Marrow fat metabolism is linked to the systemic energy metabolism

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Abstract

Recent advances in understanding the role of bone in the systemic regulation of energy metabolism indicate that bone marrow cells, adipocytes and osteoblasts, are involved in this process. Marrow adipocytes store significant quantities of fat and produce adipokines, leptin and adiponectin, which are known for their role in the regulation of energy metabolism, whereas osteoblasts produce osteocalcin, a bone-specific hormone that has a potential to regulate insulin production in the pancreas and adiponectin production in fat tissue. Both osteoblasts and marrow adipocytes express insulin receptor and respond to insulin-sensitizing anti-diabetic TZDs in a manner, which tightly links bone with the energy metabolism system. Metabolic profile of marrow fat resembles that of both, white and brown fat, which is reflected by its plasticity in acquiring different functions including maintenance of bone micro-environment. Marrow fat responds to physiologic and pathologic changes in energy metabolism status by changing volume and metabolic activity. This review summarizes available information on the metabolic function of marrow fat and provides hypothesis that this fat depot may acquire multiple roles depending on the local and perhaps systemic demands. These functions may include a role in bone energy maintenance and endocrine activities to serve osteogenesis during bone remodeling and bone healing.

Introduction

Extensive evidence indicates that bone is an integral part of a system which governs energy metabolism. Identification that central regulators of energy metabolism are critical for control of bone mass created groundwork for conceptual change in our understanding of regulation of bone homeostasis. Hypothalamic regulation of energy metabolism by leptin-, NPY-, CART-, and αMSH-dependent signaling appears to be critical for regulation of bone mass (1, 18, 20, 41). In addition, bone is under control of adrenergic signaling, which is activated by sympathetic nervous system (21, 25). Both types of adrenergic receptors, α and β, are expressed in bone where, in a type-specific manner, they regulate bone formation and bone resorption. Thus, α2-AR deficiency results in high bone mass phenotype, increased bone length and decreased expression of osteoclast-specific gene markers suggesting that this type of adrenoceptors negatively regulate bone growth and increase bone resorption by

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acting directly on osteoclasts (25). On the other hand, β1-AR and β2-AR regulate osteoblasts function, whereas β3-AR is expressed in marrow adipocytes and may control lipolysis and energy production (7, 21, 48, 59). It has been demonstrated that β2-AR positively regulates RANKL production in osteoblasts and osteoblast development by synergizing with BMP-2 signaling, whereas β1-AR regulates osteoblasts proliferation (21, 82). Tissue-specific ablation of these receptors in rodents, or use of beta-blockers in humans, is associated with increased bone mass (9, 88). Fig. 1 summarizes a contribution of factors regulating energy metabolism on bone cell development and bone remodeling.

Since the control of energy metabolism directly involves fat tissue metabolism and the fact that fat occupies significant portion of bone marrow cavity, there is a need to review available information on metabolic profile of bone fat and any evidence indicating that this particular fat depot is linked to systemic energy metabolism. The main function of fat tissue is to regulate energy homeostasis through the maintenance of energy storage and its dissipation, and production of circulating hormones which regulate energy metabolism in other organs. In contrast to extramedullar fat depots (e.g. visceral and subcutaneous fat), the function of marrow fat is largely unknown. Historically, it was considered to have supportive role in hematopoiesis by producing the necessary cytokines and energy in the form of heat for hematopoietic cell development (31, 79). Recent evidence indicates that the support for hematopoiesis is provided rather by adipo-osteogenic progenitors, which are essential for the maintenance of hematopoietic niche within the marrow (66). In contrast, the presence of lipid-filled adipocytes in the marrow cavity correlates inversely with hematopoiesis, while their absence, due to targeted suppression of mesenchymal cell differentiation toward adipocytes, correlates with increased hematopoiesis, indicating that mature marrow fat cells are negative regulators of hematopoietic micro-environment (68). However, there is certain paucity in information on metabolic activity of marrow fat. It has been hypothesized that marrow fat participates in lipid metabolism by clearing and storing circulating triglycerides, thereby acting as a localized energy reservoir for emergency situations requiring, for example, *de novo* osteogenesis (31). Indeed, gene expression profile of marrow adipocytes suggests that they possess activity of energy dissipation as well as endocrine activities, which may modulate local marrow environment supporting bone remodeling (48, 75, 76).

Marrow adipocytes originate in a mesenchymal stem cell (MSC) compartment that also produces osteoblasts. The commitment of MSCs toward either the osteoblast or adipocyte lineage is determined by a combination of extracellular and intrinsic factors that regulate cellular activities of the Wnt, TGFβ/BMP, and IGF-1 signaling pathways and lead to activation of lineage-specific transcriptional regulators including Runx2, Dlx5, and osterix for osteoblast, and PPARγ2 and a family of CAAT enhancer binding proteins for adipocytes (51, 57, 65, 71). Activation of the PPARγ2 isoform with either natural (fatty acids and ecosanoids) or artificial (TZD) ligands directs MSC differentiation toward the adipocyte lineage at the expense of osteoblast formation and results in decreased bone mass (50, 54, 65). Moreover, activation of PPARγ2 in cells of the osteoblast lineage converts them to terminally differentiated adipocytes and irreversibly suppresses their phenotype (52, 53). Marrow adipocytes are under the same transcriptional control and express similar set of genes involved in carbohydrate and lipid metabolism as extramedullar fat cells, indicating that marrow fat response to the environmental and hormonal factors might be similar to other fat depots (75). However, their localization in bone may determine their unique function and unique response to the factors modulating systemic energy metabolism.

Marrow fat metabolic functions

From the energy metabolism perspective there are two types of fat tissue. White fat or WAT, represented by subcutaneous and visceral fat, is characterized by a low number of mitochondria and serves as a primary site for triglyceride/energy storage (81). WAT also functions as endocrine tissue by producing hormones regulating energy balance including leptin and adiponectin. Brown fat or BAT, which appears as discrete tissue located along the neck, and in supraclavical, paravertebral, and perirenal regions, is rich in mitochondria and functions in basal and inducible energy expenditure (29). This is mediated by uncoupling protein 1 (UCP1), which stimulates proton leak from the mitochondrial membrane to uncouple respiration from ATP synthesis to produce heat. BAT thermogenic activity is controlled by the central nervous system via catecholamines and β-adrenergic signaling, and deiodinase 2 (Dio2)-mediated thyroid hormone conversion from thyroxine (T4) to triiodothyronine (T3). Along with its role in adaptive thermogenesis, BAT also has a function in protecting against obesity, insulin resistance and diabetes (13, 22, 44–46).

Bone marrow fat is often referred as yellow adipose tissue (YAT), because of it's yellowish appearance due to a moderate number of mitochondria, and it is suspected to have mixed white and brown fat phenotype (30, 48). Historically, marrow fat was merely considered a cellular component of bone that served a passive role by occupying space no longer needed for hematopoiesis. Marrow cavities of newborn mammals contain active hematopoietic tissue, known as "red" marrow. In the first decade of age, "red" marrow undergoes gradual replacement by fatty or "yellow" marrow, which by the second decade of human life fills almost entire cavity of long bone (63). The process begins in the periphery of the skeleton, in the terminal phalanges, it progresses to the distal and proximal long bone, and finally it occurs in the flat bone and vertebral body of the central skeleton (37, 63). In a single bone, conversion of "red' to "yellow" marrow starts in the diaphyseal region and extends toward proximal and distal metaphysis (37). Fat distribution in human skeleton is site, age, and gender specific. In adults, long bone marrow cavity is entirely filled with fat, while in iliac crest marrow constitutes 40% of fat and 60% of hematopoietic cells (78). Men have more bone marrow fat as compared to age-matched women (49), and over the adult lifespan, men and women can have more than a twofold increase in bone-marrow fat (40, 49, 61, 89). The process of fat accumulation in murine bone differs from that in human bone in respect to age and skeletal location. In C57BL/6 mice, adipocytes start to be visible in tibia and femora after peak bone mass is achieved (4–6 mo of age) (50). Moreover and in contrast to humans, they start to accumulate in proximal and/or distal metaphyseal region, and extend to the diaphyseal part of bone (Fig. 2).

The localization of bone fat to the trabecular area, where the active bone remodeling process occurs, suggests that marrow fat may be involved in this process, perhaps by providing energy for hematopoietic and mesenchymal marrow compartment (19). Indeed, an analysis of molecular signature of marrow fat showed that this fat depot expresses gene transcripts characteristic for BAT and involved in energy production (48). Relative expression of thermogenic regulators PGC1α and deiodinase 2 (Dio2) is at the levels characteristic for BAT (48). Bone marrow thermogenic activity and its response to low temperature were recognized long time ago (reviewed in (30)). It has been acknowledged that the distribution of fat in bone correlates with a body temperature gradient and is higher in the appendages, which have lower body temperature, than in the axial skeleton (31). Interestingly, in humans the fat fraction in the heel constitutes nearly 90% even at early age and does not increase with age, whereas, the fat fraction in the spine occupies 30% of marrow cavity at early age and increases to 70% at 60 years of age (58). In mice, we observe dense fat cell concentration in the distal and the proximal parts of murine tibia (Fig. 2B). Although it is a pure speculation at this point, however one can correlate the differences in fat distribution

with metabolic activity of bone and body temperature gradient. Hence, the presence of fat in the trabecular region with extensive bone remodeling and its presence in the relatively inactive distal region, which is naturally exposed to the lower temperature than the proximal part, may suggest that these two fat depots may differ metabolically.

Marrow fat may also function in a manner similar to WAT, which includes clearing and storing circulating triglycerides. The analysis of the marrow fat response to antidiabetic TZDs, which improve energy metabolism by increasing cell sensitivity to insulin and increasing lipid storage in adipocytes, suggests that YAT may function as an insulin-sensitive tissue which is involved in fatty acids metabolism (Table 1) (53, 75). Consequently, in marrow adipocytes TZD rosiglitazone upregulates the expression of genes essential for fatty acid metabolism, including fatty acid synthase, fatty acid-binding proteins, hormone-sensitive lipase, and cholesterol transporter CD36. Interestingly, although apparently a large number of genes involved in carbohydrate metabolism is upregulated, there is no change in the expression of any of the important insulin-dependent glucose transporters, including GLUT4 (75). This observation suggests that marrow fat functions in rather lipid than glucose metabolism (75). Most importantly, rosiglitazone induces in marrow adipocytes the expression of genes involved in insulin signaling, among them the insulin receptor, insulin receptor substrate-1 and FoxO1, while suppressing the expression of negative regulators of this signaling network such as Socs3 (Table 1). This profile suggests that marrow fat responds positively to insulin sensitizing conditions. In addition, TZDs upregulate in marrow fat an expression of BAT-specific gene markers (UCP1, PGC1α, Dio2, β3AR, Prdm16 and FoxC2) indicating a potential of marrow fat to provide energy. Similarly, a response of visceral fat to TZDs constitutes an increased expression of BAT-specific gene markers and increased lipid oxidization and energy production (83).

Marrow fat endocrine/paracrine function

An endocrine activity of fat cells includes production of adipokines, among them leptin and adiponectin, which regulate caloric intake and insulin sensitivity in peripheral tissues, respectively. Both adipokines are also produced in bone, however in smaller quantities as compared to WAT, and their receptors are expressed in bone cells, linking bone and fat metabolism (48). Although strong evidence points to CNS as a mediator of leptin effect on bone, the presence of leptin receptor in osteoblasts and osteoclasts, as well as leptin production by marrow adipocytes suggests receptor-mediated direct effect on bone. Indeed, animal studies demonstrated that leptin increases bone mineral density, bone mineral content, and bone formation rate, while it decreases the number and the size of bone marrow adipocytes when acting on bone peripherally (33, 34). In addition, db/db mice with leptin receptor-deficiency have reduced bone mass and bone strength, indicating that receptor mediated leptin activity can be anabolic for bone, in contrast to its activity through CNS (20, 21, 41, 85). However, human epidemiological studies correlating levels of circulating leptin with bone mass and fracture risk are not conclusive and indicate that this adipokine is rather a poor predictor of skeletal status (5, 39, 56).

In contrast, recent clinical evidence suggests that adiponectin may play an important role in the regulation of skeletal homeostasis. It has been shown that high levels of circulating adiponectin correlate with lower BMD in older men and women (4), and increased fracture risk only in older men, but not in older women (5). Interestingly, increased incidence of fractures in men occurred despite higher hip BMD and lower levels of circulating adiponectin, as compared to women, indicating that association between adiponectin and bone may be influenced by sex hormones.

In contrast to human studies, mice deficient in adiponectin show either transient increase or no effect on bone mass (69, 74, 86). *In vitro* however, adiponectin inhibits adipocyte formation, stimulates osteoblast phenotype and cell proliferation, and inhibits osteoclastogenesis (6, 86, 90). Moreover, adiponectin increases BMP-2 expression in osteoblastic cells via AdipoR1 receptor signaling pathway which includes activation of AMPK, p38 and NF-kappaB signaling (35). The direct role of adiponectin in regulation of new bone formation was demonstrated recently in the model of distraction osteogenesis (38). Intermittent administration of adiponectin to the mandibular osteodistraction site resulted in significant increase in intramembranous bone formation and an increase in overall rate of bone regeneration (38). Taken together, these results suggest that locally produced adiponectin may have a positive effect on bone, perhaps in emergency situations which require new bone formation.

Marrow fat response to physiological and pathological changes in energy metabolism

The connection between marrow fat and the systemic energy metabolism is reflected in its response to changes in energy balance. Alterations in the efficiency of energy metabolism system during aging, and in overnutrition, malnutrition, and diabetes correlate with changes in the fat volume in bone and changes in its activity. Aging process is associated with decreased efficiency of energy utilization partially due to functional impairment of fat tissue (12). A decline in peripheral fat depots size and function correlate with increased fat accumulation in bone. It is hypothesized that aging causes redistribution of lipids to cells of other organs, like bone marrow, muscle and liver, which may acquire fat-like phenotype without functioning as *bona fide* adipocytes and can lead to lipotoxicity in these organs (43). Nuclear magnetic resonance analysis of the qualitative changes in fat of lumbar vertebra showed that with aging the level of unsaturated fatty acids decreases (89). Similar changes in fat quality are observed in visceral fat with aging and metabolic diseases, which lead to accumulation of monocytes, production of inflammatory cytokines and development of insulin resistance in fat tissue (81). Despite an increase in bone fat with aging, the phenotype of marrow adipocytes changes toward lower efficiency in energy production as reflected by lower expression of brown fat gene markers: UCP1, Dio2, PGC1α and β3 adrenergic receptor (48). These data suggest that marrow fat metabolism may be subjected and is responding to the same factors which modulate extramedullar fat metabolism during aging (48).

Number of studies indicate an inverse relationship between bone mass and fat mass in bone. An increased fat content in bone correlates negatively with bone mass during aging and with decreased bone acquisition during growth (17, 32, 73, 87). The underlying mechanism includes changes in the signaling and transcriptional control of MSCs differentiation leading to their preferential differentiation toward adipocytes and at the expense of osteoblast formation (62, 70). However, it is also possible that changes in bone fat metabolism lead to lipotoxicity, which may contribute to the bone loss with aging. Indeed, increase in oxidative stress and accumulation of oxidized lipids in bone is associated with increased local inflammatory responses, resistance to anabolic effects of PTH and Wnt signaling, and osteoporotic bone loss (2, 28, 42, 72).

Overnutrition and malnutrition are two additional examples of systemic changes in energy metabolism, which affect both, bone fat volume and bone mass. In obese premenopausal women, visceral fat positively correlates with the fat content in vertebra and independently of BMD indicating that obesity and bone marrow fat accumulation are linked through the same mechanism, which is responsible for handling increased calorie intake and accumulation of energy in the form of fat (11). The same studies showed that increased fat

in vertebra correlates with decreased BMD, independently of obesity, supporting inverse relationship between adipocyte and osteoblast differentiation (11). Surprisingly, in conditions of decreased calorie intake and decrease in the amount of peripheral fat, the content of fat in bone is also increased (11, 16). Patients with anorexia nervosa have elevated marrow fat mass in vertebra and femur, which is associated with low mineral density and elevated levels of circulating Pref-1, a negative regulator of osteoblast and adipocyte differentiation (10). Similarly, caloric restriction increases fat content in murine bone (16). The 30% reduction in daily caloric intake has a deleterious effect on growing murine bone reflected by decrease in cortical and trabecular bone mass. Changes in bone mass are accompanied by increased fat accumulation in the marrow despite a decrease in peripheral fat mass. Leptin and IGF-1 levels are also decreased suggesting a possible role of these signaling in lipids accumulation in bone (16).

Diabetes is a disease of impaired glucose and fatty acids metabolism due to deficiency in insulin signaling in fat, liver and muscle. Both types of diabetes, insulin-dependent Type 1 and insulin-independent Type 2, are associated with increase of fat volume in bone. In Type 1, characterized by pancreatic β-cell failure to produce insulin, increased quantities of fat in bone correlate with low bone mass and low levels of circulating IGF-1 and deficiency in vitamin D (8, 64, 80). In contrast, in Type 2, which is associated with high levels of serum insulin but inability of peripheral tissue to respond to it, fat mass in bone is increased but this increase is not associated with lower bone mass. In a murine model of hyperinsulinemia due to insulin clearance impairment in the liver, high bone mass coincides with increased fat content (36). An analysis of metabolic profile of marrow fat of diabetic yellow agouti mice showed decreases similar to aging in the expression of brown fat specific genes involved in energy production (48). This suggests that diabetic disease not only affects peripheral fat but also bone fat and changes its function.

Interestingly, in a model of increased energy production due to deficiency in early B-cell factor 1 (Ebf1), increased bone formation and high bone mass correlates with high quantity of fat in bone (26) suggesting a positive, or at least lack of a negative, effect of fat on osteogenesis. Moreover, heterotropic bone formation is associated with accumulation of brown fat cells expressing UCP1, suggesting the role of bone fat in providing energy and supporting hematopoiesis (67). Thus, fat in bone may acquire different metabolic status dictated by systemic energy metabolism status and certain local demands of physiological importance. The above examples suggest that metabolic activity of fat is as important for bone homeostasis as its presence in bone.

Integration of bone metabolism with energy metabolism has been presented recently as a model which links anabolic effect of insulin signaling in osteoblasts with bone turnover and regulation of insulin sensitivity in peripheral organs (24, 27). Thus, in osteoblasts insulin signaling regulates an expression of Runx2 and osteocalcin production. In addition, insulin increases support for osteoclastogenesis by decreasing an expression of OPG, a decoy receptor for RANKL. As a result, insulin increases bone turnover and production of undercarboxylated osteocalcin, which in endocrine fashion regulates insulin release from β-cells in pancreas and production of adiponectin in fat tissue (14, 24, 27, 55). It is of interest whether this regulatory circuit is affected in insulin-independent Type 2 diabetes. There is limited information on the status of bone turnover in diabetes, however longitudinal histomorphometric studies by Krakauer et al. suggest that progression of diabetic disease attenuates bone turnover (47). This observation together with the role of insulin in regulation of this process poses an interesting question whether decreased bone turnover is a manifestation of insulin resistance in bone. In general, patients with Type 2 diabetes have normal or higher bone mass as compared to age-matched non-diabetic controls, however

they also have higher fracture risk indicating decrease in bone quality, which may in part result from decreased bone turnover (60). More studies need to be done in this respect.

Glucocorticoids may suppress BAT-like phenotype in marrow adipocytes

A decrease in BAT-like phenotype of marrow adipocytes with aging and diabetes (48) may account for unfavorable changes in the marrow environment affecting bone remodeling. BAT-like metabolism is controlled by β adrenergic signaling through fat-specific β3 adrenoceptor (15), which expression decreases in the bone marrow during aging and in diabetes (48). Two other adrenoceptors, β1 and β2, are expressed in osteoblasts with β2 receptor implicated in upregulation of RANKL production and increased bone resorption (59). Glucocorticoids, including endogenous cortisol, the levels of which increases with aging and diabetes (3), and which have a negative effect on bone homeostasis (84) are known to regulate adrenergic response by regulating the expression of all three forms of β adrenoceptors. Glucocorticoids inhibit the transcriptional response of the UCP1 gene to adrenergic stimulation in brown adipocytes by inhibiting the expression of β1 and β3 adrenoceptors (77). In epidydimal adipose tissue, in response to food stress, increased levels of endogeneous cortisol correlate with down-regulation of β1 and β3 adrenoceptors expression and upregulation of β2 adrenoceptor expression (23). Taking together, glucocorticoids have a dual effect on adrenergic signaling. They decrease adrenoceptor-mediated metabolic activity of brown fat and increase catabolic activity in bone. Thus, activation of glucocorticoid signaling in marrow adipocytes may lead to decrease in β3 adrenergic receptor expression and loss of BAT-like potential of marrow adipocytes, which is seen with aging and diabetes. More studies are needed to support this hypothesis.

Concluding remarks

There is an association between diseases of energy metabolism, fat content in bone and bone mass. Marrow fat is metabolically active and may acquire phenotypic characteristics of either energy producing BAT or energy storing WAT. Most importantly, it responds to changes in systemic energy metabolism. There is an increasing interest in the function of marrow fat including its capabilities to modulate marrow micro-environment to support bone remodeling and contribute to insulin-dependent fatty acid metabolism. More studies need to be done to unravel metabolic properties of this fat depot and perhaps to harness bone fat function for improving skeletal status in metabolic diseases including diabetes and osteoporosis.

Acknowledgments

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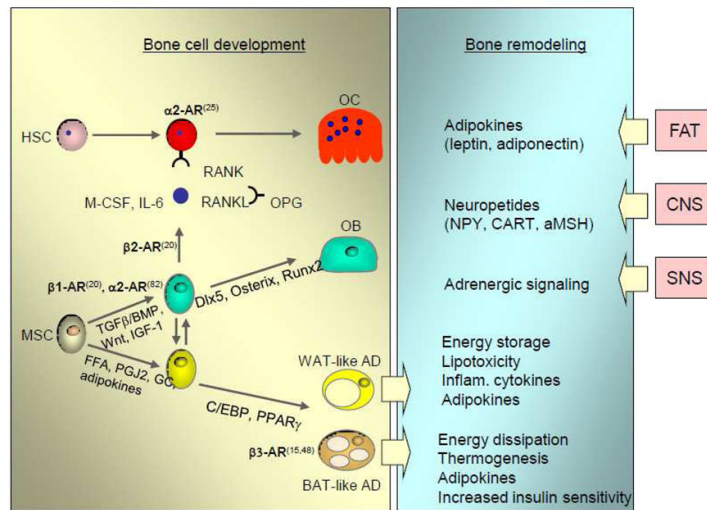
Highlights

This review summarizes available information on metabolic status of marrow fat.

Marrow fat responds to to physiologic and pathologic changes in systemic energy metabolism.

Marrow fat possesses mixed brown and white phenotype.

Marrow fat may acquire function in maintenance energy metabolism in bone.

Figure 1.
Contribution of factors regulating systemic energy metabolism on bone cell development and bone remodeling. The role of β-adrenergic signaling on osteoblast and osteoclasts development, and metabolic function of adipocytes highlighted by bold letters and referenced. Abbreviations: FFA – free fatty acids, PGJ2 – prostaglandin J2, GC – glucocorticoids.

Figure 2.
mCT renderings of murine femur (A) and tibia (B) representing longitudinal cross section of mineralized bone tissue (left panel) and fat in the same bone after decalcification and staining with osmium tetroxide (right panel).

Table 1

Expression of transcripts for insulin signaling and fatty acids metabolism in response to treatment of U-33/γ2 cells with insulin sensitizing drug rosiglitazone (75)

Functional category	Gene name	Gene symbol	Fold expression vs. U-33/c cells
Insulin signaling	Insulin receptor	IR	3.4
	Insulin receptor substrate 1	IRS1	1.9
	Forkhead box O1	FoxO1	1.8
	Suppressor of cytokine signaling 3	Socs3	−6.1
Fatty acids metabolism	Fatty acid synthase	FAS	5.5
	Fatty acid binding protein 4	FABP4	69.6
	Fatty acid binding protein 5	FABP5	82.9
	Lipoprotein lipase	LPL	3.4
	Hormone-sensitive lipase	Lipe	74.4
	CD36 antigen, cholesterol transport	CD36	351.9
	Cell death-inducing effector c/Fat specific protein 27	Cidec/FSP27	457.2