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Obesity is a concern for bone health with aging

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Abstract

Accumulating evidence supports a complex relationship between adiposity and osteoporosis in overweight/obese individuals, with local interactions and endocrine regulation by adipose tissue on bone metabolism and fracture risk in elderly populations. This review was conducted to summarize existing evidence to test the hypothesis that obesity is a risk factor for bone health in aging individuals. Mechanisms by which obesity adversely affects bone health are believed to be multiple, such as an alteration of bone-regulating hormones, inflammation, oxidative stress, the endocannabinoid system, that affect bone cell metabolism are discussed. In addition, evidence on the effect of fat mass and distribution on bone mass and quality is reviewed together with findings relating energy and fat intake with bone health. In summary, studies indicate that the positive effects of body weight on bone mineral density cannot counteract the detrimental effects of obesity on bone quality. However, the exact mechanism underlying bone deterioration in the obese is not clear yet and further research is required to elucidate the effect of adipose depots on bone and fracture risk in the obese population.

Keywords

Obesity; Osteoporosis; Bone marrow fat; Inflammation; Fracture

1. Introduction

The increase in human longevity represents a global phenomenon resulting in an aging population with profound implications for human health. The rates of diseases and conditions, typically affecting older individuals, have dramatically increased in recent years. During the past three decades, the number of older adults who are obese has doubled and the prevalence of obesity is increasing in all age groups in the United States [1,2]. An imbalance between energy intake and expenditure as well as additional factors such as age-associated hormonal changes, genetic, environmental and social factors contribute to the obesity epidemic. Obesity has direct consequences on health and increases the risks of several chronic diseases such as type II diabetes, cardiovascular disease, and cancers that compromise life quality and leads to premature death.

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Aging is associated with an accelerated decline in bone mass and strength that can culminate with osteoporosis, the major underlying cause of fracture especially in older adults. Osteoporosis or low bone mass affects more than half of the population age 50 years and beyond in the United States [3]. Even though the majority of people diagnosed with osteoporosis are women, osteoporotic fractures also occur in men as well and result in significant morbidity and mortality increased healthcare costs [4].

Accumulating evidence supports a complex relationship between adiposity and osteoporosis in the context of obesity, which goes beyond the unidirectional relationship between body weight and bone mass. Obesity adversely affects bone health by a variety of mechanisms such as an alteration of bone-regulating hormones, increased oxidative stress and inflammation, and altered bone cell metabolism. More recently, evidence indicates that obesity affects bone quality which may be a reason for a greater risk of fractures for a given bone mineral density (BMD) in the obese population [5–7]. These local interactions and endocrine regulation by adipose tissue on bone metabolism and fracture risk in obesity with aging are being addressed in this review (Figure 1).

To complete this review, a literature search on the PubMed (Medline) database was performed for studies published before August 15, 2016. The PubMed search terms included: BMD, bone quality, bone marrow fat tissue, osteoblast, osteoclast, visceral fat, obese, adipose, adipocyte, fracture and high-fat diet and fatty acid. The retrieved articles were evaluated for their relevance to the topic of this review. Relevant primary papers and review articles were searched and used for references to identify additional relevant studies.

2. Factors affecting bone cell fate in obesity

Osteoblasts and adipocytes originate in the common precursor mesenchymal stem cell (MSC). The balance between differentiation and proliferation of osteoblasts and adipocytes into one cell lineage over the other is regulated by both intra-and- extra cellular factors. Excess adipogenesis may occur when osteoblastogenesis is compromised or vice versa. For example, peroxisome proliferator–activated receptor-γ (PPARγ) and several drugs that act as ligands for PPARγ promote adipogenesis at the expense of osteoblastogenesis [8]. Antidiabetic drugs, such as thiazolidinedione improve insulin sensitivity in patients [9], but also result in excess adiposity, bone loss and increased fracture risk [10]. In addition, chronic use of steroid hormones such as glucocorticoids is shown to induce obesity and bone loss [11]. Specifically, bone loss occurs through early stimulation of osteoclast maturation and activity, and delayed reduction in osteoblastogenesis [11]. In addition, increased bone remodeling with glucocorticoids treatment occurs through reductions in sex hormones and sustained elevation of PTH [11]. Furthermore, hyperlipidemia, independent of obesity can result in the accumulation of oxidized lipids surrounding the MSC and inhibit osteoblast differentiation and bone formation [12–14]. Aging alone alters the fate of MSC in bone marrow by promoting adipogenesis and reducing osteoblastogenesis [15,16]. Enhanced expression of PPARγ in the bone marrow with aging and decreased expression of growth factors involved in osteogenesis promote adipogenesis while suppressing osteoblastogenesis will increase age-related bone loss [17]. In addition, in long-term cell culture models,

proliferation, differentiation and chromosomal stability of MSCs are altered, suggesting a direct effect of aging on the MSC [16].

2.1 Hormonal milieu in obesity

There is a fat-bone interaction that is directly influenced by adipose tissue endocrine function and other hormonal dysregulations accompanying obesity [18]. Obesity is associated with higher circulating estrogen that results from increased aromatization of androstenedione by highly expressed aromatase in the white adipose tissue [8]. This higher estrogenic state may partially attenuate bone loss in obese postmenopausal women. In addition, parathyroid hormone (PTH) has been directly associated with fat mass [19,20] and although the mechanisms responsible for this observation are less clear, PTH influences calcium metabolism and proinflammatory cytokine secretion [20] and could alter bone with greater effect on the cortical compartment [5,22]. However, circulating 25-hydroxyvitamin D (25OHD) levels are lower in the obese compared to lean individuals that are attributed to volume dilution into adipose tissue and with potential negative consequences to bone health [23–25].

Obesity increases the secretion of pancreatic hormones such as insulin, amylin, and preptin that may in turn affect bone health [26–28]. However, the mechanism whereby gut peptides affect bone health remains elusive. For example, observational studies report an inverse relationship between insulin resistance and bone strength under conditions of hyperinsulinemia [29,30]. Amylin infusion may affect osteoblast activity and appears to be attenuated under conditions of insulin-resistance [31], but overall, the role of both amylin and preptin is poorly studied. Hence, in the obese with hyperinsulinemia and insulin resistance, the anabolic effect of the pancreatic hormones could be less apparent and explain, at least partially, the higher rates of fracture in obese patients with diabetes.

2.2 Adipose-derived endocrine factors

The role of adipokines, particularly leptin and adiponectin, on bone metabolism has been examined in human and animal studies [32–37]. Leptin, a peptide hormone secreted by white adipose tissue, acts on the brain to control food intake and energy metabolism and in the absence of obesity, there is greater sensitivity to leptin with aging. However, its effects on bone are controversial. The *in vitro* data support a positive osteoblast-dependent action for leptin on osteoblast proliferation and differentiation while inhibiting osteoclastogenesis, and has been confirmed by the *in vivo* experiments using murine models [36,37]. However, these experiments also suggest that leptin regulates bone metabolism via the central nervous system by suppressing bone formation while increasing resorption [36]. Extrapolating these findings to humans is challenging considering that diet-induced obesity and hyperleptinemia both in humans and animal models are accompanied by leptin resistance, but bone loss due to high levels of leptin in obese individuals does not occur [38]. Furthermore, observational studies indicate that there is no direct relationship between leptin, bone mass, bone turnover markers, and fracture risk in humans [39,40].

Circulating adiponectin, another adipocyte-derived hormone is lower in obesity and increases with aging [41]. Adiponectin stimulates osteoblast-receptors to increase

osteoblastogenesis and indirectly inhibit osteoclastogenesis [42]. However, higher adiponectin levels are associated with greater bone loss at the lumbar spine in a 12 months longitudinal study conducted in physically active older women [43]. Furthermore, in the Health Aging and Body Composition Study, serum adiponectin was significantly higher in overweight women with fractures compared to women without fractures [40], indicating that adiponectin may be a biomarker of fracture risk [34, 40,41]. Several other adipokines, potentially involved in the development of senile osteoporosis, have been identified including resistin, fasting-induced adipose factor, visfatin, vaspin, and apelin [44]. However, the relationship between these adipokines and BMD has been inconsistent, possibly due to confounding by fat mass, BMI or body weight [35].

2.3 Cytokines

Obesity is associated with elevated systemic and local inflammation status, and obese individuals have abnormal circulating levels of inflammatory cytokines, such as interleukin-6 (IL-6), monocyte chemoattractant protein-1, and C-reactive protein (CRP) and tumor necrosis factor α (TNFα) [45]. Proinflammatory cytokines appear to modulate osteoclast differentiation and bone resorption. In patients with periodontitis, pancreatitis, inflammatory bowel disease, and rheumatoid arthritis, chronic inflammation and increased proinflammatory cytokines have been associated with bone resorption and bone loss [46,47]. Moreover, the menopause-induced bone loss has been linked to increased production of proinflammatory cytokines including TNF-α, interleukin-1 (IL-1), and IL-6 [48]. It has been shown that osteoblasts control the recruitment and activity of osteoclasts through the expression of the receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG). These inflammatory cytokines (i.e. TNF-α, IL-1, and IL-6) act by regulating RANKL/RANK/OPG pathways and stimulate osteoclast activity and bone loss [49,50].

2.4 Endocannabinoid system and bone metabolism

Our understanding of energy metabolism in recent years has allowed for a better understanding of the control of skeletal metabolism. The endocannabinoid system (ECS) including endogenous ligands *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) and their classical receptors CB_1 and CB_2 regulate energy balance, nutrient transport, metabolism and storage [51,52]. The ECS also plays a role in regulating other physiological processes such as appetite control, learning, memory, pain perception, cardiovascular homeostasis, motor control, immune responses and in bone cell activity and remodeling [53,54]. Dysregulation of ECS contributes to obesity and inflammation that may indirectly affect bone [52,54]. Importantly, bone cells are able to synthesize endocannabinoids, which may have local effects [55]. Both *in vitro* and *in vivo* studies demonstrate that cannabinoid receptors regulate bone mass in humans and mice [55,56]. The CB_1 receptor activates bone resorption by stimulating osteoclastogenesis and preventing osteoclast apoptosis [57,58]. The CB_2 receptor is also expressed in osteoclasts, but there are inconsistent findings regarding its role in osteoclastogenesis with inhibitory effects found in some studies [56,59] and stimulating effects in others [55,57,60]. Moreover, the CB_2 receptor can be found in both preosteoblasts and osteoblasts and is shown to have stimulating effects on bone formation and prevent bone loss, whereas CB_1 is low in mature osteoblasts [58,59]. Overall, inhibition of either CB_1 or CB_2 is associated with abnormal

bone phenotype and bone mass. Combined CB_1 and CB_2 deficiency enhances peak bone mass by attenuating bone resorption during growth, and in contrast predisposes mature bone to age-related osteoporosis by attenuating osteoblast differentiation and promoting adipocyte differentiation [61]. Further research should clarify the exact relationship between these model systems and the ECS with factors affecting skeletal metabolism and maintaining skeletal integrity with aging.

3. Effects of fat and obesity on bone mass and quality

3.1 White adipose tissue

Across gender and ethnicities, higher body mass index (BMI) is associated with greater visceral adiposity [62], directly linked to altered hormonal and metabolic milieu and could contribute to skeletal fragility. Altered bone quality and stiffness and a decline in bone formation have been shown in young women with more central adiposity [63]. Moreover, in older individuals changes in fat partitioning, muscle attenuation, and bone density with aging in conjunction with insulin resistance, inflammation, and dyslipidemia promoted by greater visceral fat depots could have negative consequences on bone health. A limitation of the previous studies was that most only reported the relationship between fat mass and bone, whereas newer dual-energy x-ray absorptiometry (DXA) instruments can estimate visceral adipose tissue (VAT). Advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) can more accurately measure a number of adipose depots including VAT, subcutaneous adipose tissues (SAT), and others. In studies using CT technique, conducted in middle-aged and older adults, VAT has been associated with reduced bone mass, while SAT has been found to protect bone health (Table 1), although after correcting for body weight these effects become less apparent. Others also suggest that VAT is not associated with a detrimental effect on bone microarchitecture after adjusting for BMI or weight [65]. In addition, obese postmenopausal women and those with more VAT than normal-weight postmenopausal women have lower osteocalcin levels, a bone turnover marker associated with glucose metabolism in humans [66–68].

The relationship between bone quality or bone strength and fat, examined by CT has been addressed in few studies. Gilsanz et al. [69], reported a beneficial effect for SAT on cortical bone structure and strength at the femur independent of leg length and lean mass in healthy young women, but the relationship was confounded by body weight. These same authors reported a negative association between VAT and bone geometry [69]. Recently, using trabecular bone score, a bone parameter derived from DXA images, considered a good estimation index for bone microarchitecture. Kim et al [70] reported that VAT had a detrimental effect on bone microarchitecture at the lumbar spine and a beneficial effect associated with SAT in Korean postmenopausal women. Another study conducted in a large cohort of middle-aged adults, by Zhang et al., reported an inverse relationship between VAT and cortical and trabecular bone independently of age, sex and BMI [71]. Further research addressing how different adipose depots affect bone mass and quality is required.

3.2 Bone marrow adipose tissue

The relationship between bone and fat has also been examined during the last two decades from another perspective addressing bone loss with regards to bone marrow adipose tissue (BMAT) in aging individuals. Due to its unique hormonal and metabolic regulation compared with other type of fats and its role in the bone marrow environment, pathological changes and age-related changes in BMAT could directly influence bone and trigger changes in bone health. In addition to cytokines secretion and adipokines production, exerting endocrine and central effects on bone remodeling, marrow adiposity locally affects bone cell differentiation resulting in decreased osteoblast number and enhanced osteoclastic activity [15). *In vitro* experiments showed that, within the bone marrow, adipocytes-secreted factors have a lipotoxic effect on osteoblasts [72]. In addition, since osteoblasts and adipocytes are both derived from the MSC, elevated bone-marrow adipogenesis further compromises the attenuated osteoblastogenesis capacity with aging [15,17]. Growing scientific interest in the field has led to clinical investigations on the relationship between BMAT and BMD, bone quality and fracture. Studies using non-invasive imaging methods to assess BMAT have found an inverse relationship between BMAT and BMD in both men and women [73–77] (Table 2).

Few studies have examined the relationship between BMAT and bone quality so far. Baum et al. reported lower trabecular spine volumetric BMD (vBMD) with higher BMAT in both healthy and type 2 diabetic postmenopausal women [78]. In another study conducted in older men and women, lower trabecular spine, total hip and femoral neck vBMD, and reduced vertebral compressive strength, derived from QCT with higher BMAT were found in women [74]. The relationship for these parameters did not reach statistical significance in men. In addition, cortical vBMD and BMAT were not associated at any site in men or women, possibly due to lower BMAT in cortical regions [74].

Gender differences affecting the relationship between BMAT and bone may be due to higher estrogen and testosterone levels in older men compared with postmenopausal women and the influence of sex hormone levels on bone marrow fat [79]. Longitudinal studies with measures of BMAT over time are not available. In one study, conducted over 4 years in older postmenopausal women (~74 y), found that a higher BMAT at the hip was a significant predictor of femoral neck bone loss, but changes in BMAT were not measured at follow up [73]. Finally, several studies have found higher BMAT in subjects with prevalent vertebral fracture [79].

3.3 Brown adipose tissue

Mitochondria-enriched brown adipose tissue (BAT), essential for adaptive thermogenesis appears to have a beneficial effect on bone. Endocrine and paracrine factors secreted by adipocytes with an induced BAT-like phenotype increase bone remodeling through anabolic activities [80]. Misty mice, with reduced BAT function, show altered sympathetic nervous system activity, decreased osteoblast differentiation and accelerated age-related trabecular bone loss [81]. In adult humans, BAT is located at discrete regions in the neck, supraclavicular, paravertebral, and suprarenal areas, and is reported to possibly promote bone health [80,82]. Two mechanisms have been proposed to explain the positive effect of

BAT on bone health: one is by attenuating cold-induced increases in adrenergic tone to bone, and the other is by producing factors, such as IFGBP2 (insulin like growth factor binding protein-2) and WNT10B (wingless-type MMTV integration site family, member 10B) [83]. In addition, active BAT is associated with improved metabolic status and could indirectly mediate the positive effects of BAT on bone health.

3.4 Mechanical loading: fat and lean body mass

The excess adipose tissue associated with obesity has traditionally been considered bone-protective because mechanical loading reduces apoptosis and increases proliferation and differentiation of osteoblasts and osteocytes [84–86]. Mechanical loading of bone, therefore, stimulates bone formation [87] and this occurs through the Wnt/β-catenin signaling pathway [88,89]. In a similar manner, skeletal unloading due to immobilization or inactivity will increase adipogenesis while reducing osteoblastogenesis [90]. Hence, mechanical loading due to obesity can partly explain the positive association between body weight and bone. A positive effect of adiposity on bone in the late postmenopausal years has been reported and may be attributed to higher estrogen levels, or other adipose-derived hormones rather than the mechanical loading [5,91]. However, when controlling for body weight, the positive association between body fat mass and bone mass is no longer significant [92] or is completely absent [93,94]. Moreover, some studies report a negative association between fat mass and BMD and total bone mineral content [92,95–97], especially when BMI is above 35 kg/m^2 [98]. Furthermore, Xu et al. [99] studied three generations of Finish women, and found that increasing body weight with fat accumulation is accompanied by a decline in relative bone-strength in women, but not in children. This may indicate that the beneficial effects of increased fat mass on bone, if any, does not compensate for its greater mechanical load [99]. In general, there is a strong association between lean body mass and BMD that may be due to innervation and mechanical interactions with bone. A high proportion of lean mass in an individual is probably the result of a significant amount of load bearing activity, which stimulates bone growth (100). In addition, systemic and local non-mechanical factors could also regulate bone responsiveness and sensitivity to mechanical loading due to muscle. Estrogen, GH and IGF-I decline with aging and are essential for maintaining a healthy bone-muscle unit (101). Furthermore, dietary factors, genetic influences or both, could contribute to the beneficial effect that greater lean mass has on bone. However, the positive effect of lean mass on bone in both obese and normal weight individuals is influenced by the amount of muscle mass. Low lean mass in younger individuals is associated with low BMD, while in the elderly it is also associated with poor balance, frailty and falls and increased risk of fracture [102, 103]. Importantly, although the individual risk for fracture is highest in low-body weight older individuals, the population burden of fracture is largely due to the overweight and obese [7, 104]. It may be that the effects of obesity on bone initially increases bone mass, but bone formation is unable to maintain the bone and it then causes a reduction in quality over time [105]. Overall, the greater mechanical load due to excess fat in the obese cannot be considered beneficial in preventing osteoporosis and fractures in the aging population.

4. Dietary energy and fat on bone in preclinical studies

4.1 Diet induced obesity

Studies in humans indicate that bone quality, but not mineral density or content is negatively affected by obesity or greater total or visceral adiposity. Consistent with these findings in humans, HFD-induced obesity lowers bone quality measures in rodents, but in animal studies, HFD is often associated with lowered BMD and BMC at various sites including total body, tibia, femur and spine in the majority of rodent studies [106–118] (Supplemental Table S1). Although several studies actually show a greater BMD attributed to high fat feeding [119–124] (Supplemental Table S1). It should be noted that most rodent studies showing a negative effect on bone were done in growing animals rather than after maturity, suggesting the detrimental effect of high fat feeding and obesity is especially pronounced during bone development. Whether or not these adverse effects also occur in mature bone of older animals is less clear [109–124], and may be specific to the dietary intervention such as the amount or the type of fat.

4.2. Dietary fatty acids

Optimal nutrient intake is an important factor for bone health. Research efforts have been mainly focused on dietary Ca and vitamin D due to their crucial roles in bone metabolism and skeletal health [125]. Other nutritional factors such as protein intake from diary and soy affect musculoskeletal function, and a high intake may attenuate bone loss attributed to energy restriction and weight loss [18, 126–127]. Studies report that dietary intake of vegetables and fruits rich in vitamin C, vitamin K, potassium, magnesium, as well as non-nutrient factors such as polyphenols and antioxidants that are evident in the shift toward bone retention and prevent bone loss [129–133]. For example, evidence from both *in vivo* and *in vitro* studies that dietary polyphenols, such as in blueberries, could alter MCS differentiation, suppress adipogenesis, and promote osteoblastogenesis and bone formation [131–133]. The effects of dietary fat on bone health have also been examined in clinical trials and animal studies [47,134). Dietary fat may benefit or harm bone health and appears to depend on the amount and the type of intake. Under a low or normal energy intake, dietary fat may be not detrimental to bone mineralization, possibly because it increases intestinal vitamin D and Ca absorption [135,136]. Nevertheless, excessive caloric intake from dietary fat leads to a positive energy deposition and obesity and this has been shown to negatively affect bone metabolism and compromise bone quality.

When examining the type of fatty acids, the effects of unsaturated fatty acids on bone metabolism (osteoblast vs. osteoclast) and general health may differ when compared to saturated fatty acids (SFA). For instance, in humans, long chain polyunsaturated fatty acids (PUFA) derived from fish and seafood may prevent bone loss, and the intake or serum concentration of PUFA is directly associated with BMD in older adults [134,137–140]. There is also evidence that dietary PUFA lowers fracture risk; however, observational reports are inconsistent and the association may vary among gender and ethnicities [141]. The mechanism by which PUFA, especially n-3 fatty acids, have positive effects on bone mass and quality is possibly by decreasing PGE_2 and inhibiting the receptor activator of NF-κβ ligand-induced osteoclast formation and differentiation [142,143]. Dietary n-3 PUFA also

promotes bone formation by increasing osteoblast differentiation and survival [144]. Dietary n-3 PUFA also contributes to the management and prevention of obesity, hepatic steatosis, diabetes and other obesity related complications and chronic diseases. Higher n-3 PUFA intake reduces oxidative stress and inflammation that may affect obesity related comorbidities and bone metabolism [144–147]. In addition, PUFA alters endocannobanoids production and release and CB1/CB2 gene expression, and this may be another mechanism whereby PUFA affects the fate of osteoblast and osteoclast in obesity and chronic over-activated ECS system [145, 148–150]. Furthermore, monounsaturated fatty acids (MUFA) intake from dietary olive, olive, and nuts also show a beneficial or neural effect on bone health. In a recent study from our lab, we found that MUFA attenuates BMD loss in older female mice [151], and cross-sectional studies indicate that dietary MUFA is associated with reduced fracture risk in older adults [152–154]. In contrast, despite evidence that a HFD increases intestinal fractional Ca absorption, possibly due to an altered morphology of enterocyte [136, 151, 155], the benefits of greater absorption apparently cannot always compensate for other factors influenced by HFD that affect bone. In cross-sectional data using NHANES III, it was found that SFA intake in the diet was inversely associated with hip BMD that was especially significant in men, and therefore may reduce bone mass [156]. The mechanisms that may interrupt bone metabolism due to high SFA intake have been examined in animal studies. For example, SFA prevents osteoblastogenic bone formation [157,158]. Also, a high fat diet rich in SFA also impairs lipid metabolism that may indirectly prevent osteoclast senescence and apoptosis [158–160]. Moreover, SFA mediates osteoclastogenesis and bone resorption possibly by increasing cellular oxidative stress [160,161] and the activity of inflammatory cytokines (IL1β, IL-6, TNFα) [162,163], all of which would have a negative effect on bone. Combined, these cellular and observational studies indicate that high fat feeding using different fatty acids may contribute to differential effects on bone health.

5. Obesity and fracture

Progress toward clarifying the fat-bone interaction and recent evidence reporting comparable prevalence and incidence of fragility fractures between obese and normal weight postmenopausal women [164–166] led to the reevaluation of the concept that obesity protects against osteoporosis and fracture. Recent studies strengthen the negative relationship between obesity and fracture risk too and show that obese men are also at high risk of fracture [104,164]. The relationship between BMI and fracture is site-specific. Although hip fractures occur less often in obese women than men [104], there is a greater risk of fractures for obese women at sites including the ankle, leg, humerus, and vertebrae [164]. Fracture occurrence in obese individuals may be related to a greater fat padding surrounding some sites that reduces the impact of falling while other sites are more exposed due to different patterns or forces upon falling or higher fall risk in the obese. Moreover, mechanical overloading on certain bone sites from excess body weight could predispose to fracture. Importantly, obesity has been associated with compromised bone quality, which can lead to bone structural damaging and increased fracture risk. Lower cortical BMD in the obese vs. age-matched lean individuals, as measured by peripheral QCT [5,97,166] may explain greater fracture rates at bone sites with a large proportion of cortical bone, such as

the upper arm and ankle in the obese [164]. Reduction of the cortical compartment, less apparent on trabecular bone, by excess levels of PTH in obesity [22] and other pathogenic-obesity effects (i.e. a negative paracrine effect on cortical bone quality and microstructure) may contribute to the high fracture risk in this population. Risk factors for fractures such as age, low BMD, history of previous fracture, a natural history of fracture (maternal), and use of glucocorticoids does not differ between obese and non-obese individuals [165]. In addition, reduced physical mobility and falls contribute to fracture risk in the obese [167]. Obesity-associated comorbidities such as diabetes and poor general health and other co-morbidities also influence fracture risk. When analyzing low-trauma and high-trauma fractures together, studies report more post-operative complications, longer hospital-stay and longer time for recovery post fracture when there is a higher prevalence of co-morbidities in the obese [164].

5.1 Strategies to improve bone health in the obese

Calcium and vitamin D deficiencies associated with poor dietary habits in obesity should be considered in the first place. In fact, vitamin D supplementation may need to be greater to compensate a lower serum 25OHD concentration in obese individuals mainly due to volume dilution into adipose tissue [23,168]. Weight loss is frequently used to reduce obesity-associated comorbidities and to improve overall health status. Most moderate weight-loss studies in overweight/obese individuals are accompanied by a rise in vitamin D status, and it could be hypothesized that this may contribute to the beneficial health consequences of reducing body weight [24]. However, both voluntary and involuntary weight reduction increase fracture risk in both older men and women [169–171]. Therefore, weight reduction in the obese elderly needs to consider factors that may attenuate bone loss. Several interventions such as calcium, vitamin D, proteins, and other nutrient supplementation as well as physical activity during weight reduction can attenuate loss of bone mass [127, 170, 172, 173]. Nevertheless, these factors cannot entirely prevent loss of bone mass due to weight loss [170,172,173,174]. Moreover, one important factor in the development of fractures in obese individuals is the risk of falls. It has been shown that physical function and bone health are improved with exercise [173]. However, other weight loss studies showed no effect of exercise on BMD loss [174] and falls [175]. Medication-therapy to prevent fracture is less common in the obese than normal-weight subjects [165] and could be due to the misconception that obese individuals have lower risk of fracture. Additionally, the effectiveness of anti-osteoporotic drugs in reducing fractures in the obese has generally not been examined in clinical studies. Only a few studies with low numbers of obese subjects are available and suggest similar or lower efficacy of bisphosphonates to reduce vertebral fractures in obese women compared to non-obese [176,177].

6. Conclusion

Obese individuals are not protected against osteoporosis and fracture. With the worldwide explosion of obesity and the increase in life expectancy, an increase in the number of osteoporotic fractures in obese elderly individuals is expected with slower recovery. Obesity affects bone metabolism through several pathways that could be further enhanced with aging. Dysregulation of the common progenitor stem cell, degenerative inflammation

through local cytokines action and systemic alteration through central adipokines effects, and other obesity-associated metabolic abnormalities compromise bone health by increasing adipogenesis at the expense of osteoblastogenesis, by enhancing bone resorption and reducing bone mass. The pathogenesis of fracture in obese individuals is not clear yet, but studies indicate that the positive effects of body weight on BMD cannot counteract the detrimental effects of obesity on bone quality and further research is required to elucidate the effect of ectopic adipose depots on bone and fracture risk in the obese population. Nevertheless, accumulating evidence showing that obesity could increase the risk of fracture in a growing population of elderly subjects with obesity should be considered a clinical priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviation

25OHD	25-hydroxyvitamin D
2-AG	2-arachidonoylglycerol
AEA	*N*-arachidonoylethanolamine
BAT	brown adipose tissue
BMD	bone mineral density
BMAT	bone marrow adipose tissue
BMI	body mass index
CRP	C-reactive protein
CT	computed tomography
DXA	dual-energy x-ray absorptiometry
ECS	endocannabinoid system
IL1	interleukin-1
IL-6	interleukin-6
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
OPG	osteoprotegerin
PPARδ	peroxisome proliferator–activated receptor-δ
PTH	parathyroid hormone

RNAK-L	receptor activator of NF-κB ligand
SAT	subcutaneous adipose tissues
TNFα	tumor necrosis factor α
VAT	visceral adipose tissue
vBMD	volumetric BMD

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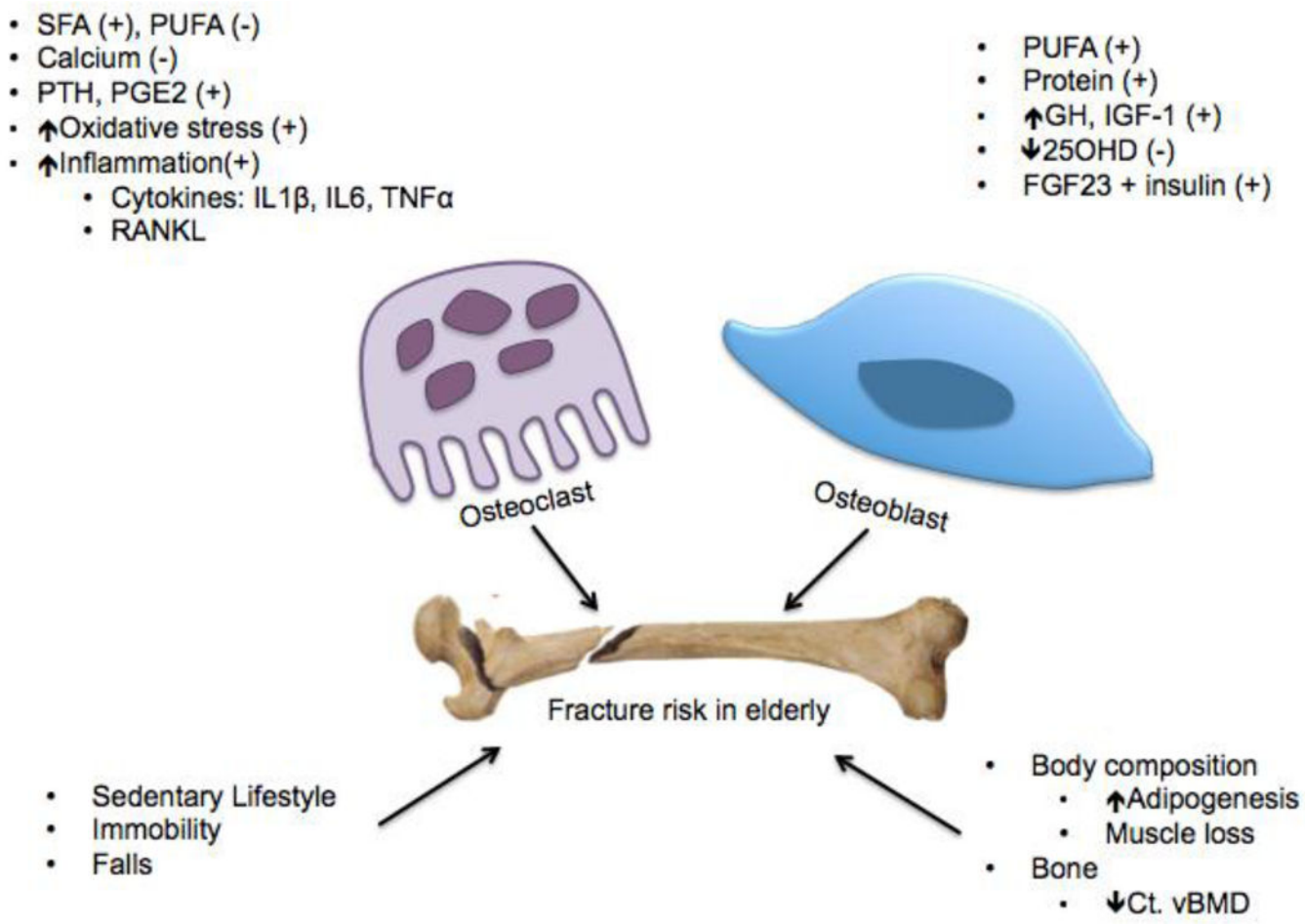

Figure 1. Mechanisms responsible for bone cell metabolism that contribute to osteoporotic fractures in obesity

Bone loss attributed to an imbalance of bone cell metabolism (osteoclast vs. osteoblast) that can contribute to osteoporotic fracture in obese individuals. In particular, factors such as high saturated fat (SFA) intake, low dietary calcium, hyperparathyroidism (PTH), and elevated oxidative stress, and inflammation will favor osteoclastogenesis and bone resorption. In contrast, dietary intake of polyunsaturated fatty acids (PUFA), protein, and supplemental vitamin D, high growth hormone (GH) and fibroblast factor 23 (FGF23) may enhance osteoblastogenesis and bone formation. Additionally, lack of physical mobility, a body composition that is high in adiposity and low in muscle mass, and compromised bone quality (Ct, cortical BMD), will also increase the risk of fracture. Factors are shown that have positive (+) and negative (−) actions on osteoporotic fractions in obesity.

Table 1

The relationship of VAT and SAT measured by computed tomography on bone parameters in healthy subjects

Study, year	Sample size	Gender, age, BMI	Outcomes	Results
Yamaguchi et al. 2009 [99]	N=125 N=187	Women, 46–82 y, 25.2 kg/m^2 Men, 28–83 y, 23.6 kg/m^2	BMD	Negative association with radius BMD and total BMD in women only. ↑ FN BMD among men with VAT area ≥100 cm^2.
Choi et al 2010 [69]	N=166 N=295	Women, 21–83 y, 22.7 kg/m^2 Men, 21–83 y, 25.2 kg/m^2	BMD	Negative correlation for VAT with LS, FN, TH BMD for both genders, but correlation was stronger in women
Yamaguchi et al. 2009 [99]	N=125 N=187	Women, 46–82 y, 25.2 kg/m^2 Men, 28–83 y, 23.6 kg/m^2	Fracture	↑ SAT in men and women without vertebral fracture with borderline significance
Liu et al. 2016 [70]	N=710	M&W 55–69 y, NA	BMD, geometry, microarchitecture	No significant VAT effect on the skeleton, after adjusting for BMI and weight.

Abbreviations: BMD bone mineral density; BMI body mass index; CT computed tomography; FN femoral neck; LS lumbar spine; TH total hip; SAT subcutaneous adipose tissue; VAT visceral adipose tissue.

Table 2

Studies examining the relationship between bone marrow fat and bone mass, bone quality and fracture

Author & year	Sample size, N	Gender, age, BMI	Method	Outcomes	Results
Griffith et al., 2005 [80]	N=82	M, 73 yrs, NA	MRI/DXA	BMF content with varying bone density	↑BMF among subjects with osteoporosis.
Griffith et al., 2006 [81]	N=103	F, 72 yrs, NA	MRI/DXA	BMF content with varying bone density	↑BMF among subjects with osteoporosis.
Yeung et al., 2005 [83]	N=53	F, 70 yrs, NA	MRI/DXA	-BMF content with varying bone density; -Fat unsaturation levels in the marrow fat with varying bone density	↑BMF among subjects with osteoporosis. Negative correlation between BMF and LS BMD. ↑Saturated lipids/unsaturated lipids in the marrow fat with ↑BMF.
Shen et al., 2012 [84]	N=280	M&F, 64 yrs, 26.5 kg/m^2	MRI/DXA		Negative association between BMF and total-body, spine and pelvic BMD.
Schwartz et al., 2013 [82]	N=257	M&F, 79 yrs, 27 kg/m^2	MRI/DXA/QCT	BMF/vBMD/fracture	↑BMF correlated with lower trabecular, but not cortical in women, but not in men. ↑BMF correlated with prevalent vertebral fracture in men (BMD adjusted).
Patsch et al., 2013 [85]	N=69	F, 63 yrs, 26 kg/m^2	MRI/DXA/QCT	BMF and composition in diabetic and healthy older women with fragility fractures vs. controls	Diabetics with fractures had the lowest marrow unsaturation and highest saturation. Healthy and diabetic fracture patients had lower vBMD than controls and diabetics without fractures.

Abbreviations: BMD bone mineral density; BMI body mass index; MRI magnetic resonance imaging; DXA dual-X ray absorptiometry; QCT quantitative computed tomography; BMF bone marrow fat; LS lumbar spine; vBMD volumetric bone mineral density.