Current Osteoporosis Reports (2024) 22:245–256
https://doi.org/10.1007/s11914-024-00864-4

Fat as a Friend or Foe of the Bone

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Accepted: 12 February 2024 / Published online: 28 February 2024

Abstract

Purpose of Review The objective of this review is to summarize the literature on the prevalence and diagnosis of obesity and its metabolic profile, including bone metabolism, focusing on the main inflammatory and turnover bone mediators that better characterize metabolically healthy obesity phenotype, and to summarize the therapeutic interventions for obesity with their effects on bone health.

Recent Findings Osteoporosis and fracture risk not only increase with age and menopause but also with metabolic diseases, such as diabetes mellitus. Thus, patients with high BMI may have a higher bone fragility and fracture risk. However, some obese individuals with healthy metabolic profiles seem to be less at risk of bone fracture.

Summary Obesity has become an alarming disease with growing prevalence and multiple metabolic comorbidities, resulting in a significant burden on healthcare and increased mortality. The imbalance between increased food ingestion and decreased energy expenditure leads to pathological adipose tissue distribution and function, with increased secretion of proinflammatory markers and harmful consequences for body tissues, including bone tissue. However, some obese individuals seem to have a healthy metabolic profile and may not develop cardiometabolic disease during their lives. This healthy metabolic profile also benefits bone turnover and is associated with lower fracture risk.

Keywords Adipose tissue · Metabolically healthy/unhealthy obesity · Adipokines · Bone marrow fat · Bone turnover · Fracture risk · Osteosarcopenia

Introduction

Obesity has become a major public health problem worldwide with a growing epidemiology, and increased burden from chronic diseases (including diabetes mellitus, hypertension, dyslipidemia, heart disease, stroke, sleep apnea, and cancer) and mortality [1]. Obesity also has economic impacts with considerable costs for health care systems and broader society [2]. Its prevalence has nearly tripled worldwide since the 1970s [3, 4, 5•] (5.5% of males and 9.8% of females) [6].

However, the relationship between obesity and cardiometabolic complications is not linear. More than 80% of individuals with type 2 diabetes are obese, but 10–30% of obese individuals have a metabolically healthy profile characterized by preserved insulin sensitivity and normal blood pressure and lipid profiles [7]. The latter are described as metabolically healthy obese (MHO). Conversely, 30% of normal-weight individuals will develop metabolic diseases during their lifetimes [8, 9•, 10].

Like obesity, osteoporosis is a major public health challenge due to its high prevalence and its association with morbidity, mortality, and healthcare costs. Osteoporosis has been diagnosed in more than 200 million people worldwide and is responsible for more than 8.9 million fractures annually, leading to an osteoporotic fracture every 3 s [11, 12]. The interaction between obesity and bone metabolism, particularly in the context of MHO, is complex and not completely understood; therefore, understanding the interaction between healthy and unhealthy fat and bone is an essential key to the optimal management of these two chronic conditions. This

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review summarizes current evidence on the metabolic and inflammatory profiles of MHO and metabolically unhealthy obese (MUHO) individuals, including their clinical phenotypes and the changes induced by these two profiles on bone. Finally, the impact of these profiles on osteoporosis treatment will be discussed.

Obesity and Cardiometabolic Risk

Obesity Definition

Obesity is an abnormal or excessive fat accumulation that presents a health risk [13]. The body mass index (BMI), a surrogate measure of body fat (BF) based on the person's weight adjusted for height, is typically used to categorize normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥ 30 kg/m^2) [14•] with morbid obesity defined as a BMI ≥ 40 kg/m^2. However, it does not consider the large variability in body adiposity and fat distributions between individuals, partially related to age, sex, and ethnicity. For instance, Asians have a higher percentage of body fat than Caucasians for the same BMI [15].

Abdominal obesity has been associated with a greater cardiometabolic risk than other locations of fat mass. Many studies have suggested that waist circumference, or the waist-to-hip ratio, may better indicate abdominal obesity than BMI [16]. Indeed, guidelines recommend measuring waist circumference when BMI is between 25.0 and 34.9 kg/m^2, with a cutoff point of 102 cm in men and 88 cm in women [17]. However, the fat distribution and its type are better prognostic health indicators than the above anthropometric measurements. Excess of visceral adipose tissue (VAT) may be more often associated with cardiovascular and metabolic disease, as well as colorectal cancer, than subcutaneous adipose tissue (SAT) [18, 19]. To date, the two gold-standard imaging methods for quantification of VAT and SAT are magnetic resonance imaging (MRI) and computed tomography (CT), which have limited use in research and clinical medicine given their cost and exposure to radiation (CT only) [20]. Dual-energy X-ray absorptiometry (DXA), initially used for osteoporosis diagnosis and monitoring, is also a validated technique to assess body composition, with lower cost and more availability [21]. These data support that there are heterogeneous obesity phenotypes among populations, depending on body fat distribution, each one with a different metabolic risk profile, leading to the concept of MHO and MUHO phenotypes [22•].

Metabolic Obesity: Pathophysiology and Definition

Adipose tissue is a dynamic organ with a major role in energy homeostasis, composed mainly of white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is involved in energy storage and includes VAT (the fat stored around internal organs), which is endocrinologically active, and SAT which is mainly metabolically inactive. In contrast, BAT is involved in energy expenditure and is mostly localized in the supraclavicular and paravertebral regions [23–25].

Accumulation of fat in visceral organs (VAT) and ectopic fat deposition (muscle, liver, heart) could lead to MUHO together with an increased risk of conditions associated with metabolic abnormalities such as hypertension, dyslipidemia, and impaired glucose metabolism, which are consequently associated with an increased risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD) [26]. In addition, excess hepatic fat (NAFLD) is a potential predictor of the MUHO phenotype and subclinical atherosclerosis [27]. Failure adipose tissue expansion (hypertrophic fat cells), occurring after a positive energy balance, results in ectopic deposition of lipids with associated lipotoxicity, abnormal proinflammatory markers secretion, high immune cell infiltration, and consequently, insulin resistance in peripheral tissues [28].

Regarding MHO, there is no universal definition for this phenotype which can explain the large variability of its prevalence (6–40% of obese individuals) [29, 30]. This subgroup of people with obesity (BMI ≥ 30 kg/m^2) is mainly characterized by the absence of insulin resistance, none of the criteria of metabolic syndrome (or some of its components) and no cardiovascular disease. Some studies also include a favorable inflammatory status according to C-reactive protein (CRP) levels [31–33]. Consequently, body composition, fat distribution, and function are critical in distinguishing metabolically healthy from metabolically unhealthy individuals.

Determinants of MHO/MUHO in the Genesis of CVD

Gender, age, genetic polymorphism, gut microbiota, and ethnicity are major etiologic factors leading to variation in fat visceral deposition, in addition to lifestyle factors [26, 34, 35••]. Despite the heterogeneity in classification, MHO individuals appear to have higher SAT levels and less visceral and ectopic fat deposition than MUHO individuals with the same BMI and usually do not develop cardiometabolic disease. Conversely, there are individuals with normal BMI and increased cardiometabolic risk36].

The quality of adipose tissue is equally important to explain the more favorable metabolic profile. MUHO might be the consequence of an impaired adipose tissue function after a chronic positive energy balance, leading to the inability of the subcutaneous adipose tissue to expand sufficiently to counter this long-term imbalance [7]. The inflammatory status also plays a key role field [37]: MHO

phenotype is associated with lower proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α, as well as lower levels of proinflammatory M1 macrophages and CD4 + T cells [37, 38].

Several adipokines produced by the adipose tissue are linked to the development of insulin resistance and T2DM [39–41]. Adiponectin, whose production is inversely correlated with adipose mass, and omentin-1 are both considered anti-inflammatory and cardioprotective adipokines and are higher in MHO subjects. Two non-cardioprotective adipokines, visfatin and resistin, are lower in MHO [42–44]. Leptin, expressed in levels proportionate to adiposity, is a product of the obesity gene with a pleiotropic effect on food intake, body weight, reproductive system, proinflammatory responses, and lipid metabolism [45]. It may act as a biomarker for cardiovascular diseases in obese individuals, as elevated plasma leptin levels are associated with proinflammatory effects, atherosclerosis, hypertension and metabolic syndrome [46]. Moreover, high serum leptin/adiponectin ratio may be a marker of "at risk" obesity, independent of waist circumference and BMI. In the literature, higher leptin levels among MUHO subjects have been found. However, some studies showed no difference between the two groups [47–49]. These few studies with contradictory results are likely secondary to other confounder parameters (differences in race, age, gender, definition of MHO used, or sample size).

In summary, the most important biological factors used to determine MHO profile are a lower amount of visceral and ectopic fat, a higher amount of subcutaneous adiposity, a decreased inflammation and fibrosis, specific adipokines secretion, and a preserved insulin sensitivity compared to MUHO profile.

Obesity and Bone Metabolism

Interaction Bone-Adipose Tissue

Osteoporosis is characterized by low bone mineral density (BMD), defined by a T-score 2.5 SD or more below the mean adult value with DXA (femoral neck measure), and progressive bone microarchitectural deterioration resulting in decreased bone strength and increased susceptibility to fractures [50]. Historically, the common belief was that obesity has a protective effect against osteoporosis [51]. Additionally, higher BMI results in lower fracture risk in the "fracture risk assessment tool (FRAX). Indeed, some studies showed a positive effect of fat on bone mass due to a higher BMD and local adipose padding in obese people compared to people with normal weight [52–54]. A low body weight is also a risk factor for fragility fracture [55]. Conversely, there is evidence that obesity has a harmful effect on bone mass [56•].

Several mechanical and biochemical mechanisms have been suggested to understand the complex communication between the adipose tissue and bone tissue. Higher body mass results in increased mechanical load on bone, leading to an increase in BMD to adapt to mechanical stress [57]. This hypothesis has been supported by precise quantitative methods (e.g., high-resolution peripheral quantitative CT) [58]. Moreover, fracture risk in obese people seems to be site-dependent: obesity is associated with higher fractures in the ankle, leg, humerus, and vertebral column, and lower fractures in the wrist, hip, and pelvis [59, 60].

Fat distribution also plays an important role. Each adipose tissue compartment has a specific metabolic profile and bone effect. VAT secretes more proinflammatory markers, negatively impacting BMD [61, 62]. Excess of SAT is associated with more leptin secretion and results in lower bone resorption and higher bone strength than excess VAT. Intramuscular fat leads to muscle performance impairment and myocyte insulin resistance [63, 64]. Additionally, brown fat (BAT) positively affects bone mass [65]. The bone marrow adipose tissue (BMAT), named yellow bone marrow, is another metabolically active adipose tissue involved in bone homeostasis and body energetic metabolism by direct or indirect effects.

Estrogens, synthesized from androgen precursors by aromatase in adipose tissue, have a crucial role in bone protection by promoting bone formation and reducing bone resorption. Obese post-menopausal women have been shown to have higher estrogen levels in blood compared with non-obese individuals [66]. Overproduction of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, results in osteoclast differentiation stimulation and bone resorption through activation of RANKL/RANK/osteoprotegerin (OPG) pathway [67, 68]. In addition, adipokines such as leptin, typically high in obesity, and adiponectin, low in obesity, as well as bone turnover markers (vitamin D, parathyroid hormone, calcium, osteocalcin), are other potential parameters involved in this interaction [69, 70].

Bone Metabolism Changes and Effects in MHO/MUHO

Bone Marrow Adipose Tissue (BMAT)

BMAT has a metabolically distinct phenotype with some similar WAT and BAT properties [71]. The degree of BMAT is not strictly related to BMI or body adipose tissue. To support these data, excess bone marrow is well described in patients with anorexia nervosa [72]. BMAT is considered a potential marker of compromised bone integrity and a major regulator of bone turnover with evidence showing an

increased amount of bone marrow adipose tissue in osteoporosis, although it is unclear what is the cause and the consequence [73, 74••]. The hypothesis is that the higher amount of bone marrow fat may decrease bone mass in obesity due to aberrant differentiation of progenitor stem cells in the bone marrow. Indeed, osteoblasts and marrow adipocytes, come from the same progenitor cell, the mesenchymal stromal cell (MSC)]. The ratio of bone marrow fat might increase with menopause, aging, and chronic renal failure, resulting in decreased bone density and enhanced fracture risk [76]. A high-fat diet might also increase BMAT in mice [77, 78]. In vitro $1,25(OH)_2D$ treatment of pre-adipocytes in culture suppresses adipogenesis [79] and enhances MSC differentiation to osteoblasts [80]. In vivo, administration of $1,25(OH)_2D$ in senescence-accelerated mice (SAM-P/6) was shown to inhibit adipogenesis and to accelerate differentiation of MSC into osteoblasts compared to placebo-treated animals [81]. This was accompanied by an increase in both cortical and trabecular bone strength [82].

The differentiation in osteoblast or adipocyte involves specific transcription factors (RUNX2 and Osterix for osteoblasts and PPARγ2 for adipocytes), and excess adipogenesis decreases bone formation [83–85]. Consequently, PPARγ suppression would result in bone formation and adipogenesis suppression [86]. Modified selection from the mesenchymal lineage to the adipogenic lineage rather than the osteogenic lineage might involve several mechanisms, such as oxidative stress, proinflammatory factors (TNF-α and IL-6) and adipokines [87, 88].

The only study that compared specific abdominal fat deposition, including lumbar bone marrow fat, between MHO/MUHO in 114 children showed no differences between the two groups [89]. Other studies showed a positive correlation between bone marrow fat and visceral fat [90–92]. Thus, MHO individuals, known to have lower visceral fat, might have lower bone marrow fat levels than MUHO individuals and, therefore, might be less at risk of osteoporosis.

Blood Biomarkers, Micronutrients, and Bone Mass

Adults with class III obesity are more at risk of having bone metabolism dysfunction, leading to an increase in bone turnover [93]. Consequently, even if there is limited literature on the bone metabolic changes in each phenotype, the detection of certain blood biomarkers and micronutrients specific to each metabolic profile would be a promising advance in the early screening of MHO/MUHO phenotypes and their bone risk fracture, in order to better target the indication for early BMD as well as therapeutic interventions (Fig. 1).

Leptin directly and indirectly affects bone through central (hypothalamic) and peripheral pathways, possibly partially explaining the contradictory results reported in vivo and in vitro [94••]. In vitro, leptin activates the differentiation of MSC to osteoblasts, enhances osteoblast proliferation, and inhibits osteoclastogenesis through increasing OPG and the RANK/RANKL/OPG pathway [95, 96]. In vivo studies demonstrate that leptin has positive or negative effects on bone tissue, depending on its site and mode of action [97–99]. Human studies are limited and reported both positive [100, 101] and negative effects [102, 103] on bone mass. Furthermore, in the clinical field, an increased level of leptin in obese patients is usually associated with high bone mass, contrary to the decreased level seen in young women with anorexia nervosa and low BMD.

Adiponectin levels are inversely correlated with central and visceral fat volumes in MHO individuals. This has been demonstrated to stimulate both bone formation and bone resorption, but its action on bone mass is controversial [104–108]. In many studies, adiponectin is inversely correlated with bone mass, although its effects on bone are unclear. Nevertheless, obesity is an inflammatory state with the secretion of inflammatory mediators (CRP, IL-1, IL-6, and TNF-α), which might be inhibitors of adipokine expression, with a known negative impact on BMD [109]. A recent meta-analysis of the

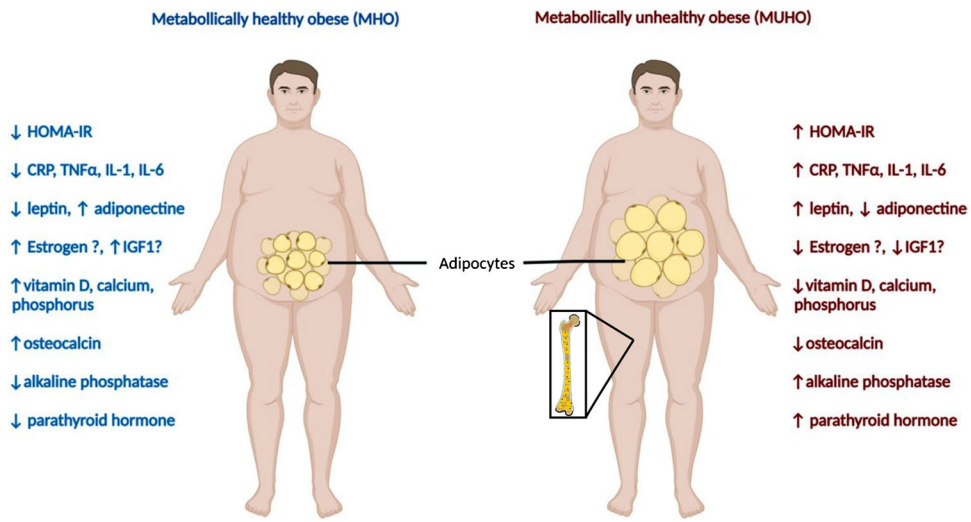

Fig. 1 Bone regulatory factors associated in MHO versus MUHO: Metabolic healthy obesity is associated with lower insulin resistance (HOMA-IR), lower inflammatory markers (CRP, TNFα, IL-1, IL-6), lower leptin and higher adiponectin, potential higher estrogen and IGF1, higher vitamin D, calcium, phosphorus, osteocalcin, and lower alkaline phosphatase, parathyroid hormone, than metabolic unhealthy obesity. In addition, increased levels of marrow adiposity are observed in MUHO individuals (prepared using BioRender software)

pooled correlations between adipokines and BMD included 47 studies and showed that leptin is correlated with BMD, adiponectin is inversely correlated with BMD, and patients with osteoporosis had lower leptin values and higher adiponectin values than patients with normal bone mass. Consequently, both adipokines might be promising blood biomarkers to predict bone fracture risk in obesity [110].

Multiple studies found an association between an increase in central adiposity, insulin resistance, and cardiometabolic disease with the menopause state [111–113]. Then, estrogen levels might be lower in MHO individuals than in MUHO individuals. Visceral obesity is associated with relative GH and IGF-1 deficiency [114]. IGF-1, a growth-promoting polypeptide, is an important determinant of cortical area in mice models [115]. Furthermore, it stimulates bone remodeling and has an anabolic effect on bone tissue. To support this finding, previous studies found a positive correlation between IGF-1 and bone mass and a negative correlation between IGF-1 and vertebral bone marrow fat in premenopausal women with or without obesity [62, 90]. These data could suggest a lower amount of IGF1 in MHO subjects.

Vitamin D plays a major role in mineral homeostasis through its essential ability to regulate calcium and phosphorus absorption, stimulating bone remodeling and modulating parathyroid hormone (PTH) and FGF-23 synthesis. Vitamin D insufficiency/deficiency is highly prevalent in the general population [116], and several studies have found a strong inverse correlation between weight and circulating vitamin D levels [117–119]. There are, however, substantial differences in the prevalence of vitamin D deficiency/insufficiency according to race/ethnic group, which is disproportionately more common in African Americans and Mexican Americans and in whom obesity is quite prevalent. Of particular interest was the finding that young Mexican American women with vitamin D insufficiency were significantly heavier and had 40% more subcutaneous and 80% more intra-abdominal fat than women with normal vitamin D levels [117]. It has been proposed that the association between obesity and vitamin D insufficiency/deficiency may be bidirectional through several potential pathophysiological mechanisms [120]. However, few studies have examined the effect of vitamin D supplementation on weight with diverging results. One study reported that high BMI might be associated with a modified response to vitamin D supplementation [121]. Another study by Ortega et al. found that baseline 25OHD levels predict the efficacy of the weight loss regimen and that the vitamin D status potentiates the effect of low caloric diet [122]. However, most studies found that in overweight and obese subjects, supplementation with vitamin D does not lead to a significant reduction in weight, percentage of fat mass, or change in fat distribution as evaluated by the waist-to-hip ratio [123–125]. Unfortunately, difficulties in controlling for the confounding effects of diet in vitamin D trials or weight reduction interventions have hindered the examination of the vitamin D/obesity link.

Moreover, since vitamin D is likely stored in body fat, simply increasing the vitamin D dosage may not be effective in overweight individuals. Nevertheless, overweight, or obese people tend to have secondary hyperparathyroidism and lower serum osteocalcin concentrations, which may, in part, be explained by low vitamin D levels leading to potential metabolic abnormalities [126, 127]. Significantly, vitamin D insufficiency/deficiency is also associated with the accumulation of muscle fat and reduction in muscle strength [128, 129], a known risk factor for falls and fractures. Overall, the combination of chronic vitamin D, calcium, and phosphorus deficiencies, particularly in obese people, enhances the risk of osteoporosis and fractures [130, 131].

Loureiro et al. [132] showed that the MHO profile in subjects with obesity class III does not protect against the abnormal secretion of bone biomarkers and micronutrients. However, among MUHO individuals, vitamin D levels are inversely correlated with BMI, and alkaline phosphatase, a marker of bone turnover regulated by vitamin D, is more concentrated. The lower vitamin D level could be partially explained by the higher abdominal fat responsible for vitamin D sequestration [133]. Moreover, there is an association between calcium, vitamin D and phosphorus in the MUHO phenotype. Thus, we can postulate that MUHO people with obesity class III have a higher risk of alterations to vitamin D, calcium, phosphorus, and PTH, promoting the development of bone disease. Sukumar et al. [134] showed that the MHO phenotype has higher serum concentrations of osteocalcin with lower serum PTH, and PTH positively correlates with body fat mass. Osteocalcin, a protein involved in bone mineralization, recently has been considered to regulate energy metabolism by increasing insulin secretion in β-cells and promoting insulin sensitivity.

In summary, early screening of these adipokines, hormones, and nutrient alterations, detected by simple blood tests, could help predict bone health in overweight or obese patients and lead to early and targeted management of bone disease.

Bone Structure and Fracture

Historically, obesity has been considered to protect against bone loss via mechanical loading under the influence of biomarkers secreted or regulated by adipocytes. Several studies tried to find an association between BMD and metabolic syndrome (MS) components, as seen in the MUHO profile, but the results have been discordant [135–137].

MHO profile is characterized by greater lean mass and lower fat mass, particularly visceral fat. Lean mass has been

considered as the strongest predictor of BMD in premenopausal women. Yamaguchi et al. [138] found that VAT area measured by CT was positively correlated with BMD in a Japanese population with T2DM, but there was no longer a significant association after correction by BMI. The effect might be due to general obesity rather than visceral fat. Recent studies showed an inverse correlation between VAT and BMD, contrary to SAT, for which negative or no association was found [61, 139–142]

Currently, only a few studies have explored the specific bone phenotype in healthy/unhealthy obesity. Mirzababaei et al. [143••] found a potential link between BMD and metabolic healthy/unhealthy phenotypes among adult obese individuals. After adjusting for age, sex, and BMI, MUHO individuals had higher total BMD and positive correlation with hip BMD compared to MHO individuals. There was no statistical association with lumbar BMD. The BMI between the groups was the same, but fat percentage, fat spine, visceral fat, and trunk fat were higher in the MUHO group. Specific skeletal sites with local mechanical load on bone may explain the higher hip BMD seen in the MUHO group.

Wang et al. [144] described the relationship between metabolic obesity and forearm BMD in young, middle-aged Chinese people and found a lower forearm BMD in men with MUHO profile and women metabolically unhealthy but with normal weight than in the MHO group. They concluded that metabolic obesity might be a better predictor of bone health than BMI alone and showed that waist circumference, LDL-c concentration and insulin resistance might be negatively associated with bone health. Additionally, Ubago et al. [145] examined the association between areal BMD (aBMD) and metabolic obesity in overweight/obese children and the role of moderate-to-vigorous physical activity (MVPA) and cardiorespiratory fitness (CRF) in this association. A higher aBMD was found in TBLH (total body less head), trunk and pelvis in MHO compared to MUHO patients and was partially explained by MVPA and CRF. Confounding variables used were more reliable in this study (TBLH lean mass) than those used by Mirzababei (BMI) and could partially explain the different findings.

A meta-analysis of seven studies with 551,224 individuals conducted by Li et al. [146] found that waist circumference and waist-to-hip ratio positively correlate with an increased risk of hip fracture. Nguyen et al. [147] showed that the abdominal adipose tissue measured by DXA has a modest contribution to the risk of hip fracture in adults over 60 years old. However, this finding could be explained by the measure of abdominal obesity combining the sum of the differential effects of subcutaneous and visceral adipose tissues on bone health. Yamaguchi et al. [138], also evaluated the fracture risk and suggested a potential protective role of VAT on vertebral fractures in patients with T2DM.

Fracture risk may depend on BMD but also on applied loads experienced during activities (local higher body masses), explaining the fracture occurrence in specific skeletal sites in obese individuals [148]. A biomechanical study found a higher risk for low-trauma and compression fracture in the spine in obese patients with the same BMI but increased waist circumference, leading to increased local pressure on the spine [149]. Gandham et al. [150] found that obesity defined by BMI is associated with a lower risk of incident fracture mediated by higher BMD but associated with a higher risk if body fat percentage was used instead of BMI. MUHO profile is often associated with T2DM as part of metabolic syndrome. Evidence suggests that influence of advanced glycation end products (AGEs) on bone matrix, complications of diabetes and medication used (ex: thiazolidinediones) probably have a major impact on bone fragility and the increased fracture risk [151].

In summary, bone fracture risk, specifically in healthy/unhealthy obese individuals, has not been studied yet, but most available studies demonstrate a negative association between visceral adipose tissue or T2DM and BMD or fracture risk, suggesting that MUHO phenotype might be associated with a higher risk of osteoporosis, than MHO phenotype.

Intervention

In longitudinal and prospective studies, almost 50% of MHO patients progress to MUHO phenotypes within 10 years [152, 153]. Prevention and reversal of this transition should be considered in therapeutic management. Thus, the development of risk prediction tools is crucial. As seen above, several biomarkers could be helpful in characterizing the metabolic obesity profile and maybe predicting this transition (Fig. 1).

Lifestyle Intervention and Prevention of Osteoporosis

Guidelines recommend weight loss by lifestyle intervention first in all obese patients, without stratifying according to MHO and MUHO phenotypes. A low-fat, healthy diet with adequate dairy, calcium, and vitamin D intake, exercise, and smoking and alcohol intake cessation should be advised. Multiple studies suggested that weight loss is associated with loss of BMD in the hip and trabecular bone [154–156]. Other studies demonstrated that BMD is not decreased, and bone geometry is preserved with moderate weight loss ($8 \pm 4\%$) [157]. Conversely, a randomized clinical trial of 101 post-menopausal women with obesity showed that an intense energy restriction was associated with a higher loss

of BMD in the hip BMD but not in the lumbar spine, compared to moderate energy restriction [158]. Clinical studies also showed a trend toward a reduction in BMAT with dietary-induced weight loss in obese patients [159••]. Given the potential role of hyperinsulinemia in converting MHO to MUHO, lower sugars and carbohydrate diet to avoid postprandial insulin increments should also be suggested [160].

Regarding physical activity, studies showed that exercise training increases the probability of having MHO phenotype [161]. Resistance exercise programs, alone or combined with aerobic exercise programs, reduce frailty and attenuate bone mass and sarcopenia in the context of a weight loss program [162, 163]. In summary, a moderate weight loss program associated with resistance alone or with aerobic exercise training is currently the best lifestyle option advised in MHO to avoid the transition to MUHO and the harmful bone effects.

Treatment Options and Bone Health

In addition to its effect on appetite and food intake, evidence suggests that GLP-1 receptor agonists (GLP-1 RA) have positive effects on bone by promoting bone formation and inhibiting bone resorption [164]. Furthermore, several studies found an increase in BMD and a decreased risk of fracture in subjects with type 2 diabetes treated with GLP-1RA compared to placebo or other antihyperglycemic drugs [165, 166]. Another hormone secreted in the upper small intestine, a glucose-dependent insulinotropic peptide, GIP, when combined with GLP-1RA, named Tirzepatide, leads to significative weight loss and improvement of nonalcoholic steatohepatitis (NASH) biomarkers and fibrosis in patients with type 2 diabetes [167]. Overexpression of GIP has shown increased bone strength in experimental studies [168]. Consequently, GLP-1 RA and GIP, leading to the improvement of metabolic syndrome and potentially preventing progression to MUHO, could be beneficial treatments for bone health when osteoporosis is superimposed.

Bariatric surgery, such as Roux-en-Y gastric bypass surgery (RYGB), promotes sustained weight loss, with an improvement of metabolic profile and inflammatory profile, and could be, consequently, a benefic therapeutic option in obesity, including MHO [169]. Nevertheless, several effects on bone have been described in the literature: A decrease in BMD with a reduction of cortical load [170, 171], and an increase of bone turnover biomarkers, both resulting in increased risk of fracture, with increased incidence between 2 and 5 years after surgery, and mainly occurring in different sites than those associated with obesity [172, 173]. Interestingly, exercise could mitigate these negative bone effects [174].

Conclusion

Despite a higher BMD, accumulating data demonstrate a negative effect of obesity on bone tissue with a site-dependent fracture risk, secondary to increased mechanical loads on some bones, excess of visceral, ectopic (including hepatic adipose tissue) and BMAT, with a metabolic profile specific to each tissue, and secretion of inflammatory cytokines, adipokines, hormones and bone remodeling factors (Fig. 1). The MHO phenotype is characterized by a more favorable body composition, distribution (less visceral, ectopic and bone marrow fat), and function than MUHO phenotype, and thus, associated with less metabolism alterations.

Understanding the mechanisms underlying these different metabolic effects is paramount to help improve the indication for early bone densitometry, develop possible intervention targets against obesity and osteoporosis, and detect early metabolic complications, including bone disease. To date, the potential determinants of MHO are not clear, however, most studies found a positive or negative correlation with inflammatory markers (CRP, cytokines, adipokines), hormones (estrogen, IGF1), and bone turnover biomarkers (vitamin D, calcium, phosphorus, PTH, osteocalcin, alkaline phosphatase), which could be therefore detected in simple blood tests.

Few data comparing bone metabolism changes and healthy/unhealthy obesity are currently available, and comparability between the studies is difficult given the lack of a universal definition for metabolically healthy obesity. The main hypothesis is that MHO is defined by excess visceral fat and the absence of metabolic syndrome features, including T2DM, associated with a better bone structure and mass, and potentially a lower risk of fracture and osteoporosis than in unhealthy obese. However, other studies are needed to confirm this hypothesis. Patients with MHO still have an indication for lifestyle management (moderate weight loss and exercises) with or without medical or surgical treatments to avoid or delay the transition to the MUHO phenotype, which may lead to a higher risk of bone metabolism-related changes.

Author contributions E.G., R.K., and G.D. wrote the main manuscript text and E.G. and G.D. prepared figure 1. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest EG, RK, and GD have no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Ethical Approval This review article does not present any previously unpublished original research, and ethical approval is therefore not applicable.

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- • Of importance
- •• Of major importance

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