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REVIEW

# The emerging role of bone marrow adipose tissue in bone health and dysfunction

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**Abstract** Replacement of red hematopoietic bone marrow with yellow adipocyte-rich marrow is a conserved physiological process among mammals. The extent of this conversion is influenced by a wide array of pathological and non-pathological conditions. Of particular interest is the observation that some marrow adipocyte-inducing factors seem to oppose each other, for instance obesity and caloric restriction. Intriguingly, several important molecular characteristics of bone marrow adipose tissue (BMAT) are distinct from the classical depots of white and brown fat tissue. This depot of fat has recently emerged as an active part of the bone marrow niche that exerts paracrine and endocrine functions thereby controlling osteogenesis and hematopoiesis. While some functions of BMAT may be beneficial for metabolic adaptation and bone homeostasis, respectively, most findings assign bone fat a detrimental role during regenerative processes, such as hematopoiesis and osteogenesis. Thus, an improved understanding of the biological mechanisms leading to formation of BMAT, its molecular characteristics, and its physiological role in the bone marrow niche is warranted. Here we review the current understanding of BMAT biology and its potential implications for health and the development of pathological conditions.

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## Introduction

At birth, long bone cavities are filled with active hematopoietic, red marrow which is for the most part composed of immune cells at different maturation stages. By the time healthy humans reach peak bone mass around the age of 25, bone marrow adipose tissue (BMAT) can, depending on the bone compartment, occupy up to 70% of marrow space, generally suggesting a rather non-pathological role for this type of fat [1]. As a rule, bones of the peripheral skeleton accumulate more adipocytes than the axial skeleton, and the distal ends of long bones are infiltrated first [2]. Aging further promotes the increase of marrow fat in the marrow cavities [3]. For instance, vertebral marrow fat of men progressively accumulates with age, whereas a sharp increase between 55 and 65 years of age is observed in women, coinciding with the onset of menopause and leaving them with an approximately 10% higher adipocyte content compared to men [4]. Marrow adipogenesis in rodents follows a comparable, if somewhat delayed, developmental pattern, making them a suitable model for research on BMAT. It should be noted that mice additionally show strong strain-specific variations in marrow fat levels and there exists a loose positive correlation of elevated BMAT presence and increasing mammal size [3].

BMAT localizes to sites of active bone formation and hematopoiesis, which suggests an involvement in skeletal remodeling and blood/immune cell production. Previously, it was suggested that marrow adipocytes are inert under physiological conditions, but may exacerbate pathological effects in states of physiological challenges such as regenerative

processes [5]. Studies in humans have revealed an inverse relationship between marrow adiposity and bone volume [1, 6] as well as a negative correlation between marrow adiposity and hematopoiesis [7]. It is not clear, however, whether BMAT is a primary cause or compensatory effect of these processes. For instance, it has also been observed that increased adiposity does not necessarily lead to decreased bone quality in mice and humans [8–10]. This is further supported by the observation that, compared to C57BL/6J mice, C3H/HeJ mice have increases in both BMAT and bone mineral density [3]. However, since C3H/HeJ mice also experience increased MAT and reduced trabecular numbers during aging, there may still be a negative correlation between MAT and bone health that remains to be investigated in more detail [11].

Bone and adipose tissues arise from mesenchymal stem cells (MSCs) [12], which acquire their respective cell fates through the activation of specific transcription factors modulating target gene expression [5]. The orchestration of a controlled regulation of cell fate commitment is critical for bone morphology and the functional microenvironment [12]. Osteogenic cells rely on the expression of transcription factors Runt-related protein-2 (Runx2) and Osterix-1 (Osx1) [13], while adipogenic cells require peroxisome proliferator-activated receptor γ (Pparγ) and CCAAT-enhancer-binding protein α (Cebpα) [14]. Upstream, transcription factor Zinc finger protein-521 (Zfp521) controls osteoblast formation, while blocking adipogenesis [15]. Zfp521 simultaneously represses its downstream target Zfp423 by binding and inhibiting the transcriptional activity of pro-adipogenic factor early B cell factor-1 (Ebf1) [16].

Marrow-resident adipocytes display a unilocular morphology, i.e., contain a single large, lipid droplet that is reminiscent of typical white adipocytes [3]. Interestingly, the presence of two distinct types of BMAT has been described, distinguishable by different lipid profiles and histologically by performic acid-Schiff staining (PFAS) [17]. PFAS-positive marrow adipocytes are widely dispersed throughout the hematopoietic tissue and disappear with hematopoietic expansion, while non-stained adipocytes accumulate regionally and remain unaffected by changes in hematopoiesis [17]. A recent study confirmed these findings, describing a regulated BMAT (rBMAT) and a constitutive BMAT (cBMAT) [11]. Postnatally, cBMAT content increases steadily and is mostly inert to external stimuli. In contrast, the inducible rBMAT accrues in skeletal regions with high hematopoiesis, i.e., the proximal limb skeleton, hips, ribs, and the lumbar/thoracic vertebrae. Regulated marrow adipocytes are smaller in diameter (31–33 μm) when compared to cBMAT (38–39 μm) and inguinal white adipocytes (65–69 μm) and seem to undergo a different transcriptional regulation as suggested by lower expression of the adipogenic transcription factors *Cebpa* and *Cebpb*. Of note, the saturation degree of fatty acids within the lipid droplets is higher in rBMAT compared to cBMAT, but comparable to white adipose tissue (WAT) in the inguinal depot [11]. Under pathological conditions such as osteoporosis and plasmacytoma, the prevailing lipid species are increasingly saturated, suggesting a switch in marrow fat type [7, 18]. It has been hypothesized that rBMAT forms initially and then matures into cBMAT [19], yet the full developmental relationship between the two BMAT types remains to be elucidated. Interestingly, the resilience of cBMAT against dissolution has led to the suggestion that it might be important for vertebrate development and functions beyond the skeleton [11, 20]. In light of the characteristics of different marrow fat types and the fact that unlike in mice, these two types do not seem to be spatially separated in bones of humans [11], the quality of local BMAT stores might be more important than its overall quantity [21], which could also help explain seemingly opposing observations in recent studies on the pathophysiological effects of BMAT.

## Developmental origin and cellular identity of bone marrow adipose tissue

BMAT in all likelihood derives from a mesenchymal origin [22] and genetic lineage tracing in mice has concomitantly revealed a non-endothelial, non-hematopoietic, mesenchymal source for marrow adipocytes [12]. These data support the hypothesis that osteogenic and adipogenic cells derive from a common MSC where distinct genetic and epigenetic factors determine the respective lineage fates [23]. All skeletal multipotent MSC populations are marked by Osx1 in neonatal bone [24], whereas analogous cells express Nestin and Leptin receptor (LepR) in adult bone [25, 26]. The entire marrow adipocyte compartment can be traced to overlapping populations of Prx1-, Osx1-, LepR-, and Adiponectin-expressing cells [12, 26–28]. Several marker combinations have been used to prospectively isolate skeletal stem cells [29, 30]. For instance, BMAT progenitors have been described as $CD45^{-}Pref1^{+}RANKL^{+}$ stromal cells [27]. Independently from this observation, we were recently able to identify defined populations of uniformly committed adipogenic progenitor cells and pre-adipocytes in murine bones [12]. Interestingly, these cell types express the same marker profile as adipogenic progenitor cell populations from classical WAT and brown adipose tissue (BAT) [31–33]. In bone they derive from a highly homogeneous population of multipotent MSCs which lack expression of the endothelial and hematopoietic lineage markers, CD31 and CD45, respectively, but express stem cell antigen-1 (Sca1), platelet-derived growth factor α (Pdgfrα), and CD24 [12]. This multipotent population can give rise to two distinct and unilaterally committed populations of osteochondrogenic progenitor cells (surface markers: $CD31^{-}CD45^{-}Sca1^{-}Pdgfr\alpha^{+}$) or adipogenic progenitor cells (surface markers: $CD31^{-}CD45^{-}Sca1^{+}Pdgfr\alpha^{+}CD24^{-}$) under

in vitro and in vivo conditions. Adipogenic progenitors further mature to a $CD31^{-}CD45^{-}Sca1^{-}Zfp423^{+}$ pre-adipocyte stage that progresses to a mature adipocyte stage (Fig. 1). In vivo transplantation studies have also shown that these maturation steps are irreversible under normal physiological conditions [12]. Whether such cell populations are also present in human bones remains to be investigated. In humans, bone-derived MSCs may contribute to at least 10% of cells in adipose tissue depots outside the bone when administered by intravenous transplantation routes, but not the other way around [34]. This contribution appears to be doubled in obesity, implying that bone harbors a reserve pool of MSCs for classical WAT. It remains to be verified whether this also occurs in a more physiological context, i.e., not involving application of exogenous MSCs.

Regarding the characteristics of mature marrow adipocytes in comparison to WAT and BAT, lineage tracing to Osx1 is unique to BMAT compared to WAT and BAT [35]. Bone marrow adipocytes are distinct in size, cytokine and adipokine expression, immunomodulatory properties, free fatty acid (FFA) content, and some aspects of stem cell marker expression [3, 11, 36, 37]. Some lack of clarity remains, as adipocytes of long bones trace to a typical white fat-like $Prx1^{+}Myf5^{-}$ origin [12, 22, 38, 39], but are capable of expressing some typical brown adipocyte genes, albeit at much lower expression levels than in BAT [40, 41]. Similarly, our own data suggest that bone-derived progenitors give rise to cells with a very limited brown-adipogenic potential [12]. On the other hand, BMAT phenotypes might be dependent on age and skeletal compartment and clearly warrant further investigation.

Congenital generalized lipodystrophy (CGL) is a rare condition defined by an almost complete loss of adipose tissue [19]. All affected genes (CGL1-4: Loss of *Agpat2*, *Bscl2*, *Cav1*, or *Ptrf*) are highly enriched in adipogenic cell populations of healthy murine bone [12]. However, only mice and humans with a loss of *Agpat2* and *Bscl2* (CGL1 and CGL2, respectively) also lack BMAT. Absence of bone fat does not

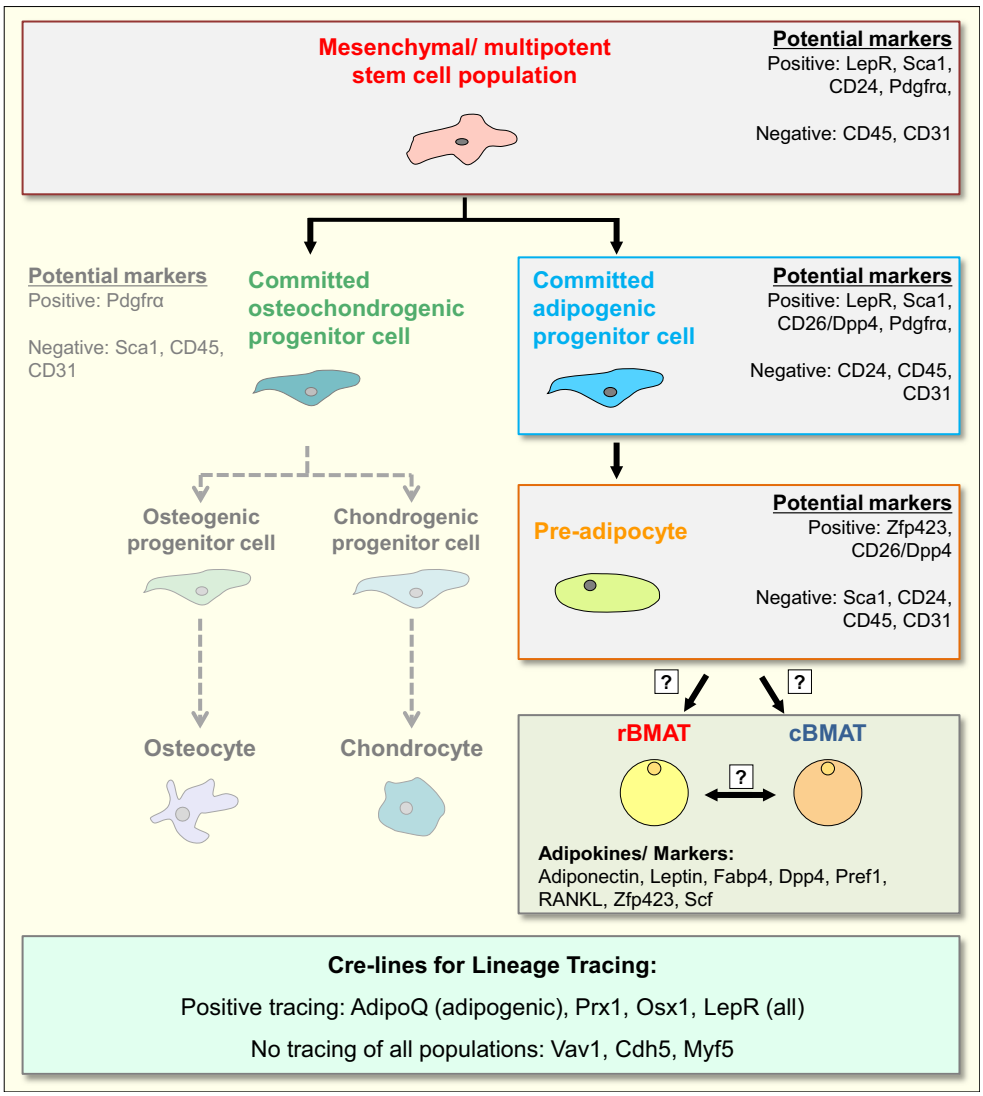


**Fig. 1** Proposed model of the cellular origin of bone marrow adipocytes. A population of stem cell-like multipotent stromal cells gives rise to distinct and unilaterally committed osteochondrogenic and adipogenic lineages. Several markers have been identified to be expressed/not expressed on the individual cellular stages and adipogenic cells of the bone in particular. Genetic lineage tracing by the Cre/loxP system further defines the developmental lineage and restricts BMAT to a mesenchymal, non-hematopoietic (Vav1), non-endothelial (Cdh5) origin that differs from traditional brown adipocytes

impair patterning of the skeleton, suggesting no role of BMAT in this process. Nonetheless, the complete lack of adipocyte-derived endocrine factors impairs bone integrity [19]. In mice, a CGL4 model specifically reduces rBMAT, but not cBMAT [11], while CGL3 has no effect on any marrow adipose tissue type [11]. These findings further emphasize the existence of variations in genetic determinants of BMAT and WAT/BAT formation and function.

## Pathophysiological regulation of bone marrow adipose tissue

Adipocyte development in the bone marrow compartment is regulated by different physiological and pathological processes. With advancing age, depots of BMAT increase in size and number in healthy individuals [42]. Obesity can be a potent driver of bone marrow adipocyte formation in particular in correlation with visceral WAT expansion [43]. Studies in mice show that feeding of a high-fat diet (HFD) rapidly initiates the expansion of BMAT by the activation of adipogenic progenitor cell proliferation [12]. Interestingly, caloric restriction (CR) and conditions such as anorexia nervosa also favor accumulation of marrow adipocytes [19]. Although CR generally counters aging and disease, it is not fully elucidated whether this also applies to bone tissue. For instance, in the growth phase of juvenile mice, CR leads to high marrow adiposity and low bone mass [44]. In patients recovered from anorexia nervosa, marrow adipocytes are depleted suggesting that marrow adipogenesis under these conditions is reversible [45]. While acute starvation does not affect BMAT [46], severe starvation beyond normal CR leads to a loss of bone marrow lipid content [47], altogether indicating that it might be able to serve as energy reservoir in specific situations. Cold exposure selectively reduces rBMAT in mice [11], but effects on bone mass depend on the level of brown adipose tissue (BAT) activation [48]. In contrast, housing at temperatures close to thermoneutrality (32 °C), which inactivates brown adipocytes, seems to be less detrimental to bone mass than room temperature (22 °C), which is a mild cold stimulus in mice [49]. Other physiological changes also regulate BMAT: ovariectomy- and menopause-induced estrogen deficiency favors adipocyte differentiation in the bone and is correlated with osteoporosis and increased fracture risk [3, 50]. Similarly, reduced mechanical stimulation due to extended bed rest induces a persistent bone loss and increased BMAT levels, which are retained even during subsequent exercise programs [51]. In line with the reversible nature of marrow adipogenesis, animal studies have shown that exercise reverses ovariectomy-, HFD-, and rosiglitazone-mediated BMAT accumulation [52–55]. Rosiglitazone and other thiazolidinediones (TZDs) are Pparγ-agonists with potent insulin-sensitizing effects, thereby improving systemic glucose homeostasis. As a common side effect, TZDs induce BMAT accumulation, which is paralleled by a decrease in BMD [56–58]. In mice, the effects of such Pparγ-agonists depend on dosage, age, and genetic background [59, 60]. For instance, the C3H/HeJ strain is highly responsive to rosiglitazone-induced bone loss, while C57BL/6J (B6) mice increase bone marrow adiposity without changes in trabecular bone parameters under TZDs [59]. In summary, the list of BMAT-regulating factors is constantly growing (see also Table 1). Other drivers of red-to-yellow marrow conversion include cancer, chemotherapy, radiation therapy, and hematopoietic malignancies as discussed further below [2, 67, 85, 86].

## Endocrine and paracrine regulation of bone marrow adipose tissue

Many hormones involved in metabolic control also regulate marrow adipogenesis (Fig. 2). High systemic levels of growth hormone favor bone over marrow adipocyte formation [71]. Similarly, obese women show an inverse association between vertebral BMAT and circulating insulin-like growth factor-1 (Igf1) levels, which is in congruence with the essential role of Igf1-receptor signaling for bone development [43]. Glucocorticoids, for instance excessive cortisol levels in Cushing's disease patients, induce marrow adiposity [71, 72]. In the same line, a recent article demonstrated that parathyroid hormone (Pth) stimulates an osteogenic fate. The authors showed that a loss of Pth-receptor activation in mice and humans increases BMAT, inducing the release of osteoclastogenesis-promoting RANKL and thereby promoting bone loss [37]. Increasing BMAT is also observed in response to elevated fibroblast growth factor 21 (Fgf21) levels which can be positively correlated with low bone mass in older men [76, 77]. An increment of osteocyte-derived Sclerostin secretion positively correlates with vertebral BMAT amounts in men [82]. In support of this observation, genetic ablation and pharmacological blockage of Sclerostin prevent BMAT and ameliorate osteoporotic conditions [83, 84]. Moreover, female rats treated with testosterone have less bone marrow fat and high bone mass [49, 75].

Adiponectin may act in an anti-osteogenic manner by hampering osteoblast proliferation in short-term conditions, while long-term effects include enhanced bone mass and inhibition of BMAT formation by decreasing sympathetic tone, i.e., pro-adipogenic β3-adrenergic signaling, through central signaling mechanisms of the brain [81]. Intriguingly, BMAT significantly contributes to circulating Adiponectin levels during CR, which may mediate some of the beneficial effects of this dietary intervention [20]. TZD treatment similarly leads to elevated Adiponectin in serum, but it is not clear whether this is due to a general expansion of WAT mass [60]. It also remains to be investigated whether other drivers of BMAT-formation also lead to increased bone-derived Adiponectin secretion or whether these factors induce different types of BMAT.

**Table 1** List of parameters with general associations of BMAT and bone mass in human and rodents

| Condition | Factor | Reference | Effect on BMAT | Effect on bone mass |
|---|---|---|---|---|
| Physiological/Environmental | Aging | [2, 3, 7, 12] | Increased | Decreased |
| | Exercise/disuse | [53–55] | Decreased/increased | Increased/increased |
| | Caloric restriction/excessive CR | [20, 44]/[47, 61] | Increased/decreased | Decreased/decreased |
| | Acute starvation | [46] | Unchanged | Decreased |
| | Cold exposure | [11, 49] | Decreased | Varying |
| | Menopause | [10, 21, 50] | Increased | Decreased |
| Disease | Osteoporosis | [18, 62, 63] | Increased | Decreased |
| | Obesity | [6, 8, 9, 12] | Increased | Varying |
| | Diabetes, type I | [3, 64, 65] | Increased, unchanged | Decreased |
| | Diabetes, type II | [3, 64–66] | Increased, unchanged | Varying |
| | CGL, type I | [11, 19] | Decreased | Decreased |
| | CGL, type II | [11, 19] | Decreased | Decreased |
| | CGL, type III | [11, 19] | Unchanged | Decreased |
| | CGL, type IV | [11, 19] | Unchanged, decreased | Decreased |
| | Anorexia nervosa | [3, 20] | Increased | Decreased |
| | Aplastic/chronic anemia | [2, 7] | Increased/decreased | Decreased, unchanged |
| | Myeloma | [2, 67–69] | Increased | Decreased |
| | Leukemia | [2, 69] | Increased (in young: decreased) | Decreased |
| | Prostate cancer | [67, 70] | Increased | Decreased |
| Hormones | Growth hormone/Igf1 | [43, 71] | Decreased | Increased |
| | Glucocorticoid | [3, 72, 73] | Increased, unchanged | Decreased |
| | Estrogen | [50, 63, 74] | Decreased | Increased |
| | Testosterone | [50, 75] | Decreased | Increased |
| | Fgf21 | [76, 77] | Increased | Decreased |
| | Leptin | [78–80] | increased | decreased |
| | Adiponectin | [20, 60, 72, 81] | Varying | Varying |
| | Parathyroid hormone | [37] | Decreased | Increased |
| | Sclerostin | [82–84] | Increased | Decreased |
| Treatments | Chemotherapy | [20, 27, 85] | Increased | Decreased |
| | Radiation therapy | [12, 27, 85–87] | Increased | Decreased |
| | BADGE (Pparγ-agonist) | [87–89] | Decreased | Unchanged, increased |
| | Exendin-4 (Glp1-receptor agonist) | [90, 91] | Decreased | Increased |
| | Romosozumab (anti-Sclerostin antibody) | [82–84] | Decreased | Increased |
| | Bisphosphonate | [92] | Decreased | Increased |
| | Dpp4 inhibition | [12, 93] | Decreased | Increased |
| | TZDs (glitazones) | [56, 58, 59] | Increased | Decreased |

Additionally, BMAT could also be a source of significant amounts of Leptin, an adipokine that regulates fertility, appetite, and energy metabolism [94, 95]. Hypothalamic activity of Leptin increases sympathetic tone and favors marrow adipogenesis over osteogenesis. Locally, however, it may drive osteogenic fates by binding to LepR on osteoblasts [78], whereas other findings imply that activation of LepR signaling in MSCs promotes adipogenesis and impairs fracture healing [79]. In mice lacking Leptin (ob/ob), increased BMAT is observed and this correlates negatively with BMD of the axial skeleton [80]. Further indications of a potential metabolic involvement of bone come from the observation that the pancreatic hormone insulin binds to osteoblasts and thereby contributes to whole-body glucose homeostasis [96]. Specifically, insulin suppresses the expression of Osteoprotegerin (*Opg*) in osteogenic cells, an inhibitor of the differentiation of bone-resorbing osteoclasts. This stimulates bone degradation leading to a lower site-restricted pH, which in turn leads to decarboxylation of osteoblast-derived Osteocalcin (Ocn). The undercarboxylated form of Ocn promotes insulin secretion

and enhances insulin sensitivity in liver, muscle, and WAT [96, 97]. In line with the important metabolic functions of Ocn, known pathologies of reduced bone quality and elevated marrow adiposity correlate with diminishing levels of this skeleton-derived hormone [98, 99]. A recent report shows that osteogenic cell-derived Lipocalin-2 (Lcn2) also controls energy metabolism by stimulating insulin secretion and decreases food intake through binding to melanocortin-4 receptor of neurons in the hypothalamus [100]. This finding is in contrast to two earlier studies that found no effect on appetite in mice lacking Lcn2 systemically [101, 102]. Adipose tissue is a known source of Lcn2, but conditional, adipocyte-specific ablation of Lcn2 driven by the *Adipoq* gene promoter did not show any effects. Whether BMAT-derived Lcn2 contributes to systemic metabolic effects remains to be determined, since only young mice on a C57BL/6J genetic background known to have negligible amounts of marrow adipocytes were investigated [100]. Lastly, BMAT has been described as a source of Dipeptidyl peptidase-4 (Dpp4), which as a locally secreted negative regulator inhibits the regenerative processes of bone healing and hematopoiesis [12, 103] (Fig. 2).

## Implications for bone health and pathology

The potential functions of BMAT include production of adipokines, including several (pro-inflammatory) cytokines, and paracrine effects by direct contact to adjacent cells supporting a pro-adipogenic, bone-resorbing environment which is potentially mediated by lipotoxicity [104]. This is underpinned by the change of bone marrow cytokine profiles with aging [105]. In vitro data show that fatty acids impair osteoblast differentiation [106, 107] and that saturated palmitic acid reduces mineralization by impairing pro-osteogenic Wnt-signaling and related pathways [108]. In accordance with this observation, the fracture risk in postmenopausal women is increased with higher levels of saturated fatty acids in bone marrow fat [21]. Osteoporosis is characterized by an imbalance of bone formation and bone resorption, which is initiated by increased osteoclast activity and a reduced function of osteoblasts due to a clonal switch of MSCs from osteogenesis to adipogenesis during aging [3, 62, 63, 109]. Osteoporosis is particularly prevalent in women after menopause when increased osteoclastogenesis, BMAT accumulation, and fracture risk are evident [109, 110]. In obese, postmenopausal women, a low BMD is associated with high serum levels of Dpp4, a protease that can also be released form adipogenic cells as an adipokine [111]. Importantly, clinically approved Dpp4-inhibitors attenuate bone loss in male diabetic rats [93], decrease fracture risk in diabetic humans [112], and are a promising strategy to improve fracture healing outcomes in healthy, non-diabetic mice [12]. Among the Dpp4-substrates, the incretin hormones glucagon-like peptide-1 (Glp1) and gastric inhibitory polypeptide (Gip) are rapidly inactivated by Dpp4 and play a central role in metabolism [90]. Activation of the Glp1 receptor promotes osteogenesis, which can also be achieved with the synthetic agonist exendin-4, making it a therapeutic target for osteoporosis treatment [91].

Diabetes mellitus increases the risk of osteoporosis and bone fragility in humans [64]. Individuals with diabetes mellitus type 2 present a higher prevalence of fractures and fatty acid saturation in BMAT [21, 66] and experimental data show that type 2 diabetic mice suffer from bone loss and

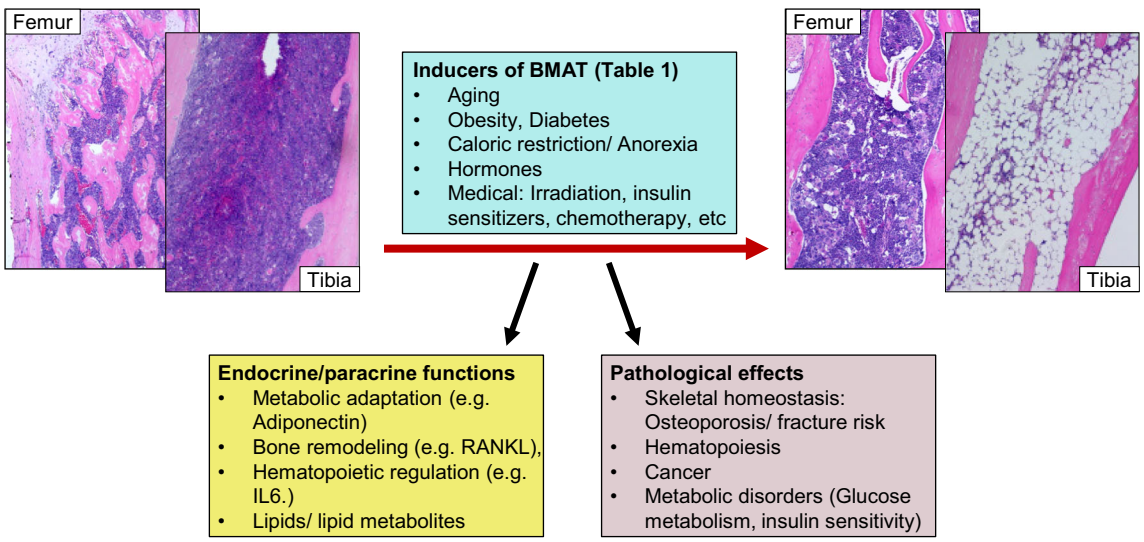


**Fig. 2** The red, predominantly hematopoietic bone marrow is converted into yellow, adipocyte-rich marrow as a normal physiological process, also in response to environmental and pathological cues. BMAT exerts endocrine and paracrine functions, which have been mainly associated with negative effects for local and systemic processes. During caloric restriction, BMAT contributes to significant amounts of circulating Adiponectin, thereby potentially improving metabolic conditions

increased bone marrow adiposity [113]. Interestingly, prevention of BMAT accumulation during diabetes mellitus type 1 or after ovariectomy does not prevent bone loss, suggesting additional non-adipocyte-related mechanisms for impairment of bone integrity in diabetics [88, 114]. Under certain circumstances and depending on the BMAT type, bone marrow adipocytes might be supportive, as evidenced by the observation that BMAT-deficiency increases bone loss during unloading [115].

The hematopoietic niche within bones comprises diverse cell types of which osteo-lineage, endothelial, and mesenchymal stromal cells have been assigned hematopoiesis-supportive functions (reviewed in [116]). Obesity, which may induce BMAT, has been shown to negatively affect immune cells [117], but it also promotes white blood cell production through increased circulating Leptin levels [118, 119]. A recent study showed that a 2-week HFD reduces long-term hematopoietic stem cell (HSC) numbers and shifts lymphoid to myeloid differentiation, which leads to a changed bone structure with fewer osteoblasts and more adipocytes [120]. Moreover, blocking BMAT formation by treatment with the Pparγ-agonist bisphenol A diglycidyl ether (BADGE) rescues this phenotype and is potentially mediated by a change in gut microbiota composition [120]. This is in line with the finding that CR impairs lymphoid differentiation after irradiation following hematopoietic reconstitution [121], two mediators of strong BMAT induction. TZD treatment has no effect on the composition of the hematopoietic compartment, leading to the hypothesis that BMAT plays only a minor role during hematopoiesis [122]. In vitro co-culture experiments of bone-derived adipogenic cells and HSCs have yielded supportive as well as inhibitory effects for HSC maintenance [122, 123]. The first in vivo study investigating the role of BMAT for hematopoiesis concluded that marrow adipocytes failed to support hematopoiesis, since HSC number and quiescence were negatively related to adipocyte amount in the bone marrow [87]. Strikingly, genetic ablation of adipocyte development, or application of BADGE, leading to decreased BMAT and also classical adipose depots, rescues impaired hematopoietic recovery after radiation and chemotherapy [27, 85, 87, 89]. Consistent with these observations, our own analyses show that lineage-committed adipogenic progenitor cells co-injected into tibia bones with HSCs following lethal irradiation significantly inhibited the local engraftment of HSCs in competitive reconstitution assays. Conversely, multipotent MSCs isolated simultaneously enhanced hematopoietic reconstitution [12]. Interestingly, a recent study proposed BMAT as an important source of stem cell factor (Scf), a critical HSC niche factor [116], at least during hematopoietic reconstitution [27]. The authors show a reduced hematopoietic recovery in conditional, *Adipoq*-Cre driven Scf-knockout mice. According to the study, Adiponectin is expressed in all marrow adipocytes and a small subset (ca. 5%) of $LepR^+$ cells, which expands after irradiation [27]. A potential explanation for apparent discrepancies might be that the stromal cells targeted by *Adipoq*-Cre could be involved in some of the observed effects, as $LepR^+$ cells are highly heterogeneous and contain unilaterally committed osteochondrogenic and adipogenic cells, and also hematopoiesis-supporting multipotent MSCs [12]. Taken together, these data imply a highly context-specific role for bone marrow adipocytes in hematopoiesis and warrant further investigation with stronger emphasis on the definition of potentially distinct BMAT types, closely defined subpopulations of mesenchymal cells, and their distinct micro-anatomical localizations.

Cancer coincides with aging, obesity, and BMAT accumulation [124]. Marrow adipocytes are believed to be involved with the progression of myeloma and support bone metastases of prostate cancer, potentially linking marrow adiposity to an inflammation-induced pathophysiology [68–70]. Possible mechanisms include lipid exchange between cells, support of osteoclastogenesis, and contribution to osteolysis through the production of chemokine (C-X-C motif) ligand-1 (CXCL1) and CXCL2 [67, 70, 125]. Interestingly, certain tumor types depend on the local bone marrow status as blood cancers develop in red marrow spaces due to decreased vascularization in BMAT [2]. During stress-related disorders like anemia of chronic disease and childhood leukemia, the hematopoietic marrow becomes hyperplastic, leading to reduced or delayed local adipocyte emergence [2]. Leptin and Adiponectin have potentially opposing roles in cancer progression and thus provide an additional perspective to the endocrine function of BMAT [124]. Together with the observation that CR reduces the incidence of some cancers [126], and despite driving increased marrow adiposity, this underlines the need for a more accurate distinction of a beneficial or detrimental involvement of the prevailing BMAT type in bone-related pathologies.

## Future perspectives

Depending on the molecular context, BMAT has pleiotrophic functions and can affect bone and marrow health by exerting beneficial as well as pathological effects (Fig. 2). This clearly emphasizes the need for a more detailed characterization of distinct types of BMAT and the stem/progenitor cells that can give rise to marrow-resident adipocytes. Recent findings highlight its involvement in human health and disease through paracrine and endocrine properties that are worth further examination. Marrow adipocytes that accumulate under physiological or homeostatic conditions may serve as a way to modulate energy-costly hematopoiesis and bone remodeling processes [127]. In contrast, improving osteogenesis by reducing BMAT during pathogenic conditions may not only increase skeletal health, but also other metabolic processes on the

systemic level. Supportive clinical evidence along these lines comes from the use of estrogen replacements [74], bisphosphonate [92], and Sclerostin antibodies [84]. Novel candidates are synthetic Glp1-receptor agonists [91] and Dpp4-inhibitors [12] that require further investigation. One major drawback in the field is the lack of BMAT-specific in vivo models. Genetically engineered mice and adipocyte-ablating agents in most cases affect other adipose depots alongside BMAT, making it difficult to deduce the direct contribution of marrow-resident adipocytes. To this end, a detailed analysis of murine BMAT stem/progenitor cells may contribute to novel discoveries. The translation of such findings to the human context will be critical, as is the improvement of non-invasive BMAT analysis and quantification tools for clinical studies. In summary, the research of BMAT holds a significant clinical potential and will contribute to a better understanding of physiological and pathological processes of the musculoskeletal system.

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