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Bone marrow adipose tissue: formation, function and regulation

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Abstract

The human body requires an uninterrupted supply of energy to maintain metabolic homeostasis and energy balance. To sustain energy balance, excess consumed calories are stored as glycogen, triglycerides and protein, allowing the body to continue to function in states of starvation and increased energy expenditure. Adipose tissue provides the largest natural store of excess calories as triglycerides and plays an important role as an endocrine organ in energy homeostasis and beyond. This short review is intended to detail the current knowledge of the formation and role of bone marrow adipose tissue (MAT), a largely ignored adipose depot, focussing on the role of MAT as an endocrine organ and highlighting the pharmacological agents that regulate MAT.

Over half a century ago, a fundamental movement occurred, recognising adipose tissue as a metabolically active tissue [1]. Prior to this, adipose tissue was considered to be a metabolically inert organ whose function was solely for the store of triglyceride, protection, insulation and cosmetic importance. Composed of mature adipocytes, endothelial cells, immune cells, pre-adipocytes, and adipose progenitor/stem cells (stromal vascular fraction), mammalian adipose tissue is typically classed as two distinct subtypes, white adipose tissue (WAT) or brown adipose tissue (BAT). These are further subdivided into regional depots based on structural organisation, cellular size, biochemical profiles and biological function [2] (Figure 1.). Characterised by the presence of adipocytes with large mono-locular lipid droplets specialised for lipid storage and release, WAT is dispersed throughout the body in specific regional depots, differing in origin, structural organisation, cellular size, and biological function [2,3]. The largest WAT depots are found both viscerally and subcutaneously. Heterogeneous in nature, visceral WAT accumulation is associated with elevated cardiometabolic risk whilst subcutaneous accumulation has been reported to have a neutral repercussion [4,5]. Indeed, subcutaneous fat transplanted into the visceral cavity improves glucose metabolism in mice, suggesting that subcutaneous fat is intrinsically different from visceral fat [6]. In contrast to WAT, BAT is specialised for the mediation of

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thermogenesis via uncoupled respiration, and is composed of adipocytes with smaller, multi-locular lipid droplets and increased mitochondria expressing uncoupling protein 1 (UCP1). Once thought to exist only in small mammals and new-borns [7], positron emission tomography-computed tomography scans (PET-CT) using the ^{18}F -fluoro-2-deoxy-D-glucose tracer have identified metabolically active BAT, which becomes active upon cold exposure, in supraclavicular adipose tissue depots of healthy adult humans. Brown adipose tissue has also been shown to be inversely correlated with body-mass index [8–11]. It is important to highlight that in addition to WAT and BAT, the identification of so-called beige/ brite adipose tissue has sparked much research interest in the last decade. Beige adipose tissue is an inducible thermogenic adipose tissue, believed to form in WAT sporadically upon exposure to various environmental activators such as chronic cold exposure (as summarised in recent reviews [12,13]). Resembling brown adipocytes in terms of displaying some thermogenic capacity, a subset (10%–15%) of beige adipocytes arise from MYH11-positive smooth muscle-like precursors [14,15] (Figure 2.). The activation of beige and brown fat is associated with a reduction in metabolic disease and several studies have identified secreted and systemic factors that regulate “browning”, which may provide a promising therapeutic targets for obesity, diabetes and other metabolic diseases [16–18].

The metabolic and endocrine importance of WAT is currently firmly established. More recently, the markers and pathways associated with the formation and function of brown and beige adipose tissue are undergoing extensive study due to the promising therapeutic potential of these tissues. However, the scientific community are is only just beginning to unravel the role of the third major depot of adipose tissue, marrow adipose tissue (MAT).

Identified over a century ago, MAT is situated within the marrow cavity in a distinct and organised manner, constituting 70% of bone marrow (BM) volume and accounting for approximately 10% of total fat mass in healthy adult humans [19,20]. Marrow adipose tissue show a similar distribution in rodents and other animals, predominating in the arms and legs but being sparse (or non-existent) in the spine and more central skeleton [21](Figure 1.). Largely overlooked since its discovery, MAT was not recognised as an adipose depot until the *mid*-late twentieth century [22] and MAT research began to attract further interest only in the 1970s, when it was shown that the developmental origin and lipid composition of marrow adipocytes is distinct to that of white adipocytes [23,24](comprehensively reviewed in [25]).

Theories regarding the putative role of MAT have fluctuated throughout the last 40 years, whereby MAT accumulation has been associated with osteoporosis, ageing, type 1 diabetes, Cushings disease, oestrogen deficiency and anorexia nervosa [26–30] (Figure 2.). Due to recent advances in medical research and the introduction of new imaging modalities available in both clinical and preclinical studies, including magnetic resonance spectroscopy, PET-CT, and osmium tetroxide staining coupled with micro-computerised tomography, we are now better equipped to quantify MAT in a rapid and reproducible manner [31]. The use of the osmium staining technique was recently applied to whole tibiae from male C57BL/6J and C3H/HeJ mice, revealing that MAT exists in two distinct populations: ‘regulated’ MAT (rMAT), which appears in proximal skeletal sties shortly after postnatal development and consists of adipocytes interspersed with active haematopoiesis; and constitutive MAT

(cMAT), which forms in early postnatal stages in distal regions, contains larger adipocytes resembling those in WAT, and remains largely preserved upon systemic challenges. Furthermore, rMAT and cMAT subtypes differ in lipid composition and gene expression [32]. The role of these MAT subpopulations have yet to be defined, however it has been suggested that cMAT may have an important function in early in vertebrate development, whilst rMAT may influence hematopoiesis and/or skeletal remodeling [32].

At the time of writing (February 2016), much MAT research is focusing on fundamental questions regarding the formation, genetic determinants, relationship to bone formation and haematopoiesis, and endocrine roles of MAT in skeletal and whole body metabolism. The current thinking is that the origin of MAT is distinct to that of both WAT and BAT. Marrow adipose tissue is thought to be derived from progenitors that express osterix (*Sp7*), a transcription factor essential for osteoblastogenesis and bone formation in mice. Recent evidence identifies MAT as an endocrine organ, contributing to the elevated serum levels of adiponectin during caloric resection (CR) [20,33,34] (Figure 2.). Hereafter we will discuss and highlight regulators of MAT expansion and depletion, inclusive of diseases, hormones, pharmacological agents and environmental factors.

Expansion of Bone Marrow Adipose Tissue

In lean states such as CR or in pathological conditions such as anorexia nervosa MAT is elevated [35]. The accumulation of adipose tissue is somewhat counterintuitive given that in catabolic states other depots of adipose tissue are being mobilised for energy utilisation. The paradox to why this occurs remains unclear (comprehensively reviewed [35]), but it has been suggested that MAT may occupy BM cavity space that ordinarily would be occupied by trabecular bone; that MAT may accumulate as an adaptation for surviving starvation; or that MAT secretes adipokines, such as adiponectin, that can increase insulin sensitivity and promote appetite [25]. These possibilities are worthy targets for future MAT research.

In humans, radiotherapy or chemotherapy for cancer is known to increase MAT formation, coupled with reduced bone mass and increased fracture risk. These pathological changes are also observed in aging and other age-related conditions such as estrogen deficiency and increased oxidative stress. It has been suggested that mechanisms underlying MAT elevation are due to a switch in lineage commitment of BM mesenchymal stem cells down the adipogenic lineage (reviewed [36]). Furthermore, recent data from patients undergoing cancer therapy for ovarian or endometrial cancer shows that these patients display lumbar vertebral MAT expansion and elevated serum adiponectin levels, despite no change in total adiposity [20]; this is further evidence emphasising the potential endocrine nature of MAT. The mechanisms for this cancer therapy-associated MAT accumulation still remain elusive, however Cawthorn *et al.* speculate that the increased adiponectin derives from MAT expansion and may act to limit tumour growth [20,37]. Moreover, MAT increases during treatment with pharmacologic agents such as glucocorticoids, thiazolidinediones (TZD) and fibroblast growth factor-21 (FGF21) [38–42]. Glucocorticoids have anti-proliferative and anti-inflammatory properties via the inhibition of cytokines and adhesion molecules and are exploited and successfully used clinically in treating disorders of heightened immunity and autoimmune diseases [43,44]. Exogenous glucocorticoid administration in humans results in

femoral MAT expansion that is correlated with steroid intake [45]. Moreover, mice deficient in 11 β -hydroxysteroid dehydrogenase 1 (11 β HSD1), an isoenzyme that interconverts active glucocorticoids with inert 11-keto forms, have a complete lack marrow adipocytes, indicative that 11 β HSD1 is required for MAT formation in mice [46]. Thus, in circumstances of MAT expansion exemplified by CR, circulating active glucocorticoids (corticosterone in mice and rats; cortisol in humans and other species) are increased [47,48], suggestive of a role for glucocorticoids in MAT expansion during CR. This is further supported by recent observations that, unlike in most species, CR in rabbits causes neither MAT expansion nor increased circulating glucocorticoids [49]. It is also of note that in states of chronic glucocorticoid excess, exemplified in Cushing's disease (CD), whereby a tumour manifests within in the pituitary producing adrenocorticotrophic hormone or in the adrenal producing cortisol, patients present with profound body compositional changes, with alterations in fat distribution, muscle mass and adipokine profiles leading to elevated adiponectin serum levels. The elevation in serum adiponectin may be associated with increased MAT in patients with CD, which decreases in remission; however this decrease in MAT is not coupled with decreased adiponectin, suggesting further complexity that remains to be elucidated [29].

Thiazolidinediones (TZD) are agonists for peroxisome proliferator-activated receptor-gamma (PPAR γ) which regulates lipid metabolism and systemic insulin sensitivity. Routinely used as an anti-diabetic agent, exogenous TZD treatment has been linked to osteoporosis and increased risk of bone fractures in patients with diabetes and prediabetes. Notably, TZDs also lead to increased MAT [50–52]. However the mechanism whereby TZD influences bone quality and MAT expansion is not well understood and is therefore under current investigation [53].

Fibroblast growth factor-21 is an endocrine and paracrine hormone that is expressed in the liver and WAT. Upon exogenous administration, FGF21 enhances insulin sensitivity, decreases plasma glucose and triglyceride, reduces body weight and decreases bone mass. This also occurs with genetic gain of function of FGF21 [39,54,55]. Conversely, in FGF21-deficient mice adipose depots are depleted due to the inhibition of PPAR γ sumoylation, leading to a decrease in its transcriptional activity such that TZD-induced bone loss is prevented [55,56]. Interestingly, MAT was decreased in the FGF21-deficient mice while FGF21 treatment was shown to potentiate the differentiation of BM mesenchymal stem cells to adipocytes *ex vivo*, thereby inhibiting osteoblastogenesis. Thus, these observations are indicative of a direct role for FGF21 in stimulating BM adipogenesis [55].

Finally, MAT is also known to increase in clinical conditions such as ageing-associated bone loss, osteoporosis and osteopenia deficiency, and type 1 diabetes, which has been discussed extensively in a previous review [19].

Decline of Bone Marrow Adipose Tissue

In contrast to MAT expansion, far less is currently known about the decline of MAT (Figure 2.). Patients with Lipodystrophy, Gauchers disease and hypertensive heart failure also present with decreased MAT. Briefly, Lipodystrophy is often accompanied by pathologic

accumulation of lipid in the liver and low circulating leptin and adiponectin. Patients with type 1 congenital generalised lipodystrophy (CGL1) and *BSCL2*-linked lipodystrophy (CGL2) present with decreased MAT; however, MAT in patients with acquired generalised lipodystrophy, CGL3 or CGL4 is often preserved. Lipodystrophy in humans has been previously comprehensively reviewed, but the authors highlighted that the preservation in MAT may prevent the severe onset of diabetes and insulin resistance in CGL [25].

The most prevalent lysosomal storage disease, Gauchers, is an autosomal-recessive inherited disorder caused by a deficiency or absence of β -glucocerebrosidase (β -glucosidase). Infiltration of the BM by lysosome-engorged macrophages (Gaucher cells) results in secondary damage to the bone, including mild osteopenia, osteonecrosis, osteoporosis, osteosclerosis, epiphyseal collapse, osteoarthritis, bone infarcts, fractures and BM volume expansion with cortical thinning [57,58]. Marrow fat expansion accompanies the increased BM volume, but the role of MAT in this disease remains unknown. Similarly, patients with hypertensive heart failure present with elevated red marrow, suggestive of loss of MAT [59]. This may warrant further research into the relationship between MAT, haematopoiesis and cardiovascular function. It has also been suggested that type-two diabetes decreases MAT and pioglitazone, a TZD, has been shown to increase MAT in type 2 diabetes patients without effecting bone mineral density (BMD). It is important to note that the relationship between MAT and BMD still is inconclusive, with inconsistencies in clinical studies [60,61].

Postmenopausal women receiving estrogen replacement show decreased BM adipocyte number and size, as well as decreased MAT, suggesting that locally generated androgens and oestrogens can exert regulatory action on bone marrow cells [62,63]. Finally, MAT is thought to decline in excessive CR, implying that MAT may initially accumulate as an adaptation for surviving less severe phases of starvation, but that upon terminal illness or chronic starvation MAT becomes utilised as fuel.

Perspective

In the last decade, there has been increasing interest in the formation, function and potential endocrine roles of MAT. Indeed, the formation of MAT in mice occurs in two distinct temporal waves that are spatially separated, suggesting that MAT is a functional organ that can undergo pathologic changes and respond to disease [25,32]. Furthermore, data from animal and human models support the notion that MAT is significantly associated with skeletal health [19]. The limited nature of the study of MAT, however, has seen many questions remain unanswered. For example, is MAT unique from white, brown and beige adipose tissue? Where does MAT originate from? Do rMAT and cMAT differ in function and or / origin? Does MAT have a local role in the skeletal microenvironment? Is MAT involved locally / systemically in skeletal pathology? To this end, whole-body physiology in mouse models and comprehensive clinical studies is paving the way to unravelling the role of MAT in the future. The potential therapeutic implications of MAT may have enormous implications, underscoring the importance of future study of MAT.

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References

1. Feller DD, Feist E. Metabolism of adipose tissue. II. Incorporation of propionate carbon into lipides by slices of adipose tissue. *J Biol Chem.* 1957; 228:275–284. [PubMed: 13475316]
2. Fruhbeck G. Overview of adipose tissue and its role in obesity and metabolic disorders. *Methods Mol Biol.* 2008; 456:1–22. [PubMed: 18516549]
- 3. Chau Y-Y, Bandiera R, Serrels A, Martínez-Estrada OM, Qing W, Lee M, Slight J, Thornburn A, Berry R, McHaffie S, et al. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. *Nat Cell Biol.* 2014; 16:367–375. The authors demonstrate that there is a major ontogenetic difference between visceral and subcutaneous white adipose tissue. [PubMed: 24609269]
4. Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB, Jerosch-Herold M, Lima JA, Ding J, Allison MA. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA Study. *JACC Cardiovasc Imaging.* 2014; 7:1221–1235. [PubMed: 25440591]
5. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev.* 2000; 21:697–738. [PubMed: 11133069]
6. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial Effects of Subcutaneous Fat Transplantation on Metabolism. *Cell metabolism.* 2008; 7:410–420. [PubMed: 18460332]
7. Lean ME. Brown adipose tissue in humans. *Proc Nutr Soc.* 1989; 48:243–256. [PubMed: 2678120]
8. Hany TF, Gharehpapagh E, Kamel EM, Buck A, Himms-Hagen J, von Schulthess GK. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. *Eur J Nucl Med Mol Imaging.* 2002; 29:1393–1398. [PubMed: 12271425]
9. van Marken Lichtenbelt WD, Vanhomerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. *N Engl J Med.* 2009; 360:1500–1508. [PubMed: 19357405]
10. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009; 360:1509–1517. [PubMed: 19357406]
11. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med.* 2009; 360:1518–1525. [PubMed: 19357407]
12. Kajimura S, Spiegelman BM, Seale P. Brown and Beige Fat: Physiological Roles beyond Heat Generation. *Cell Metab.* 2015; 22:546–559. [PubMed: 26445512]
13. Sidossis L, Kajimura S. Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. *J Clin Invest.* 2015; 125:478–486. [PubMed: 25642708]
14. Shabalina IG, Petrovic N, de Jong JM, Kalinovich AV, Cannon B, Nedergaard J. UCP1 in brite/beige adipose tissue mitochondria is functionally thermogenic. *Cell Rep.* 2013; 5:1196–1203. [PubMed: 24290753]
- 15. Long JZ, Svensson KJ, Tsai L, Zeng X, Roh HC, Kong X, Rao RR, Lou J, Lokurkar I, Baur W, et al. A smooth muscle-like origin for beige adipocytes. *Cell Metab.* 2014; 19:810–820. The authors report that a subset of beige cells arise from a smooth muscle-like origin using *in vivo* fate mapping. [PubMed: 24709624]
16. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. *Nat Med.* 2013; 19:1252–1263. [PubMed: 24100998]
17. Villarroya F, Vidal-Puig A. Beyond the sympathetic tone: the new brown fat activators. *Cell Metab.* 2013; 17:638–643. [PubMed: 23583169]
18. Wu J, Cohen P, Spiegelman BM. Adaptive thermogenesis in adipocytes: is beige the new brown? *Genes Dev.* 2013; 27:234–250. [PubMed: 23388824]

19. Fazeli PK, Horowitz MC, MacDougald OA, Scheller EL, Rodeheffer MS, Rosen CJ, Klibanski A. Marrow fat and bone--new perspectives. *J Clin Endocrinol Metab.* 2013; 98:935–945. [PubMed: 23393168]
- 20. Cawthorn WP, Scheller EL, Learman BS, Parlee SD, Simon BR, Mori H, Ning X, Bree AJ, Schell B, Broome DT, et al. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. *Cell Metab.* 2014; 20:368–375. The authors reveal that marrow adipose tissue is an endocrine organ that contributes to increased serum adiponectin during caloric restriction in mice and cancer therapy in humans. [PubMed: 24998914]
21. Kricun ME. Red-yellow marrow conversion: its effect on the location of some solitary bone lesions. *Skeletal Radiol.* 1985; 14:10–19. [PubMed: 3895447]
22. Zakaria E, Shafir E. Yellow bone marrow as adipose tissue. *Proc Soc Exp Biol Med.* 1967; 124:1265–1268. [PubMed: 4290465]
23. Tavassoli M. Marrow adipose cells. Histochemical identification of labile and stable components. *Arch Pathol Lab Med.* 1976; 100:16–18. [PubMed: 56163]
24. Tavassoli M. Ultrastructural development of bone marrow adipose cell. *Acta Anat (Basel).* 1976; 94:65–77. [PubMed: 961340]
25. Scheller EL, Rosen CJ. What's the matter with MAT? Marrow adipose tissue, metabolism, and skeletal health. *Annals of the New York Academy of Sciences.* 2014; 1311:14–30. [PubMed: 24650218]
26. Justesen J, Stenderup K, Ebbesen EN, Mosekilde L, Steiniche T, Kassem M. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. *Biogerontology.* 2001; 2:165–171. [PubMed: 11708718]
27. Devlin MJ, Cloutier AM, Thomas NA, Panus DA, Lotinun S, Pinz I, Baron R, Rosen CJ, Bouxsein ML. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. *J Bone Miner Res.* 2010; 25:2078–2088. [PubMed: 20229598]
28. Takeshita S, Fumoto T, Naoe Y, Ikeda K. Age-related marrow adipogenesis is linked to increased expression of RANKL. *J Biol Chem.* 2014; 289:16699–16710. [PubMed: 24753250]
29. Geer EB, Shen W, Strohmayer E, Post KD, Freda PU. Body Composition and Cardiovascular Risk Markers after Remission of Cushing's Disease: A Prospective Study Using Whole-Body MRI. *The Journal of Clinical Endocrinology and Metabolism.* 2012; 97:1702–1711. [PubMed: 22419708]
30. Botolin S, McCabe LR. Bone loss and increased bone adiposity in spontaneous and pharmacologically induced diabetic mice. *Endocrinology.* 2007; 148:198–205. [PubMed: 17053023]
- 31. Scheller EL, Troiano N, VanHoutan JN, Bouxsein MA, Fretz JA, Xi Y, Nelson T, Katz G, Berry R, Church CD, et al. Use of Osmium Tetroxide Staining with Microcomputerized Tomography to Visualize and Quantify Bone Marrow Adipose Tissue In Vivo. *Methods in enzymology.* 2014; 537:123–139. The authors describe a new technique to visualize and quantify marrow adipose tissue in a three dimensional manner using osmium tetroxide microcomputerized tomography. [PubMed: 24480344]
- 32. Scheller EL, Doucette CR, Learman BS, Cawthorn WP, Khandaker S, Schell B, Wu B, Ding SY, Bredella MA, Fazeli PK, et al. Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. *Nat Commun.* 2015; 6:7808. The authors describe region-specific variation in marrow adipose tissue development, defining the proximal marrow adipose tissue as 'regulated' and the distal marrow adipose tissue as 'constitutive'. [PubMed: 26245716]
33. Chen J, Shi Y, Regan J, Karuppaiah K, Ornitz DM, Long F. Osx-Cre targets multiple cell types besides osteoblast lineage in postnatal mice. *PLoS One.* 2014; 9:e85161. [PubMed: 24454809]
34. Liu Y, Strecker S, Wang L, Kronenberg MS, Wang W, Rowe DW, Maye P. Osterix-cre labeled progenitor cells contribute to the formation and maintenance of the bone marrow stroma. *PLoS One.* 2013; 8:e71318. [PubMed: 23951132]
35. Devlin MJ. Why does starvation make bones fat? *Am J Hum Biol.* 2011; 23:577–585. [PubMed: 21793093]

36. Georgiou KR, Hui SK, Xian CJ. Regulatory pathways associated with bone loss and bone marrow adiposity caused by aging, chemotherapy, glucocorticoid therapy and radiotherapy. *American Journal of Stem Cells*. 2012; 1:205–224. [PubMed: 23671809]
37. Dalamaga M, Diakopoulos KN, Mantzoros CS. The Role of Adiponectin in Cancer: A Review of Current Evidence. *Endocrine Reviews*. 2012; 33:547–594. [PubMed: 22547160]
38. Combs TP, Berg AH, Rajala MW, Klebanov S, Iyengar P, Jimenez-Chillaron JC, Patti ME, Klein SL, Weinstein RS, Scherer PE. Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. *Diabetes*. 2003; 52:268–276. [PubMed: 12540596]
39. Kharitonov A, Wroblewski VJ, Koester A, Chen YF, Clutinger CK, Tigno XT, Hansen BC, Shanafelt AB, Etgen GJ. The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. *Endocrinology*. 2007; 148:774–781. [PubMed: 17068132]
40. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL. Rosiglitazone Causes Bone Loss in Mice by Suppressing Osteoblast Differentiation and Bone Formation. *Endocrinology*. 2005; 146:1226–1235. [PubMed: 15591153]
41. Ackert-Bicknell CL, Shockley KR, Horton LG, Lecka-Czernik B, Churchill GA, Rosen CJ. Strain-specific effects of rosiglitazone on bone mass, body composition, and serum insulin-like growth factor-I. *Endocrinology*. 2009; 150:1330–1340. [PubMed: 18948404]
42. Tornvig L, Mosekilde L, Justesen J, Falk E, Kassem M. Troglitazone Treatment Increases Bone Marrow Adipose Tissue Volume but Does not Affect Trabecular Bone Volume in Mice. *Calcified Tissue International*. 2001; 69:46–50. [PubMed: 11685433]
43. Almawi WY, Hess DA, Rieder MJ. Multiplicity of glucocorticoid action in inhibiting allograft rejection. *Cell Transplant*. 1998; 7:511–523. [PubMed: 9853580]
44. Fan H, Morand EF. Targeting the side effects of steroid therapy in autoimmune diseases: the role of GILZ. *Discov Med*. 2012; 13:123–133. [PubMed: 22369971]
45. Vande Berg BC, Malghem J, Lecouvet FE, Devogelaer JP, Maldague B, Houssiau FA. Fat conversion of femoral marrow in glucocorticoid-treated patients: a cross-sectional and longitudinal study with magnetic resonance imaging. *Arthritis Rheum*. 1999; 42:1405–1411. [PubMed: 10403268]
46. Justesen J, Mosekilde L, Holmes M, Stenderup K, Gasser J, Mullins JJ, Seckl JR, Kassem M. Mice deficient in 11beta-hydroxysteroid dehydrogenase type 1 lack bone marrow adipocytes, but maintain normal bone formation. *Endocrinology*. 2004; 145:1916–1925. [PubMed: 14715714]
47. Lawson EA, Klibanski A. Endocrine abnormalities in anorexia nervosa. *Nat Clin Pract Endocrinol Metab*. 2008; 4:407–414. [PubMed: 18542109]
48. Iqbal J, Macdonald LJ, Low L, Seckl JR, Yau CW, Walker BR, Hadoke PW. Contribution of endogenous glucocorticoids and their intravascular metabolism by 11beta-HSDs to postangioplasty neointimal proliferation in mice. *Endocrinology*. 2012; 153:5896–5905. [PubMed: 23125311]
49. Cawthorn WP, Scheller EL, Parlee SD, Pham HA, Learman BS, Redshaw CM, Sulston RJ, Burr AA, Das AK, Simon BR, et al. Expansion of Bone Marrow Adipose Tissue During Caloric Restriction Is Associated With Increased Circulating Glucocorticoids and Not With Hypoleptinemia. *Endocrinology*. 2016; 157:508–521. [PubMed: 26696121]
50. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem*. 1995; 270:12953–12956. [PubMed: 7768881]
51. Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med*. 2004; 351:1106–1118. [PubMed: 15356308]
52. Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. *Diabetes Care*. 2007; 30:1574–1576. [PubMed: 17363747]
53. Beck GR, Khazai NB, Bouloux GF, Camalier CE, Lin Y, Garneys LM, Siqueira J, Peng L, Pasquel F, Umpierrez D, et al. The effects of thiazolidinediones (TZD) on human bone marrow stromal cell differentiation in vitro and in TZD-treated patients with type 2 diabetes. *Translational research : the journal of laboratory and clinical medicine*. 2013; 161:145–155. [PubMed: 23022285]
54. Canto C, Auwerx J. Cell biology. FGF21 takes a fat bite. *Science*. 2012; 336:675–676. [PubMed: 22582248]

55. Wei W, Dutchak PA, Wang X, Ding X, Wang X, Bookout AL, Goetz R, Mohammadi M, Gerard RD, Dechow PC, et al. Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor gamma. *Proc Natl Acad Sci U S A*. 2012; 109:3143–3148. [PubMed: 22315431]
56. Dutchak PA, Katafuchi T, Bookout AL, Choi JH, Yu RT, Mangelsdorf DJ, Kliewer SA. Fibroblast growth factor-21 regulates PPARgamma activity and the antidiabetic actions of thiazolidinediones. *Cell*. 2012; 148:556–567. [PubMed: 22304921]
57. Maas M, Hollak CEM, Akkerman EM, Aerts JMFG, Stoker J, Den Heeten GJ. Quantification of Skeletal Involvement in Adults with Type I Gaucher's Disease: Fat Fraction Measured by Dixon Quantitative Chemical Shift Imaging as a Valid Parameter. *American Journal of Roentgenology*. 2002; 179:961–965. [PubMed: 12239046]
58. Pastores GM, Meere PA. Musculoskeletal complications associated with lysosomal storage disorders: Gaucher disease and Hurler-Scheie syndrome (mucopolysaccharidosis type I). *Curr Opin Rheumatol*. 2005; 17:70–78. [PubMed: 15604908]
59. Shillingford JP. The Red Bone Marrow in Heart Failure. *Journal of Clinical Pathology*. 1950; 3:24–39. [PubMed: 15404597]
60. Grey A, Beckley V, Doyle A, Fenwick S, Horne A, Gamble G, Bolland M. Pioglitazone increases bone marrow fat in type 2 diabetes: results from a randomized controlled trial. *Eur J Endocrinol*. 2012; 166:1087–1091. [PubMed: 22408124]
61. Paccou J, Hardouin P, Cotten A, Penel G, Cortet B. The Role of Bone Marrow Fat in Skeletal Health: Usefulness and Perspectives for Clinicians. *J Clin Endocrinol Metab*. 2015; 100:3613–3621. [PubMed: 26244490]
62. Rosen CJ, Ackert-Bicknell C, Rodriguez JP, Pino AM. Marrow Fat and the Bone Microenvironment: Developmental, Functional, and Pathological Implications. *Critical reviews in eukaryotic gene expression*. 2009; 19:109–124. [PubMed: 19392647]
63. Syed FA, Oursler MJ, Hefferan TE, Peterson JM, Riggs BL, Khosla S. Effects of Estrogen Therapy on Bone Marrow Adipocytes in Postmenopausal Osteoporotic Women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2008; 19:1323–1330.
64. Bartelt A, Heeren J. Adipose tissue browning and metabolic health. *Nat Rev Endocrinol*. 2014; 10:24–36. [PubMed: 24146030]
65. Peirce V, Carobbio S, Vidal-Puig A. The different shades of fat. *Nature*. 2014; 510:76–83. [PubMed: 24899307]
66. Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev*. 2013; 93:1–21. [PubMed: 23303904]

1. Bone marrow adipose tissue is distinct from white and brown adipose tissue.
2. Bone marrow adipose tissue exists in two distinct populations
3. Bone marrow adipose tissue is an endocrine organ

Figure 1. Location of the principal white, brown, beige and marrow fat depots in mice and humans

In human adults and rodents the main white adipose tissue depots are subdivided into subcutaneous and visceral adipose tissue. Visceral adipose tissue surrounds the vital organs and is further subdivided into **1.** Pericardial and epicardial in the thoracic cavity and **2.** Retroperitoneal, **3.** Omental, **4.** Mesenteric and **5.** Gonadal in the abdominal cavity. Subcutaneous white adipose tissue is located **6.** Intramuscularly and out-with the abdominal and thoracic cavities, here exemplified by **7.** gluteofemoral adipose tissue (human) and inguinal adipose tissue (mouse). Inguinal adipose tissue is composed of both white and beige adipocytes and can be highly influenced by environmental and dietary factors. Brown adipose tissue is located **8.** Deep within the neck (humans) and in the interscapular region (rodent), with both of these depots containing classical brown adipocytes. Humans also contain some brown adipose tissue supercalivcularly (**9.**), although this may also contain white and beige adipocytes. **10.** Marrow adipose tissue shows a similar distribution in rodents and humans, predominating in the arms and legs but being sparse (or non-existent) in the spine and more central skeleton. **Adapted from [64,65].**

Figure 2. Bone marrow, white, beige and brown fat developmental origins, functions and regulators

Originating from mesenchymal stem cells that express *Pdgfra*, white adipocytes are enriched in several markers, including *HoxC9* and *Tcf21*. White adipose tissue (WAT) is involved in physiological and metabolic processes such as glucose homeostasis and lipid metabolism [66]. White adipose tissue expansion and breakdown is induced by pathological, hormonal, therapeutic and environmental, cues including obesity, diabetes, anorexia nervosa and growth hormone. Beige adipocytes originate predominantly from *Pdgfra*-positive, *MYF5*-negative mesoderm precursors, with a subset of beige adipocytes arising from *MYH11*-positive smooth muscle-like precursors [15], and from the transdifferentiation of differentiated white adipocytes. Beige adipocytes are enriched in markers such as *Ucp1*, *Pgc1a*, *Cidea*, *Cited*, *Cd137*, *Tbx*, *Tmem26*, *Hoxc9*, *Cd137* and their differentiation is induced by cues such as cold exposure and exercise. Classical brown adipocytes originate from *MYF5*-positive dermomyotomes and express *Ucp1*, *Pgc1a*, *Cidea*, *Zic1*, *Dio2* [13,16]. Proliferation and breakdown of beige and brown adipocytes is very similar, however irisin has been found to have selective actions in beige adipocytes only. The origin of bone marrow (BM) adipocytes remains unclear: it has been suggested that BM adipocytes differentiate from mesenchymal stem cells and upon formation may transdifferentiate into beige and white adipocytes. We leave the question open if regulated and constitutive marrow adipocytes have different origins (discussed further in text). BM adipocytes proliferate in conditions such as anorexia nervosa and type 1 diabetes. Indeed, therapeutic agents that increase MAT, including glucocorticoids and thiazolidinediones, also effect on bone formation. **Adapted from** [13,15,16,65,66].