MECHANISMS IN ENDOCRINOLOGY

Bone marrow adiposity and bone, a bad romance?

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Abstract

Bone marrow adipocytes (BMA-) constitute an original and heterogeneous fat depot whose development appears interlinked with bone status throughout life. The gradual replacement of the haematopoietic tissue by BMA arises in a well-ordered way during childhood and adolescence concomitantly to bone growth and continues at a slower rate throughout the adult life. Importantly, BM adiposity quantity is found well associated with bone mineral density (BMD) loss at different skeletal sites in primary osteoporosis such as in ageing or menopause but also in secondary osteoporosis consecutive to anorexia nervosa. Since BMA and osteoblasts originate from a common mesenchymal stem cell, adipogenesis is considered as a competitive process that disrupts osteoblastogenesis. Besides, most factors secreted by bone and bone marrow cells (ligands and antagonists of the WNT/ β -catenin pathway, BMP and others) reciprocally regulate the two processes. Hormones such as oestrogens, glucocorticoids, parathyroid and growth hormones that control bone remodelling also modulate the differentiation and the activity of BMA. Actually, BMA could also contribute to bone loss through the release of paracrine factors altering osteoblast and/or osteoclast formation and function. Based on clinical and fundamental studies, this review aims at presenting and discussing these current arguments that support but also challenge the involvement of BMA in the bone mass integrity.

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Introduction

The last decades have witnessed compelling evidence for fat influence on skeletal health. Among others, the two main adipokines leptin (1) and adiponectin (2) exert direct and indirect effects on bone mass. Moreover, clinical studies have drawn attention to the complex relationships between adipose tissues, their distribution

and bone mineral density (BMD) (3), the main parameter used to diagnose osteoporosis and to assess fracture risk. A low BMI is a predisposing factor for fractures and, indeed, decreased BMD associated with an enhanced risk of fracture is a common comorbidity of anorexia nervosa (4). In obesity and type 2 diabetes, a higher incidence rate

Invited author's profile

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of fractures is reported despite normal or higher BMD (5, 6). Understanding the involvement of fat depots on bone integrity is increasingly needed considering the growing prevalence of obesity and type 2 diabetes notably in the ageing population.

Bone development and renewal rely on the activities of osteoclasts and osteoblasts, which resorb and form the mineralized matrix, respectively. During the developmental stages, both cells act rather independently to shape and allow the growth of bone. Once the peak bone mass is achieved, its maintenance throughout the adult life mainly involves the bone remodelling process to remove the old and damaged bone and to contribute to whole body calcium homeostasis. Bone remodelling consists in the sequential activities of the activated osteoclasts followed by the recruited osteoblasts: bone resorption and formation are thus timely and locally coupled so that the amount of removed bone is balanced by the amount of newly formed one (7). With ageing, bone remodelling progressively becomes uncoupled with an insufficient formation response to the resorption level. This uncoupling phenomenon is also prominent in the setting of menopause when the increase in bone formation fails to compensate for the rapid and continuous bone resorption. The resulting bone mass loss and micro architectural deterioration, mainly at trabecular but also cortical sites, characterize osteoporosis and lead to fragility fractures (7). Current osteoporosis treatment includes anti-catabolic or anabolic drugs used alone or in combination, which unfortunately cannot prevent all types of fractures and may be inefficient on the long term (8, 9).

The control of bone remodelling is multifactorial and driven by hormones such as oestrogens, parathyroid hormone, growth hormone, glucocorticoids but also numerous local factors. Indeed, bone cells such as the osteocytes (the osteoblast-derived cells imbedded within the bone matrix) and bone marrow (BM) cells tightly regulate their respective activities. BM also provides an essential environment by hosting the haematopoietic stem cells of which the myeloid precursors that are activated into osteoclasts and the bone marrow mesenchymal stem cells (BM-MSC) that give rise to osteoblasts (7). Among other haematopoietic, stromal, endothelial and neuronal cells, bone marrow adipocytes (BMAs) have recently emerged as an active component of the bone and the BM environment (10, 11).

BM adiposity represents up to 5% of total fat mass in healthy adults and constitutes an original and heterogeneous fat depot whose characteristics differ from

the more commonly studied brown or subcutaneous and visceral white adipose tissues (10). BMA reside within the cavities of long bones and vertebrae in close vicinity of trabeculae. Different waves of BMA arise during bone growth and bone remodelling in humans and animal models (12). Importantly, the amount of BM adiposity is negatively associated with BMD in primary osteoporosis such as in ageing or menopause but also in secondary osteoporosis such as in anorexia nervosa. More evidence highlight how BMA differentiate from BM-MSC in response to typical regulators of bone remodelling and can also be a paracrine source of factors regulating osteoclastogenesis and/or osteoblastogenesis. In this review, clinical and fundamental data are collated to address both the pathophysiological conditions and the main BM and endocrine factors that interfere with the development and the activities of BMA, in order to discuss the current arguments that support but also challenge the involvement of BMA in the bone mass integrity.

Physiological and pathological conditions associated with BMA development

BMA develop throughout life in close connection to bone status

BM adiposity first develops during childhood and adolescence. The gradual replacement of the active haematopoietic BM by adipocytes was primarily reported to start in the appendicular skeleton: already present in the phalanges at the first year of life, BMA spread in the diaphysis up to the metaphysis of long bones during the following decades (13, 14). Besides, a very rapid accrual of BM adiposity has recently been described in the lumbar vertebrae during the first 2 years of life (15). Thus, BMA development appears as a physiological process concomitant to bone growth, which suggests its involvement in the acquisition of the peak bone mass. Indeed, in pre-pubertal girls, femoral BM fat content is positively associated with total bone mineral content (13). Perturbations in the peak bone mass achievement are believed to have adverse long-term effects on adulthood bone health as feared in paediatric osteoporosis (16) or with anorexia nervosa, a prevalent disorder in adolescent girls (4). However, BM fat development in femoral and tibial metaphysis remains strongly associated with age in adolescent girls suffering a mild-to-moderate anorexia nervosa, and, BM fat fraction is still positively correlated with BMD in the youngest patients identified as skeletally

immature (17). Moreover, reviewing the skeletal phenotype of various lipodystrophy types, Scheller and Rosen conclude that none of adipose tissues is instrumental in the basic bone formation. Nevertheless, maintenance of BM adiposity development could contribute to bone protection against cyst formation during adolescence and pathological fractures in adulthood (14). Yet, analyses of BM fat remain scarce in very young subjects and non-existent in childhood osteoporosis to our knowledge. As murine models of osteogenesis imperfecta (18) or Marfan syndrome (19) exhibit altered BMA development, investigating BM adiposity in paediatric bone disorders could also clarify its involvement in bone accrual and skeletal integrity later in life.

In the young adults with mature skeleton, the remaining haematopoietic sites within the proximal metaphysis of femur and humerus (20) and the lumbar vertebrae (21, 22) are progressively invaded by BMA. The increase rate of BMA accumulation is then slow with a ~6% increase of fat per decade as assessed in vertebrae (21). BM adiposity proportion is higher in men than in women at least up to the menopause age (20, 22). Importantly, in that ageing-related step, BM accumulation is negatively associated with BMD (22, 23) and with trabecular bone quantity (24, 25) at different skeletal sites. Thus, even though BM adiposity development appears as a continuous physiological process throughout life, a switch in its association with bone mass occurs with the bone growth arrest. Whether this switch is causal, consecutive or unrelated to the physiological bone status has to be determined and could propel research on BM adiposity.

Two BMA subpopulations for different periods of development in rodents

The use of osmium tetroxide staining visualized by nano- and micro- CT has recently documented the developmental process of BM adiposity in rodents and leads to the definition of two BMA subpopulations. In 1- to 4-week-old mice, distal tibiae and caudal vertebrae rapidly display an expansion of adipocytes. This first early developed subset – whose amount remains relatively stable during pathophysiological challenges or ageing – has been referred as to constitutive BMA (cBMA) (12). From 12-week-old and beyond, a second subset develops within the middle and proximal tibia, a site characterized by the presence of cancellous bone and high remodelling. Despite differences in the developmental rates between mouse strains, the amount of this BMA subpopulation correlates negatively with the trabecular number of proximal tibia.

This BMA subset – which arises scattered among the haematopoietic cells – has been referred to as regulated BMA (rBMA) (12) since its development is observed and modulated with ageing (12, 26, 27) or pathophysiological conditions (12, 27, 28). Importantly, the rBMA are reported to phenotypically differ from cBMA by a smaller size and a lower content in unsaturated fatty acids (12). The rBMA have been proposed to be preferentially distributed within the mid-to-proximal tibia, the femur and the lumbar vertebrae though cBMA could also be present in some of these areas (11). Actually, this recent classification into two subtypes might be oversimplified. Regarding its definition, for example, the ‘unresponsive cBMA’ can significantly expand within the distal part of the tibia–fibula junction following ovariectomy (S Lucas, personal communication). Moreover, as indicated through the characterization of BM-MSC-derived adipocytes, a greater heterogeneity in BMA properties can be expected according to the bone region (epiphysis, metaphysis and diaphysis) (29) or the bone type (long bones versus vertebrae) as well as the pathophysiological conditions as emphasized in the following sections. Extrapolation of such classification to humans also remains elusive. Indeed, some striking differences have to be considered when comparing animal models and human pathophysiological conditions. Compared to humans, the relative proportion of BM adiposity appears lower in mouse models (12). The mouse skeleton maturity is delayed to the adulthood since femoral (30) and vertebral (31) longitudinal growth continues to slowly increase up to the age of 6 and 10 months respectively, which is a period associated with rBMA development. Finally, females exhibit a much more enrichment in tibial rBMA than males (11, 29). Whether this trait is related to the early and fast trabecular bone loss occurring in these females (27, 28) has not been assessed yet but deserves further investigations considering the close associations between BMA and bone remodelling.

BM adiposity is associated with bone loss

From the initial biopsy analyses to the most adapted MRI or spectroscopy techniques, BM adiposity content has been shown to increase with ageing in various cross-sectional studies (23, 24). Importantly, the relative amount of BM adiposity has been negatively associated with bone quantity measured as areal BMD using whole body or regional DEXA (dual energy X-ray absorptiometry) or trabecular bone volume using QCT (quantitative CT). The BM fat proportion locally measured has been found to be inversely correlated with the trabecular bone

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volume in iliac crest biopsies (24), with the trabecular BMD in lumbar vertebrae (25, 32, 33, 34) and with the pelvic BMD (23, 35). In some studies, the relative BM fat proportion measured at a specific site (often the spine) can even be negatively associated with the whole body BMD (23, 35) or other bone site BMD (33, 34), which is surprising considering the expected heterogeneity of BMA development and phenotype according to the site and the potential interference of BMA in the local bone remodelling. This inverse relationship has been reported in young or old men and women (23, 24, 35, 36), even though post-menopausal women can exhibit the most consistent association compared to old men (33, 34). Indeed, women experience a rapid loss of bone and a spurt of BMA development at menopause (22). Importantly, the vertebral BM fat content is increased in osteopenic and osteoporotic subjects compared to those with normal BMD in aged men (37) and post-menopausal women (34, 38, 39). Higher BM adiposity levels are also depicted in conditions where bone density is reduced secondary to anorexia nervosa (40), immobilization (41), glucocorticoid (42) or some thiazolidinedione (43) treatments. Moreover, a few studies indicate a relationship between BM fat content and prevalent vertebral fractures as reviewed in (44). Interestingly, in post-menopausal women, the unsaturation level of the vertebral BM lipid fraction is decreased compared to controls (38) and is inversely associated with fragility fractures (45). In line with the phenotype of rBMA in rodents (12), these data suggest that, besides expansion, the metabolic profile of BMA could also play an essential role in bone alterations.

Enhanced BM adiposity formation is reported in animal models of ageing (27), ovariectomy (28), calorie restriction (46), skeletal unloading (47) or following glucocorticoid (48) or rosiglitazone (49) administration. In most studies, stimulating BMA development is accompanied with a reduced bone quantity, and these animal models provide useful insights in the underlying connections between bone and BM fat. However, a few studies report a failure to improve bone parameters by impairing BMA development notably in the ovariectomy model (50, 51, 52). Besides challenging the current view of an inverse relationship between BM adiposity and bone mass, other issues can be gleaned from these studies. Firstly, the genetic or pharmacological manipulations used to hamper BM adipogenesis also reduce the amount of extramedullary fat depots (51, 52), which may interfere with the bone integrity restoration. Indeed, specifically targeting the BM adipogenesis process has become a

critical issue. Secondly, bone formation stimulation is only reported in the ovary-intact rats whose BM adiposity was the lowest following a PPARG antagonist treatment (52) raising the hypothesis that BM adiposity has to be amply curtailed below a certain threshold to beneficially impact on bone. Thirdly, as emphasized earlier, BMA development is strain-, gender- and age dependent. It is thus expected that the effects of BM adiposity on bone mass exhibit strong age-related variations notably according to the onset of ovariectomy-induced oestrogen deficiency, which should be performed when animals are skeletally mature.

BM adiposity status in other bone defects

BM adiposity is induced in mice (53) and patients (54) following irradiation, which triggers bone loss and other skeletal alterations. Cancer cells in the BM also disrupt bone formation and resorption leading to bone lesions. Though not yet demonstrated, BMA could also support the progression of multiple myeloma cells or bone metastatic cells as discussed in (55, 56) respectively.

In obesity and type 2 diabetes, a higher risk of fractures is reported at some specific bone sites despite increased or unchanged BMD. These conditions elicit a low bone turnover and likely compromise bone quality (5, 6). The development of BM adiposity in obesity has been poorly addressed: vertebral BM fat content is found unchanged compared to control (57) and related (32) or not (57, 58) with the amount of visceral fat. In contrast, BMA consistently accrue in the long bones of high-fat feeding rodents while skeletal changes vary according to the studies (59, 60). Interestingly, BMA accumulation is more pronounced in aged animals (61). In type 2 diabetic patients, BM fat content is reported unmodified (62, 58) or increased (63) according to the skeleton site, but yet is positively associated with HbA1c levels (58, 63). In accordance, bariatric surgery, which causes a lowering of both body weight and bone mass, reduces BM fat fraction only in patients with improved glycaemic control (64).

In conclusion, and as already discussed (10), BM adiposity strikingly differs from the main fat depots and its levels are modulated by different cues. Moreover, BM fat development can dissociate from bone mass alterations in some conditions such as growth and body weight loss in obesity. Yet, BM adiposity accretion is strongly age-related and often associated with BMD deficit supporting its involvement in bone remodelling uncoupling.

Potential mechanisms underlying the detrimental impact of BMA on bone

As confirmed by lineage tracing studies in mice (61), osteoblasts and BMA originate from a common BM-MSC that can give rise to independent precursors committed either to the osteochondrogenic or the adipogenic lineages. Moreover, several factors reciprocally regulate adipogenesis and osteoblastogenesis. Consequently, an unbalanced shift toward adipogenesis is considered as a detrimental process for osteoblastogenesis and the maintenance of bone mass.

Besides, first *in vitro* and *ex vivo* characterizations support that BMA are active cells releasing several factors interfering with bone remodelling. Primary BMA from ageing mice can synthesize several pro-apoptotic cytokines (65) and inflammatory factors such as TNFA and IL6 (26). Primary human (66) and murine (67) BMA also express the pro-osteoclastogenic factor RANKL, which promotes osteoclast precursor differentiation through direct cell contact (66). *In vitro* co-culture (68) or conditioned medium (63, 69) models point out a paracrine activity of BMA. BM-MSC-derived adipocytes can release saturated fatty acids that negatively impact osteoblast function and survival (68). Finally, adipocytes, derived from BM stromal or mesenchymal stem cells (both referred as to BM-MSC in the review), can secrete factors altering osteoblastogenesis and favouring adipogenesis as described in the next section.

The balance between osteoblastogenesis and adipogenesis is indeed orchestrated by multiple signals, cytokines, hormones and metabolic factors acting in an autocrine/paracrine or an endocrine mode on MSC. All these factors are involved in the regulation of the lineage commitment and/or differentiation programmes of MSC, which require the activation of specific transcription factors such as osterix and RUNX2 for osteoblastogenesis and PPARG2 and CEBPA for adipogenesis. In that matter, PPARG appears as a critical molecular regulator since targeting *PPARG* expression or activation interferes with the differentiation programme of both adipogenesis and osteoblastogenesis as exemplified in (70, 71).

The local control of osteoblastogenesis and adipogenesis in the bone marrow

Among many signalling pathways, WNT/ β -catenin and bone morphogenetic proteins (BMP) signalling play prominent roles in the control of osteoblastogenesis and adipogenesis.

WNT/ β -catenin signalling

The canonical WNT/ β -catenin signalling pathway has been well established to play pro-osteogenic (72, 73) and anti-adipogenic (73, 74) effects on MSC. Briefly, WNT/ β -catenin signalling activation begins by the binding of WNT ligands with cell surface Frizzled receptors and requires the involvement of LDL receptor-related proteins 5,6 (LRP5/6) as co-receptors. This leads to β -catenin protein stabilization, accumulation then translocation to the nucleus where the protein acts as co-factor for stimulating specific gene targets (75). Thus, the regulation of WNT/ β -catenin signalling output is coordinated by a family of WNT secreted glycoprotein agonists found expressed by osteoblasts (72), preadipocytes (74) or BM-MSC (76). In addition, the pathway is negatively regulated by a variety of secreted antagonists: secreted Frizzled receptor proteins (SFRPs) including SFRP1 expressed by BM preadipocytes (73) and SFRP4 expressed in BM-MSCs (76) and BMA (26); Dickkopf-1 (DKK1) synthesized by BM-MSCs (76), BM preadipocytes (73), osteoblasts (77), and osteocytes (70); sclerostin secreted by osteocytes (78).

Both pro-osteogenic and anti-adipogenic effects of WNT/ β -catenin signalling have been demonstrated in various cell models by activating the pathway via inhibition of glycogen synthase kinase 3 beta (GSK3B) in BM-MSC (79) or β -catenin stabilization in the multipotent murine mesenchymal stem cell lines ST2 or C3H10T1/2 (80). Of note, in the 3T3-L1 cell line, WNT/ β -catenin signalling and PPARG are reciprocally regulated to control adipogenesis (74). Most over experiments have modified the expression or availability of WNT agonists or antagonists. WNT3A treatment increases osteogenesis in BM-MSC (81) and in C3H10T1/2 cells for which adipogenesis is also inhibited (80, 81). Overexpression of *Wnt1*, *Wnt10a* or *Wnt10b* in ST2 cells attenuates adipogenesis and augments osteogenesis while depletion displays opposite effects (82). As for WNT antagonists, SFRP1 treatment of ST2 cells inhibits osteogenesis and stimulates adipogenesis (73). Next, DKK1 treatment stimulates adipogenesis of 3T3-L1 preadipocytes (74) while *Dkk1* depletion results in decreased adipogenesis of D1 MSCs and pro-osteogenic effect on MC3T3-E1 cells and primary BM-MSCs (77). Finally, SOST addition exerts pro-adipogenic effects on primary murine and human BM-MSC (83).

The pro-osteogenic role of WNT/ β -catenin signalling has also been substantiated *in vivo* with reported functional mutations of *LRP5* resulting in lower bone mass in humans (81) and in mouse models (72, 80) associated

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with decreased osteoblast proliferation and bone formation activity. Moreover, deletion or overexpression of *Sfrp1* (84), *Dkk1* (77), *Sfrp4* (85), *Sost* (86) increases or decreases, respectively, trabecular bone volume and osteoblast number. Neutralizing antibodies against SOST, alone or in combination with those against DKK1, are clinically assessed for the treatment of osteoporosis (8, 9). Besides bone volume alterations, *in vivo* β -catenin ablation in early cells of the osteoblast lineage increases BM adipogenesis (87). Additionally *Sost* deficiency (83) or *Wnt10b* overexpression (88) raises trabecular bone volume but lowers BM adiposity.

Besides its implication in the regulation of BM-MSC differentiation process, the Wnt/ β -catenin signalling promotes bone formation through several mechanisms. The pathway modulates the proliferation of preosteoblasts (72), controls the induction of apoptosis in osteoblasts and osteocytes (84); stimulates bone matrix synthesis and mineralization (77) and regulates osteoclastogenesis notably by promoting the osteoblast production of osteoprotegerin (89). Considering its critical roles, the Wnt/ β -catenin signalling is obviously a local downstream mediator of several bone-regulating hormones as developed in the 'Systemic control' section.

BMP signalling

BMPs are extracellular cytokines that are part of the transforming growth factor-beta (TGFB) superfamily and regulate numerous physiological processes including bone cell differentiation, bone formation, development and remodelling (90, 91). The most widely investigated BMP member consists in BMP2 that is produced by BM-MSC (92) or osteoblasts (93). The signalling is initiated through BMP binding to BMPR2 receptors, which led to the further activation of BMPR1 (90). The activated downstream components encompass many pathways and regulate lineage commitment and differentiation (94). In contrast to the WNT/ β -catenin signalling, BMP signalling stimulates both osteoblastogenesis and adipogenesis according to the availability of appropriate inductors in culture media (92, 95), the BMP concentration as the signalling may finely tune the MSC fate (96) and likely according to the activation of the proper receptor subtypes (BMPR1A versus BMPR1B) though their specificity for lineage differentiation remains unclarified (97). Importantly, both differentiation processes remain mutually exclusive (98). *In vitro*, pro-osteogenic and pro-adipogenic effects of BMP signalling are mainly evidenced

by investigations of BMP2 treatment on C3H10T1/2 (90, 95) and ST2 cells (80).

Interestingly, both BMP and WNT/ β -catenin pathways play either antagonist (81) or cooperative (69) roles at various steps along bone cell lineage fate, differentiation and maturation. At early step, BMP signalling activation regulates MSC commitment to either osteoblastic or adipogenic lineages (95). Next, WNT/ β -catenin pathway activation is required to conduct osteochondrogenic progenitors to preosteoblasts (99). By then, both BMP signalling and Wnt/ β -catenin signalling cooperate to promote osteoblast differentiation (94, 98) and self-renewal (99), respectively. In the end, Wnt/ β -catenin and BMP pathways exert opposite effects during osteoblast maturation: BMP signalling activation is still required to stimulate terminal osteogenic differentiation (95) and proper bone formation (91); meanwhile, WNT/ β -catenin signalling has to be inhibited in line with the late increased expression of the WNT antagonist SOST (78). Actually, osteocytes orchestrate bone formation via subtle variations of WNT/ β -catenin and BMP signalling to modulate osteoblast activity in response to their microenvironment (100). Nevertheless, the pro-osteogenic role of BMP signalling is well substantiated *in vivo*: *Bmpr1* or *Bmp2* depletions in mice respectively result in low bone mass (90) or deficient fracture healing (101) while treatment with the BMP signalling antagonist gremlin (102) impaired bone formation.

Other local signals and factors

Most over-secreted factors are pro-osteogenic and display anti-adipogenic properties. The cytokine Hedgehog (HH) stimulates the commitment of murine MSC into osteoblastic lineage at the expense of adipogenesis (103). Its anti-adipogenic activity only occurs during the maturation phase in human BM-MSC (104). Moreover, HH signalling is reported to interact with BMP (93) and WNT/ β -catenin signalling (81). TGFB is another cytokine with pro-osteogenic effect (105) and an anti-adipogenic role as reported in human BM-MSC (106). Fibroblast growth factor 2 (FGF2) – expressed by MSC, osteoblasts and osteocytes – also exerts pro-osteogenic and anti-adipogenic effects: *Fgf2*-deficient mice exhibit increased BM adiposity and decreased BMD (107, 108); conversely, FGF2 treatment abrogates the loss in bone formation (109) and reduces the adipogenic lineage potential of murine BM-MSC (110). The pro-osteogenic factor oncostatin produced by osteoblasts and osteocytes

also has anti-adipogenic property on differentiating BM-MSCs (111).

Next, inflammatory cytokines, in serum or locally produced by various bone cells including BMA (26, 65), are associated with increased bone resorption notably in the setting of oestrogen decline (7). Interleukin -1 (IL1), -6 (IL6), -11 (IL11) and TNFA are well documented for their inhibitory effects on adipogenesis as shown in murine (112) and human BM-MSC (108). However, distinct osteogenic effects are reported according to one cytokine to another. Both IL6 and IL11 display pro-osteogenic effects on BM-MSC (112, 113), and *Il11* expression in murine BM-MSC is inversely correlated to impaired bone formation during ageing (113). As reviewed in (107), contradictory effects are described for TNFA with both inhibitory and promoting activities on osteoblast differentiation. Lipocalin 2, recently found to be secreted by osteoblasts and myeloid cells, may upregulate osteoblastogenesis at the expense of adipogenesis as suggested in human BM-MSC (108). MCP1 has recently been reported as a factor released from BMA in type 2 diabetes to promote adipogenesis and partly alter osteoblastogenesis (63).

In contrast, the cell differentiation regulator DLK1/PREF1, produced by several BM cells, exerts both anti-osteogenic and anti-adipogenic roles as evidenced in human BM-MSC (114).

Remarkably, the BMA-secreted chemerin is one of the few factors which was demonstrated *in vitro* to be required for adipogenesis while negatively regulating osteoblastogenesis of murine BM-MSC (115). The involvement of two main adipokines, leptin and adiponectin, has obviously been investigated. Of note, the first phenotyping of primary mature adipocytes isolated from human (116) and murine (26) bone marrow samples strongly support that BMA express very low levels of leptin and adiponectin compared to extramedullary fat depots, notably in ageing (26) and in the post-menopausal status (S Lucas, personal communication). So far, a strong secretion of adiponectin from BMA has only been demonstrated in calorie-restricted mice and has been associated with a systemic metabolic adaptation (88). Considering that BMA may not be a relevant local source of these two adipokines, leptin and adiponectin effects are thus discussed in the 'Metabolic hormones' section relative to the 'Systemic control'.

Collectively, most local characterized factors are pro-osteogenic with anti-adipogenic activities and can be dysregulated in diverse pathological conditions affecting

BMD. Interestingly, BM adipogenesis appears intimately interlinked with the bone microenvironment and partly regulated by several osteocyte-, osteoblast- and MSC-secreted factors. Moreover, the fact that BM preadipocytes and adipocytes can synthesize SFRP1, chemerin and MCP1 suggests that BMA themselves contribute to the control of their expansion (Fig. 1).

Figure 1

Potential mechanisms underlying the detrimental impact of BMA on bone remodelling. As shown on the top, bone marrow adipocytes (BMA) and osteoblasts arise from a common mesenchymal stem cell (MSC). Local osteogenic factors such as the WNT ligands WNT1 (synthesized by osteoblasts) and WNT10B impair adipogenesis. The local effects of leptin and adiponectin are still discussed (as mentioned in the text). The WNT antagonists such as sclerostin (secreted by osteocytes), DKK1 (synthesized by MSC, osteoblasts and osteocytes) or SFRP1 (secreted by MSC and bone marrow preadipocytes) inhibit osteoblastogenesis and promote adipogenesis. Oestrogen deficiency, parathyroid hormone (PTH) deficiency or glucocorticoid excess promote adipogenesis. These conditions could also alter the activity of BMA (as mentioned in the text). As shown at the bottom, BMA could support osteoclastogenesis through the synthesis of RANKL, TNFA and IL6. BMA could also preferentially release saturated fatty acids that alter osteoblast function and survival. Finally, BMA could stimulate its own expansion by secreting SFRP1 and chemerin, which are both pro-adipogenic and anti-osteoblastogenic.

The systemic control of BM osteoblastogenesis and adipogenesis

Sex steroids

Oestrogens and androgens stimulate the growth spurt and promote bone mass acquisition at puberty through the growth hormone/insulin-like growth factor-1 (GH/IGF1) axis stimulation and direct effects on bone cells. Sex steroids also contribute to bone mass maintenance in adulthood by slowing bone remodelling and tuning bone resorption and formation in a balanced mode (117). MSC, osteoblasts, osteocytes, myeloid precursors and osteoclasts express the two oestrogen receptor ESR1 and ESR2 and the androgen receptor AR. Mouse models of global or cell-specific deletions of each receptor have clarified the involvement of sex steroids, which is rather complex and vary according to the cortical or trabecular bone compartment, the cell type, the age and the sex (as deeply discussed in (117, 118)).

The decline of oestrogen (more specifically 17 β -oestradiol, E2) production at menopause triggers bone mass loss and is the main factor contributing to osteoporosis in women. The discovery in men that testosterone is converted to E2 by aromatization and that serum bioavailable oestrogen level is a consistent independent predictor of BMD also supports the potential contribution of oestrogen deficiency in the age-related bone loss in men (118). In humans and animals, both oestrogen and androgen deficiency results in increased bone remodelling: bone resorption and to a lesser degree formation are stimulated which leads to a net decrease of bone mass.

As already emphasized, menopause (22) or ovariectomy and orchidectomy in animals (27) leads to a strong BM adiposity accrual. Studies in growing or skeletally mature rodents indicate a rapid increase of BM fat in femur or proximal tibia (as soon as 4 weeks (28, 51)) that continues to expand up to 2–3 months following ovariectomy (51, 119, 120). Following ovariectomy, the changes in trabecular bone and the activity of osteoclasts and osteoblasts appear earlier than BMA development (121). Nevertheless, BMA amount continues to rise as the bone loss worsens (120) and a reciprocal relationship between BMA content and bone formation rate is observed (122). In premenopausal women with surgical bilateral oophorectomy, BMD reduction and BM fat accretion rapidly and concomitantly occur in the lumbar vertebrae and continue to evolve accordingly up to 21 months (123).

E2 exerts protective effects on bone via multiple mechanisms that notably involve suppression of bone resorption by inducing osteoclast apoptosis, reducing osteoclastogenic cytokine production and stimulating osteoprotegerin expression in osteoblasts. E2 also reduces osteoblast and osteocyte apoptosis (as reviewed in (117)). Importantly, in several murine BM stromal cell lines (98, 124), murine (98) or human BM-MSC (125), E2 promotes osteoblastogenesis and inhibits adipogenesis. The pro-osteoblastogenic effect of E2 relies on various molecular pathways such as the WNT (126) or BMP-4 (127) signalling pathways. Studies using BM stromal cells from several murine ER deletion models support that E2 suppresses the adipocyte lineage commitment and reduces adipocyte lipogenesis through ESR1 (128, 129). Moreover, E2 administration in ovariectomized rodents (119, 130) or in post-menopausal women (131, 132) rapidly decreases the amount of BM adiposity by preventing the BM adipocyte number accrual and reducing the adipocyte size. This can be observed before any restoration of the trabecular bone volume suggesting a high E2 sensitivity of the BM adiposity component.

Altogether many data consistently support the hypothesis that oestrogen deficiency diverts MSC differentiation from osteoblastogenesis toward adipogenesis, and this mechanism could significantly contribute to bone loss. Yet, as already discussed, early adipogenesis blocking failed to ameliorate bone parameters in ovariectomized rodents (50, 51, 52). On the other hand, oestrogen deficiency could also alter mature osteoblast and adipocyte functions and future studies should therefore better address the BMA functions in the unbalanced bone remodelling following oestrogen decline.

Glucocorticoids

Even though a physiological level of glucocorticoids is instrumental in normal bone development, hypercortisolism or long-term glucocorticoid-based therapies are the most common cause of secondary osteoporosis and predispose to increased fractures in trabeculae-enriched bones (133). Following a transient resorption stimulation, bone formation is reduced, which becomes a clinical outcome in glucocorticoid-induced osteoporosis (GIOP). Besides their systemic impact on several hormonal axes, glucocorticoids exert direct effects on many bone and BM cells: MSC, osteoblasts and adipocytes express the nuclear glucocorticoid receptor

and the two enzymes *11 β -HSD* that intracellularly metabolize glucocorticoids (134, 135, 136). As shown in the long bones of glucocorticoid-treated animals (77, 137), BM adiposity accrual is concomitant to (or even precede (48)) the decrease in BMD, trabecular bone or osteoblast number.

Both *in vitro* and *in vivo*, glucocorticoid excess impairs osteogenesis notably by promoting osteoblast apoptosis (as reviewed in (99)) but also by inhibiting osteoblast differentiation through a GSK3B-mediated reduction of β -catenin activity (137). Pharmacological doses of glucocorticoids also stimulate osteoblast expression of several WNT signalling inhibitors such as DKK1 whose inhibition can prevent bone loss (77, 136). While a low concentration of dexamethasone is a common osteoinducer for cultured BM-MSC, increased concentrations trigger adipogenesis (138). Glucocorticoid signalling also seems crucial *in vivo* since *Hsd11b1* deletion abrogates BM adipogenesis (134). The glucocorticoid-induced disruption of BM-CSM differentiation leading to increased expression of *Pparg2* or *Cebpa* has been linked to epigenetic regulations through the downregulation of WNT signalling (139, 140). However, both increased adipogenesis and unchanged osteogenesis have been reported in BM-MSC from a mouse GIOP model (27). These data point out that glucocorticoid excess does not always compromise BM-MSC commitment toward osteoblastogenesis in agreement with (138). Moreover, dexamethasone can regulate *in vitro* or *ex vivo* BMA functions by stimulating their lipolysis (68), upregulating RANKL expression (66) or perturbing adiponectin and leptin secretion (68, 141).

Deleterious glucocorticoid impact on bone mass involves several cell types and cellular mechanisms that include BM-MSC differentiation shift toward adipogenesis and the contribution of mature BMA to the altered bone remodelling through released factors. Of note, BM fat involvement remains poorly examined in GIOP and deserves further investigations.

Parathyroid hormone

Parathyroid hormone (PTH) is a major regulator of calcium homeostasis partly through its direct stimulating actions on bone remodelling. As exemplified with primary hyperparathyroidism, continuous exposure to high levels of PTH results in the increase of bone resorption that exceeds bone formation, thus leading to bone loss. The stimulated osteoclast activity appears to rely on the

unbalanced production of RANKL and osteoprotegerin by osteoblasts and osteocytes, which express the main receptor PTH1R (142). In contrast, intermittent administration (once daily) of PTH – or its short fragment PTH1-34 teriparatide – promotes bone formation to a greater extent than resorption. This anabolic effect increases trabecular bone mass in various animal models (142) and teriparatide is thus used to treat osteoporosis and to prevent fractures (8, 9). Indeed, intermittent PTH administration decreases sclerostin expression by osteocytes, prevents osteoblast apoptosis (142) and promotes osteoblast differentiation from BM-MSC via BMP signalling enhancement (143) or via β -catenin stabilization through a LRP6/PTH1R complex (144). Lineage tracing studies in mice also revealed that teriparatide reactivates quiescent lining cells (145) or stimulates osteoblast precursor proliferation (146) to become active osteoblasts.

Several evidence support that PTH also elicits bone anabolic effect by inhibiting adipogenesis. Intermittent teriparatide exposure of human BM-MSC reduces adipocyte differentiation even in pro-adipogenic conditions (147). PTH treatment of ovariectomized rats increases BMD but lowers BM adiposity (148). In mice, *Pth1r* ablation in mesenchymal progenitors results in both reduced trabecular and cortical bone volume and a marked increase of BMA (67). Moreover, withdrawal of intermittent teriparatide administration increases the density of BMA that partly derive from osteoblast precursors; such cell fate switch is associated with a suppressed β -catenin activity (146). Finally, teriparatide administration rapidly improves bone density and reduces BM fat fraction at lumbar spine in post-menopausal women (149) and lowers BMA number in the iliac crest of osteoporotic men (67).

Altogether, PTH appears as a critical factor to determine the cell fate between osteoblast and adipocyte. Besides, the loss of PTH signalling increases several adipocyte factors and stimulates RANKL synthesis in murine BMA (67) supporting that PTH can also alter the activity of BMA.

The GH/IGF1 axis

The GH/IGF1 axis is an important regulator of growth and peak bone mass achievement and contributes to bone maintenance in adulthood (150). Serum levels of GH and its downstream mediator IGF1 decline with ageing in association with bone loss suggesting their involvement in osteoporosis pathogenesis (9, 150). Moreover adult-onset

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GH deficiency is associated with reduced BMD and a higher risk of fractures; GH replacement therapy increases BMD on the long term (reviewed in (9)).

IGF1 is a peptide with insulin-like properties, mainly produced by the liver under the GH control but also by osteoblasts in tight collaboration with the PTH. IGF1 activity is mediated by the IGF1 receptor (IGF1R) and is highly dependent on its bioavailability and transport by binding proteins (150).

In vitro data are scarce and support that IGF1 stimulates MSC proliferation and promotes both adipogenic and osteoblastogenic differentiation (151, 152). IGF1 signalling in osteoblasts is also critical for bone mineralization as evidenced by multiple murine models (150). BM adiposity has been poorly assessed *in vivo*: IGF1 appears ineffective on BMA levels in mice with *Igf1* liver deficiency and following administration in hypophysectomized rats (153), which suggests that the IGF1 pathway is not critical for BM adipogenesis.

GH is expected to elicit IGF1-independent effects since BM-MSC, osteoblasts, osteocytes, osteoclasts and adipocytes express the receptor for GH (150). The reported direct effects of GH are scarce but include the proliferation and the osteogenic differentiation of human osteoblast-like cells (154). GH differently influences adipocyte differentiation according to the cell type. In GH-deficient dwarf rats (155) and in hypophysectomized rats (153), both number and size of BMA are increased while trabecular bone, osteoblast number or mineralization perimeter are decreased. In both models, GH administration improves bone parameters and lowers BMA density and diameter, whereas IGF1 administration has barely any impact on BMA. Surprisingly, divergent results were obtained from the *in vitro* study of BM-MSC from hypophysectomized rats supporting that lack and restoration of GH level decreases and increases the preadipocyte pool respectively (153, 156). Besides, GH administration in obese premenopausal women increases serum bone formation markers and BM fat in vertebrae (157). Further studies are thus required to clarify if reduced GH signalling is really involved in the reciprocal changes of bone and fat.

Metabolic hormones

Several other hormones interact with bone mass and BM adiposity including leptin and adiponectin whose influences are complex. Leptin raises a tremendous interest since either hyperleptinemia in obesity or hypoleptinemia in anorexia nervosa could underlie the increase in bone fragility observed in these two

conditions. Leptin actions on bone mass have been believed to be mediated mainly through a hypothalamic relay, which stimulates the sympathetic tone and regulates several hormonal axes such as the sex steroids, cortisol and GH ones (1). Besides leptin exerts peripheral effects, which can now be regarded as more dominant than the central effects as proposed in (158, 159, 160). Leptin notably impacts on the lineage commitment of both human (161) and murine (162) BM-MSC *in vitro*. Lineage tracing studies have actually shown that most BM stromal cells express the main leptin transducing receptor (LEPR), which post-natally give rise to osteoblasts and adipocytes (163). Though controversial (163), osteoblasts and BMA can express LEPR (164). Various rodent models including leptin or *Lepr* disruption with or without leptin administration have been extensively studied and, yet, data are conflicting. Pioneer studies promoted that leptin negatively regulates bone mass through the sympathetic nervous system to inhibit osteoblast proliferation (165). In contrast, re-evaluation of the *Ob/Ob* and *Db/Db* models indicate that leptin positively impacts bone mass with variations according to the skeleton site (i.e. long bones versus vertebrae) and the bone region (i.e. trabecular or cortical site) (158, 166). Furthermore, peripheral as well as central leptin administration enhances bone formation by increasing both the number and activity of osteoblasts (1, 158). Concomitantly to trabecular bone reduction, an increase in BMA density is found in the long bones of *Ob/Ob* (166) and *Db/Db* mice (164) while BM adiposity is unchanged in lumbar vertebrae. Subcutaneous leptin administration in *Ob/Ob* mice lowers the number of BMA and improves bone formation (167). Most *in vitro* studies support that leptin favours osteogenesis over adipogenesis as exemplified in (161). However, the lineage commitments of murine BM-MSC harbouring different disruptions in leptin signalling are quite variable (162). Characterization of the model with *Lepr* deletion specifically in BM-MSC has recently challenged this view. The study supports that leptin directly acts on MSC to inhibit osteogenesis and to drive adipogenesis in normal conditions and during high-fat diet; nevertheless, LEPR signalling seems unnecessary for irradiation-induced adipogenesis (160). Besides partly explaining the regional impact of leptin signalling, the study provides interesting clues regarding the disconnected effect of leptin administration on decreasing BM adiposity with no change in osteoblast number as observed during immobilization (168) or calorie restriction (169). Importantly, it highlights how permissive the pathophysiological context is for leptin impact on BMA adiposity.

Adiponectin, whose plasma levels vary in the opposite of leptin ones, has obviously focused a lot of attention. Adiponectinemia can be found inversely correlated with BMD at different bone sites in anorexia nervosa (170), post-menopausal women and men (171) and in type 2 diabetes (172). Adiponectin actions on bone mass are centrally mediated or direct since osteoblastic and osteoclastic cells express the receptor ADIPOR1 (2). Various murine models have been investigated with very inconsistent outcomes regarding bone mass as reviewed in (2). Briefly, adiponectin decreases bone resorption through both central and peripheral mechanisms (173). Bone formation can be stimulated when adiponectin acts centrally to reduce the sympathetic tone (174) and inhibited when adiponectin directly targets osteoblasts (173) with an age-dependent partitioning of these opposite pathways (174). To further illustrate the complexity, either adiponectin overexpression (175) or deletion (174) results in the increase of BM adiposity. *In vitro* studies confuse the issue since the adipokine is reported to prevent adipogenesis (176) and to favour osteoblast differentiation (177) of murine BM-MSC. Altogether data are thus difficult to reconcile. One may speculate that, as supported for leptin action and in (173), the pathophysiological conditions determine adiponectin targets and actions. The adiponectinaemia rise induced by calorie restriction has indeed been shown to be triggered by BMA to contribute to the metabolic adaptation of skeletal muscle (88).

Finally, fibroblast growth factor 21 (FGF21), which is mainly a hepatokine but can also be released by adipose tissue, has also recently been identified as a negative bone regulator by inhibiting osteoblastogenesis and stimulating adipogenesis in murine BM-MSC (178).

Conclusions and perspectives

BM-MSC commitment toward adipogenesis or osteoblastogenesis results from a complex interplay of both local and systemic factors. In most states with uncoupled bone remodelling and osteoporosis, BM adipogenesis is stimulated while osteoblastogenesis is impaired (Fig. 1). Though the two processes can independently be modulated (e.g. growth versus ageing, glucocorticoid excess (179), leptin impact (160)), much attention has been brought to the relationship of BMA with impaired bone formation. Yet, activation of the resorption process itself can promote BM adipogenesis (180) and anti-resorptive (181) treatment can reverse

BM adiposity in post-menopausal women. In line with their RANKL production (66, 67), BMA may thus play an unexpected and yet relevant role in the unbalanced bone remodelling by disrupting the osteoclast–osteoblast tandem classically considered in the resorption process regulation. This additional level of BMA involvement in bone metabolism through resorption definitively deserves further investigations and could clarify the independent modulation sometimes observed between osteoblastogenesis and adipogenesis.

Latest studies highlight the BMA heterogeneity, which is greater than previously anticipated notably regarding its location in either skeleton site (appendicular versus axial) or bone region (trabecular versus cortical). However, BM fat measurements in clinical studies remain mostly performed in the lumbar vertebrae (32, 33, 45, 58, 62). Discrepancies between fundamental and clinical studies as exemplified in the obesity situation could be unravelled by further examination of other relevant skeleton sites. Fracture sites in obesity and type 2 diabetes can actually differ from the primary osteoporosis typical ones (5, 6) and clinical analysis of BM adiposity at these specific sites could better define if the BMA component is involved in these metabolic situations as recently exemplified (63).

Moreover, BMA development and properties also vary according to the pathophysiological context. Ageing, which exacerbates ovariectomy (130) or high-fat feeding (61) effects, is most likely a determinant context that encompasses a functional decline of BM-MSC (179, 61) and an array of dysregulated mediators. Besides, BMA secretions could interfere with bone remodelling in a regulated manner (66, 67) (Fig. 1). Thus, as initially proposed (10), the BMA are most likely highly regulated cells whose phenotype and function should be considered according to each analysed pathophysiological condition and carefully extrapolated. With more investigations on these important issues, BM adiposity could become a reliable indicator of bone integrity in the management of osteoporosis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

T R and S L contributed to the design of the review, critically revised it, approved the final version to be published and agreed to be accountable for all aspects of the work. S L made the figure.

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