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BONE MARROW AND ADIPOSE TISSUE (B LECKA-CZERNIK AND G DUQUE, SECTION EDITORS)

Osteoporosis and Bone Marrow Adipose Tissue

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Abstract

Purpose of Review This review focuses on the recent findings regarding bone marrow adipose tissue (BMAT) concerning bone health. We summarize the variations in BMAT in relation to age, sex, and skeletal sites, and provide an update on noninvasive imaging techniques to quantify human BMAT. Next, we discuss the role of BMAT in patients with osteoporosis and interventions that affect BMAT.

Recent Findings There are wide individual variations with region-specific fluctuation and age- and gender-specific differences in BMAT content and composition. The Bone Marrow Adiposity Society (BMAS) recommendations aim to standardize imaging protocols to increase comparability across studies and sites. Water-fat imaging (WFI) seems an accurate and efficient alternative for spectroscopy (^{1}H-MRS). Most studies indicate that greater BMAT is associated with lower bone mineral density (BMD) and a higher prevalence of vertebral fractures. The proton density fat fraction (PDFF) and changes in lipid composition have been associated with an increased risk of fractures independently of BMD. Therefore, PDFF and lipid composition could potentially be future imaging biomarkers for assessing fracture risk. Evidence of the inhibitory effect of osteoporosis treatments on BMAT is still limited to a few randomized controlled trials. Moreover, results from the FRAME biopsy sub-study highlight contradictory findings on the effect of the sclerostin antibody romosozumab on BMAT.

Summary Further understanding of the role(s) of BMAT will provide insight into the pathogenesis of osteoporosis and may lead to targeted preventive and therapeutic strategies.

Keywords Osteoporosis · Bone marrow adipose tissue · Lipid composition · Imaging · Fractures · Bone mineral density · Clinical trials

Abbreviations

BMAT	bone marrow adipose tissue
BMSCs	bone marrow stromal cells
BMAds	bone marrow adipocytes
^{18}F FDG-PET	positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose
MRI	magnetic resonance imaging
^{1}H-MRS	proton magnetic resonance spectroscopy
WFI	water-fat imaging
BMAS	international bone marrow adiposity society
DXA	dual-energy X-ray absorptiometry
BMD	bone mineral density

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BMAd.Dm	bone marrow adipocyte diameter
CT	computed tomography
CSE-WFI	chemical shift encoding-based water-fat imaging
BMFF	bone marrow fat fraction
SFF	signal fat fraction
PDFF	proton density fat fraction
PRESS	point-resolved spectroscopy
STEAM	stimulated echo acquisition mode
DECT	dual energy computed tomography
SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue
ZOL	zoledronic acid
RCT	randomized clinical trial
Ad.V/TV	adipose tissue volume/total tissue volume
N.Ad/Ma.Ar	adipocyte number
PPARγ2	peroxisome proliferator-activated receptor γ2 gene

Introduction

Bone marrow adipose tissue (BMAT) is localized in the bone cavity as part of the bone marrow (BM). It derives from bone marrow stromal cells (BMSCs) capable of differentiation into different cell types, including bone marrow adipocytes (BMAds). The presence and distribution of BMAT through the skeleton changes during aging, starting with red BM filled with mostly hematopoietic cells at birth, which in adulthood are replaced by yellow BM filled with BMAds in distal parts of the appendicular skeleton [1, 2], accounting for approximately 70% of BM volume. BMAT is unique because it is the only tissue where adipocytes and bone cells are juxtaposed. Recent animal studies demonstrated the presence of two types of BMAds: "regulated" BMAds interspersed in proximal and axial parts of the skeleton and "constitutive" BMAds predominately present in the distal part of the skeleton. Regulated and constitutive BMAds show different metabolic activity in rodents [3]. However, their presence in humans still requires further investigation.

Over the last decade, increased interest in human BMAT has led to several important findings. Human BMAT shares some characteristics with peripheral white adipose tissue (e.g., unilocular lipid droplets, adipokine secretion, insulin signaling etc.). At the same time, it manifests several different molecular characteristics in terms of lipid composition, lipid handling and responsiveness to metabolic stimuli [4•, 5••, 6••]. Attané et al. [5••] reported that human BMAds and peripheral adipocytes differ in proteins involved in cholesterol metabolism and lipolysis, suggesting the contribution of different lipid species in regulating BMSC differentiation. In addition, using positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F FDG-PET) scanning, Suchacki et al. [6••] demonstrated that human BMAT is functionally distinct from brown adipose tissue with higher basal glucose uptake but no response to insulin. Further, BMAT can contribute to circulating levels of adiponectin under caloric restriction and can secrete other bioactive molecules (e.g., dipeptidyl peptidase-4, lipocalin-2), which may have systemic effects on whole-body metabolism [4•]. However, more clinical studies are needed to decipher the direct role of BMAT in the regulation of whole-body metabolism in humans.

Examining and understanding the connection between BMAT and bone health has recently emerged as an exciting area of research. This was made possible by the development of BMAT imaging. Magnetic resonance imaging (MRI) is considered the reference noninvasive imaging modality to quantify in vivo BMAT in humans [7••, 8•]. Although proton magnetic resonance spectroscopy (^{1}H-MRS) has long been considered the gold standard, water-fat imaging (WFI) seems an efficient alternative. The recent International Bone Marrow Adiposity Society (BMAS, https://bma-society.org) recommendations aim to standardize imaging protocols in order to increase comparability across studies and different sites [7••, 8•]. Using MRI in combination with dual-energy X-ray absorptiometry (DXA), several studies indicate that greater BMAT is associated with lower bone mineral density (BMD) and a higher prevalence of vertebral fractures [9]. Prospective data on lipid composition and bone health, including BMD and fracture outcomes, are now available [10•, 11]. It is now well established that several osteoporosis treatments and non-pharmacological interventions decrease BMAT and increase BMD [9]. However, the influence of diet and exercise on BMAT has remained unclear, and the effect of the sclerostin antibody romosozumab on human BMAT is still unknown.

This review focuses on the recent findings available to medical bone specialists regarding BMAT and bone health. This review has been divided into four parts. The first part deals with BMAT variations with age, sex, and skeletal sites. The second part of this paper provides an update on BMAT imaging modalities in humans. The third part focuses on the usefulness/importance of BMAT assessment in patients with osteoporosis. The fourth part presents the three critical interventions that impact BMAT: diet, exercise, and osteoporosis treatments.

BMAT Variations with Age, Sex, and Skeletal Sites

In humans, BMAT represents approximately 10% of total body fat mass [4•]. Kugel et al. reported an age-related increase in vertebral BMAT in both males and females, with males having approximately 6–10% more BMAT than females of comparable age between the ages of 20 and 60 years

[12]. Thereafter (i.e., in the years following menopause), vertebral BMAT increases sharply in females [13]. In males, vertebral BMAT rose gradually throughout life. Vertebral BMAT in females over 60 years of age is approximately 10% higher than in males, pointing to a reversal of the sex difference in BMAT reported in subjects aged less than 60 years. However, there are wide individual variations with region-specific fluctuation and age- and gender-specific differences in BMAT [14–16]. In a cross-sectional study involving 40 healthy adults (26 male and 14 female), Beekman et al. reported distinct, age- and gender-dependent distribution of BMAT throughout the human skeleton in different sites (tibia, femur, pelvis, spine) using WFI [14]. BMAT increases from spine to tibia, from the cervical to the lumbar spine, and from proximal to distal in femora, while it shows a small but significant decrease within the tibia. These detailed analyses revealed that in women BMAT was positively correlated with age in the spine, pelvis, and proximal femur, while in men only in the spine [14]. In a seminal paper published in 2007 by Hwang S et al., a complete MRI study of marrow adipose tissue distribution in entire human skeleton as a function of age was performed [15]. The normal distribution of red and yellow marrow in the skeleton changes with age in a predictable sequence: red marrow converts to yellow marrow from the peripheral to the central skeleton and superimposed on that sequence, red marrow converts to yellow proceeding from diaphysis to metaphysis in long bones [15]. Up to now, far too little attention has been paid to BMAT assessment in other skeletal sites besides the lumbar spine, and prospective studies examining BMAT variations with age, sex and skeletal sites are still lacking.

BMAT Quantification in Humans

Histology of BMAT

Historically, histology represents the main tool for evaluating bone/BM and histomorphometry a key methodology for bone and BMAT analysis in clinical settings [7••, 17••]. BMAT and BMAds can be evaluated on decalcified sections from paraffin-embedded BM biopsies that offer the advantage of access to retrospective collections, especially in the clinical setting where this procedure is the standard [8•, 18]. Paraffin-embedded samples can be used for immunohistochemistry and BMAT histomorphometry according to standard procedures and nomenclature [7••, 17••, 18]. However, the integrity of the BM is not always optimal. Embedding procedures that do not require decalcification (e.g., methacrylate embedding media) can also be used, particularly for transiliac bone biopsy when bone histomorphometry is needed [19]. Even though in hard plastic-embedded samples immunohistochemistry is a challenge, distortion and shrinking up of the tissues are less than in decalcified paraffin-embedded samples [7••]. Of note, as both paraffin- and methacrylate-based embedding procedures dissolve the lipids within the vacuole, BMAds (as the adipocytes of the peripheral white adipose tissue) appear as "ghosts" making possible, on histological sections, quantitation studies but not in-depth morphological analysis of lipid droplets and their lipid content and composition. To stain lipids in BMAds (and potentially in other marrow cells that may contain lipids), Oil red O-, Sudan black- or Nile blue sulfate-stained cryosections or marrow smears should be used [20]. Examples of histological images of bone/BM are shown in Fig. 1.

Compared to other human fat depots, BMAds are not organized in lobules. Thirty to 70% of the area of a histologic section of hematopoietic marrow obtained at the iliac crest of a healthy adult consists of BMAT, and the mean diameter of BMAds (BMAd.Dm) is around 50 μm, which is lower compared to that of subcutaneous or visceral adipocytes [21]. As in white adipose tissue, BMAds show a single centrally located large fat vacuole and a narrow rim of cytoplasm containing a flattened nucleus, ribosomes, strands of endoplasmic reticulum, and several mitochondria and are in intimate contact with vascular channels, macrophages and stromal, osteogenic and hematopoietic cells [1, 7••, 18, 21]. Even though histology and histomorphometry are the gold standards for evaluating BMAT, BM and bone biopsies are painful and invasive procedures that bring patients discomfort. Therefore, the recent advances in noninvasive imaging techniques and the demonstration of the high concordance between them and histology in the quantification of BMAT [22] overcome these limitations and contribute significantly to the progress in translational and clinical studies.

Noninvasive Quantification of BMAT

In humans, different imaging modalities [MRI- or computed tomography (CT)-based techniques] can be used to quantify BMAT (i.e., the "generic term" BM fat fraction, BMFF as a %) in vivo. Accurate, standardized methods to quantify BMAT are necessary to evaluate the clinical implications of BMAT, and knowledge of the differences between methods is essential for inter-study comparison [7••]. The advantages and disadvantages of the different techniques are described below, and summarized in Table 1.

BMAT can be quantified non-invasively with MRI methods like WFI also called chemical shift encoding-based WFI (CSE-WFI) and ^{1}H-MRS.

– The MRI technique WFI uses the signal of hydrogen atoms, containing one single proton (^{1}H) in its nucleus, to create an image. The signal emitted by hydrogen atoms differs, depending on the physical surrounding of the hydrogen atoms, like in water or fat. The different signals

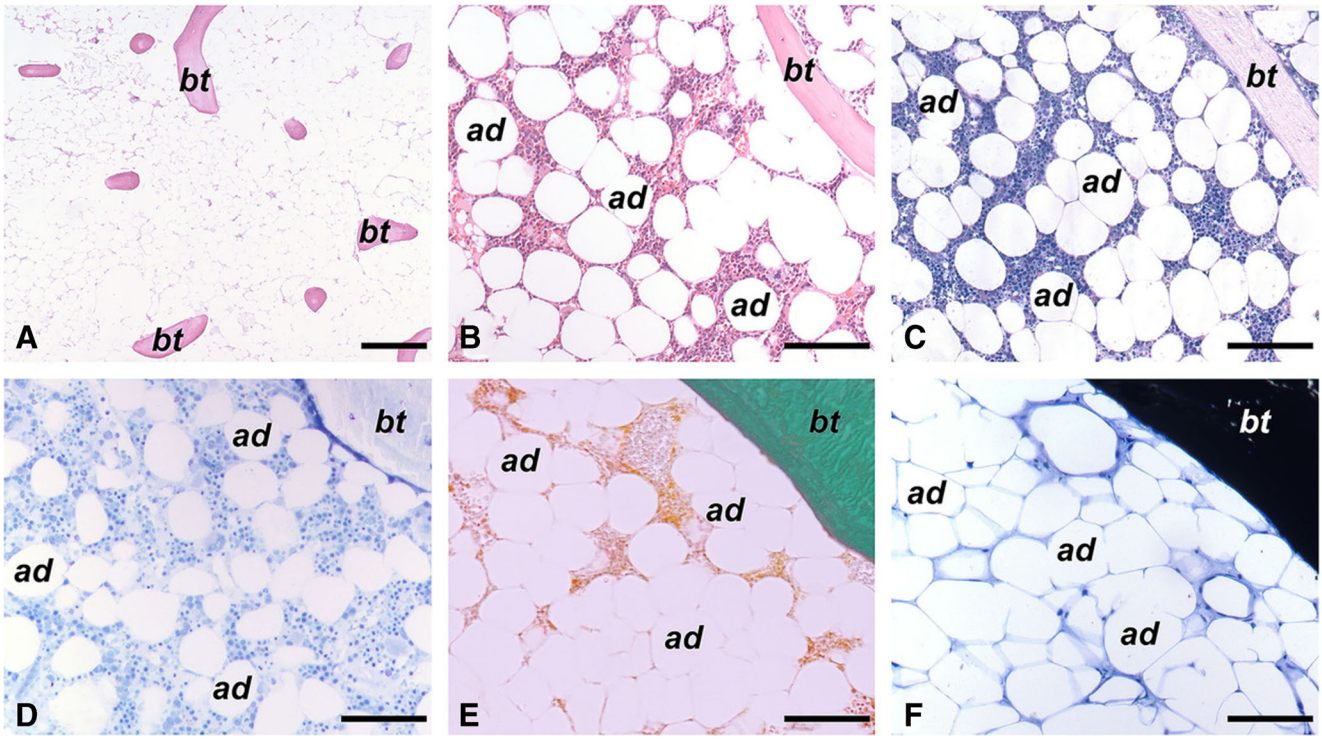

Fig. 1 Histological view of human bone/BM as viewed in decalcified paraffin-embedded (**A** and **B**) and in undecalcified plastic-embedded (**C**–**F**) samples. As both embedding methods dissolve the lipids, the BMAds (ad) appear as "ghosts" [7••] within the marrow spaces. Panel A shows a haematoxylin-eosin stained section of osteoporotic bone. The cancellous bone volume and the connectivity of the bone trabeculae are extremely reduced and the marrow spaces are extensively occupied by adipose tissue. Panels **B**-**F** illustrates the bone/BM organ as viewed after staining with haematoxylin-eosin (**B**), May-Grünwald-Giemsa (**C**), azure II-methylene blue (**D**), Goldner's trichrome (**E**) and von Kossa (**F**, counterstained with methylene blue). The last three stains are commonly used for the qualitative and quantitative histological evaluation of bone tissue and can be also used for the *in situ* assessment of BMAT and BMAds. Bars: 250 μm in A and 100 μm in B-F; *bt*: bone trabecula; *ad*: BMAd

from hydrogen atoms in water and fat can be used to calculate Signal Fat Fraction (SFF as a %), which is a "generic term" specific to MRI techniques. After correcting this SFF for confounding factors like T2* decay, T1 bias, and the multiple peaks of the fat spectrum, the proton density fat fraction (PDFF) can be derived, i.e., the ratio of the unconfounded fat signal to the sum of the unconfounded fat and water signals [7••]. PDFF is more stable over scanners and sites [7••, 23–25]. A disadvantage of PDFF is that correction for the abovementioned confounding factors makes the algorithm to calculate the PDFF substantially more complicated. Furthermore, it is possible to characterize the triglyceride composition of BMAT (i.e., number of double bonds with WFI) to assess the degree of lipid saturation/unsaturation of BMAT [14, 26]. Commercially available sequences for quantifying

Table 1 Advantages and disadvantages of imaging methods used to assess BMAT

Method	Advantages	Disadvantages
CSE-WFI	Quantification of BMFF or PDFF in large parts of the skeleton, vendor specific PDFF quantification methods available for liver fat quantification can be applied for BMAT PDFF measurements	Standardization of methods is lacking
^{1}H- MRS	Quantification of BMFF or PDFF and bone marrow fatty acid composition, upcoming standardization of post-processing of the acquired spectra	Relatively small sampling area, relatively time consuming
DECT	Quantification of BMFF and BMD simultaneously, able to correct for underestimation of BMD due to BMAT	Radiation exposure, less suitable for younger subjects
^{18}F FDG PET	Able to assess metabolic activity of the bone marrow, potentially combined with CT or MRI	Radiation exposure, less suitable for younger subjects

Abbreviations: *^{1}H-MRS* proton magnetic resonance spectroscopy; *CSE-WFI* Chemical shift encoding-based water-fat imaging; *DECT* dual-energy computed tomography; *^{18}F FDG-PET* positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose; *BMAT* bone marrow adipose tissue; *BMFF* bone marrow fat fraction; *PDFF* proton density fat fraction; *BMD bone mineral density*

the PDFF have been developed for the liver, and these sequences can also be used to quantify the PDFF within the BM [7••].

– ^{1}H-MRS can be used to quantify the BMFF, the PDFF and the amount of saturated and unsaturated fatty acids within the BM. With single voxel spectroscopy, a voxel is placed on the area of interest and a spectrum is measured showing the difference in resonance frequencies of hydrogen atoms in water, saturated and unsaturated fatty acids. Fat fractions can be calculated by quantifying the area under the different fat and water peaks, and the amount of unsaturated fatty acids, expressed as the unsaturation index, can be determined. As with WFI, biases need to be considered during post-processing to derive the PDFF. The unsaturated lipid peaks can be challenging to discriminate from the spectrum, especially when using a 1.5T scanner [11]. Two spectroscopy methods commonly used are point-resolved spectroscopy (PRESS) and stimulated echo acquisition mode (STEAM). STEAM is potentially more accurate in quantifying the PDFF [25] and shows more reproducible unsaturation measurements [27]. Disadvantages of this technique are the small sampling area, the relatively long scanning times, and the expertise required to post-process the acquired spectra [28•]. Recently Karampinos et al. have optimized their Matlab script [29, 30] for the accurate quantification of the PDFF using ^{1}H-MRS, and released a new version called ALFONSO [www.github.com/BMRRgroup/alfonso, [31••] that could greatly improve standardization of PDFF quantified using ^{1}H-MRS.

Dual-energy CT (DECT) can be used to quantify BMAT (the "generic term" BMFF) and BMD at the same time [32, 33]. The different attenuation of fat and water at the different energies used for scanning can be used to determine the BMFF. Furthermore, DECT can be used to correct for the underestimation of BMD measurements caused by BMAT [34], which is especially interesting when evaluating treatments that affect both BMD and BMAT. Exposure to ionizing radiation makes this method less suitable for repeated quantification of BMAT, especially in younger subjects.

^{18}F FDG-PET can be used to assess the metabolic activity of BM as it assesses glycolytic activity. Mostly, a (low dose) CT scan is acquired simultaneously with FDG-PET for attenuation correction, which also allows for quantification of BMD besides the metabolic activity of the marrow area. Low metabolic activity of the lumbar spine BM is associated with low BMD [35]. ^{18}F FDG-PET can also be acquired in combination with MRI, in which case PDFF could be obtained besides the metabolic activity of the BM. As with DECT, the exposure to ionizing radiation makes ^{18}F FDG-PET less suitable for evaluating BMAT in younger subjects.

Although a large amount of research has been carried out on BMAT imaging in humans, there is a need to standardize imaging protocols in order to increase comparability across studies and different skeletal sites. With this goal in mind, BMAS recommendations should be followed [7••, 8•]. A multi-center study on BMAT imaging in humans is currently not available.

Osteoporosis and BMAT Changes

MRI has been used to demonstrate the well-documented inverse association between SFF/PDFF and BMD. Several cross-sectional studies have applied ^{1}H-MRS and/or WFI for measuring the PDFF at the lumbar spine; fewer have investigated the proximal femur. Sollmann et al. recently reviewed the current literature on quantitative MRI methods and related findings in osteoporosis at the lumbar spine and proximal femur from a methodological and clinical perspective [28•]. An example of a SFF map of the lumbar spine of postmenopausal women with and without osteoporosis is shown in Fig. 2. In a study including 50 postmenopausal women (mean age: 70 years; 15 with normal BMD, 15 with osteopenia, 20 with osteoporosis) and 12 young women as control subjects (mean age: 28 years), Yeung et al. observed that PDFF measured with ^{1}H-MRS at the spine was significantly elevated in osteoporotic and osteopenic subjects compared to normal subjects and young controls. Moreover, the fat unsaturation index was significantly lower in osteoporotic and osteopenic subjects compared to normal subjects and young controls, and an inverse correlation was observed between the PDFF and the unsaturation index (r=−0.53, P< 0.0001) [36].

Quantitative CT measurements of bone (spine and hip) can provide insights into the aspects of bone that are associated with BMAT. In the Iceland AGES-Reykjavik cohort, higher PDFF was found to be associated with lower trabecular spine, total hip and femoral neck—but not cortical-volumetric BMD (vBMD) in older women. In men, there were no statistically significant associations between PDFF and vBMD (both trabecular and cortical) either at spine, total hip or femoral neck [37]. The largest longitudinal analysis of the relationship between BMAT and change over time in BMD has been published by Woods *et al.* in 2020 [11]. The authors found that each 1 SD increase in baseline PDFF was associated with a 0.9 mg/cm^3/year greater loss of spine trabecular BMD (p=0.02), and a 1.2 mg/cm^3/year greater loss of femoral neck trabecular BMD (p=0.02) in women. Among men, there were no associations between PDFF and changes in BMD over time. More recently, Woods et al. showed that greater BM unsaturated lipid content was associated with greater trabecular BMD [10•].

Clinical studies indicate that greater BMAT is associated with a higher prevalence of vertebral fractures [18, 37, 38]. In

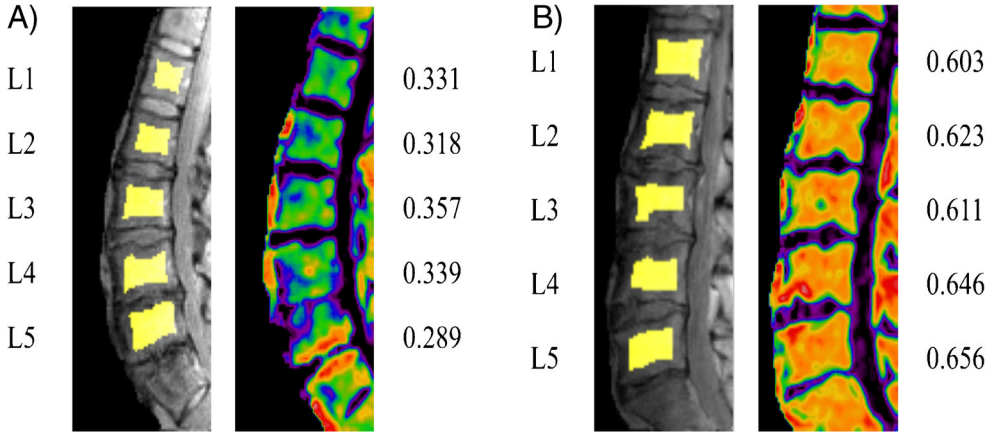

Fig. 2 Chemical shift encoding-based water-fat imaging (CSE-WFI), showing sagittal images with the regions of interest and fat signal fraction map (SFF) of the lumbar spine of **A** a 52 year old postmenopausal female with low bone marrow adipose tissue (BMAT): SFF = 32.7% and normal bone mineral density (BMD quantified by quantitative CT): 129.1 mg/cm^3 (normal BMD > 120 mg/cm^3) and **B** a 60-year-old postmenopausal female with high BMAT: SFF = 62.8% and low BMD 69.2 mg/cm^3 (osteoporotic range BMD < 80 mg/cm^3). CSE-WFI courtesy of E.M. Akkerman - Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands

bone biopsies of postmenopausal women, patients with vertebral fractures had higher BMAT than subjects without fractures, with similar bone volume [18]. Recently, Gassert et al. showed that PDFF quantified using CSE-WFI can differentiate between osteoporotic/osteopenic patients with and without vertebral fractures [38]. Furthermore, BMAT composition seems to be associated with fracture risk [10, 39]. Patsch et al. showed for the first time that prevalent fragility fractures in postmenopausal women were associated with −1.7% (95% CI, −2.8 to -0.5%) lower unsaturation levels and +2.9% (95% CI, 0.5 to 5.3%) higher saturation levels quantified using ^{1}H-MRS at the lumbar spine [39]. Recently, Woods et al. showed that greater BM saturated lipid content was associated with higher odds of both prevalent and incident vertebral fractures, this association did not significantly alter after adjustment for lumbar spine BMD, and BM unsaturated lipid content was associated with a lower risk of incident radiographic vertebral fractures after adjustment for lumbar spine BMD [10•]. This could indicate that, if PDFF and lipid composition are associated with an increased risk of fractures independently of BMD, PDFF, and lipid composition could potentially be future imaging biomarkers for assessing fracture risk.

The reader of this review should bear in mind that most of the current knowledge on BMAT and bone health is based on the Iceland AGES-Reykjavik cohort. There is still a need to confirm their findings in other cohorts. Moreover, much of the research up to now has been focused on BMAT assessment at the lumbar spine. Future studies should also report measurements of PDFF and lipid composition at the proximal femur or other anatomical sites of clinical significance. Finally, imaging in humans examining the relationship between BMAT and bone health is exciting, but the usefulness for clinicians in the day-to-day management of patients with osteoporosis is still far.

Interventions to Modulate BMAT

Dietary Intervention

BMAT and its relevance to bone health during dietary interventions remain largely unknown. Cordes et al. did not find a change in BMFF of L5 using ^{1}H-MRS in 20 obese postmenopausal women after a 4-week calorie restriction (800 kcal per day; mean weight loss of 7%), although a decrease was observed in other fat depots [40].

Fazeli et al. have recently demonstrated in 23 healthy volunteers that the BMFF of L4 increased during short-term high-calorie feeding and fasting [41••]. Data on lipid composition showed a significant increase in the BMAT saturation index of L4 during high caloric feeding. During fasting, there were opposite changes in the axial and peripheral skeleton. The BMAT saturation index of L4 increased, while the femoral BMAT saturation and unsaturation index decreased, and the tibial BMAT unsaturation index decreased [42••].

Exercise

Interestingly, bone response to exercise includes changes in BMAT, which may contribute to the beneficial effect of exercise on BMD [43]. Bertheau et al. reported in a population-based study that at least 2 h of physical activity per week was required to reduce the BMFF [44]. Physical activity seems to affect BMAT preferentially at the spine in contrast to the proximal femur. Belavy et al. studied the effect of aerobic and resistance exercises, targeting major muscle groups on back pain reduction and lumbar BMAT in a 6-month single-blinded randomized controlled trial in 40 patients (men and women) with back pain [45]. This trial provided the first prospective evidence in humans that a

moderate exercise intervention may modulate lumbar spine SFF at 3 months but not at 6 months. The effect of exercise on SFF may be more prominent in males than females [45].

BMAT Variations with Osteoporosis Treatments

Due to the variable characteristics of BMAT based on location, metabolic activity, lipotoxic effect or response to hormones and growth factors, targeting this tissue as a therapeutic approach to osteoporosis with active pharmacological compounds has been challenging [46]. Nevertheless, several clinical trials have tested the effect of a number of compounds, demonstrating a therapeutic effect on one or some components of BM and bone structure. Overall, those therapeutic approaches have been aimed at some of the following objectives [46, 47]:

1. A reduction in fat volumes (i.e., adipocyte number, diameter, etc.) within the BM, which is expected to favor an increase in bone volumes and improvement in bone quality;
2. A predominant differentiation of BMSCs into osteoblasts at the expense of adipocytes;
3. Reducing the local lipotoxic effect of BMAT would reduce osteoclastic activity and facilitate bone homeostasis, while improving its positive impact on energy metabolism.

Although some of the new noninvasive techniques described in a previous section of this review offer unique opportunities to accurately measure these effects, testing these therapeutic effects in humans is particularly challenging. Here we will summarize the very few clinical trials that have tested the effect of several compounds on BMAT, including their effect on BMD and/or quality.

Teriparatide Teriparatide, also known as 1-34 parathyroid hormone, is commonly used to treat osteoporosis in postmenopausal women. In vitro and in vivo studies have suggested an inhibitory effect of teriparatide on adipogenesis [48–50]. With this effect in mind, Yang et al. [51] tested the effect of the usual anabolic dose of teriparatide (20μg/d subcutaneously) on BMFF, subcutaneous (SAT), and visceral adipose tissue (VAT) of postmenopausal osteopenic women (n= 135; mean age 64.1 ± 8.9 years) randomly assigned to receive teriparatide or placebo for 12 months. In addition to the already reported bone anabolic effect, the treatment group showed a reduced PDFF (–3.5% at 6 months; –5.9% at 12 months, all $p < 0.01$). PDFF was negatively associated with SAT (r = –0.479) and positively associated with VAT (r = 0.531) and VAT/SAT (r = 0.415, all $p < 0.05$). Overall, although the anabolic effect of teriparatide on bone has been usually associated with an increase in osteoblastogenesis, this clinical trial provides novel data supporting an additional effect of teriparatide on BMAT in humans, which seems to be specific to BM. Further studies on osteoporotic subjects with higher BMAT are still indicated.

Zoledronic Acid (ZOL) In two BMAT animal models, administering ZOL, a potent anti-resorptive, has reduced BMAT volumes. This has been observed in animal models with high levels of BMAT, such as ovariectomized rats [52] and methylprednisolone-treated rabbits [53]. In humans, only one randomized clinical trial (RCT) has been conducted in 100 postmenopausal women with osteoporosis who were randomly given either a single dose of ZOL (5 mg) or placebo [54]. Main outcome measures included BMD by DXA, vertebral PDFF by ^{1}H-MRS, and bone turnover markers. Twelve months post-treatment, PDFF was reduced by 8.1% in the ZOL-treated women and increased by 3.0% in the controls (all $p < 0.05$). Considering that, as in previous RCTs testing the effect of ZOL on BMD, ZOL-treated patients did not show a marked increase in BMD (2.8, 2.0, and 1.7% in the lumbar spine, femoral neck, and total hip), thus suggesting that the observed effect on PDFF could be an additional beneficial effect of ZOL on bone, which deserves further investigation.

Estrogens Estrogens have been reported as strong regulators of adipogenesis both in vitro and in vivo [55], with postmenopausal women showing higher BMAT [56, 57]. Limonard et al. [57] measured spine BMFF every week for 6 consecutive weeks in 6 postmenopausal women before, during, and after 2 weeks of oral 17-β estradiol treatment (2 mg/day). BMFF decreased by 0.05 (95% CI, 0.01 to 0.09) from 0.48 (95% CI, 0.42 to 0.53) to 0.43 (95% CI, 0.34 to 0.51) during 17-β estradiol administration ($p < 0.001$) and increased again after cessation. Although limited by a small sample size, this study concludes that 17-β estradiol regulates BMAT, and this effect seems independent of bone mass. In another study performed by Syed et al., paired bone biopsies were obtained from a subset of postmenopausal osteoporotic women at baseline and after treatment with placebo (n=27) or estrogen (n=29) for 1 year [58]. Bone marrow adipose tissue parameters (adipocyte volume/tissue volume, adipocyte number, and adipocyte perimeter) increased significantly in the placebo group whereas estogen therapy was able to either prevent or even reverse these changes [58].

Raloxifene Raloxifene, a selective estrogen receptor modulator, is used as a treatment for postmenopausal osteoporosis due to its moderate effect on bone turnover, primarily via the regulation of osteoclastogenesis and osteoclastic activity. To determine whether raloxifene also affects BMAT, Beekman et al. [19] analyzed bone biopsies from the MORE trial (baseline and after 2 years of treatment; n=53; age 68.2 ± 6.2 years), which originally investigated the effects of raloxifene 60 or

120 mg per day versus placebo on bone metabolism and fracture incidence in patients with postmenopausal osteoporosis. Although the authors found that high BMAT volume and larger adipocyte size were associated with prevalent vertebral fractures, raloxifene did not affect BMAT and instead tended to increase adipocytes number compared to placebo.

Oral Bisphosphonates In vitro and in vivo studies have demonstrated an inhibitory effect of oral bisphosphonates risedronate [59] and alendronate [60] on adipogenesis. To our knowledge, no RCTs have tested the effect of alendronate on BMAT. Regarding risedronate, Duque et al. [61] analyzed trans-iliac bone biopsies from the VERT study, a randomized, placebo-controlled clinical trial that evaluated the effects of risedronate treatment 5 mg/day on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis. Paired bone biopsies were obtained from a subset of patients at baseline and after treatment with placebo or risedronate for 3 years (n = 14 per group) (Fig. 3). In the placebo group, adipose tissue volume/total tissue volume (Ad.V/TV), number (N.Ad/Ma.Ar) and diameter (Ad.Dm) of adipocytes significantly increased after 3 years (~15%, $p < 0.01$). In contrast, Ad.Dm unchanged, and Ad.V/TV and N.Ad/Ma.Ar significantly reduced (~20%) in the risedronate group at 3 years ($p < 0.01$). These changes were associated with a significant reduction in Peroxisome proliferator-activated receptor γ2 (PPARγ2) expression in the BM of risedronate-treated women. These results suggest that, additionally to the strong direct inhibitory effect of risedronate on osteoclasts, an inhibitory effect on BMAT was also observed. However, further studies are needed to explore whether this effect impacts lipotoxicity or the metabolic activity of BMAT.

Sclerostin Antibody Romosozumab Testing the effect of sclerostin-neutralizing antibody (3 mg/kg or 50 mg/kg, weekly) on BMAT of 8-week-old male and female rats was mainly associated with a decrease in total tissue adiposity by "increasing trabecular bone, resulting in an overall reduction in the space in which adipocytes can reside" [62]. Surprisingly, in the FRAME biopsy sub-study in patients receiving romosozumab or placebo, no significant difference in total adipocyte volume, number or density between placebo and romosozumab groups was observed at months 2 and 12 [63]. Moreover, no relationship between Ad.V/TV and the bone formation rate could be evidenced, and romosozumab did not modify the size or shape of the BMAds after 2 or 12 months. These findings suggest that the modeling-based formation observed at month 2 resulted from a reactivation of bone lining cells rather than a preferential commitment of the precursors to osteogenic over adipogenic cell lineages [63].

In summary, evidence of the inhibitory effect of osteoporosis treatments on BMAT is still limited to a few RCTs. The main remaining question is whether, as in the teriparatide study reported above, the reduction in BMAT observed in the treated groups is due mainly to a reduction in the space in which BMAds can reside. However, although this is plausible in teriparatide-treated subjects, it is a less likely observation in humans treated with anti-resorptives where the gain in BMD is insufficient to explain this space occupying mechanism, thus suggesting that there is an additional beneficial effect from inhibiting BMAT that requires further investigation. Very recently, results from the FRAME biopsy sub-study highlight contradictory findings about romosozumab effect on BMAT between humans and animals [62, 63]. In addition, it is still unknown whether denosumab has an impact on BMAT. With the development of more accurate techniques to non-invasively quantify and characterize BMAT in humans, future larger clinical trials are warranted.

Conclusion

Thanks to the development of noninvasive techniques to quantify and characterize BMAT in humans, examining and

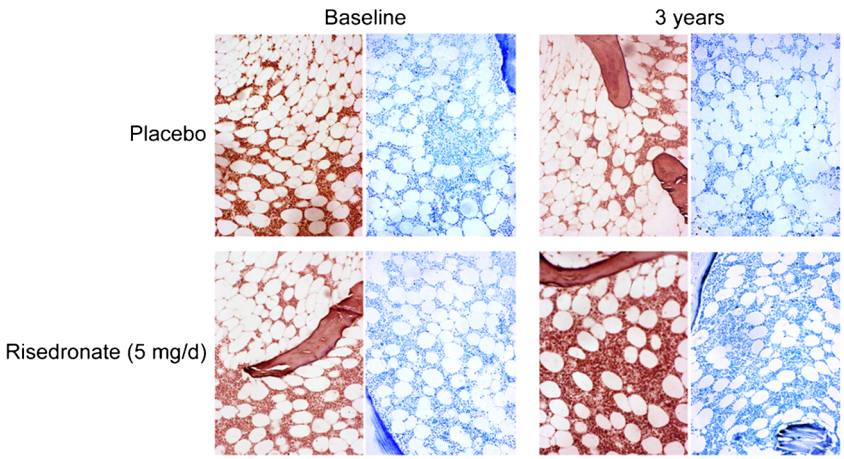

Fig. 3 Representative serial sections of hematoxylin/eosin (left panels) and toluidine blue (right panels) from a patient either on placebo or on risedronate at the start (baseline) and end of treatment (3 years). Photomicrographs taken at ×40 magnification

understanding the connection between BMAT and skeletal health remains an exciting area of research. However, there is still a need to define the normal physiological values of BMAT and to increase functional understanding in relation to age, gender, skeletal location, and lipid composition. In order to achieve this goal, imaging protocols need to be standardized to increase comparability across studies and different skeletal sites. Findings on the associations between BMD and BMAT are consistent, particularly for BMD assessed by DXA. However, there is still uncertainty on the exact role of BMAT in skeletal health, and its association with fractures remains to be determined. Future more extensive clinical trials are warranted to evaluate BMAT changes following pharmacological and non-pharmacological interventions in metabolic bone diseases.

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Declarations

Conflict of Interest None of the authors have financial or non-financial interests that are directly or indirectly related to this manuscript.

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- • Of importance
- •• Of major importance

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