Bone 118 (2019) 8–15

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Marrow adiposity and bone: Review of clinical implications

Julien Paccou [a,b,*], Guillaume Penel [a], Christophe Chauveau [c], Bernard Cortet [a,b], Pierre Hardouin [c]

[a] Université de Lille, Université Littoral Côte d'Opale, PMOI EA 4490 faculté de chirurgie dentaire, place de Verdun, 59000 Lille, France
[b] Service de rhumatologie, CHRU, 59000 Lille, France
[c] Univ. Littoral Côte d'Opale, Univ. Lille, EA 4490, PMOI, Physiopathologie des Maladies Osseuses Inflammatoires, F-62300 Boulogne-sur-Mer, France

ARTICLE INFO

Article history:
Received 25 November 2017
Revised 9 February 2018
Accepted 13 February 2018
Available online 2 March 2018

Keywords:
Marrow adiposity
Bone mineral density
Fractures
Diabetes mellitus
Obesity
Bariatric surgery

ABSTRACT

There is growing interest in the relationship between bone marrow fat (BMF) and skeletal health. Progress in clinical studies of BMF and skeletal health has been greatly enhanced by recent technical advances in our ability to measure BMF non-invasively. Magnetic resonance imagery (MRI) with or without spectroscopy is currently the standard technique for evaluating BMF content and composition in humans. This review focuses on clinical studies of marrow fat and its relationship with bone.

The amount of marrow fat is associated with bone mineral density (BMD). Several studies have reported a significant negative association between marrow fat content and BMD in both healthy and osteoporotic populations. There may also be a relationship between marrow fat and fracture (mostly vertebral fracture), but data are scarce and further studies are needed. Furthermore, a few studies suggest that a lower proportion of unsaturated lipids in vertebral BMF may be associated with reduced BMD and greater prevalence of fracture. Marrow fat might be influenced by metabolic diseases associated with bone loss and fractures, such as diabetes mellitus, obesity and anorexia nervosa. An intriguing aspect of bariatric (weight loss) surgery is that it induces bone loss and fractures, but with different impacts on marrow fat depending on diabetic status.

In daily practice, the usefulness for clinicians of assessing marrow fat using MRI is still limited. However, the perspectives are exciting, particularly in terms of improving the diagnosis and management of osteoporosis. Further studies are needed to better understand the regulators involved in the marrow fat-bone relationship and the links between marrow fat, other fat depots and energy metabolism.

1. Introduction

With the increase in population age and the prevalence of obesity, it is important to understand the relationship between adipose tissue and bone mass, bone quality and fractures [1,2]. Greater body weight or body fat mass are known to have a positive effect on bone mineral density (BMD), but obesity is not always protective against fractures (e.g., ankle and lower limb fractures). Furthermore, the association between fractures and obesity seems to be site-dependent [3–5]. The connection between fat and bone is complex since the associations between adiposity and bone are age-, gender-, menopausal status-, adipose depot- and bone compartment-specific [6,7].

In the past decade, a new approach to evaluating the bone-fat relationship has emerged, focusing on bone marrow adiposity (BMA). Marrow adiposity is a specific fat depot—with properties distinct from those of other fat depots—found in bone cavities in the immediate vicinity of sites of bone remodeling activity. In addition, marrow adiposity and bone are increasingly recognized as being capable of mutual regulation [8,9]. As imaging techniques become more sophisticated, the role of marrow adiposity on skeletal health can be studied directly and non-invasively. As such, BMA can now be quantified non-invasively using magnetic resonance imaging (MRI), either with or without spectroscopy [10,11]. Moreover, whereas the term "bone marrow fat" (BMF) is used in MRI studies, BMA is used in bone histomorphometric studies and as a general term referring to fat inside the bones. Using MRI with spectroscopy (MRS) in combination with dual energy x-ray absorptiometry (DXA), several studies have reported an association between BMF and BMD in patients with osteoporosis, as well as in populations of individuals with metabolic diseases such as obesity and diabetes mellitus [12–15]. It is conceivable therefore, that marrow adiposity may be driving bone loss—at least in part—and contributing to osteoporosis [6]. However, during puberty, both marrow fat and osteoblast differentiation increase, suggesting that marrow fat may be necessary for osteoblasts to produce new bone.

This review focuses on the knowledge available to medical bone specialists regarding the usefulness of bone marrow fat evaluations and their applications in the management of osteoporosis. Furthermore, this article review draws on animal data to fill in the gaps where

* Corresponding author at: Service de rhumatologie, Hôpital Roger Salengro, Rue Emile Laine, CHRU, 59037 Lille Cedex, France.
E-mail address: julien.paccou@chru-lille.fr (J. Paccou).

https://doi.org/10.1016/j.bone.2018.02.008
8756-3282/

human data are unavailable, and to provide some mechanistic insights which may be relevant for the results from human studies. Due to restrictions on the length of the reference list, the reader is also referred to other reviews by our team on the same topic (16,17).

2. Bone marrow fat variations with age, sex and menopause

At birth, bone cavities are filled mainly with red hematopoietic marrow. During childhood, red marrow is gradually replaced by fatty yellow marrow [18]. Despite wide individual variations, there is, globally, a positive correlation between BMF and age [19,20]. Kugel et al. reported an age-related increase in vertebral BMF in both males and females, with males having approximately 6–10% more fat than females of comparable age between the ages of 20 and 60 years [21]. Thereafter, vertebral BMF increases sharply in females between 55 and 65 years of age, i.e., in the years following menopause [22]. In males, vertebral BMF content rose gradually throughout life. Vertebral BMF content in females over 60 years of age was approximately 10% higher than in males, pointing to a reversal of the sex difference in BMF content reported in subjects aged <60 years [21,22].

3. Bone marrow fat evaluation using MRI

Historically, clinical measures of marrow adiposity required a bone biopsy. Progress in clinical studies of BMA and skeletal health has been greatly enhanced by recent technical advances in our ability to measure marrow fat non-invasively using MRI [10]. Three techniques have been used to evaluate BMF content, namely magnetic resonance spectroscopy (MRS), T1-weighted MRI and the Dixon method. For these three techniques, results are expressed as a percentage. Satisfying correlations have been found between the three methods [23].

Most of the recent clinical studies on the relationship between BMD and BMF have used MRS to analyse separate water and fat signals of BMF (*BMF content*) at the vertebrae or hip [24,25], with or without MR perfusion imaging (to assess *BMF perfusion*) [26,27]. MRS has also been used to measure lipid saturation (*BMF composition*, i.e., the presence and type of hydrogen bindings) in bone marrow [14]. The resulting spectrum shows peaks corresponding to water, saturated lipids, unsaturated lipids and residual lipids (Fig. 1) [11,14,28]. In MRS measurements, BMF is expressed as a percentage. To evaluate vertebral BMF, the measurement is acquired on one or more of the lumbar vertebral bodies (L1–L4). A single voxel is placed in the centre of the vertebral body [10]. The percentage of BMF is calculated using the large lipid peak at 1.3 ppm (ppm) (saturated lipids or *SL*), disregarding the much smaller lipid peaks at 5.3 (unsaturated lipids or *UL*) and 2.0 (residual lipids or *RL*) [10]. Fat content is then calculated as: fat content (%) = [(Ifat/(Ifat + Iwater)] × 100%. Furthermore, BMF content has also been reported using three of these lipid peaks [28]. In that case, fat content is calculated as: fat content (%) = [(I*UL* + I*RL* + I*SL*)/(I*UL* + I*RL* + I*SL* + I*water*)] × 100%. With MRS, it is also possible to assess the degree of lipid saturation in marrow [28]. The unsaturation index is then calculated as: UL (%) = [I*UL*/(I*UL* + I*RL* + I*SL*)] × 100%. The saturation index can also be calculated as: SL (%) = [I*SL*/(I*UL* + IRL + I*SL*)] × 100%. To date, there is currently no standardized protocol for BMF imaging using MRI with or without spectroscopy.

Finally, peripheral quantitative computed tomography (pQCT) has been used to assess marrow fat density at the tibia (mg/cm^3), but this technique requires exposure to relatively high levels of radiation [29]. Thus, further studies are needed to determine valid and reliable methods for measuring marrow adiposity with greater precision using pQCT or QCT, and a validation study should be conducted through comparison with MRI.

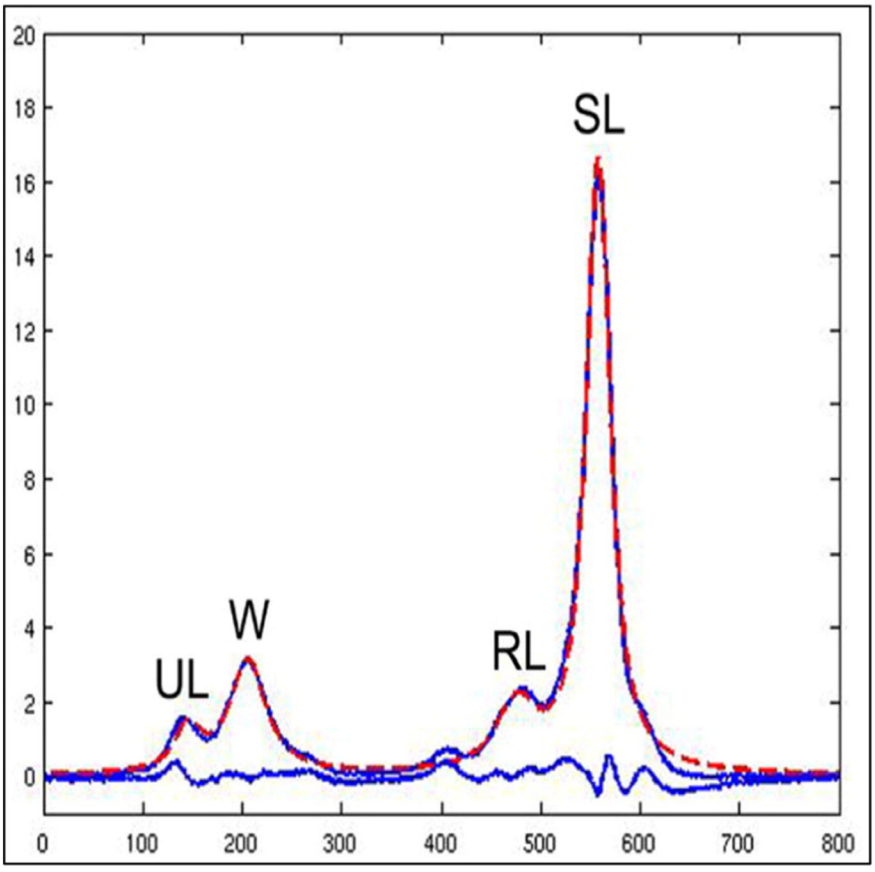

Fig. 1. Evaluation of bone marrow fat using MRI with spectroscopy. The resulting spectrum shows 4 peaks corresponding to water (W), saturated lipids (SL), unsaturated lipids (UL) and residual lipids (RL). Adapted from [11].

4. Bone marrow fat and bone mineral density by DXA: an inverse relationship

In most clinical studies in healthy populations, BMF has been measured using T1-weighted whole-body MRI. Several studies have reported a significant negative association between BMF content and BMD in healthy men [15,30] and women [13,15,30]. In a study including 560 healthy men and women (younger group, age 18.0–29.9 years; older group, age 50.0–88 years), Shen et al. observed an inverse relationship between BMF and BMD in an anatomically matched region (i.e., pelvic BMF and pelvic BMD), a non-anatomically matched region (i.e., pelvic BMF and spine BMD), and regional and whole-body (i.e. pelvic BMF and whole body BMD), after adjusting for body composition [30].

Higher BMF content as measured by MRS has been found in osteoporotic populations vs. osteopenic/normal populations. These findings have been reported in Chinese men and women aged 55 years and older when compared to those with low (osteopenic) or normal BMD matched for age [24,25]. More recently, in 51 postmenopausal women (54–73 years), BMF content measured by MRS was found to be significantly higher in patients with osteoporosis/osteopenia compared with controls, after adjustment for age and body mass index (BMI) ($p < 0.05$) [11]. Similar results were found in 78 postmenopausal women (55–81 years) [31]. However, all these results were obtained in Chinese populations [11,24,25,31] and data in Caucasian populations are scarce.

It is important to note that the inverse relationship between BMF and BMD is more than just a statistical association. As BMF increases, there are also histologic changes within fat tissue assessed by bone biopsy [32,33]. However, the general statement that the amount of marrow fat is always associated with BMD should be qualified. Indeed, there is no evidence to suggest that direct reciprocal relationship exists between marrow fat and bone during puberty or after bariatric surgery.

5. Marrow fat, volumetric BMD and bone microarchitecture: beyond DXA, measurements of bone using single energy quantitative computed tomography

Although bone density assessed by DXA is a robust predictor of fracture risk, DXA measurements provide only areal estimates of density, and since DXA cannot distinguish cortical and trabecular bone, the technique is limited. Quantitative computed tomography (QCT) measurements of bone (spine and hip) can provide insights into the aspects of bone that are associated with marrow adiposity. In the Iceland AGES-Reykjavik cohort, higher marrow fat was found to be associated with lower trabecular spine, total hip and femoral neck—but not cortical—volumetric BMD (vBMD) in older women [34]. In men, there were no statistically significant associations between BMF and vBMD (both trabecular and cortical) either at spine, total hip or femoral neck [34]. In another study involving women (13 healthy participants and 13 diabetics patients), mean vertebral BMF (L1-L3, %) was found to correlate inversely with trabecular spine vBMD (L1-L3, mg/ml) in healthy participants (−0.578; $p = 0.049$) [14]. Bredella et al. [35] found that vertebral BMF as measured by MRS also correlated inversely with trabecular spine vBMD ($r = -0.39$, $p = 0.007$) in 47 premenopausal women of various BMIs (range: 18–41 kg/m2, mean 30 ± 7 kg/m^2), and the correlation remained significant after controlling for visceral adipose tissue (VAT) ($p = 0.03$).

Data on peripheral QCT (pQCT) measurements of bone (distal radius and tibia) and their relationships with BMF content are scarce. Sheu et al. [36] found no correlation between BMF and trabecular and cortical BMD in 118 non-diabetic elderly men (80.6 ± 4.6) involved in the MrOS study.

In a cross-sectional study, 35 obese men (mean age, 33.8 ± 6.4 years; mean BMI, 36.5 ± 5.8 kg/m2) were included to evaluate determinants of bone microarchitecture assessed using high resolution peripheral QCT (HR-pQCT) of the distal radius [37]. Vertebral BMF content assessed by MRS correlated inversely with cortical vBMD ($r = -0.42$, $p = 0.02$), cortical area ($r = -0.45$, $p = 0.01$) and trabecular thickness ($r = -0.38$, $p = 0.03$), and the correlation remained significant after controlling for lumbar BMD assessed by DXA ($p < 0.04$) [37]. No data were available regarding distal tibia.

Finally, although published data are scarce and difficult to compare, higher vertebral BMF content seems to be associated with lower trabecular spine vBMD assessed using QCT in women. Additional studies are needed to better evaluate the relationship between BMF, vBMD and microarchitecture assessed by pQCT and HR-pQCT.

6. Marrow fat and fracture: Data are scarce

Little data are available on the relationship between marrow adiposity and fractures. Previous studies have reported an association between prevalent vertebral fractures and higher bone marrow adiposity assessed by iliac crest biopsy [32] and BMF content assessed using MRS [20]. Some human imaging studies suggest that alterations in BMF assessed using MRS may contribute to "bone weakness" (prominent Schmorl's nodes, endplate depression, vertebral wedging, and vertebral compression) independently of BMD [38,39]. Moreover, marrow adiposity parameters measured by iliac crest biopsy (number, size and volume of adipocytes) were found to be higher in 64 premenopausal women with idiopathic osteoporosis (defined by low-trauma fractures ($n = 45$) or low BMD ($n = 19$)) versus 40 controls, after adjustment for age and BMI [40].

More recently, in a cohort of 257 older adults (118 men, 139 women; mean age 79 years (SD 3.1)), those with prevalent morphometric vertebral fractures (21 men, 32 women) had higher mean BMF (57.3% vs. 53.6%, $P = 0.003$) in models adjusted for age and gender. However, no association was found between BMF content and history of clinical fractures (all fractures) or analyses limited to fragility fractures (hip, proximal humerus, and clinical spine) either in men or women [41]. In a study reported by Patsch et al. [28], no association was found between low-trauma fractures and BMF content in a cohort of 69 diabetic and non-diabetic postmenopausal women (with or without fragility fracture; $n = 33$ versus $n = 36$).

Radiographic vertebral fractures might be associated with higher BMF content independently of BMD [38,39,41]. To date, no prospective studies evaluating the relationship between BMF and fractures are available.

7. Lipid composition of marrow fat: association with bone density and fracture?

Marrow fat composition and content may be relevant for skeletal health. The relative amounts of saturated and unsaturated lipids in marrow fat can be measured non-invasively with MRS, thereby providing a means of evaluating this aspect of BMF composition. A few studies suggest that a lower proportion of unsaturated lipids in vertebral marrow fat may be associated with reduced BMD [25] and greater prevalence of fracture [28].

In a study conducted by Yeung et al. [25] involving 50 postmenopausal women (66–81 years) and 12 controls (18–43 years), the fat unsaturation index was significantly lower in osteoporotic (0.091 ± 0.013) and osteopenic (0.097 ± 0.014) subjects compared to normal subjects (0.114 ± 0.016) and young controls (0.127 ± 0.031). Moreover, an inverse correlation was observed between the fat content and the unsaturation index ($r = -0.53$, $P < 0.0001$). These results were confirmed in another study conducted by Li et al. using a new imaging technique permitting the evaluation of marrow fat composition ex vivo [42]. Bone marrow samples were

obtained by iliac crest aspiration during surgical procedures. In a cohort of 24 postmenopausal women (65–89 years), subjects with lower BMD ($n = 17$, osteopenic and osteoporotic subjects together) had significantly lower mono-unsaturated and unsaturated levels ($p = 0.003$ and $p = 0.039$ respectively) compared to controls ($n = 7$) using ex vivo high-resolution magic angle spinning proton nuclear MRS [42].

Patsch et al. [28] evaluated the association between vertebral BMF and fragility fractures in 69 diabetic and non-diabetic postmenopausal women. In their study, no association was found between fragility fractures and vertebral BMF content as previously mentioned. However, an association was found with low BMF unsaturation levels (−1.7% [95% CI: -2.8% to −0.5%], $p = 0.005$), independently of age, race, and spine vBMD.

8. Marrow fat, obesity and other fat depots: Data are lacking or inconsistent

An important area of clinical investigation would be to consider the relationship between marrow fat and other fat depots such as total body, visceral and subcutaneous fat. To our knowledge, only one study has explored the relationship between obesity and BMF content and composition. Bone marrow fat content and unsaturation index were similar in obese ($n = 23$) and non-obese ($n = 27$) premenopausal women (38.5 ± 0.1 vs. 38.6 ± 0.1%, $p = 0.994$; 0.162 ± 0.065 vs. 0.175 ± 0.048, $p = 0.473$, respectively) [43]. Data are lacking regarding the relationship between marrow fat and total body and subcutaneous fat, and the relationship between marrow fat and visceral fat appears to be inconsistent. Indeed, some, but not all, studies [44,45] have reported a positive association between marrow fat and visceral fat [35]. Positive correlations between BMF and visceral fat ($r = 0.34$; $p = 0.02$) were reported in 23 obese premenopausal women (body mass index: 34.4 ± 4.9 kg/m^2) (Fig. 2) [35]. However, in other studies, no such association was found [44,45], or the authors used CT [46] or T1-weighted MRI [15], neither of which is in keeping with the current standard practice for evaluating marrow fat. Consequently, further studies are needed to effectively evaluate the relationship between marrow fat and other fat depots using MRS or the Dixon method at the lumbar spine in homogeneous populations of obese and non-obese men and women.

9. Weight loss, anorexia nervosa and bariatric surgery: What about marrow fat?

9.1. Weight loss

Several studies have examined the longitudinal effects of weight loss on BMD in humans and confirmed a reduction in bone mass [47,48]. However, studies on the longitudinal effect of weight loss on BMF in humans are scarce [49]. Cordes et al. [50] did not find a change in marrow fat in 20 obese postmenopausal women during a 4-week diet intervention (800 kcal per day; mean weight loss 7%), although a decrease was observed in other fat depots (e.g. visceral fat, subcutaneous fat…).

9.2. Anorexia nervosa

Anorexia nervosa (AN) is a serious disorder—with non-negligible rates of mortality and morbidity—which can affect bone tissue with a loss in bone mass [51,52]. Studies have shown that BMF content increases in AN [53,54]. The most notable finding is that, despite a severe depletion of body fat (both VAT and SAT), AN is associated with an increase in BMF content (as measured by MRS) [53,54]. Women with AN ($n = 10$, 29.8 ± 7.6 years) have higher lumbar and femoral BMF content levels than normal-weight age-matched controls (n = 10, 29.2 ± 5.2 years), and BMF content correlates inversely with BMD assessed using DXA after controlling for BMI [53]. In a study focusing on BMF composition assessed using MRS, similar BMF composition measurements were found in patients with AN ($n = 14$, age 29.5 ± 1.9 years) compared to 12 age-matched normal-weight controls [54]. This paradoxical increase in marrow fat at a time when SAT and VAT are markedly reduced raises important questions about the functional consequences of this process. These changes may represent a protective compensatory mechanism for skeletal health. Moreover, in women with anorexia nervosa, marrow fat decreases and then returns to levels comparable to those found in healthy controls, highlighting the issue of reversibility of marrow adiposity [55].

9.3. –Bariatric surgery

Bariatric surgery procedures provide the most effective and lasting weight-loss strategy for the treatment of severe obesity, but the clinical impact on BMD and fractures may be detrimental [56,57]. In a recent

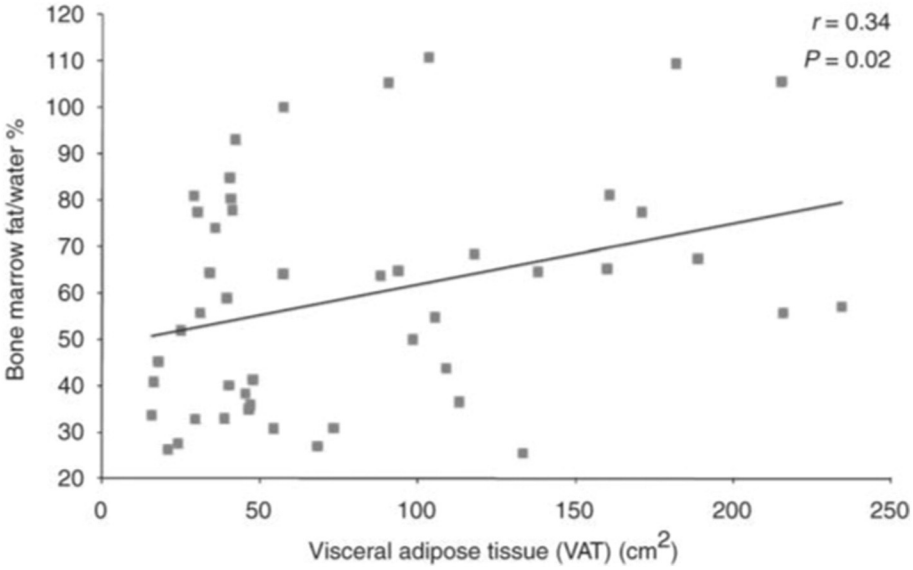

Fig. 2. Relationship between marrow fat and visceral fat in obese premenopausal women. Adapted from [35].

study, Roux-en-Y gastric bypass (RYGB) surgery was found to be associated with a 43% increase in the risk of nonvertebral fracture compared with adjustable gastric banding [58].

In a pilot study involving morbidly obese diabetic ($n = 6$) and nondiabetic women ($n = 5$) undergoing RYGB surgery, Schafer et al. examined the effects of RYGB on vertebral BMF content using MRS [59]. Six months post-operatively, in those without diabetes, BMF was maintained on average after RYGB (+0.9%), despite dramatic declines in overall fat mass. In those with diabetes, RYGB significantly reduced BMF content (−7.5% [95% CI: −15.2 to +0.1%], $p = 0.05$) [59]. With an extended cohort of 30 women (14 women with diabetes and 16 without), the same team examined vertebral BMF content and BMD changes over a period of 6 months post-RYGB [45]. Participants lost a mean 27.3 ± 6.8 kg in weight and 19.3 ± 4.8 kg in total body fat. In the women with diabetes, RYGB significantly reduced BMF content (−6.5% [95% CI: −13.1 to 0%], $p = 0.05$), whereas in the non-diabetic women, BMF content was stable (+1.8% [95% CI −1.8 to +5.4%], $p = 0.29$). In the cohort overall (diabetic and non-diabetic women), greater declines in HbA1C were associated with declines in marrow fat ($r = 0.50$, $p = 0.01$). Not only was marrow fat content associated with spine vBMD at baseline ($r = -0.72$, $p < 0.01$), but longitudinal changes in marrow fat content and spine vBMD were also inversely related ($r = -0.58$, $p < 0.01$) (Fig. 3) [45]. However, the skeletal effects of bariatric surgery are complex and, in another bariatric study, the authors did not report any changes in BMF content in subgroups of participants who had had RYGB, although they did find an association between sleeve gastrectomy and an increase in marrow fat [60].

10. Diabetes, skeletal health and marrow fat: possible gender differences

Diabetes is an independent risk factor for fragility fractures at skeletal sites such as the hip, spine, and distal forearm [61–63]. Only a small number of studies have investigated marrow fat content and composition in patients with diabetes mellitus compared to non-diabetes patients. The literature suggests that diabetes may be a state of elevated BMF content.

Intriguingly, this relationship may differ by gender. Indeed, in a study involving 13 postmenopausal women with diabetes mellitus and 13 age- and body mass index-matched healthy controls, BMF was similar in the diabetic women and healthy controls, whereas unsaturation levels were significantly lower in the diabetic group [14]. Similar results were reported by Patsch et al., who found no association between diabetic status and BMF content in a cohort of 69 postmenopausal women (mean age 63 ± 5 years), whereas diabetes was associated with lower unsaturation levels [28]. Kim et al. [45] did not identify higher marrow fat content in diabetic versus nondiabetic women.

Sheu et al. [36] found that BMF content was higher in men with diabetes than those without (59.2 ± 3.5 vs. 54.8 ± 3.3, $p = 0.036$), but this result did not remain significant after excluding 2 men receiving thiazolidinediones. No BMF composition measurements were available in this study.

Furthermore, in women with diabetes mellitus, higher HbA1c levels were associated with higher BMF content, suggesting that BMF may influence or may be influenced by glucose metabolism and glycemic control [14]. This result was confirmed in another study conducted by Yu et al. [44] at the lumbar spine ($r = 0.61$; $p = 0.004$) and femoral metaphysis ($r = 0.47$; $p = 0.03$) (Fig. 4). Furthermore, BMF content was found to correlate negatively with insulin and HOMA-IR ($r = -0.342$, $r = -0.352$, respectively, $p = 0.01$) in 50 obese ($n = 23$) and non-obese ($n = 27$) premenopausal women, confirming the link between glucose metabolism and marrow adiposity [43].

11. Osteoporosis treatments decrease marrow adiposity

Increased bone marrow adiposity in postmenopausal women might be due, at least in part, to estrogen deficiency [22]. Indeed, in a cohort of 29 postmenopausal osteoporotic women, one-year transdermal estrogen therapy resulted in significant decreases in bone marrow adipocyte volume (adipocyte volume/tissue volume in bone biopsy), and prevented the increase in adipocyte number as compared to placebo-treated controls ($n = 27$) [64]. In another bone biopsy study, similar findings—decrease in adipocyte volume/tissue volume and prevention of the increase in adipocyte number—were observed in 24 postmenopausal women after 3 years of risedronate (5 mg/day) compared to placebo [65]. In a pilot study, teriparatide was administered at 20 μg daily for 18 to 24 months to 21 premenopausal women with unexplained fragility fractures or low BMD. After 12 months, adipocyte area, perimeter, and volume/marrow volume, as assessed by bone biopsies, had decreased, with no change in adipocyte number [66]. In another study, postmenopausal osteopenic women were randomly assigned to receive teriparatide ($n = 90$) or placebo ($n = 45$) for 12 months. Teriparatide effectively lowers marrow fat assessed using T1-weighted MRI in postmenopausal osteopenic women at 12 months (−5.9%) (Fig. 5). However, these results should be interpreted with two important caveats: MRI with or without spectroscopy is not able to determine whether it is marrow adipocyte size or number, or both, which is reduced; and PTH treatment may have an effect on lipolysis (marrow adipocytes size, but not number, was reduced). Moreover, a

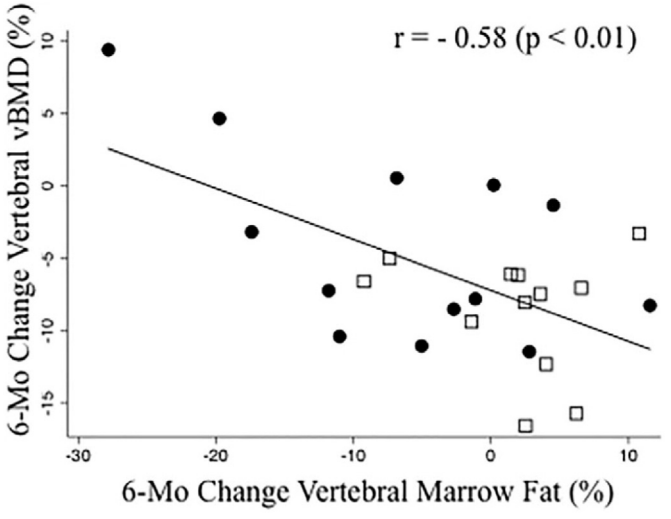

Fig. 3. Correlation between vertebral marrow fat content and vertebral volumetric BMD with 6-month changes in diabetic (dark circles) and nondiabetic populations (white squares) Adapted from [45].

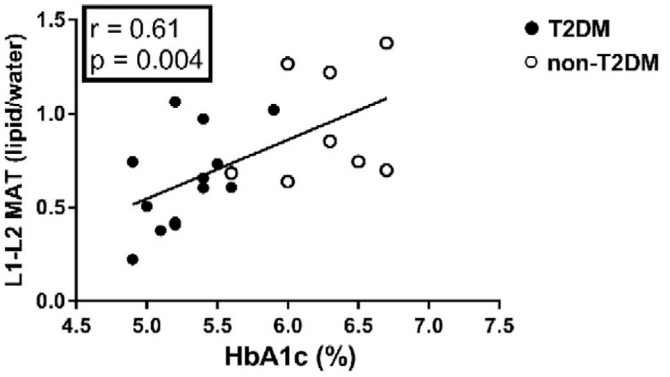

Fig. 4. Relationship between HbA1C and marrow fat in diabetic and nondiabetic populations Adapted from [44].

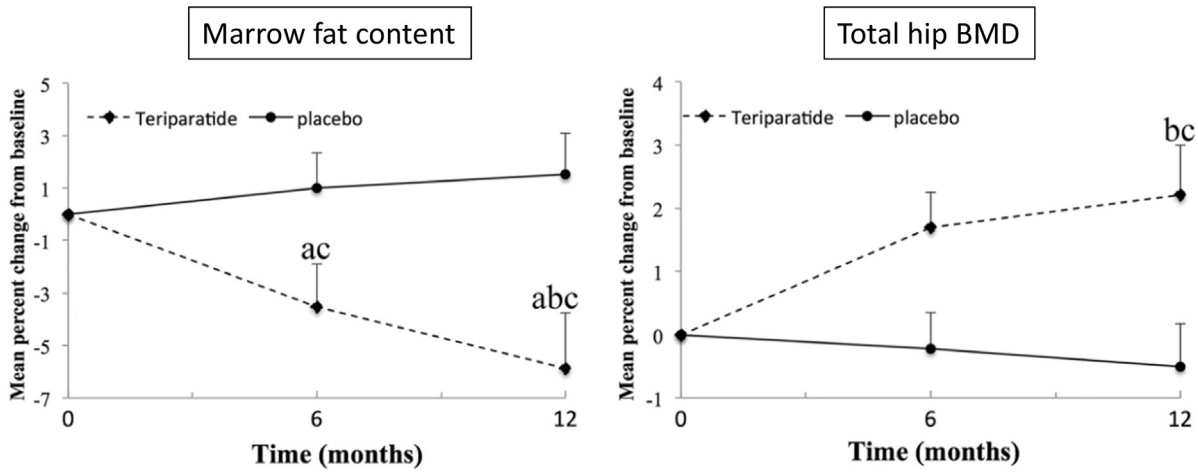

Fig. 5. Influence of teriparatide administration onmarrow fat content and total hip BMD (a) $p < 0.05$ vs. previous time point; (b) $p < 0.05$ vs. baseline within group; (c) $p < 0.05$ vs. placebo group at the same time point. Adapted from [66].

positive association was found between marrow fat content and VAT ($r = 0.531$, $p = 0.008$) [67].

12. Marrow adiposity variations: Effects of exercise and pharmacologic agents such as rosiglitazone and glucocorticoids

12.1. Exercise

Interestingly, bone response to exercise includes changes in marrow adiposity, which may contribute to the beneficial effect of exercise on bone mass [68,69]. For example, female athletes (17–40 yrs.) involved in weight-bearing impact sports (impact group, $n = 122$) have lower marrow adiposity (tibial bone marrow density assessed using pQCT) compared with athletes involved in non-impact loading sports (non-impact group, $n = 57$) and non-athletic controls (control group, $n = 41$) [68]. Furthermore, in all young women, marrow adiposity is a predictor of bone strength, independently of loading history, body size, or body composition [68]. Moreover, in eight week-old female C57BL/6 mice, BMF accumulation accelerated by a high fat diet was suppressed by exercise (voluntary access to running wheels) after 6 weeks [69]. In this study, femoral BMF was assessed by micro-scanner as well as bone parameters, and mice were divided in regular-diet and high fat-diet groups with or without exercise (4 groups, $n = 5$ per group). Interestingly, exercise significantly increased bone quantity in both diet groups [69]. Taken together, these studies suggest that the beneficial effect of exercise on bone density might be mediated by a decrease in marrow adiposity and a concomitant increase in osteoblastogenesis.

12.2. –Pharmacologic agents

Thiazolidinediones (TZDs) are oral anti-diabetes agents that act mainly as insulin-sensitizers by activating the nuclear peroxisome proliferator-activated receptor γ (PPARγ). In humans, rosiglitazone – a PPARγ-agonist – is known to increase marrow adiposity and fracture risk [70]. In mice, activation of PPARγ by rosiglitazone stimulates the differentiation of adipocytes over osteoblasts from MSC, increases the number of adipocytes, decreases the number of osteoblasts, and decreases BMD [71].

In the rabbit model of glucocorticoid-induced bone loss, there was a remarkable increase in marrow adiposity but a reduction in BMD compared with the controls. Interestingly, a single dose of early zoledronic acid can reverse the marrow adiposity to its original level completely [72].

13. Conclusions and perspectives

Examining and understanding the link between marrow adiposity and bone is a tremendous area of research. Findings on the associations are consistent, particularly for BMD assessed using DXA and spine trabecular vBMD using QCT. However, its association with bone fractures remains to be determined and prospective studies are needed to evaluate the association between BMF and fractures, the most common clinical consequence of osteoporosis. Furthering our understanding of the mechanism of this association could lead to a better diagnostic approach to osteoporosis.

Osteoporosis treatments (e.g. estrogen, teriparatide…) have been found to decrease bone marrow adiposity and increase BMD. This might be of significance for further studies focusing on populations of individuals with metabolic diseases (e.g. diabetes, obesity, anorexia nervosa…), in which BMF content and/or composition abnormalities have been demonstrated.

Further studies are also needed to better understand the impact of weight loss surgery on marrow adiposity depending on diabetic status and type of bariatric surgery (e.g. RYGB, sleeve gastrectomy…).

Finally, the relationship between marrow fat and other fat depots (e.g. total body fat, visceral fat…) needs to be properly evaluated.

Regarding technical issues, the priority is to standardize the protocol for BMF imaging using MRI with or without spectroscopy. Examining lipid composition (unsaturation level) in terms of its association with skeletal health (e.g. BMD, fracture…) and diabetic status might also be important.

Although the regulation of the marrow fat-bone relationship is not completely understood, there is evidence suggesting that the GH-IGF1 axis may be involved [35,45] as much as adipokines such as adiponectin [43,44,73–75]. Furthermore, bone marrow adiposity may influence or may be influenced by glucose metabolism and glycemic control [14,43,44].

Finally, In the Iceland AGES cohort [76], Ma et al. found that higher circulating sclerostin was associated with higher marrow fat in men but not women, suggesting that osteocyte activity may also influence marrow fat.

Further research is needed to understand the mechanisms underlying the marrow adiposity-bone interaction and its possible regulation by glucose metabolism and sclerostin (Fig. 6). Ultimately, understanding the role of marrow adiposity in bone metabolism could lead to the development of strategies for the prevention and treatment of osteoporosis.

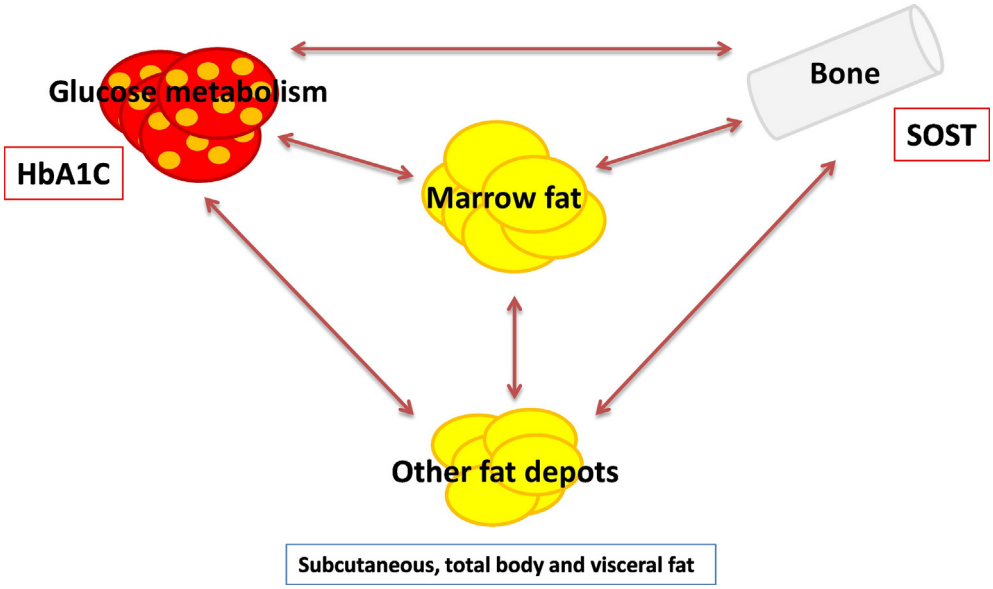

Fig. 6. Relationships between marrow fat, bone, other fat depots and glucose metabolism.

References

[1] S. Migliaccio, E.A. Greco, F. Wannenes, L.M. Donini, A. Lenzi, Adipose, bone and muscle tissues as new endocrine organs: role of reciprocal regulation for osteoporosis and obesity development, Horm. Mol. Biol. Clin. Invest. 17 (2014) 39–51.

[2] E. Dolan, P.A. Swinton, C. Sale, A. Healy, J. O'Reilly, Influence of adipose tissue mass on bone mass in an overweight or obese population: systematic review and meta-analysis, Nutr. Rev. 75 (2017) 858–870.

[3] J.E. Compston, N.B. Watts, R. Chapurlat, C. Cooper, S. Boonen, S. Greenspan, et al., Obesity is not protective against fracture in postmenopausal women: GLOW, Am. J. Med. 124 (2011) 1043–1050.

[4] K. Hind, M. Pearce, F. Birrell, Total and visceral adiposity are associated with prevalent vertebral fracture in women but not men at age 62 years: the Newcastle thousand families study, J. Bone Miner. Res. 32 (2017) 1109–1115.

[5] H. Johansson, J.A. Kanis, A. Odén, E. McCloskey, R.D. Chapurlat, C. Christiansen, et al., A meta-analysis of the association of fracture risk and body mass index in women, J. Bone Miner. Res. 29 (2014) 223–233.

[6] O. Sadeghi, P. Saneei, M. Nasiri, B. Larijani, A. Esmaillzadeh, Abdominal obesity and risk of hip fracture: a systematic review and meta-analysis of prospective studies, Adv. Nutr. 8 (2017) 728–738.

[7] M.J. Devlin, C.J. Rosen, The bone–fat interface: basic and clinical implications of marrow adiposity, Lancet Diabetes Endocrinol. 3 (2015) 141–147.

[8] A.G. Veldhuis-Vlug, C.J. Rosen, Mechanisms of marrow adiposity and its implications for skeletal health, Metabolism 67 (2017) 106–114.

[9] E.L. Scheller, W.P. Cawthorn, A.A. Burr, M.C. Horowitz, O.A. MacDougald, Marrow adipose tissue: trimming the fat, Trends Endocrinol. Metab. 27 (2016) 392–403.

[10] D.C. Karampinos, S. Ruschke, M. Dieckmeyer, M. Diefenbach, D. Franz, A.S. Gersing, et al., Quantitative MRI and spectroscopy of bone marrow, J. Magn. Reson. Imaging (2017 Jun 1)https://doi.org/10.1002/jmri.25769.

[11] X. Li, D. Kuo, A.L. Schafer, A. Porzig, T.M. Link, D. Black, et al., Quantification of vertebral bone marrow fat content using 3 Tesla MR spectroscopy: reproducibility, vertebral variation, and applications in osteoporosis, J. Magn. Reson. Imaging 33 (2011) 974–979.

[12] T.A.L. Wren, S.A. Chung, F.J. Dorey, S. Bluml, G.B. Adams, V. Gilsanz, Bone marrow fat is inversely related to cortical bone in young and old subjects, J. Clin. Endocrinol. Metab. 96 (2011) 782–786.

[13] W. Shen, J. Chen, M. Punyanitya, S. Shapses, S. Heshka, S.B. Heymsfield, MRI-measured bone marrow adipose tissue is inversely related to DXA-measured bone mineral in Caucasian women, Osteoporos. Int. 18 (2007) 641–647.

[14] T. Baum, S.P. Yap, D.C. Karampinos, L. Nardo, D. Kuo, A.J. Burghardt, et al., Does vertebral bone marrow fat content correlate with abdominal adipose tissue, lumbar spine bone mineral density, and blood biomarkers in women with type 2 diabetes mellitus? J. Magn. Reson. Imaging 35 (2012) 117–124.

[15] W. Shen, R. Scherzer, M. Gantz, J. Chen, M. Punyanitya, C.E. Lewis, et al., Relationship between MRI-measured bone marrow adipose tissue and hip and spine bone mineral density in African-American and Caucasian participants: the CARDIA study, J. Clin. Endocrinol. Metab. 97 (2012) 1337–1346.

[16] P. Hardouin, V. Pansini, B. Cortet, Bone marrow fat, J. Bone Spine. 81 (2014) 313–319.

[17] J. Paccou, P. Hardouin, A. Cotten, G. Penel, B. Cortet, The role of bone marrow fat in skeletal health: usefulness and perspectives for clinicians, J. Clin. Endocrinol. Metab. 100 (2015) 3613–3621.

[18] B.C. Vande Berg, J. Malghem, F.E. Lecouvet, B. Maldague, Magnetic resonance imaging of normal bone marrow, Eur. Radiol. 8 (1998) 1327–1334.

[19] P. Meunier, J. Aaron, C. Edouard, G. Vignon, Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies, Clin. Orthop. 80 (1971) 147–154.

[20] F.W. Wehrli, J.A. Hopkins, S.N. Hwang, H.K. Song, P.J. Snyder, J.G. Haddad, Cross-sectional study of osteopenia with quantitative MR imaging and bone densitometry, Radiology 217 (2000) 527–538.

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

[22] J.F. Griffith, D.K. Yeung, H.T. Ma, J.C. Leung, T.C. Kwok, P.C. Leung, Bone marrow fat content in the elderly: a reversal of sex difference seen in younger subjects, J. Magn. Reson. Imaging 36 (2012) 225–230.

[23] W. Shen, X. Gong, J. Weiss, Y. Jin, Comparison among T1-weighted magnetic resonance imaging, modified dixon method, and magnetic resonance spectroscopy in measuring bone marrow fat, J. Obes. 2013 (2013), 298675. .

[24] J.F. Griffith, D.K.W. Yeung, G.E. Antonio, F.K.H. Lee, A.W.L. Hong, S.Y.S. Wong, et al., Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast-enhanced MR imaging and MR spectroscopy, Radiology 236 (2005) 945–951.

[25] D.K.W. Yeung, J.F. Griffith, G.E. Antonio, F.K.H. Lee, J. Woo, P.C. Leung, Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: a proton MR spectroscopy study, J. Magn. Reson. Imaging 22 (2005) 279–285.

[26] J.F. Griffith, D.K.W. Yeung, J.C.S. Leung, T.C.Y. Kwok, P.C. Leung, Prediction of bone loss in elderly female subjects by MR perfusion imaging and spectroscopy, Eur. Radiol. 21 (2011) 1160–1169.

[27] J.F. Budzik, G. Lefebvre, H. Behal, S. Verclytte, P. Hardouin, P. Teixeira, A. Cotten, Bone marrow perfusion measured with dynamic contrast enhanced magnetic resonance imaging is correlated to body mass index in adults, Bone 99 (2017) 47–52.

[28] J.M. Patsch, X. Li, T. Baum, S.P. Yap, D.C. Karampinos, A.V. Schwartz, et al., Bone marrow fat composition as a novel imaging biomarker in postmenopausal women with prevalent fragility fractures, J. Bone Miner. Res. 28 (8) (2013) 1721.

[29] J.C. Gibbs, Z.M. Brown, A.K. Wong, B.C. Craven, J.D. Adachi, L.M. Giangregorio, Measuring marrow density and area using peripheral quantitative computed tomography at the tibia: Precision in young and older adults and individuals with spinal cord injury, J. Clin. Densitom. (2017)https://doi.org/10.1016/j.jocd.2017.02.002 (pii: S1094-6950(16)30258-X.).

[30] W. Shen, J. Chen, M. Gantz, M. Punyanitya, S.B. Heymsfield, D. Gallagher, et al., MRI-measured pelvic bone marrow adipose tissue is inversely related to DXA-measured bone mineral in younger and older adults, Eur. J. Clin. Nutr. 66 (2012) 983–988.

[31] G.Y. Tang, Z.W. Lv, R.B. Tang, Y. Liu, Y.F. Peng, W. Li, et al., Evaluation of MR spectroscopy and diffusion-weighted MRI in detecting bone marrow changes in postmenopausal women with osteoporosis, Clin. Radiol. 65 (2010) 377–381.

[32] J. Justesen, K. Stenderup, E.N. Ebbesen, L. Mosekilde, T. Steiniche, M. Kassem, Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis, Biogerontology 2 (2001) 165–171.

[33] S. Verma, J.H. Rajaratnam, J. Denton, J.A. Hoyland, R.J. Byers, Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis, J. Clin. Pathol. 55 (2002) 693–698.

[34] A.V. Schwartz, S. Sigurdsson, T.F. Hue, T.F. Lang, T.B. Harris, C.J. Rosen, et al., Vertebral bone marrow fat associated with lower trabecular BMD and prevalent vertebral fracture in older adults, J. Clin. Endocrinol. Metab. 98 (2013) 2294–2300.

[35] M.A. Bredella, M. Torriani, R.H. Ghomi, B.J. Thomas, D.J. Brick, A.V. Gerweck, et al., Vertebral bone marrow fat is positively associated with visceral fat and inversely associated with IGF-1 in obese women, Obesity 19 (2011) 49–53.

[36] Y. Sheu, F. Amati, A.V. Schwartz, M.E. Danielson, X. Li, R. Boudreau, J.A. Cauley, Osteoporotic fractures in men (MrOS) research group. Vertebral bone marrow fat, bone mineral density and diabetes: the osteoporotic fractures in men (MrOS) study, Bone 97 (2017) 299–305.
[37] M.A. Bredella, E. Lin, A.V. Gerweck, M.G. Landa, B.J. Thomas, M. Torriani, et al., Determinants of bone microarchitecture and mechanical properties in obese men, J. Clin. Endocrinol. Metab. 97 (2012) 4115–4122.
[38] D. Schellinger, C.S. Lin, J. Lim, H.G. Hatipoglu, J.C. Pezzullo, A.J. Singer, Bone marrow fat and bone mineral density on proton MR spectroscopy and dual-energy X-ray absorptiometry: their ratio as a new indicator of bone weakening, Am. J. Roentgenol. 183 (2004) 1761–1765.
[39] D. Schellinger, C.S. Lin, H.G. Hatipoglu, Fertikh D. Potential, Value of vertebral proton MR spectroscopy in determining bone weakness, AJNR Am. J. Neuroradiol. 22 (2001) 1620–1627.
[40] A. Cohen, D.W. Dempster, E.M. Stein, T.L. Nickolas, H. Zhou, D.J. McMahon, et al., Increased marrow adiposity in premenopausal women with idiopathic osteoporosis, J. Clin. Endocrinol. Metab. 97 (2012) 2782–2791.
[41] A.V. Schwartz, S. Sigurdsson, T.F. Hue, T.F. Lang, T.B. Harris, C.J. Rosen, et al., Vertebral bone marrow fat associated with lower trabecular BMD and prevalent vertebral fracture in older adults, J. Clin. Endocrinol. Metab. 98 (2013) 2294–2300.
[42] X. Li, K. Shet, K. Xu, J.P. Rodríguez, A.M. Pino, J. Kurhanewicz, et al., Unsaturation level decreased in bone marrow fat of postmenopausal women with low bone density using high resolution magic angle spinning (HRMAS) 1H NMR spectroscopy, Bone 105 (2017) 87–92.
[43] F. Ermetici, S. Briganti, A. Delnevo, P. Cannaò, G.D. Leo, S. Benedini, et al., Bone marrow fat contributes to insulin sensitivity and adiponectin secretion in premenopausal women, Endocrine (2017 Jun 17)https://doi.org/10.1007/s12020-017-1349-7.
[44] E.W. Yu, L. Greenblatt, A. Eajazi, M. Torriani, M.A. Bredella, Marrow adipose tissue composition in adults with morbid obesity, Bone 97 (2017) 38–42.
[45] T.Y. Kim, A.V. Schwartz, X. Li, K. Xu, D.M. Black, D.M. Petrenko, et al., Bone marrow fat changes after gastric bypass surgery are associated with loss of bone mass, J. Bone Miner. Res. (2017 Aug 9)https://doi.org/10.1002/jbmr.3212 [Epub ahead of print].
[46] N. Di Iorgi, S.D. Mittelman, V. Gilsanz, Differential effect of marrow adiposity and visceral and subcutaneous fat on cardiovascular risk in young, healthy adults, Int. J. Obes. 32 (2008) 1854–1860.
[47] K.E. Ensrud, R.L. Fullman, E. Barrett-Connor, J.A. Cauley, M.L. Stefanick, H.A. Fink, et al., Voluntary weight reduction in older men increases hip bone loss: the osteoporotic fractures in men study, J. Clin. Endocrinol. Metab. 90 (2005) 1998–2004.
[48] D.T. Villareal, K. Shah, M.R. Banks, D.R. Sinacore, S. Klein, Effect of weight loss and exercise therapy on bone metabolism and mass in obese older adults: a one-year randomized controlled trial, J. Clin. Endocrinol. Metab. 93 (2008) 2181–2187.
[49] A. Bosy-Westphal, W. Later, B. Schautz, M. Lagerpusch, K. Goele, M. Heller, et al., Impact of intra- and extra-osseous soft tissue composition on changes in bone mineral density with weight loss and regain, Obesity 19 (2011) 1503–1510 Silver Spring Md.
[50] C. Cordes, M. Dieckmeyer, B. Ott, J. Shen, S. Ruschke, M. Settles, et al., MR-detected changes in liver fat, abdominal fat, and vertebral bone marrow fat after a four-week calorie restriction in obese women, J. Magn. Reson. Imaging 42 (2015) 1272–1280.
[51] I. Legroux-Gérot, J. Vignau, M. d'Herbomez, R.M. Flipo, B. Cortet, Predictive factors of change in BMD at 1 and 2 years in women with anorexia nervosa: a study of 146 cases, Osteoporos. Int. 23 (2012) 2855–2861.
[52] Legroux-Gérot I, Vignau J, Viltart O, Hardouin P, Chauveau C, Cortet B. Adipokines and bone status in a cohort of anorexic patients. Under revision for Joint Bone Spine (ref: BONSOI-D-17-00330R1).
[53] M.A. Bredella, P.K. Fazeli, K.K. Miller, M. Misra, M. Torriani, B.J. Thomas, et al., Increased bone marrow fat in anorexia nervosa, J. Clin. Endocrinol. Metab. 94 (2009) 2129–2136.
[54] M.A. Bredella, P.K. Fazeli, S.M. Daley, K.K. Miller, C.J. Rosen, A. Klibanski, et al., Marrow fat composition in anorexia nervosa, Bone 66 (2014) 199–204.
[55] P.K. Fazeli, M.A. Bredella, L. Freedman, B.J. Thomas, A. Breggia, E. Meenaghan, et al., Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa, J. Bone Miner. Res. 27 (2012) 1864–1871.
[56] C.W. Lu, Y.K. Chang, H.H. Chang, et al., Fracture risk after bariatric surgery: a 12-year nationwide cohort study, Medicine 94 (2015), e2087. .
[57] A. Lalmohamed, F. de Vries, M.T. Bazelier, et al., Risk of fracture after bariatric surgery in the United Kingdom: population based, retrospective cohort study, BMJ 345 (2012), e5085. .
[58] E.W. Yu, M.P. Lee, J.E. Landon, K.G. Lindeman, S.C. Kim, Fracture risk after bariatric surgery: roux-en-Y gastric bypass versus adjustable gastric banding, J. Bone Miner. Res. 32 (2017) 1229–1236.
[59] A.L. Schafer, X. Li, A.V. Schwartz, L.S. Tufts, A.L. Wheeler, C. Grunfeld, et al., Changes in vertebral bone marrow fat and bone mass after gastric bypass surgery: a pilot study, Bone 74 (2015) 140–145.
[60] M.A. Bredella, L.B. Greenblatt, A. Eajazi, M. Torriani, E.W. Yu, Effects of Roux-en-Y gastric bypass and sleeve gastrectomy on bone mineral density and marrow adipose tissue, Bone 95 (2017) 85–90.
[61] L.J. Melton, C.L. Leibson, S.J. Achenbach, T.M. Therneau, S. Khosla, Fracture risk in type 2 diabetes: update of a population-based study, J. Bone Miner. Res. 23 (2008) 1334–1342.
[62] A.V. Schwartz, D.E. Sellmeyer, K.E. Ensrud, J.A. Cauley, H.K. Tabor, P.J. Schreiner, et al., Older women with diabetes have an increased risk of fracture: a prospective study, J. Clin. Endocrinol. Metab. 86 (2001) 32–38.
[63] N. Napoli, E.S. Strotmeyer, K.E. Ensrud, D.E. Sellmeyer, D.C. Bauer, A.R. Hoffman, et al., Fracture risk in diabetic elderly men: the MrOS study, Diabetologia 57 (2014) 2057–2065.
[64] F.A. Syed, M.J. Oursler, T.E. Hefferanm, J.M. Peterson, B.L. Riggs, S. Khosla, Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women, Osteoporos. Int. 19 (2008) 1323–1330.
[65] G. Duque, W. Li, M. Adams, S. Xu, R. Phipps, Effects of risedronate on bone marrow adipocytes in postmenopausal women, Osteoporos. Int. J. Establ. Result Coop. Eur. Found Osteoporos. Natl. Osteoporos. Found USA 22 (2011) 1547–1553.
[66] A. Cohen, E.M. Stein, R.R. Recker, J.M. Lappe, D.W. Dempster, H. Zhou, et al., Teriparatide for idiopathic osteoporosis in premenopausal women: a pilot study, J. Clin. Endocrinol. Metab. 98 (2013) 1971–1981.
[67] Y. Yang, X. Luo, X. Xie, F. Yan, G. Chen, W. Zhao, et al., Influences of teriparatide administration on marrow fat content in postmenopausal osteopenic women using MR spectroscopy, Climacteric 19 (2016) 285–291.
[68] T. Rantalainen, R. Nikander, A. Heinonen, T. Cervinka, H. Sievänen, R.M. Daly, Differential effects of exercise on tibial shaft marrow density in young female athletes, J. Clin. Endocrinol. Metab. 98 (2013) 2037–2044.
[69] M. Styner, W.R. Thompson, K. Galior, G. Uzer, X. Wu, S. Kadari, et al., Bone marrow fat accumulation accelerated by high fat diet is suppressed by exercise, Bone 64 (2014) 39–46.
[70] S.E. Kahn, S.M. Haffner, M.A. Heise, W.H. Herman, R.R. Holman, N.P. Jones, et al., Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, N. Engl. J. Med. 355 (2006) 2427–2443.
[71] S.O. Rzonca, L.J. Suva, D. Gaddy, D.C. Montague, B. Lecka-Czernik, Bone is a target for the antidiabetic compound rosiglitazone, Endocrinology 145 (2004) 401–406.
[72] G.-W. Li, S.-X. Chang, J.-Z. Fan, Y.-N. Tian, Z. Xu, Y.-M. He, Marrow adiposity recovery after early zoledronic acid treatment of glucocorticoid-induced bone loss in rabbits assessed by magnetic resonance spectroscopy, Bone 52 (2013) 668–675.
[73] A.M. Pino, S. Ríos, P. Astudillo, M. Fernández, P. Figueroa, G. Seitz, et al., Concentration of adipogenic and proinflammatory cytokines in the bone marrow supernatant fluid of osteoporotic women, J. Bone Miner. Res. 25 (2010) 492–498.
[74] W.P. Cawthorn, E.L. Scheller, B.S. Learman, S.D. Parlee, B.R. Simon, H. Mori, et al., Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction, Cell Metab. 20 (2014) 368–375.
[75] E.L. Scheller, A.A. Burr, O.A. MacDougald, W.P. Cawthorn, Inside out: bone marrow adipose tissue as a source of circulating adiponectin, Adipocyte. 5 (2016) 251–269.
[76] Y.H. Ma, A.V. Schwartz, S. Sigurdsson, T.F. Hue, T.F. Lang, T.B. Harris, et al., Circulating Sclerostin associated with vertebral bone marrow fat in older men but not women, J. Clin. Endocrinol. Metab. 99 (2014) E2584–90.