HHS Public Access

Author manuscript

Endocrinol Metab Clin North Am. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Endocrinol Metab Clin North Am. 2017 March ; 46(1): 41–50. doi:10.1016/j.ecl.2016.09.004.

Bone-Fat Interaction

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SYNOPSIS

Marrow adipose tissue (MAT) is a recently identified endocrine organ capable of modulating a host of responses. Given its intimate proximity to the bone microenvironment, the impact marrow adipocytes exert on bone has attracted much interest and scientific inquiry. While many questions and controversies still remain relative to marrow adipocytes, multiple conditions/ disease states in which alterations occur in MAT have provided clues about their function. In general, the consensus in the field is that MAT is inversely associated with bone density and quality. Although further investigation is warranted, MAT has clearly been demonstrated as an active dynamic depot that contributes to bone turnover and overall metabolic homeostasis.

Keywords

Marrow adipose tissue; marrow fat; adiposity; bone marrow

Introduction

Osteoporosis and low bone mass (i.e., osteopenia) are major public health concerns affecting a staggering 54 million in the U.S.[1] Moreover, as the nation's demographic continues to shift towards an older population these statistics are projected to continue to rise.[2] Approximately 2 million osteoporotic-related fracture occur each year, costing the nation $17 billion per year.[2] In addition to the financial burden, osteoporosis-related fractures often lead to multiple comorbidities (i.e., hypertension, deficiency anemias, fluid and electrolyte imbalance)[3], and patients frequently experience diminished quality of life due to immobility, pain, and isolation.[4] While therapeutic treatment options have significantly aided in the management of osteoporosis, some patients still experience undesirable, adverse side-effects,[5-7] and therefore, continued development of refined options is necessary. As this

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DISCLOSURE STATEMENT
The authors have nothing to disclose.

quest continues, it is imperative to gain further insight in to the cellular and molecular responses occurring within the bone niche.

Bone is an incredibly dynamic tissue that undergoes continuous remodeling involving bone resorbing osteoclasts, bone forming osteoblasts, and mechanical sensing osteocytes. While much of bone biology has focused on these primary cell types, the bone marrow compartment also provides a unique environment in which communication between various cells can directly and indirectly impact the bone. One such cell population that has attracted much attention and scientific inquiry in the past decade are marrow adipocytes, often referred to as marrow adipose tissue (MAT) and/ or yellow adipose tissue (YAT). These adipocytes can be found interspersed throughout the marrow compartment. Recently, two "types" of MAT, constitutive MAT (cMAT) and regulated MAT (rMAT), have been described based on their (1) cellular morphology, (2) region specificity, and (3) fatty acid composition.[8] Both in human and mouse tissues cMAT is described as containing large adipocytes localized at the distal tibia, and primarily composed of unsaturated lipids.[8] Conversely, rMAT is mainly found in the proximal tibia, interspersed with active hematopoiesis, and composed of saturated lipids.[8] Although our understanding of MAT has advanced significantly in the past decade, many questions still remain. It is therefore the aim of this review is to provide the most current opinions relative to MAT and bone, while providing a brief overview of clinical scenarios in which MAT is altered.

Current Controversies and Fundamental Questions

Lineage of Bone Marrow Adipocytes

Unlike peripheral adipocytes or white adipose tissue (WAT), which are primarily derived from mesenchymal stem cells (MSC) through vascular infiltration,[9, 10] the definitive lineage of marrow adipocytes remains largely unknown and controversial. For example, while these cells have classic adipocyte functions and pathology by their hallmark ability to store lipids, bone marrow adipocytes express the osteoprogenitor marker osterix, encoded by the *Sp7* gene.[11] Given the expression of *Sp7*, one theory, is that the development of marrow adipocytes results from a shift in allocation of MSCs from the osteoblast lineage towards the adipocyte lineage, subsequently decreasing bone formation.[12-14] Another possibility is that the marrow adipocyte could arise from bone lining cells, poorly characterized flat fibroblastic cells that express some markers of the osteogenic lineage (e.g. Sp7).

In addition to demonstrating features characteristic of WAT and *Sp7*, marrow adipocytes also exhibit some brown adipose tissue (BAT) transcriptional markers and target genes (i.e., *Prdm16*, *FoxC2*, *Pgc1a*, *Dio2*, *β3AR*, and *Ucp1*).[15] Some literature also describes fibroblast adventitial reticular cells of the venous sinusoids accumulating lipids to "convert" to adipocytes. Under these circumstances, marrow adipocytes are presumed to primarily function as space-fillers in the marrow cavity for inactive or reduced numbers of hematopoietic cells,[16, 17]. Another, more recent discovery completely shifts the idea that bone marrow adipocytes exclusively develop from MSCs pools and suggests they may arise from hematopoietic stem cells (HSCs). These data demonstrate that HSCs have the ability to hone to non-tissue resident fat depots, differentiate to adipocytes, and undergo *de novo* generation.[9, 18] Moreover, the identification of differential bone marrow adipose depots (i.e.,

cMAT and rMAT) has given rise to the possibility that adipocytes within the marrow space are a heterogeneous population, derived from multiple sources. Nonetheless, the controversy surrounding the origin of bone marrow adipocytes underscores the complexity of these unique cells and further investigation is warranted.

Bone Marrow Adipocyte Function

Aside from the lineage tracing of marrow adipocytes, the next fundamental question that arises is that of MAT function. Our understanding of marrow adipocytes now extends well beyond their historical role as passive, "space-filling" support for the hematopoietic microenvironment. While marrow adipocytes have a defined function as regulators of hematopoietic activity,[19] evidence also suggests MAT impacts systemic metabolism as well as bone turnover. Given their adipose pathology and biology, bone marrow adipocytes store fatty acids, and therefore, can impact global metabolism either by clearance of circulating fats and/or by their mobilization. Additionally, the recent identification of MAT as an endocrine organ capable of producing hormones such as adiponectin and leptin strongly suggests bone marrow adipocytes regulate systemic metabolism.[20, 21] While the impact of marrow adipocytes on bone appears to be complex, evidence also indicates that an inverse relationship exists between MAT and skeletal mass (Table 1). As described in the previous section, one theory could involve the "see-saw" effect between osteoblasts and adipocytes, however, it is likely more complicated than proposed. The predominant localization of marrow adipocytes to the trabecular compartment of bone suggests their direct interaction facilitates bone turnover.[8] Although many questions still remain, clinical scenarios in which MAT is altered has allowed investigators to gain further insight into how this novel organ impacts bone and fracture risk.

Clinical Scenarios of Altered MAT and their Bone Phenotype

Anorexia Nervosa

Anorexia nervosa is a prevalent psychiatric disorder characterized by extreme self-imposed starvation as well as the subsequent weight loss and depletion of energy stores. A striking health consequence of anorexia nervosa is an ~7-fold increase in fracture risk which is predominantly due to significant bone loss and decreased bone turnover.[22-24] Another, somewhat paradoxical feature of anorexia nervosa is that despite the lack of peripheral fat, the bone medullary space experiences a dramatic but reversible increase in MAT.[25, 26] Histological and pathological evaluation of the bone marrow cavity is characterized by hypoplasia accompanied by the accumulation of adipocytes and a pink gelatinous material.[27] This gelatinous material tends to surround adipocytes and is thought to be a result of fat atrophy during severe starvation. The progression of these changes within the marrow space appears to primarily depend on body weight loss or weight gain with treatment.[28] As a cautionary note, serous changes occurring in the bone marrow of patients with anorexia nervosa can often mask stress fracture during routine MRI.[29] Anorexia nervosa patients also experience decreases in serum leptin,[30, 31] insulin-like growth factor (IGF)-1[31] as well as increases in adiponectin[20] and preadipocyte factor (Pref)-1[32]. Whether the relationship of these various biomarkers is directly associated with MAT and their precise mechanisms of action remain to be further elucidated in patients with anorexia nervosa, however, they all

have documented effects on bone metabolism. Furthermore, some of the bone loss, and the excess marrow adiposity is reversible, when eating resumes normally and weight is restored.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is another condition which patients experience dramatic bone loss and increased risk of fracture,[33-35] however, the MAT phenotype appears to be slightly more ambiguous. Mouse models of T1DM (i.e., streptozotocin or STZ-induced) have been characterized as an appropriate model based on their (1) ablation of β-cells and subsequent attenuation of insulin production; (2) decreased body weight; (3) hyperglycemia; and (4) significant bone loss.[36] Additionally, these animal models have consistently demonstrated increased marrow adiposity.[36-40] Despite these observations in animal models, assessment of MAT in T1DM patients has yielded less impressive results. For example, T1DM patients with severe sensory polyneuropathy revealed a slight shift in T1 waves of routine MRI, indicative of marrow fat, in the tibia compared to matched controls.[41] However, the author's noted that while this signaling shift was significant it was not overtly abnormal.[41] Somewhat consistent with this finding, Slade et al.,[42] reported no differences in marrow adiposity from any site tested (e.g., vertebrae, femur epiphysis, femur metaphysis, and tibia metaphysis) between control and T1DM patients. An unexpected and key finding to this study was that serum lipids (e.g., cholesterol, cholesterol/HDL ratio, LDL, and triglycerides) demonstrated a strong relationship with marrow adiposity, not duration of T1DM or HbA_{1C}.[42] Taken together, these studies reveal that further clinical studies are warranted to fully understand whether MAT is altered clinically during T1DM.

Obesity and Type 2 Diabetes Mellitus

One of the most striking health consequences related to the prevalence of obesity (body mass index or BMI ≥30 kg/m^2 in adults) has been the staggering increase in cases of type 2 diabetes (T2DM), and while not all type 2 diabetics are overweight or obese, the majority of the cases occur in this population.[43] Understanding the bone phenotype in obese individuals and patients with T2DM has been extremely complex and outside of the scope of the current review, however, the current stance within the field is that type 2 diabetics experience an increased risk of fracture, independent of BMD.[44-52] In one study it appears that visceral fat in otherwise healthy women correlated with vertebral marrow adiposity, however bone density was not reported.[53] In addition to marrow visceral fat, bone marrow fat content was also shown to be associated with intramyocellular and intrahepatic lipids, as well as serum cholesterol and triglycerides, both of which are elevated during obesity.[54] One logical explanation of increased MAT during obesity would be that cells within the marrow compartment are exposed to or come in contact with more fatty acids, and therefore, readily accumulate and store these substrates. Given the intimate relationship between obesity and T2DM, similar changes in MAT have also been documented. Interestingly, one study noted that while total lipids were not different between type 2 diabetics and control subjects, patients with T2DM had higher saturated fat in the marrow compartment.[55] Moreover, T2DM patients with previous fracture had the highest saturated fatty acids and lowest unsaturated fatty acids.[55] These data suggest that bone marrow fat composition may serve as a novel tool to assess fracture risk within T2DM patients. It is also interesting to note that weight-loss from roux-un-Y gastric bypass reduces MAT after 6 months only in diabetic

patients and not non-diabetic group.[56] Although the implications of obesity and T2DM on bone health remains somewhat controversial, these data further implicate the role of MAT as a regulator of systemic metabolism.

Aging and Gonadal-Deficiency

Age-related changes in bone (i.e., decreased BMD, increased risk of fracture) are often thought of as the most classic alterations occurring in the skeleton. Aside from affecting an enormous portion of the population, age-related and gonadal deficiency osteoporosis have a strong historical presence in the bone literature In 2000, Schellinger and colleagues[57] used proton MR to determine that fat content within the vertebra (L2) increased with age, and, interestingly, men had higher fat content than women. These results were independently corroborated shortly thereafter.[58] In addition to the age-associated increase in bone marrow adipocytes and decrease in BMD, bone formation rates have also been inversely correlated to MAT.[59] These data provide evidence that as the adipocyte portion increased within the bone marrow cavity, osteoblast activity decreased. Moreover, the composition of marrow fat in age-related osteoporosis appears to be preferentially composed of unsaturated fatty acids.[60]

As aging progresses in women, gonadal deficiency or menopause is a natural physiological consequence. As such, the inverse relationship between BMD and MAT also exists in postmenopausal women.[61] The changes in marrow adiposity are most evident in the axial skeleton and it has been reported that the increase in MAT can occur quickly after withdrawal of estrogen or decrease rapidly in response to exogenous estrogen.[62] Furthermore, the fatty acid composition of MAT in postmenopausal women also follows a similar profile demonstrating lower saturated fatty acids and increased monounsaturated fatty acids, particularly in participants with previous fracture.[63] This is particularly interesting given the opposite observation in T2DM. It is also important to note that the treatment of postmenopausal osteoporosis with the bisphosphonates risendronate and zoledronate not only significantly reduces the risk of fracture, but can also decrease MAT.[64, 65] Collectively, these data clearly demonstrate that an inverse relationship exists between bone density and MAT in age-related and postmenopausal osteoporosis.

Disuse and Unloading of the Skeleton

Mechanical loading of the skeleton is crucial to overall bone health and quality. This is namely demonstrated in the severe loss of bone experienced by astronauts and cosmonauts during spaceflight as well as in bedridden patients.[66] Likewise, loading of the skeleton by gravity and weight-bearing exercises has shown to increase BMD and decrease fracture risk.[67] While clinical data remains relatively scarce due to the uniqueness and vulnerability of the primary populations affected by disuse, Trudel et al.,[68] demonstrated that 60 days of bedrest increased fat accumulation in vertebral bone marrow. The authors go on to describe that the elevated MAT remained even after a year of recovery (reambulation or normal physical activity).[68] It should also be noted this increase in bone marrow adiposity has also been documented in rodent models of disuse (i.e., hindlimb suspension)[69] and during microgravity/ spaceflight. Additionally, when mechanical stress or loading is introduced to bone in the form of exercise, it appears to decrease MAT while increasing BMD.[70, 71] While

more research is needed to fully elucidate how mechanical stress, or the lack thereof, effect MAT, the decrease of BMD appears to be accompanied by an increase in marrow adiposity.

Other Clinical Scenarios

The most extensively studied clinical diseases and conditions that alterations in have been studied MAT are outlined above, however, other research alludes to unique scenarios in the clinic that MAT is also altered. For example, bone loss and increased fracture risk is associated with alcoholism, it has also been demonstrated in rodent models that alcohol consumption dramatically increases vertebral fat accumulation.[72] Treatment options for various conditions and disease states can also impact marrow adiposity and bone. One such example of this is from radiation exposure used to treat various cancers. Exposure of the bone marrow compartment to radiation is sometimes targeted as in Hodgkin's lymphoma, but can also occur secondary due to the proximity of the targeted area, as in many pelvic cancers. None-the-less, radiation treatment causes direct damage to red and white blood cells often eradicating blood-related cancers, however, the repopulation of the marrow compartment is accomplished by adipocyte replacement.[73-75] Perhaps consequently to this massive expansion of MAT, the risk fracture to the irradiated area is often 3-times that of non-irradiated populations.[76] While this is by no means an all-inclusive list of clinical scenarios in which MAT is altered, it is imperative to continue to collect this data to gain further insight into how this novel tissue can impact multiple disease states. The advent of techniques such as MRI spectroscopy in larger clinical trials is likely to provide greater insight into the pathophysiology of MAT.

Future Considerations/ Summary

Marrow adipose tissue is an active dynamic depot that contributes to overall metabolic homeostasis. Understanding both its function and origin will go a long way in terms of determining how marrow adipocytes sense energy needs in the organism and how these cells respond to environmental and nutrient stress. Importantly, defining if these adipocytes are unique in their fatty acid transport and in their adipokine secretion should help to clarify the role of MAT in bone acquisition and maintenance.

References

(1). NOF. America's Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation. 2002. Ref Type: Generic

(2). The Surgeon General. Bone Health and Osteoporosis: A Report of the Surgeon General. Oct 14. 2004

(3). Nikkel LE, Fox EJ, Black KP, Davis C, Andersen L, Hollenbeak CS. Impact of comorbidities on hospitalization costs following hip fracture. J Bone Joint Surg Am. 2012; 94(1):9–17. [PubMed: 22218377]

(4). Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002; 359(9319):1761–1767. [PubMed: 12049882]

(5). Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. Med J Aust. 2005; 182(8): 417–418. [PubMed: 15850440]

(6). Rizzoli R, Reginster JY, Boonen S, et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcif Tissue Int. 2011; 89(2):91–104. [PubMed: 21637997]

(7). Schilcher J, Koeppen V, Aspenberg P, Michaelsson K. Risk of atypical femoral fracture during and after bisphosphonate use. N Engl J Med. 2014; 371(10):974–976. [PubMed: 25184886]

(8). Scheller EL, Doucette CR, Learman BS, et al. Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. Nat Commun. 2015; 6:7808. [PubMed: 26245716]

(9). Gavin KM, Gutman JA, Kohrt WM, et al. De novo generation of adipocytes from circulating progenitor cells in mouse and human adipose tissue. FASEB J. 2016; 30(3):1096–1108. [PubMed: 26581599]

(10). Majka SM, Barak Y, Klemm DJ. Concise review: adipocyte origins: weighing the possibilities. Stem Cells. 2011; 29(7):1034–1040. [PubMed: 21544899]

(11). Liu Y, Strecker S, Wang L, et al. Osterix-cre labeled progenitor cells contribute to the formation and maintenance of the bone marrow stroma. PLoS One. 2013; 8(8):e71318. [PubMed: 23951132]

(12). Song L, Liu M, Ono N, Bringhurst FR, Kronenberg HM, Guo J. Loss of wnt/beta-catenin signaling causes cell fate shift of preosteoblasts from osteoblasts to adipocytes. J Bone Miner Res. 2012; 27(11):2344–2358. [PubMed: 22729939]

(13). Velletri T, Xie N, Wang Y, et al. P53 functional abnormality in mesenchymal stem cells promotes osteosarcoma development. Cell Death Dis. 2016; 7:e2015. [PubMed: 26775693]

(14). Takada I, Suzawa M, Matsumoto K, Kato S. Suppression of PPAR transactivation switches cell fate of bone marrow stem cells from adipocytes into osteoblasts. Ann N Y Acad Sci. 2007; 1116:182–195. [PubMed: 17656564]

(15). Krings A, Rahman S, Huang S, Lu Y, Czernik PJ, Lecka-Czernik B. Bone marrow fat has brown adipose tissue characteristics, which are attenuated with aging and diabetes. Bone. 2012; 50(2): 546–552. [PubMed: 21723971]

(16). Bianco P, Costantini M, Dearden LC, Bonucci E. Alkaline phosphatase positive precursors of adipocytes in the human bone marrow. Br J Haematol. 1988; 68(4):401–403. [PubMed: 3377984]

(17). Bianco P, Riminucci M, Kuznetsov S, Robey PG. Multipotential cells in the bone marrow stroma: regulation in the context of organ physiology. Crit Rev Eukaryot Gene Expr. 1999; 9(2):159–173. [PubMed: 10445154]

(18). Majka SM, Miller HL, Sullivan T, et al. Adipose lineage specification of bone marrow-derived myeloid cells. Adipocyte. 2012; 1(4):215–229. [PubMed: 23700536]

(19). Naveiras O, Nardi V, Wenzel PL, Hauschka PV, Fahey F, Daley GQ. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009; 460(7252):259–263. [PubMed: 19516257]

(20). Cawthorn WP, Scheller EL, Learman BS, et al. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. Cell Metab. 2014; 20(2):368–375. [PubMed: 24998914]

(21). Dib LH, Ortega MT, Fleming SD, Chapes SK, Melgarejo T. Bone marrow leptin signaling mediates obesity-associated adipose tissue inflammation in male mice. Endocrinology. 2014; 155(1):40–46. [PubMed: 24169547]

(22). Misra M, Klibanski A. Anorexia nervosa and osteoporosis. Rev Endocr Metab Disord. 2006; 7(1-2):91–99. [PubMed: 16972186]

(23). Vestergaard P, Emborg C, Stoving RK, Hagen C, Mosekilde L, Brixen K. Fractures in patients with anorexia nervosa, bulimia nervosa, and other eating disorders--a nationwide register study. Int J Eat Disord. 2002; 32(3):301–308. [PubMed: 12210644]

(24). Fazeli PK, Klibanski A. Bone metabolism in anorexia nervosa. Curr Osteoporos Rep. 2014; 12(1):82–89. [PubMed: 24419863]

(25). Bredella MA, Fazeli PK, Miller KK, et al. Increased bone marrow fat in anorexia nervosa. J Clin Endocrinol Metab. 2009; 94(6):2129–2136. [PubMed: 19318450]

(26). Ecklund K, Vajapeyam S, Feldman HA, et al. Bone marrow changes in adolescent girls with anorexia nervosa. J Bone Miner Res. 2010; 25(2):298–304. [PubMed: 19653811]

(27). Cornbleet PJ, Moir RC, Wolf PL. A histochemical study of bone marrow hypoplasia in anorexia nervosa. Virchows Arch A Pathol Anat Histol. 1977; 374(3):239–247. [PubMed: 142350]

(28). Abella E, Feliu E, Granada I, et al. Bone marrow changes in anorexia nervosa are correlated with the amount of weight loss and not with other clinical findings. Am J Clin Pathol. 2002; 118(4): 582–588. [PubMed: 12375646]

(29). Tins B, Cassar-Pullicino V. Marrow changes in anorexia nervosa masking the presence of stress fractures on MR imaging. Skeletal Radiol. 2006; 35(11):857–860. [PubMed: 16308715]

(30). Cawthorn WP, Scheller EL, Parlee SD, et al. Expansion of Bone Marrow Adipose Tissue During Caloric Restriction Is Associated With Increased Circulating Glucocorticoids and Not With Hypoleptinemia. Endocrinology. 2016; 157(2):508–521. [PubMed: 26696121]

(31). Devlin MJ, Cloutier AM, Thomas NA, et al. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. J Bone Miner Res. 2010; 25(9):2078–2088. [PubMed: 20229598]

(32). Fazeli PK, Bredella MA, Freedman L, et al. Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa. J Bone Miner Res. 2012; 27(9):1864–1871. [PubMed: 22508185]

(33). Hui SL, Epstein S, Johnston CC Jr. A prospective study of bone mass in patients with type I diabetes. J Clin Endocrinol Metab. 1985; 60(1):74–80. [PubMed: 3964795]

(34). Piepkorn B, Kann P, Forst T, Andreas J, Pfutzner A, Beyer J. Bone mineral density and bone metabolism in diabetes mellitus. Horm Metab Res. 1997; 29(11):584–591. [PubMed: 9479561]

(35). Kemink SA, Hermus AR, Swinkels LM, Lutterman JA, Smals AG. Osteopenia in insulin-dependent diabetes mellitus; prevalence and aspects of pathophysiology. J Endocrinol Invest. 2000; 23(5):295–303. [PubMed: 10882147]

(36). Botolin S, McCabe LR. Bone loss and increased bone adiposity in spontaneous and pharmacologically induced diabetic mice. Endocrinology. 2007; 148(1):198–205. [PubMed: 17053023]

(37). Botolin S, Faugere MC, Malluche H, Orth M, Meyer R, McCabe LR. Increased bone adiposity and peroxisomal proliferator-activated receptor-gamma2 expression in type I diabetic mice. Endocrinology. 2005; 146(8):3622–3631. [PubMed: 15905321]

(38). Botolin S, McCabe LR. Inhibition of PPARgamma prevents type I diabetic bone marrow adiposity but not bone loss. J Cell Physiol. 2006; 209(3):967–976. [PubMed: 16972249]

(39). Motyl KJ, McCabe LR. Leptin treatment prevents type I diabetic marrow adiposity but not bone loss in mice. J Cell Physiol. 2009; 218(2):376–384. [PubMed: 18932203]

(40). Motyl KJ, Raetz M, Tekalur SA, Schwartz RC, McCabe LR. CCAAT/enhancer binding protein beta-deficiency enhances type 1 diabetic bone phenotype by increasing marrow adiposity and bone resorption. Am J Physiol Regul Integr Comp Physiol. 2011; 300(5):R1250–R1260. [PubMed: 21346244]

(41). Poll LW, Chantelau EA. Routine MRI findings of the asymptomatic foot in diabetic patients with unilateral Charcot foot. Diabetol Metab Syndr. 2010; 2:25. [PubMed: 20412561]

(42). Slade JM, Coe LM, Meyer RA, McCabe LR. Human bone marrow adiposity is linked with serum lipid levels not T1-diabetes. J Diabetes Complications. 2012; 26(1):1–9. [PubMed: 22257906]

(43). National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults- The evidence report. Obes Res. 1998; 6(Suppl 2)

(44). Valerio G, Galle F, Mancusi C, et al. Prevalence of overweight in children with bone fractures: a case control study. BMC Pediatr. 2012; 12:166. [PubMed: 23088687]

(45). Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab. 2001; 86(1):32–38. [PubMed: 11231974]

(46). van Daele PL, Stolk RP, Burger H, et al. Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med. 1995; 122(6):409–414. [PubMed: 7856988]

(47). Nicodemus KK, Folsom AR. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care. 2001; 24(7):1192–1197. [PubMed: 11423501]

(48). de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. Osteoporos Int. 2005; 16(12):1713–1720. [PubMed: 15940395]

(49). Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. Diabetes Care. 2006; 29(7):1573–1578. [PubMed: 16801581]

(50). Farr JN, Drake MT, Amin S, Melton LJ III, McCready LK, Khosla S. In Vivo assessment of bone quality in postmenopausal women with type 2 diabetes. J Bone Miner Res. 2013

(51). Cole ZA, Harvey NC, Kim M, et al. Increased fat mass is associated with increased bone size but reduced volumetric density in pre pubertal children. Bone. 2012; 50(2):562–567. [PubMed: 21600324]

(52). Goulding A, Taylor RW, Jones IE, McAuley KA, Manning PJ, Williams SM. Overweight and obese children have low bone mass and area for their weight. Int J Obes Relat Metab Disord. 2000; 24(5):627–632. [PubMed: 10849586]

(53). Bredella MA, Torriani M, Ghomi RH, et al. Vertebral bone marrow fat is positively associated with visceral fat and inversely associated with IGF-1 in obese women. Obesity (Silver Spring). 2011; 19(1):49–53. [PubMed: 20467419]

(54). Bredella MA, Gill CM, Gerweck AV, et al. Ectopic and serum lipid levels are positively associated with bone marrow fat in obesity. Radiology. 2013; 269(2):534–541. [PubMed: 23861502]

(55). Patsch JM, Li X, Baum T, et al. Bone marrow fat composition as a novel imaging biomarker in postmenopausal women with prevalent fragility fractures. J Bone Miner Res. 2013; 28(8):1721–1728. [PubMed: 23558967]

(56). Schafer AL, Li X, Schwartz AV, et al. Changes in vertebral bone marrow fat and bone mass after gastric bypass surgery: A pilot study. Bone. 2015; 74:140–145. [PubMed: 25603463]

(57). Schellinger D, Lin CS, Fertikh D, et al. Normal lumbar vertebrae: anatomic, age, and sex variance in subjects at proton MR spectroscopy--initial experience. Radiology. 2000; 215(3):910–916. [PubMed: 10831721]

(58). Kugel H, Jung C, Schulte O, Heindel W. Age- and sex-specific differences in the 1H-spectrum of vertebral bone marrow. J Magn Reson Imaging. 2001; 13(2):263–268. [PubMed: 11169833]

(59). Verma S, Rajaratnam JH, Denton J, Hoyland JA, Byers RJ. Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis. J Clin Pathol. 2002; 55(9):693–698. [PubMed: 12195001]

(60). Yeung DK, Griffith JF, Antonio GE, Lee FK, Woo J, Leung PC. Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: a proton MR spectroscopy study. J Magn Reson Imaging. 2005; 22(2):279–285. [PubMed: 16028245]

(61). Li GW, Xu Z, Chen QW, et al. Quantitative evaluation of vertebral marrow adipose tissue in postmenopausal female using MRI chemical shift-based water-fat separation. Clin Radiol. 2014; 69(3):254–262. [PubMed: 24286935]

(62). Limonard EJ, Veldhuis-Vlug AG, van DL, et al. Short-Term Effect of Estrogen on Human Bone Marrow Fat. J Bone Miner Res. 2015; 30(11):2058–2066. [PubMed: 25982922]

(63). Miranda M, Pino AM, Fuenzalida K, Rosen CJ, Seitz G, Rodriguez P. Characterization of Fatty Acid Composition in Bone Marrow Fluid From Postmenopausal Women: Modification After Hip Fracture. Journal of Cellular Biochemistry. 2016 In press.

(64). Duque G, Li W, Adams M, Xu S, Phipps R. Effects of risedronate on bone marrow adipocytes in postmenopausal women. Osteoporos Int. 2011; 22(5):1547–1553. [PubMed: 20661545]

(65). Yang Y, Luo X, Yan F, et al. Effect of zoledronic acid on vertebral marrow adiposity in postmenopausal osteoporosis assessed by MR spectroscopy. Skeletal Radiol. 2015; 44(10):1499–1505. [PubMed: 26130070]

(66). LeBlanc AD, Spector ER, Evans HJ, Sibonga JD. Skeletal responses to space flight and the bed rest analog: a review. J Musculoskelet Neuronal Interact. 2007; 7(1):33–47. [PubMed: 17396004]

(67). Kodama Y, Umemura Y, Nagasawa S, et al. Exercise and mechanical loading increase periosteal bone formation and whole bone strength in C57BL/6J mice but not in C3H/Hej mice. Calcif Tissue Int. 2000; 66(4):298–306. [PubMed: 10742449]

(68). Trudel G, Payne M, Madler B, et al. Bone marrow fat accumulation after 60 days of bed rest persisted 1 year after activities were resumed along with hemopoietic stimulation: the Women International Space Simulation for Exploration study. J Appl Physiol (1985). 2009; 107(2):540–548. [PubMed: 19478189]

(69). Hamrick MW, Shi X, Zhang W, et al. Loss of myostatin (GDF8) function increases osteogenic differentiation of bone marrow-derived mesenchymal stem cells but the osteogenic effect is ablated with unloading. Bone. 2007; 40(6):1544–1553. [PubMed: 17383950]

(70). Rantalainen T, Nikander R, Heinonen A, Cervinka T, Sievanen H, Daly RM. Differential effects of exercise on tibial shaft marrow density in young female athletes. J Clin Endocrinol Metab. 2013; 98(5):2037–2044. [PubMed: 23616150]

(71). Styner M, Thompson WR, Galior K, et al. Bone marrow fat accumulation accelerated by high fat diet is suppressed by exercise. Bone. 2014; 64:39–46. [PubMed: 24709686]

(72). Maddalozzo GF, Turner RT, Edwards CH, et al. Alcohol alters whole body composition, inhibits bone formation, and increases bone marrow adiposity in rats. Osteoporos Int. 2009; 20(9):1529–1538. [PubMed: 19238309]

(73). Ramsey RG, Zacharias CE. MR imaging of the spine after radiation therapy: easily recognizable effects. AJR Am J Roentgenol. 1985; 144(6):1131–1135. [PubMed: 3873791]

(74). Casamassima F, Ruggiero C, Caramella D, Tinacci E, Villari N, Ruggiero M. Hematopoietic bone marrow recovery after radiation therapy: MRI evaluation. Blood. 1989; 73(6):1677–1681. [PubMed: 2713500]

(75). Cao X, Wu X, Frassica D, et al. Irradiation induces bone injury by damaging bone marrow microenvironment for stem cells. Proc Natl Acad Sci U S A. 2011; 108(4):1609–1614. [PubMed: 21220327]

(76). Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. JAMA. 2005; 294(20):2587–2593. [PubMed: 16304072]

(77). Gorman E, Chudyk AM, Madden KM, Ashe MC. Bone health and type 2 diabetes mellitus: a systematic review. Physiother Can. 2011; 63(1):8–20. [PubMed: 22210975]

(78). Schwartz AV, Vittinghoff E, Bauer DC, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA. 2011; 305(21):2184–2192. [PubMed: 21632482]

(79). Schwartz AV, Sigurdsson S, Hue TF, et al. Vertebral bone marrow fat associated with lower trabecular BMD and prevalent vertebral fracture in older adults. J Clin Endocrinol Metab. 2013; 98(6):2294–2300. [PubMed: 23553860]

KEY POINTS

- In general, an inverse relationship exists between marrow fat and bone density.
- Multiple diseases associated with increased fracture risk also present with increased marrow adipose tissue.
- Composition of marrow adipose tissue differs between anatomical sites.
- Exact stem cell lineage and precise function of marrow adipocytes remains controversial.

Table 1

Relationship between marrow adiposity, bone mineral density, and fracture risk in various clinical conditions.

	Marrow Adiposity	Bone Mineral Density	Fracture Risk	References
Anorexia Nervosa	↑	↓	↑	**22, 23, 25**
Type 1 Diabetes Mellitus	*Inconclusive*	↓	↑	**35, 42, 47**
Type 2 Diabetes Mellitus	*Inconclusive*	No Change or ↑	↑	**55, 77, 78**
Aging	↑	↓	↑	**1, 57, 79**
Gonadal Deficiency	↑	↓	↑	**61, 62**
Unloading	↑	↓	↑	**66, 68**