Bone 119 (2019) 57–64

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review Article

Fat-bone interaction within the bone marrow milieu: Impact on hematopoiesis and systemic energy metabolism

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ARTICLE INFO

Article history:
Received 2 March 2018
Accepted 13 March 2018
Available online 15 March 2018

Keywords:
Bone marrow milieu
Bone marrow adipose tissue
White adipose tissue
Hematopoeisis
Mesenchymal stem cells
Hematopoeitic stem cells
Adipocytes
Adipokines
Bone mineral density

ABSTRACT

The relationship between fat, bone and systemic metabolism is a growing area of scientific interest. Marrow adipose tissue is a well-recognized component of the bone marrow milieu and is metabolically distinct from current established subtypes of adipose tissue. Despite recent advances, the functional significance of marrow adipose tissue is still not clearly delineated. Bone and fat cells share a common mesenchymal stem cell (MSC) within the bone marrow, and hormones and transcription factors such as growth hormone, leptin, and peroxisomal proliferator-activated receptor γ influence MSC differentiation into osteoblasts or adipocytes. MSC osteogenic potential is more vulnerable than adipogenic potential to radiation and chemotherapy, and this confers a risk for an abnormal fat-bone axis in survivors following cancer therapy and bone marrow transplantation. This review provides a summary of data from animal and human studies describing the relationship between marrow adipose tissue and hematopoiesis, bone mineral density, bone strength, and metabolic function. The significance of marrow adiposity in other metabolic disorders such as osteoporosis, diabetes mellitus, and estrogen and growth hormone deficiency are also discussed. We conclude that marrow adipose tissue is an active endocrine organ with important metabolic functions contributing to bone energy maintenance, osteogenesis, bone remodeling, and hematopoiesis. Future studies on the metabolic role of marrow adipose tissue may provide the critical insight necessary for selecting targeted therapeutic interventions to improve altered hematopoiesis and augment skeletal remodeling in cancer survivors.

Contents

Abbreviations: BADGE, bisphenol A diglycidyl ether; BAT, brown adipose tissue; BMD, bone mineral density; cMAT, constitutive marrow adipose tissue; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplantation; MAT, marrow adipose tissue; MSC, mesencymal stem cell; PPAR-c, peroxisome proliferator-activated receptor-c; PPAR- γ, peroxisomal proliferator-activated receptor γ; rMAT, regulated marrow adipose tissue; Sp7, Ostirix; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TZD, thiazolidinediones; UCP1, uncoupling protein 1; WAT, white adipose tissue.

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https://doi.org/10.1016/j.bone.2018.03.012
8756-3282/

1. Introduction

Marrow adipose tissue is a well-recognized component of the bone marrow microenvironment and is metabolically distinct from other subtypes of adipose tissue. The functional significance of marrow adipose tissue remains unknown. However, growing evidence suggests an inverse association between marrow adipocytes and measures of hematopoiesis, as well as bone mineral density [1]. Recent advances in imaging modalities have provided improved tools to measure marrow adiposity; to investigate the underlying physiology; and to study the function of this intriguing fat depot. This review summarizes our current understanding of the following: (1) the role of stem cell interaction in the bone marrow niche in regulating hematopoiesis, marrow adiposity and bone formation; (2) current delineated subtypes of adipose tissue and their physiologic function; and (3) marrow adipose tissue as a distinct endocrine organ with future therapeutic implications.

2. Stem cells and the bone marrow niche

The bone marrow microenvironment provides a critical regulatory milieu for the differentiation of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). HSCs are the developmental origin of the hematopoietic system and comprise 0.001% of total bone marrow cells [2]. They arise from dorsal aortic section of the aorta-gonad-mesonephros region to populate the fetal liver and subsequently migrate to the spleen and eventually to the bone marrow [3]. Differentiated hematopoietic cells include erythrocytes, platelets, and white blood cells, that give rise to innate and adaptive immune function [4]. MSCs, on the other hand, are the origin of connective tissue cells such as osteoblasts, adipocytes, chondrocytes and myocytes. In addition to the remodeling and repair of various organ systems, MSCs play a critical role in maintaining the HSCs population within the bone marrow microenvironment [5].

The endosteal bone surface is the principal component of the hematopoietic niche, and plays an influential role in HSC differentiation and interaction with osteoblasts, osteoclasts, and MSCs [6]. While the primary function of osteoblasts is to secrete osteoid for bone mineralization, these cells also play a major role in HSC regulation [7]. Osteoblasts prevent HSC mobilization from the bone marrow niche and promote HSC quiescence through the secretion of soluble stromal-cell derived factor 1 (also known as CXCL12) and angiopoietin-1 [8,9]. Osteoblasts and MSCs are closely coupled to HSC proliferation, and increases in osteoblast population lead to concomitant increases in HSC numbers [7,10]. This expansion is mediated by osteoblastic Notch signaling [7] and other factors such as osteopontin [11], Wnt, N-cadherin, thrombopoietin [12], and angiopoietin [13]. The delicate interaction between these cell populations is further highlighted in conditions such as inflammation, obesity, aging [14], type 1 diabetes mellitus [15], or cancer therapy that change the number and activity of osteoblasts and MSCs, and invariably demonstrate an effect on HSCs [16]. Additionally, knockout of MSC severely impairs the maintenance of HSC progenitors and their ability to home to the bone marrow, further highlighting the critical role that MSCs play in HSC maintenance [17]. Therefore, the complex cellular interactions in conjunction with the properties of the bone marrow microenvironment form the marrow regulatory *niche* that influences the actions and activities of these marrow progenitor cells.

On the other hand, osteoclasts are multinucleated cells that arise from hematopoietic cells and are predominantly responsible for bone resorption. In addition to bone remodeling, osteoclasts are also involved in HSC mobilization within the bone marrow milieu through enzymatically cleaving CXCL12 [18]. Thus, a competitive balance between osteoblasts and osteoclasts is necessary for the regulation of HSC in the marrow microenvironment (Fig. 1). Osteoclast-mediated bone resorption increases calcium levels and this further enables HSCs (via calcium receptors) to navigate and lodge within the bone marrow endosteal surface [19]. While the size of the HSC population is closely associated with osteoclast numbers, bisphosphonate therapy, which drastically slows osteoclast activity, results in curtailed osteoblast-mediated increases in HSC numbers [20]. Hence, bisphosphonate treatment increases the risk of impaired hematopoietic engraftment, as functional osteoclasts are required for the regulation of hematopoiesis both independently and through co-operation with other marrow cells.

Accumulating evidence indicates that multiple niches are required for each hematopoietic process [1]. The physical and functional interaction of the different niches and cells residing within the bone marrow (i.e. changes in the bone marrow composition with enhanced adiposity) can affect HSC and hematopoiesis. For example, osteoblast lineage Gsα-dependent signaling allows for normal B-cell development, thus emphasizing the importance of bone-cell interaction on B-cell fate [21]. Similar to HSCs, B-cells require exposure to CXCL12 during development. CXCL12 is critical for the maintenance of multipotent progenitors in differentiation to the B-cell lineage. By intercalating within the hematopoietic milieu and disrupting the cellular composition of the bone marrow niche, adipocytes displace and interfere with the connection between HSCs and other niche cells to exert a negative influence on hematopoiesis. Thus, even small changes in the microenvironment, such as enhanced bone marrow adiposity, can affect a particular niche or disrupt cellular trafficking [22].

Adipocytes share the bone marrow milieu with osteoblasts, MSCs, osteoclasts, and vascular cells. The role of adipocytes on hematopoiesis in this niche is complex, though predominantly characterized as inhibitory [1,23]. The increased bone marrow adiposity seen after chemotherapy and radiation treatment is antagonistic to hematopoietic recovery [1]. The peroxisome proliferator-activated receptor-c (PPAR-c) inhibitor bisphenol A diglycidyl ether (BADGE) prevents bone marrow adipocyte formation in vitro and in vivo in mice models of streptozocin-induced diabetes [1,24]. Administration of BADGE to lethally irradiated mice two weeks after bone-marrow transplantation results in the inhibition of bone marrow adipocyte formation, with robust cellular engraftment and higher peripheral white blood cell counts [1]. This suggests that PPAR-c inhibitors, or other adipocyte inhibitors, might serve as adjuvants to hematopoietic recovery following hematopoietic stem cell transplantation (HSCT) (Fig. 2).

β-catenin signaling and activation of the canonical Wnt pathway, targeted by most cancer treatment regimens, play a critical role in MSC differentiation and are required for hematopoietic regeneration following injury [25]. Total body irradiation, used as part of the treatment regimens in allogeneic HSCT, is associated with enhanced marrow adiposity, suggesting that MSC interaction with HSCs within the bone marrow niche is required for successful engraftment [26,27]. We previously demonstrated markedly increased marrow adiposity, abnormal bone microarchitecture, and abnormal fat distribution in long-term childhood HSCT recipients after total body irradiation [26]. Importantly, these patients also had occult vertebral compression fractures as well as widespread vertebral deformities, highlighting the fracture risk associated with increased marrow adiposity.

Bone marrow adipocytes may directly modify HSC differentiation through paracrine effects [28–30], and adipocyte-derived factors including adiponectin, leptin, prostaglandins, and sex steroids can regulate hematopoiesis [31,32]. Bone and fat cells share a common MSC within the bone marrow. Human cell culture studies suggest that MSC osteogenic potential is more vulnerable to radiation and chemotherapy than adipogenic potential. Consequently, hormones and transcription factors such as growth hormone, leptin, and peroxisomal proliferator-activated receptor γ (PPAR-γ) can influence MSC differentiation into either osteoblasts or adipocytes. Secreted by adipocytes, leptin regulates appetite and energy metabolism. Leptin also plays a critical role in skeletal metabolism through sympathetic neuronal signaling within the hypothalamus [33]. Recent data indicate that human bone marrow adipocytes produce leptin in a regulated manner that becomes suppressed during caloric restriction and systemic inflammation [34].

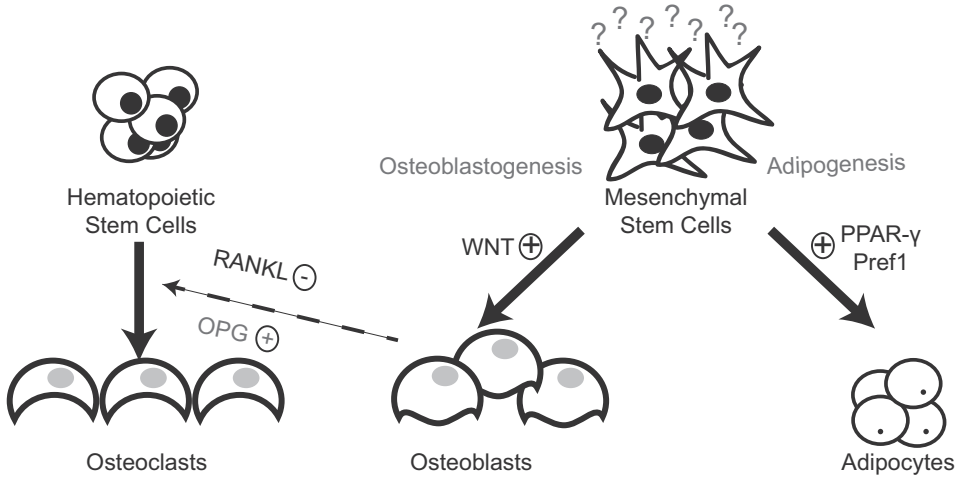

Fig. 1. The endosteal bone surface is the principal component of the hematopoietic niche, and plays an influential role in hematopoietic stem cell (HSC) differentiation and interaction with osteoblasts, osteoclasts, and mesenchymal stem cells (MSCs). Osteoblasts and MSCs are closely coupled to HSC proliferation. Knockout of MSC severely impairs the maintenance of HSC progenitors and their ability to home to the bone marrow, further highlighting the critical role that MSCs play in HSC differentiation. Activation of the canonical Wnt pathway, targeted by most cancer treatment regimens, play a critical role in MSC differentiation. Hormones and transcription factors such as Pref 1, growth hormone, leptin, and peroxisomal proliferator-activated receptor γ (PPAR- γ) can influence MSC differentiation into either osteoblasts or adipocytes. Osteoclasts are multinucleated giant cells that arise from hematopoietic cells and are predominantly responsible for bone resorption. In addition to bone remodeling, osteoclasts are also involved in HSC mobilization within the bone marrow milieu through enzymatically cleaving soluable stromal-cell derived factor 1 or CXCL12. The receptor activator of NF-κB ligand (RANKL) plays a critical role in osteoclast formation, and the biological activity of RANKL is moderated by osteoprogerin (OPG), a physiological decoy receptor. Thus, a competitive balance between osteoblasts and osteoclasts is necessary for the regulation of HSC in the bone marrow milieu.

While the systemic function of marrow-adipose tissue derived leptin has yet to be determined, increasing evidence suggests that leptin produced by bone marrow adipocytes acts predominantly as an autocrine and paracrine factor within the bone marrow milieu to influence hematopoiesis and osteoblastogenesis [30,35].

3. Adipose tissue an intriguing endocrine organ

Adipose tissue is a metabolically active tissue comprised of mature adipocytes, endothelial cells, immune cells, pre-adipocytes, and adipose progenitor cells. Mammalian adipose tissue is traditionally classified into two distinct subtypes: white adipose tissue (WAT); and brown adipose tissue (BAT), and further divided into regional depots based on structural organization, cellular composition, biochemical profile, and biological function [36]. The traditional role of WAT is long-term energy storage. Excess energy stimulates lipogenic enzymes that synthesize triglycerides for storage [37], while reduced caloric intake stimulates enzymatic lipid hydrolysis and release of free fatty acids from fat stores into the blood stream for metabolism by other organs [38]. WAT is dispersed throughout the body. The largest WAT depots are located within the visceral and subcutaneous regions and exhibit notable region-specific metabolic differences. In general, the expansion of visceral adipose tissue is associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiometabolic disease and the metabolic syndrome [39]. In mice, transplanting subcutaneous fat into the visceral cavity improves glucose metabolism, further highlighting the intrinsic difference

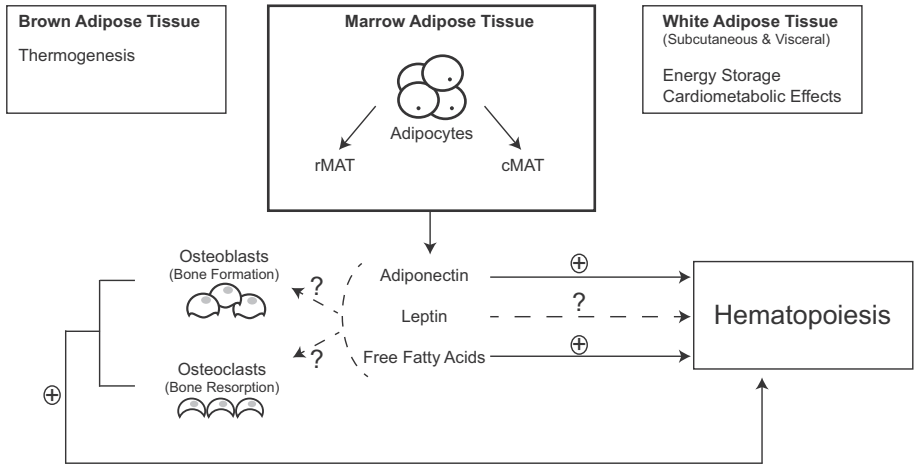

Fig. 2. Mammalian adipose tissue is currently classified into distinct subtypes of white adipose tissue (WAT), brown adipose tissue (BAT), and marrow adipose tissue (MAT). Not shown in this figure, is another subtype referred to as "beige" adipose tissue further described in the review text. These adipose tissues are further divided into regional depots based on structural organization, cellular composition, biochemical profile, and biological function. MAT has endocrine and paracrine functions. Recent gene profiling of marrow-derived adipocytes reveal different gene patterns, further highlighting its difference from WAT and BAT. MAT is further divided into two distinct subtypes: regulated MAT (rMAT) and constitutive MAT (cMAT). rMAT is predominantly located in the proximal skeletal sites and interspersed within regions of active hematopoiesis, while cMAT is found predominantly in the distal skeletal regions with no corresponding interspersed areas of active hematopoiesis. MAT expresses and secretes adiponectin to exert systemic metabolic effects. However, many systemic effects of adiponectin and other MAT-derived endocrine factors have yet to be delineated. Local production of leptin or adiponectin might influence osteoblast and osteoclast function. The positive and negative effects of these factors are indicated by "+" or "−", while inconclusive effects by a "?". Future clinical studies are needed to better delineate the paracrine and endocrine functions of MAT as potential targeted interventions for treatment of various hematopoietic, metabolic and skeletal disorders.

of these two fat depots [40]. Visceral adipocytes are also more responsive to lipolytic signals which upregulate the transport of free fatty acids, while subcutaneous adipocytes serve as stable energy reserves [41]. During periods of caloric excess, WAT mass expands through adipocyte hypertrophy and hyperplasia by terminal differentiation of committed pre-adipocytes into mature adipocytes, a process dependent on PPAR-γ [41]. As WAT deposits expand in states of obesity, the fat tissue undergoes remodeling to facilitate tissue expansion. Dead adipocytes are removed by adipose tissue macrophages that infiltrate the fat tissue in response to adipocyte death [42], and these macrophages contribute to an increased inflammatory profile in WAT depots present in states of obesity and often associated with the development of insulin resistance [43].

In contrast to WAT, BAT appears as discrete adipose tissue located along the neck, supraclavicular, paravertebral, and peri-renal regions. Brown adipocytes originate from MYF-5 positive dermomyotomes and become active upon cold exposure [44,45]. BAT is rich in mitochondria and functions in basal and inducible energy expenditure by uncoupling protein 1 (UCP1) [46], which stimulates proton leak from the mitochondrial membrane to uncouple respiration from ATP synthesis and produce heat. BAT's thermogenic activity is typically controlled by catecholamines, including the β-adrenergic signaling, as well as thyroid hormone [47]. BAT inversely correlates with body mass index [48] and, along with its role in adaptive thermogenesis, also functions in protecting against obesity, insulin resistance and T2DM [49]. In the past decade, a "third" fat tissue (the so-called "beige" adipose tissue) has been described and sparked much research interest. Beige adipose tissue is an inducible thermogenic adipose tissue that forms in WAT after exposure to different environmental triggers, including chronic cold exposure [50]. Beige fat resembles BAT in terms of displaying thermogenic activity, and originates from mesenchymal stem cells that express Pdgfrα, MYF5-negative mesoderm precursors, with a subset (approximately 15%) originating from MYH11-positive smooth muscle-like precursors [44,51]. Unlike the firmly established metabolic and endocrine role of WAT in various physiologic states and disorders, markers and pathways associated with brown and beige adipose tissue are currently under active investigation. There is growing scientific interest in activating these specific fat tissues as potential therapeutic options to reduce metabolic disorders. Additional studies are needed to better elucidate metabolic properties and systemic regulating factors for "browning" of WAT as future therapeutic targets for treating obesity, T2DM and other metabolic disorders in cancer survivors [45].

4. Marrow adipose tissue, a distinct fat tissue

Situated within the bone marrow cavity, marrow adipose tissue (MAT) accounts for approximately 10% of the total fat mass in healthy adult humans [52]. The origin of bone marrow adipocytes remains unclear and it is thought that these adipocytes differentiate from MSCs located within the bone marrow cavity, where they subsequently differentiate into white and beige adipose tissue. During early childhood, bone marrow is predominantly composed of hematopoietic tissue [53]. However, in both males and females, exponential accumulation of MAT begins at birth, starting with the distal bones [53], with males demonstrating greater amounts of MAT compared to females [54]. By age 25 years, approximately 70% of the human bone marrow consists of MAT, with continued gradual accumulation of MAT throughout life [52]. While MAT was originally recognized as a distinct adipose depot by the mid to late twentieth century [55], recent advances in medical research along with newer imaging modalities such as magnetic resonance spectroscopy, positron emission tomography-computed tomography (PET-CT), and osmium tetroxide staining coupled with micro-CT, have provided the necessary tools to study the function and physiology of this unique fat depot [56].

MAT's origin is distinct to both WAT and BAT and is derived from progenitors that express osterix (Sp7), a transcription factor essential for osteoblastogenesis and bone formation [57]. Recent gene profiling comparing adult bone marrow-derived adipocytes to epididymal adipocytes also reveal different gene patterns, further highlighting MAT differences from WAT and BAT [58]. For example, bone marrow adipocytes demonstrate low expression of adipocyte-specific genes such as PPARγ, but high expression of genes associated with early adipocyte differentiation (C/EBPβ, RGS2), as well as genes that regulate bone cell function (SFRP4, TNFα, TFG) [59].

The distinct developmental origin and lipid composition of marrow adipocytes has generated new-found scientific interest into the role and metabolic function of MAT [60]. Similar to WAT, the lipid content of MAT is entirely composed of triglycerides [23], but, unlike WAT, the MAT fatty acid component consists of saturated, monounsaturated, and polyunsaturated fat [52]. Fatty acid metabolism is critical for HSC and MSC proliferation and function. During times of metabolic need, adipose tissue lipases break down triglycerides to release free fatty acids for use as an energy source to regulate osteoblasts, osteoclasts, and hematopoietic cell populations [61]. In humans, the fatty acid composition of MAT is significantly higher in saturated fat content, which is distinct from fatty acid composition of subcutaneous WAT [62]. The difference in fatty acid content of adipocytes located within hematopoietic dominant regions of the bone marrow compared to non-hematopoietic regions suggest that bone marrow adiposity influences hematopoiesis by providing local source of fatty acids [23,60]. Thus bone marrow adiposity can also influence hematopoiesis by providing a local source of fatty acids.

Theories regarding the functional role of MAT have varied over the past few decades, particularly as MAT accumulation is associated with aging, osteoporosis, type 1 diabetes mellitus (T1DM),T2DM, anorexia nervosa, estrogen and growth hormone deficiency [52]. During states of nutritional deprivation, MAT and WAT show marked differences, with varying responses to nutritional cues. In human models of caloric restriction, such as anorexia nervosa, MAT stores are increased compared with healthy weight controls, while WAT stores are low [63–65]. The mechanism of how caloric restriction triggers the development of MAT is unclear and a signal, such as the hormone ghrelin released systemically or locally, may trigger other hormonal responses to induce marrow adipogenesis [66]. The increased MAT stores seen in anorexia nervosa and caloric restriction have been discussed extensively in prior reviews [57,65].

MAT exists in two distinct subtypes designated as constitutive and regulated MAT, each with different characteristics and function [60]. Regulated MAT (rMAT) is predominantly located in proximal skeletal sites and is interspersed within regions of active hematopoiesis. In contrast, constitutive MAT (cMAT) forms in the distal skeletal regions in early postnatal life and remains largely unchanged in the face of systemic or environmental challenges. The distinct metabolic role and function of these MAT subtypes are further highlighted by variations in lipid composition and gene expression [60]. However, future studies are required to better delineate the role of these distinct MAT subpopulations, where cMAT may serve an important function in early vertebrate development, in contrast to rMAT's role in hematopoiesis and skeletal remodeling [56,60].

5. Is marrow adipose tissue an endocrine organ?

Increases in MAT with aging and other clinical conditions such as anorexia nervosa, T1DM, T2DM, glucocorticoid treatment and cancer therapy raises the fundamental question regarding the function of this unique adipose tissue. MAT expresses and secretes adiponectin and this exerts systemic metabolic effects, prompting investigators to classify it as a functional endocrine organ [57]. In humans, low circulating levels of adiponectin are present in states of obesity, and enhanced WAT is a well-established biomarker of insulin resistance and cardiovascular disease [67]. Conversely, serum adiponectin concentrations increase in lean states, such as caloric restriction in humans with anorexia

nervosa [68]. Reduced circulating levels of adiponectin in obesity likely derives from reduced adiponectin expression and secretion due to mitochondrial dysfunction from increased inflammation, hypoxia, as well as endoplasmic reticulum stress [67]. Findings in animal models collectively suggest that MAT expansion is required for increased adiponectin production during periods of caloric restriction, supporting the conclusion that MAT contributes to the increases in circulating adiponectin measured in this context. In addition, the increased adiponectin concentrations seen during caloric restriction may also play a role in skeletal muscle adaptation [57]. However, the consequences of adiponectin production from MAT have yet to be fully delineated.

6. Fat and bone: the role of adipose tissue and the skeleton

MAT is found across all skeletal sites in humans, and compromises up to 15% of total fat stores in adults [57]. Skeletal homeostasis is actively mediated through MAT interaction with osteoblasts [69–71]. While endosteal adipocytes are rare in neonates, these cells steadily accumulate throughout the lifespan and occupy a greater proportion of the bone marrow cavity in the axial skeleton with aging [72]. MAT is increased in metabolic disorders with low bone mass (e.g. T1DM or anorexia nervosa) [63,73]. As noted, osteoblasts and adipocytes derive from a common pool of mesenchymal progenitors, superficially suggesting a simple tradeoff between bone and fat mass. Pref-1, a member of the epidermal growth factor-like family of proteins, is a known regulator of adipocyte and osteoblast differentiation [65]. Wren et al. were the first to report an inverse association between femoral cortical bone area and MAT in both young and older subjects [74]. Furthermore, an inverse relationship between bone mineral density (BMD) and MAT was also demonstrated in groups of healthy Caucasian women [75] and middle-age Caucasian and African American men and women [76]. Yet, the negative association of high marrow adiposity and low bone mass is variable and far from a simple inverse relationship. In healthy individuals, marrow adipocytes increase rapidly in long, axial bones around peak skeletal mass acquisition during puberty. As noted previously, males have greater amounts of MAT when compared with females, despite higher BMD [54,72]. Several animal models have also demonstrated high bone mass despite increased marrow adipose tissue [52,77]. These findings suggest that simultaneous accumulation of bone mass and MAT can occur, and that the MAT in healthy individuals somehow differs from the marrow fat accumulation seen in various disease processes, including cancer survivors following radiation and chemotherapy. Similarly, the relationship between WAT and bone is equally complex and highly dependent on the location of the fat depot. High body mass confers greater mechanical loading and enhanced bone mass, yet greater visceral WAT has deleterious effects on bone and contributes to osteoporosis by disrupting bone remodeling through the release of inflammatory cytokines, such as IL6 and TNFα [78]. In our study of long-term HSCT survivors following total body irradiation, MAT volume was two-fold greater when compared with age- and sex-matched controls. The enhanced MAT was also associated with greater visceral adiposity and fat infiltration of muscle, reduced bone volume fraction, and abnormal bone microarchitecture [26]. Similarly, adult patients receiving pelvic radiation therapy in combination with chemotherapy experience significant bone marrow cell depletion, bone loss with increased fracture risks, and enhanced MAT [79].

Increased MAT is present in osteoporosis, and MAT is an important indicator of bone integrity [80]. Iliac bone biopsies in osteoporotic individuals demonstrate increased MAT volume and decreased trabecular bone volume compared with age-matched controls, suggesting increased fracture risk in individuals with increased MAT [81,82]. Similarly, Wehrli et al. demonstrated that enhanced vertebral adiposity is an independent predictor of fracture risk [83]. Lower proportion of unsaturated lipid content is noted in MAT of individuals with osteoporosis and osteopenia based on proton spectroscopy imaging [84]. However, it is not known whether marrow fat saturation or unsaturation contributes to increased fracture risks.

Mechanical loading also serves as an important player in the bone-fat interaction for skeletal homeostasis. PPAR-γ is required for adipocyte differentiation, and treadmill running in rats prevents ovariectomy-induced bone loss by limiting PPAR-γ expression [85]. Unloading in humans and animal models is associated with increased MAT and low bone mass [86]. In rat models exposed to hind limb unloading, impaired bone acquisition and greater marrow adiposity is seen, and these abnormalities normalize upon skeletal reloading [87,88]. At the cellular level, MSCs subjected to subtle mechanical signals in vivo demonstrate an increased propensity towards osteoblastogenesis, even if situated in highly adipogenic environments [89,90]. Similarly, in vitro stretching of MSCs reduces PPAR-γ signaling and adipogenesis, even during PPAR-γ activation [91]. Interestingly, β-catenin signaling is also increased during mechanical stretching and serves as an important mechanosensitive regulatory mechanism in the stem cell niche and a further explanation of how exercise can influence the bone marrow microenvironment [92]. Recent intervention studies in healthy children demonstrate increases in BMD along with significant decreases in femoral MAT with activity [93,94].

Lastly, in addition to exercise, growth hormone serves as another key factor in the bone-fat interaction, particularly as growth hormone is secreted in response to exercise [95]. During aging, the bone marrow cavity gradually becomes filled with adipocytes and bone is lost. Concomitantly, levels of growth hormone also decline. In mice and humans with growth hormone deficiency, adipocytes accumulate within the bone marrow cavity and these levels normalize with growth hormone replacement [96]. In these individuals, growth hormone replacement is also accompanied by parallel increases in osteoblast activity and increased BMD [96].

7. Marrow adipose tissue and metabolic disorders

T1DM is a significant risk factor for impaired cortical geometry, low bone mass, and fractures [73,97]. Increased MAT is present in patients with T1DM regardless of disease severity [98], yet it is still unclear if marrow adipocyte infiltration in these patients plays a central role in bone loss. In animal models of streptozocin-induced T1DM, expression of proadipocyte genes such as PPARγ was increased in long bones along with reduced expression of osteocalcin [99,100]. Interestingly, subsequent treatment with PPARγ antagonist, BADGE, in these animal models prevented the accumulation of marrow adiposity, without improvement in the accompanied skeletal loss [100]. These investigations suggest that the PPARγ-mediated interaction between bone formation and enhanced marrow adiposity is probably not the sole mechanism responsible for bone loss in T1DM. On the other hand, treatment with thiazolidinediones (TZD), agonists of the PPARγ receptors and strong inducers of MAT, are linked with bone loss in the appendicular skeleton of rodents [47,101]. Yet, conflicting results are noted in humans with respect to TZD treatment and marrow adipose tissue expansion, suggesting need for more detailed investigation [102].

Skeletal fragility is also a well-recognized feature of T2DM even in the presence of normal BMD [103]. Despite elevated fracture risks, increased MAT is not consistently present in patients with T2DM. To date, studies using magnetic resonance spectroscopy suggest an increased saturated to unsaturated lipid ratio within the marrow cavity of women with T2DM who have fractures [104]. While marrow adiposity is not a feature of insulin resistance, in women with T2DM who have hemoglobin A1C levels >7%, higher levels of MAT were noted compared with those who have levels ≤ 7%, alluding that perhaps MAT is affected by glycemic control [105].

The decline in estradiol and dihydrotestosterone levels, as seen with aging or as a consequence of cancer therapy, increases expression of PPARγ and differentiation of MSCs into adipocytes. In animal models following ovariectomy, adipocyte infiltration and marked increase in

bone marrow adiposity are seen [106]. In addition, postmenopausal women undergoing estrogen treatment demonstrate a decline in bone marrow adipocyte number and size as well as in MAT, suggesting a regulatory action of estrogen and androgens on bone marrow cells [107]. Finally, mice deficient in 11β-hydroxysteroid dehydrogenase 1, an isoenzyme that interconverts active glucocorticoids to its inert 11-keto forms, lack marrow adipocytes, suggesting a role for active glucocorticoids in MAT expansion [108]. Hence, the increased MAT seen in anorexia nervosa may also reflect an impact of elevated circulating cortisol levels [109,110].

8. Future directions and therapeutic implications of marrow adiposity

Over the past few decades, the majority of studies have focused on discerning the basic function and endocrine role of MAT, an intriguing source of adiposity in mammals. Animal studies indicate that MAT is an endocrine organ capable of undergoing pathologic changes and evolving in the presence of various disease states. The bone marrow niche regulates hematopoiesis and osteoblastogenesis. Factors influencing this process occur through delicate cellular, physical and chemical interactions within the bone marrow microenvironment. Thus, even small changes to the niche composition (e.g. cancer therapy) can have profound impacts on hematopoiesis, adiposity and skeletal health. While data from animal and human studies support the hypothesis that MAT is associated with skeletal remodeling, many questions still remain unanswered regarding the source, origin, and function of MAT and the local role of MAT in the skeletal microenvironment. Although animal studies have informed our basic understanding of MAT, future comprehensive clinical studies are needed to determine its relevance in treating metabolic disorders, improving skeletal health, and enhancing hematopoiesis. These efforts will provide the foundation for future targeted therapeutic interventions with the aim to address altered hematopoiesis and maximize skeletal remodeling in different patient groups including survivors of cancer and bone marrow transplantation.

Disclosure Summary

The authors have no financial relationships to disclose relevant to this article.

Funding sources

This review was supported by the NIH grant K07 CA166177 (SMM).

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