating levels of DLK1 (also known as preadipocyte factor-1, Pref-1), a regulator of adipocyte and osteoblast differentiation that is higher in women with anorexia vs. control women.(43) Consistent with this concept, DLK1 levels fall, bone marrow adipose fraction decreases, and bone mass increases as women recover from anorexia.(23)

Experiments in model organisms are an essential complement to human studies and continue to provide key insights into the mechanisms linking MAT and bone. Rodent models of anorexia nervosa consistently support an inverse association of leptin and marrow adiposity, although the link between leptin and bone mass is more complex.(27) Hypoleptinemia secondary to caloric restriction leads to high MAT and lower trabecular bone mass in young but not older rodents.(44-46) Interestingly, β -adrenergic blockade during caloric restriction in rats was recently shown not only to mitigate both low bone mass and high MAT, but also to blunt the starvation-induced decrease in serum leptin,(47) implying central regulation of bone mass and MAT in caloric restriction. Hypoleptinemia and leptin insensitivity are also associated with high marrow adiposity in ob/ob and db/db mice, which lack leptin and the leptin receptor, respectively. In the ob/ob mouse, Hamrick et al. showed that leptin treatment both decreases marrow adiposity and increases bone formation, suggesting a possible role for leptin in mediating the balance between bone and fat.(48) However, a subsequent study found that leptin stimulation of VMH receptors reduced both peripheral white adipocytes and marrow adipocytes without affecting osteoblast surface area, implying leptin affects bone formation and marrow adiposity via distinct pathways.(49)

Diabetes mellitus

High marrow adipose has also been shown in Type 1 diabetes (T1D), along with impaired cortical bone geometry.(3, 28, 29) In contrast, high MAT is not seen in Type 2 diabetes (T2D), in which fracture risk is elevated despite normal to high BMD.(17, 50) However, a difference in MAT composition in T2D was recently revealed by magnetic resonance spectroscopy (MRS): the marrow cavity contains relatively more saturated lipid in women with T2D, and less unsaturated lipid in the subset of women with T2D who also have prior fractures.(51) While these findings are intriguing, it is not yet known how marrow saturation or unsaturation might be related to the overall amount of fat, or to fracture risk.

Animal models of Type 1 diabetes are consistent with human data, exhibiting hypoleptinemia, high MAT, and low bone mass. This would be consistent with the paradoxical response of the marrow to global substrate deficiency, i.e. enhanced marrow adiposity. Studies of streptozotocin-induced diabetes in BALB/c and non-obese diabetic (NOD) mice found that in both models, the proximal tibia exhibited marked increases in marrow adipocyte number and levels of peroxisome proliferator-activated receptor gamma (PPARG) and FABP4 mRNA, along with decreases in trabecular and cortical bone mineral density and bone volume fraction, as well as in osteocalcin mRNA.(52, 53) Treatment with leptin or with a PPARG antagonist, bisphenol A diglycidyl ether (BADGE), prevented accumulation of marrow adiposity but not bone loss, suggesting these phenomena result from partially independent mechanisms in diabetes.(54, 55) In contrast, BADGE treatment in wildtype adult mice, with or without concurrent vitamin D, increased bone formation and decreased marrow adipogenesis.(56) The implication is that there is a PPARG-mediated tradeoff between bone formation and marrow adipocyte formation, but that this is not the only mechanism responsible for low bone mass in type I diabetes.

In Type II diabetes mellitus, insulin resistance and obesity are well recognized features. Bone mineral density is usually normal or slightly elevated, but fracture risk is increased.(57, 58) The mechanisms responsible for skeletal fragility in this disorder are still being investigated, although cortical porosity is one feature that may impair bone strength, particularly in the appendicular skeleton where fractures are most prevalent.(37, 59) Marrow adiposity is not a feature of generalized insulin resistance, although B6 mice given a high fat diet for 12 weeks after wean show a modest increase in marrow adipocytes in the tibia as measured by osmium micro CT (personal communication, Casey Doucette). On the other hand, the thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, are very strong inducers of MAT and bone loss in the appendicular skeleton of rodents. (60, 61) In vitro, the TZDs are extremely potent stimulators of adipogenesis in mesenchymal progenitor cells, and are inhibitors of osteogenesis.(62) In humans, some studies suggest that marrow adiposity occurs in response to TZDs, although in others this was not found.(63, 64)

Unloading

Accumulation of bone marrow adipose is associated with skeletal unloading in humans, e.g. paralysis.(12, 26, 27) Recently, the Women International Space Simulation for Exploration study showed that 60 days of bedrest increased bone marrow adiposity, and that the increase persisted for a year after reambulation.(19) A subsequent study in men found that resistive

exercise, alone or in combination with low magnitude total body vibration, inhibited MAT accumulation, although effects on bone mass were not reported and the sample size was modest.(65)

In support of the notion that mechanical loading plays a role in bone-fat interactions, skeletal unloading is associated with high marrow adiposity and low bone mass in animal models. Early studies of rats exposed to microgravity in spaceflight or terrestrial hindlimb unloading showed that impaired bone mineral acquisition and greater marrow adiposity reverted to normal upon reloading in both models.(66-69) A recent study of hindlimb unloading sufficient to induce bone loss and high MAT found that treatment with sclerostin antibody reduced bone loss, but had no effect on marrow adipose,(21) suggesting bone loss and high MAT are mediated independently in this model.

On a mechanistic level, unloaded rats exhibited reduced bone formation and lower levels of RUNX2, osteocalcin, and type 1 collagen mRNA, but more marrow adipocytes and higher levels of PPARG, lipoprotein lipase, and FABP4 (fatty acid binding protein 4, also known as adipocyte protein 2 (aP2)). Both gene expression and bone formation were normalized following transforming growth factor-beta2 (TGF-B2) treatment.(70) Subsequent experiments showed that unloading increased CCAAT/enhancer-binding protein alpha and beta (CEBPA and CEBPB) expression, which in turn increased PPARG2 expression, but that TGF-B2 prevented unloading-induced changes in gene expression and activity.(71)

Osteoporosis

As first noted by Meunier,(72) increased marrow adipose tissue is seen in osteoporosis. Transiliac biopsies of premenopausal women with idiopathic osteoporosis or osteopenia revealed more numerous, voluminous marrow adipocytes compared to controls, although only controls had the expected positive correlation of MAT and age and negative correlations of MAT, bone formation and bone volume.(25) A recent study in the AGES-Reykjavik cohort found that higher MAT was negatively related to trabecular BMD measured by QCT in women, and positively related to existing vertebral fractures in men.(18)Both osteoporosis and osteopenia were associated with a lower proportion of unsaturated lipid, as assessed by proton magnetic resonance spectroscopy ((1)H-MRS).(20)

One of the lingering questions about MAT and bone is whether MAT accumulation precedes, follows, or parallels bone loss. In most rodent models, aging is associated with significant marrow adiposity, and this has been linked with low trabecular bone mineral density in rodents(73) as well as in humans,(18) suggesting this is a mutually exclusive process. On the other hand, female C57BL6 mice start losing trabecular bone as early as eight weeks of age and yet increased marrow adiposity does not become apparent until much later in life.(10, 74, 75) In a model of glucocorticoid-induced osteoporosis in rabbits, longitudinal assessment of marrow lipid fraction and bone mineral density in the proximal femur indicated the increase in MAT preceded the decrease in bone mineral density, and quantitative histology showed that an initial increase in the number of marrow adipocytes was followed by an increase in adipocyte diameter.(76) Interestingly, while concurrent zoledronic acid treatment was sufficient to eliminate the glucocorticoid-induced increases in adipocyte number and diameter, bone mineral density was only partially restored.(77)

Summary and Potential Therapeutic Implications

To summarize, in humans, there are conflicting data about whether marrow adipose and bone mass are positively or negatively correlated. While adolescents gain both simultaneously,(13, 21) MAT and bone seem to be inversely related later in adulthood. (39-42) Data from animal models generally support the idea that marrow adiposity is inversely correlated with bone mass in certain metabolic diseases, although there are exceptions: the ob/ob mouse phenotype includes high MAT and high axial but low appendicular bone mass, despite the total absence of leptin,(78) and comparison of the C3H and C57Bl/6J strains demonstrates that bone mass and MAT are frequently but not always inversely correlated, particularly in the latter strain.(9) In the former, high bone mass (trabecular and cortical) coexists with increased marrow adipose tissue across the lifespan.

Both human and animal data also indicate that high marrow adiposity arises via multiple mechanisms. Accumulation of marrow adipose appears to result at least in part from hypoleptinemia in anorexia nervosa and Type 1 diabetes, but mechanical unloading is a likely candidate in bedrest and perhaps in age-related osteoporosis. Ghrelin levels, which are increased in anorexia, can stimulate marrow adiposity.(79) The resulting marrow adipocytes also exhibit differing degrees of plasticity in response to metabolic signals. Anorexia-induced marrow adiposity ameliorates with weight gain, whereas MAT in unloading and diabetes appears more persistent despite re-ambulation or insulin treatment, respectively. Part of this may be related to how MAT is defined, since it is possible that there are two types of marrow adipose tissue, constitutive (i.e. seen consistently in the distal femur) and 'regulated' in the diaphysis and proximal femur and tibia (i.e. variably present in response to metabolic perturbations).(80) Thus in addition to identifying the specific pathways underlying marrow adipocyte formation in healthy individuals and in metabolic disease, more work is needed to understand the mechanisms that lead to regression of different marrow adipose compartments and its ultimate distribution following recovery.

What are the potential diagnostic and therapeutic implications from our knowledge of marrow adiposity and its interaction with the niche elements? There are several intriguing possibilities. First, a major clinical sequel from the treatment of malignant diseases with chemotherapy and radiation is osteoporotic fractures.(35) Most patients treated for hematopoietic and solid tumors (e.g. lymphoma, leukemia) require these therapeutic approaches for potential cures. But the resulting osteopenia and increased skeletal fragility later in life, particularly for children treated early, is a major co-morbidity.(81) Many of these patients have persistent marrow adiposity on bone biopsy or by MRI, and their bone density is usually well below age-matched controls. Lifelong treatment with anti-osteoporosis drugs is not a palatable or cost effective option. However, if an agent could early on alter the lineage allocation in the irradiated marrow to favor osteogenesis, this could have huge therapeutic implications downstream and tremendous cost savings. Second, Type 1 diabetes mellitus is associated with skeletal fragility particularly in individuals with the disease for more than two decades. The fundamental concern in these patients is the low bone mass and the reduced bone formation. But an increase in marrow adiposity is another characteristic feature. Once again, developing drugs that would enhance osteogenesis and reduce marrow adipose infiltration should have a major impact on skeletal morbidity in this

chronic disease. Finally, if MAT has a specific spectroscopic signal of greater fat saturation on MRI in high risk patients with age related osteoporosis or Type 2 diabetes mellitus, then screening affected individuals, particularly those with normal bone density, may prove a cost effective means of identifying patients to treat with osteoporosis medications.(20, 51)

In sum, it is critical to understand cell fate in the marrow, and its implications for physiologic and pathologic states. Marrow adiposity provides a window of opportunity to understand the remodeling of the marrow niche and its potential manipulation for treating chronic diseases.

Acknowledgments

This work was supported by USPHS R24 NIDDK 092759.

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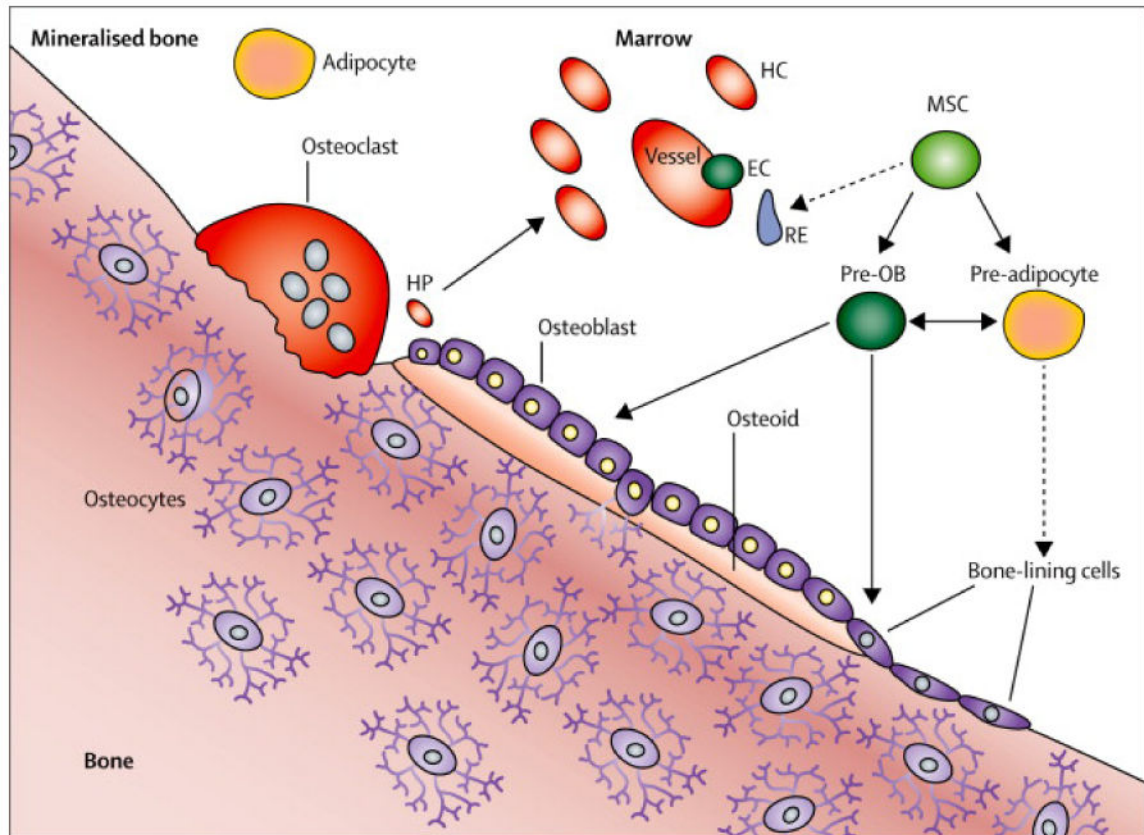


Figure 1. Bone-fat interactions in the bone marrow microenvironment

The bone marrow microenvironment includes osteoblasts, bone lining cells, pre-osteoblasts, pre-adipocytes, endothelial cells, reticuloendothelial cells that might be the earliest progenitor for mesenchymal stromal cells, osteoclasts that resorb bone, haematopoietic cells, haematopoietic progenitor cells, and, within the bone matrix, osteocytes. The communication between osteocytes and bone lining cells and osteoblasts organises the bone remodelling process. Mesenchymal stromal cells can differentiate into pre-osteoblasts or pre-adipocytes and these early cells can be plastic. The haematopoietic progenitors are intimately associated with the endosteal osteoblasts, and both are involved in blood cell differentiation. Bone lining cells are fibroblast-like cells; their function is not known, although it is likely these cells become osteoblasts, and express markers of osteoblasts and osteocytes. These cells could become adipocytes in response to injury. Dotted lines indicate hypothesised pathways; solid lines indicate known pathways. Pre-OB=pre-osteoblasts. EC=endothelial cells. RE=reticuloendothelial cells. MSCs=mesenchymal stromal cells. HC=haematopoietic cell. HP=haematopoietic progenitor. Adapted from DiGirolamo and colleagues,⁷ by permission of Macmillan Publishing Ltd.

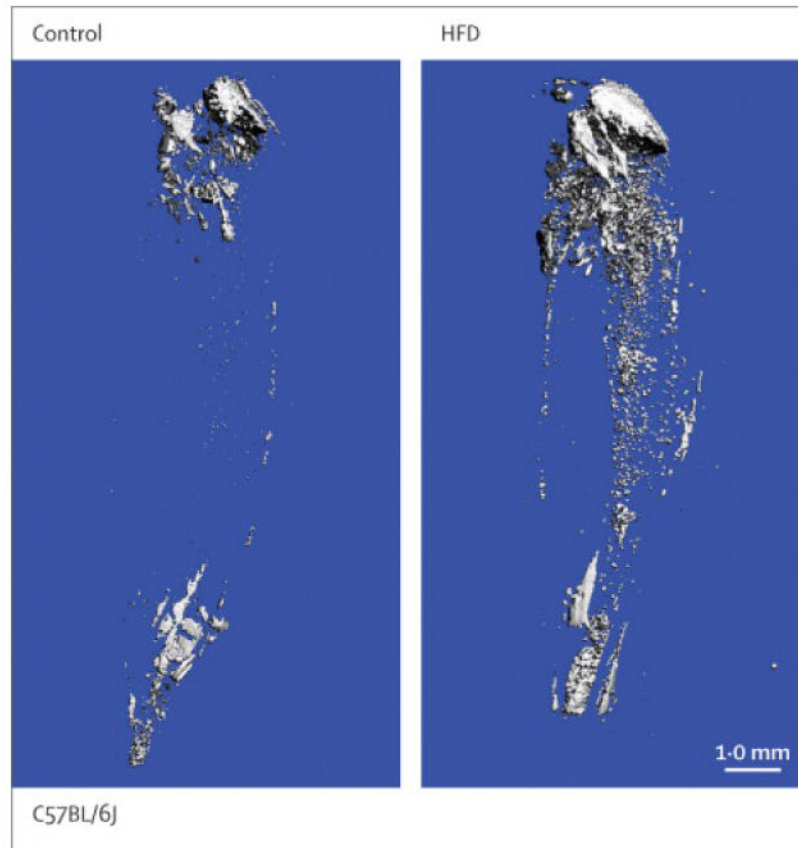


Figure 2. Osmium tetroxide (OsO₄) staining of bone marrow fat visualized by microcomputed tomography. Representative images from the tibia show that compared to normal diet (Control, left panel), marrow adiposity is increased only marginally by high fat diet (HFD, right panel).

Table 1
Relationships of marrow adipose and bone mass in humans

Condition	Marrow adipose	BMD	Ameliorated by treatment?	References
Puberty	Increased	Increased	N/A	Kricun 1985,(21) Moore 1990(13)
Aging	Increased	Decreased	N/A	Tuljapurkar 2011(15)
Starvation	Increased	Decreased	Yes	Abella 2002,(22)Bredella 2009,(14)Ecklund 2010,(16)Fazeli 2012(23)
Osteoporosis	Increased	Decreased	Yes	Cohen 2012,(24) Duque 2011,(25) Schwartz 2013,(18)Yeung 2005(20)
Unloading	Increased	Decreased	No	Dudley-Javorski 2008,(26)Minaire 1984,(27) Qin 2010,(12)Trudel 2009(19)
Type 1 diabetes	Increased	Decreased	No	Moyer-Mileur 2008,(28) McCabe 2007, 2011(3, 29)