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Review Article

Obesity, osteoporosis and bone metabolism

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Abstract

Obesity and osteoporosis have become major global health problems over the last decades as their prevalence is increasing. The interaction between obesity and bone metabolism is complex and not fully understood. Historically, obesity was thought to be protective against osteoporosis;however, several studies have challenged this belief. Even though the majority of the studies suggest that obesity has a favourable effect on bone density, it is unclear what the effect of obesity is on skeletal microarchitecture. Additionally, the effects of obesity on skeletal strength might be site-dependent as obese individuals are at higher risk of certain fractures. Several mechanical, biochemical and hormonal mechanisms have been proposed to explain the association between the adipose tissue and bone. Mechanical loading has positive effects on bone health, but this may not suffice in obesity. Low-grade systemic inflammation is probably harmful to the bone and increased bone marrow adipogenesis may lead to decreased bone mass in obese individuals. Finally, visceral abdominal fat may exert different actions to the bone compared with the subcutaneous fat. Achieving a better understanding of the association between adipose and bone tissue may help to identify new molecular therapeutic targets that will promote osteoblastic activity and/or inhibit adipogenesis and osteoclastic activity.

Keywords: Adipose Tissue, Bone Mineral Density, Obese, Overweight, Skeletal Microarchitecture

Introduction

Obesity has become a major health issue and a global epidemic. Its worldwide prevalence has been doubled in the last three decades[1]. This issue poses a burdensome public health issue as well as a major health risk factor for the individual. The problem is intense in the middle-age and older-age groups with the combined overweight and obese population in some countries accounting for the majority of the people. Additionally, alarming rates of obesity and overweight are observed in children[2].

Osteoporosis, a systemic skeletal disease, is characterized by low bone mineral density and progressive deterioration of the bone microarchitecture. Its major consequences are bone fragility and risk of fracture[3]. Osteoporosis affects more than 200 million people globally, with high health cost involved[4]. In the US alone, osteoporosis is responsible for 1.3 million fractures, with 500,000 vertebral, 250,000 hip and 240,000 wrist fractures, costing $10 billion per annum[5].

The accretion in the prevalence of both conditions prompts the need to understand better the association between obesity and osteoporosis. Traditionally, it was thought that obesity has a protective effect on the bone. This belief has influenced clinical practice. Body mass index (BMI) is part of the fracture risk assessment tool (FRAX), and higher BMI leads to lower fracture risk[6]. However, over the last few years, epidemiological and clinical studies have challenged this belief. Some studies indicate that abdominal adiposity is associated with osteopenia and osteoporosis, whereas other studies indicate that this association is probably more complex and site-dependent, with a lower risk for certain types of fractures but higher risk for others.

In this narrative review, the available literature is critically appraised, and the mechanical and molecular mechanisms

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associated with the dynamic interaction between obesity and skeleton are discussed.

Methods

The electronic databases PubMed (Medline), Embase and Scopus were searched using the terms: "osteoporosis", "osteopenia", "obesity", "metabolic syndrome", "fracture", "bone mineral density/BMD". Additional terms used included "pathophysiology", "epidemiology", "leptin", adiponectin", and "resistin". The search was limited to publications in English from inception until January 30, 2020.

Definitions

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health[7,8]. BMI is an imperfect, but a widely used measure of obesity as it provides a crude measure. It is defined as a person's height in kilograms divided by the square of his/her height in metres. The World Health Organisation (WHO) defines obesity as a BMI of 30 kg/m^2 or higher, while a person with a BMI of 25-30 kg/m^2 is considered as overweight[9]. An alternative definition of adiposity based on body fat percentage is not well-established[10].

Osteoporosis is defined as the T-score of the bone mineral density (BMD) of 2.5 SD or more below the mean adult value (measured at the femoral neck). Osteopenia is measured using BMD with a T-score between 1.0 and 2.5. The recommended site for diagnosis is the proximal femur with dual energy X-ray absorptiometry (DXA). Other sites, however, can be used for fracture prediction such as the lumbar spine or the wrist[11,12].

Pathophysiology

Adipose tissue had long been viewed as a passive energy reservoir. However, since the discovery of leptin and other adipokines, the notion has changed: adipose tissue considered as an endocrine organ with a critical role in energy homeostasis. Various molecular pathways have been proposed by which adipose tissue communicates with the bone. This interplay is active and dynamic, involving multiple factors, such as leptin, adiponectin, pro-inflammatory cytokines, and vitamin D. Additionally, the bone tissue affects metabolic parameters, including body weight control, through bone-derived factors, such as osteocalcin and osteopontin.

In general, there is a double association between the adipose tissue and the bone: mechanical and metabolic.

Mechanical association

Mechanical loading

Biochemical markers of bone turnover are lower in obese compared with lean subjects[13]. This difference seems to be more relevant for bone-resorption markers compared with bone formation ones[13]. During adulthood, these effects help in maintaining the bone mass. During menopause, higher body weight seems to decelerate bone loss[14].

The most plausible mechanism explaining the increased BMD in obese individuals is the increased mechanical loading and strain associated with obesity. With few exceptions (such as marked sarcopenia), obese people have increased body fat mass as well as increased lean mass. That leads not only to passive loading but to increased muscle strain with favourable effects on bone geometry and modelling[15].

If physical loading was the sole mechanism contributing to the increased BMD, then an increase in bone size by bone apposition should be expected. However, the findings do not always confirm this hypothesis: bone size at the radius and the tibia estimated by high-resolution peripheral quantitative computed tomography (CT) does not differ between obese and normal-weight controls[14]. These findings suggest that, even though the loading factor is an aspect of the bone-fat association, it is not sufficient to explain the interaction fully.

Obesity and falls

Several studies over the last few years have highlighted that excessive body weight is associated with falls, especially in older people. This high incidence of falls has high medical and economic costs[16]. The aetiology of falls in obese and overweight people is multifactorial. First, obesity can cause or exacerbate chronic health problems, such as diabetes, cardiovascular disease, arthritis, hypoventilation syndrome, sleep apnoea and hypertension[17]. These conditions are strongly associated with peripheral neuropathy, autonomic dysfunction with orthostatic hypotension and instability as well as general weakness, all predisposing to falls[17]. Second, the excessive body weight is linked with reduced ability in performing daily tasks, such as walking unaided or climbing up stairs, which again increases the risks of falls[18]. Third, increased body weight adds pressure on the heels, which compromises postural stability and balance ability[19]. Fourth, central adiposity in older women, measured by the waist-to-hip ratio, plays a major independent role as a fall-related indicator[20], as it compromises the stability of body center.

Over the last few years, new clinical entities have been described attempting to explain the complex physiological association between obesity and falls. "Dynapenic obesity" is characterised by loss of muscle strength due to obesity. It is associated with limited mobility[21], and contributes to an increased risk of falls[22]. "Sarcopenic obesity"[23] is characterised by loss of muscle mass due to obesity. Sarcopenia is positively associated with an increased risk of falls[24], because of postural instability and reduced physical activity[25], as well as a loss of bone mineral density and osteoporosis, leading to an increased fracture risk in older adults[26].

In a recent meta-analysis of 31 observational studies, obese older adults had an increased risk of falls compared with non-obese counterparts[27]. Furthermore, obesity was associated with an increased risk of multiple falls[27]. There

was no evidence, however, of an association between obesity and fall-related injuries[27]. On the other hand, there is emerging evidence on the role of obesity in hospitalization following falls. A study examining the effect of obesity on hospitalization and disabilities following falls demonstrated that older adults with obesity class 1 or 2 are more likely to develop a disability following a fall compared with older adults of normal weight[28]. Furthermore, obese older adults have lower quality of life following a fall compared with adults of similar age and normal weight[29].

The impairment of protective responses and the pattern of falling observed in obese individuals contribute to the site-specificity of fracture risk[30]. Obesity is protective against hip fracture in women but carries a high risk of fractures at other sites. One reason for the low frequency of hip fractures may be the presence of fat tissue (padding) surrounding the pelvis and the femur that reduces the impact of falling[31]. The pattern of falling tends to be different in obese and overweight individuals compared with lean ones: the former are prone to fall backward or sideward, whereas the latter to fall forward[32]. Exaggeration of introversion and extroversion of the ankle and lower leg in obese subjects may be also responsible for the high prevalence of fractures at these sites. Obese women experience more fractures in the ankle[33], leg[34], humerus[35], and vertebral column[36] and fewer in the wrist[37], hip[35] and pelvis[35].

In summary, the current evidence suggests that obesity increases the risk of falls and multiple falls in people aged >60 years with high chances of residual disability and lower quality of life; however, there is insufficient evidence of an association of obesity with fall-related injuries or fractures.

Metabolic association

Oestrogens

Adipose tissue is one of the major sources of aromatase, an enzyme also expressed in the gonads, which synthesises oestrogens from androgen precursors. Oestrogens are steroid hormones that have a key role in the maintenance of skeletal homeostasis, promoting bone formation and reducing bone resorption; therefore, protecting the bone. Obese post-menopausal women have been shown to have higher serum concentrations of oestrogens compared with non-obese controls[38]. These findings may partly explain the positive association between BMD and BMI. However, it has become apparent that oestrogens are not the only regulator of bone mass.

Leptin

Leptin is the product of the ob (Lep) gene. It is a cytokine-like hormone, produced primarily by the adipocytes. It plays a key role in the energy homeostasis and appetite control, mainly by inducing satiety in the hypothalamus. Leptin concentrations are typically elevated in obesity, which is a leptin-resistant condition[39]. Hyperleptinaemia is an independent risk factor for cardiovascular disease through hyperinsulinaemia and insulin resistance[40]. The effects of leptin on the bone are complex[41,42]. It has both direct and indirect effects exerted by central-hypothalamic and peripheral pathways. Both positive and negative actions have been reported on BMD and *in vivo* studies have produced conflicting results. *In vitro*, leptin stimulates the differentiation of stromal cells to osteoblasts[43], increases the proliferation of osteoblasts and inhibits osteoclastogenesis, while mature osteoclasts seem to be unaffected[44]. Furthermore, deficiency in leptin signalling, caused by knockout of its receptor gene, leads to a reduction in bone volume and BMD[45]. *In vivo* studies suggest that the effect of leptin might depend on its site and mode of action. It has been proposed that peripheral administration of leptin leads to increased bone mass by stimulating bone formation and inhibiting bone resorption[46], while central administration of leptin, as an intracerebroventricular infusion, induces bone loss in both leptin-deficient and wild-type mice[47]. This negative central effect seems to be exerted through the activation of the sympathetic system. Leptin inhibits the expression of the hypothalamic neuropeptide Y (NPY), which is essential not only for the regulation of food consumption and energy but also for bone remodelling[48]. Human data is even more conflicting, possibly due to the limitations of the studies. Different studies have reported both positive roles of leptin[49,50] and profoundly negative ones[51,52]. In summary, it seems unlikely that the hyperleptinaemia observed in obese individuals has a negative effect on the bone.

Adiponectin

Low adiponectin concentrations are a common feature of obesity, diabetes and insulin resistance[53]. They improve following weight loss, and they exert a protective role in the cardiovascular system and glucose metabolism[54]. *In vivo* and *in vitro* studies suggest that adiponectin has a favourable role on bone mass by stimulating osteoblastogenesis and suppressing osteoclastogenesis[55]. These findings indirectly indicated that higher adiponectin concentrations, following weight loss and fat reduction, may improve BMD. On the contrary, adiponectin concentrations are inversely correlated to C-reactive protein (CRP), IL-6 and TNF-α concentrations. These inflammation markers are potent inhibitors of adiponectin expression[56]. This can indirectly indicate that chronic inflammatory processes, including central and visceral adiposity, can have a negative impact on bone quality.

TNF-α and IL-6

Adiposity is associated with pro-inflammatory cytokines, such as TNF-α and IL-6. The expression of TNF-α correlates with body fat percentage and insulin resistance in humans[57]. It induces bone loss through osteoclastogenesis via the activation of the NFκB in obesity by raising c-fms, receptor activator of nuclear factor kappa-B ligand (RANK) and RANK ligand (RANKL) concentrations[58]. RANKL is the primary osteoclastogenic cytokine factor, promoting the resorptive

activity of osteoclasts[59,60]. Furthermore, TNF-α reduces the production of osteoprotogerin (OPG), which is the inhibitor of RANKL, leading to higher RANKL concentrations, and, as a consequence, to further bone loss[61]. Finally, TNF-α directly modulates the RANKL-induced signalling pathways, leading to a synergistic activity with RANKL, which promotes further osteoclastic resorption[62]. This property seems to be unique among the cytokines.

IL-6 is another cytokine with a wide range of actions. Obesity and insulin resistance lead to up-regulation of its production[63] by several cells, including adipocytes and fibroblasts[64]. Similarly to TNFα, IL-6 promotes osteoclastogenesis and bone resorption. Furthermore, IL-6 stimulates osteoblast proliferation and pre-osteoblast differentiation[65].

The emerging evidence suggests that inflammatory cytokines play a critical role in bone loss[66]. Obesity is associated with low-grade chronic inflammation; the latter is more pronounced in central and visceral adiposity, which is characterized by higher CRP, TNF-α and IL-6 concentrations. This marked inflammatory response may be responsible for the accelerated bone loss observed in obesity.

Resistin

Resistin is produced by visceral adipocytes and macrophages. Its concentrations are elevated in obesity and associated with glucose tolerance and insulin resistance[67]. It has been suggested that it might also affect bone turnover. However, it is less clear if that effect is positive or negative, as it seems to increase osteoblast proliferation but also osteoclast proliferation and cytokine release[68].

High-fat diet and bone microenvironment

Probably the commonest model to study the impact of adiposity on bone metabolism is obesity induced by a high-fat diet (HFD). Data from animal models suggest a negative effect of obesity on bone metabolism. This negative effect is likely exerted through alterations in bone microenvironment as well as systemic inflammation. A critical finding was that obesity induced by HFD is associated with increased bone quantity (larger bone size and mineral content) but decreased bone quality (lower size-independent mechanical properties)[69]. Another study showed that the deterioration in trabecular bone micro-architecture in mice fed with HFD is critical and is observed at early stages and this can eventually lead to reduction in trabecular bone density[70]. Additionally, obesity induced by HFD causes increased bone resorption[71] but increased bone marrow adiposity as well[72]. The bone microenvironment in adiposity seems to be associated with bone resorption.

Fat bone marrow and osteoporosis

The emerging data over the last years have given rise to the hypothesis that a bone marrow rich in fat may be responsible for osteoporosis. The fat in bone marrow is a reflection of ageing. It is also a phenomenon frequently observed in systemic adiposity as well as osteoporosis, especially in postmenopausal women[73]. It is not entirely clear what is the primary cause of bone marrow fat deposition. A plausible mechanism is the differentiation of parenchymal cells to adipocytes rather than osteoblasts.

Adipocytes and osteoblasts derive from a common progenitor, a pluripotential, bone marrow-derived mesenchymal stem cell (BMSC)[74]. This stem cell has an equal propensity for differentiation into adipocytes or osteoblasts as well as other cells (endothelial, fibroblasts, chondrocytes). This differentiation is complex and controlled by several transcription factors. The process is characterised by plasticity and various mechanisms of regulation of the transcription[75].

The differentiation seems to be irreversible and is associated with the switching of differentiated cells from one lineage (osteoblasts) to another (adipocytes)[76]. There is evidence that this occurs during disease[77]. Additionally, there is an inverse association between fat production in the bone marrow and bone formation in osteoporosis; in patients with a high bone mass, reduced adipogenesis has been observed[78]. The dominant hypothesis currently is that the inability of the BMSCs to differentiate into osteoblasts leads to increased differentiation into adipocytes.

The accumulating evidence provides new insight into the pathogenesis of osteoporosis and its association with various metabolic diseases. However, it is not yet fully understood what the factors influencing this transdifferentiation are. Oestrogens seem to play a pivotal role in this process[79-81]. Mesenchymal cells from bone marrow in postmenopausal women with osteoporosis appear to have more adipose differentiating properties compared with those from controls with normal bone mass. Furthermore, analysis of the bone marrow of rats following oophorectomy has revealed pronounced fatty infiltration[75]. Newer studies have shown that oestrogens suppress adipogenic differentiation via Wnt signalling[82], a system crucial for bone metabolism. Oestrogens seem to induce both osteogenesis and suppression of adipogenesis[83,84]. These findings, observed both *in vivo* and *in vitro*, suggest that oestrogens play a key role in the process, and states of oestrogens deficiency, such as menopause, may lead to unbalanced differentiation towards adipocytes within the bone marrow.

Another factor involved is peroxisome proliferator-activated receptor-γ (PPARγ). It plays a key role in inducing adipogenesis[85]. States of PPARγ insufficiency are characterised by increasing differentiation of osteoblasts[86]. On the contrary, mutations of the PPARγ observed in systemic obesity as well as states of enhanced expression of PPARγ (e.g. aged mice) demonstrate fat infiltration of the bone marrow and reduced differentiation of the common progenitor to the osteoblasts[87,88].

In summary, fat infiltration of the bone marrow has been associated with osteoporosis. This may be caused by unbalanced differentiation of the common progenitor towards adipocytes rather than osteoblasts under the influence of various factors in a highly complex process. However, it is not

fully understood yet what these factors are and whether the fat bone marrow is a cause or a consequence of osteoporosis.

Vitamin D

Vitamin D deficiency is prevalent among obese individuals. The impact of low vitamin D concentrations on the musculoskeletal system is well-documented. Obese people have lower serum 25(OH)D concentrations compared with normal-weight people, and serum 25(OH)D is inversely associated with body weight, BMI and fat mass[89-91]. Serum 25(OH)D concentrations are approximately 20% lower in obese people compared with those of normal weight[90-92]. The prevalence of vitamin D in obese individuals is between 40-80%, higher compared with normal-weight individuals[90,93].

Interestingly, supplementation with vitamin D seems to be much more effective in increasing vitamin D concentrations in non-obese adults and children compared with obese[94,95]; nevertheless, a meta-analysis showed no effect on body weight or fat mass[96]. The more effective restoration of vitamin D concentrations in normal-weight individuals compared with obese is likely due to the sequestration of vitamin D in the fat stores. Another factor involved is possibly the secondary hyperparathyroidism. Up to 43% of the morbidly obese adults suffer from secondary hyperparathyroidism with a further negative impact on skeletal health[97,98].

In other clinical situations, low total 25(OH) concentrations would lead to decreased dietary calcium absorption, increased bone turnover and lower BMD. However, adults with obesity seem to have lower bone turnover compared with normal weight, and higher BMD with thicker and denser cortices[14]. However, the opposite is observed in children and adolescents, where obesity has a negative impact on bone strength, another alarming consequence of childhood obesity[99,100].

It is not entirely clear what are the reasons for the lack of adverse effects of vitamin D deficiency on bone in obese adults. One hypothesis is that obese vitamin D-deficient adults may develop compensatory mechanisms for the negative impact of vitamin D[101]. These mechanisms include factors, such as leptin, mechanical loading or oestrogens. An alternative theory is that obese individuals are not truly vitamin D deficient. This theory suggests that, albeit serum 25(OH)D concentrations are lower, total body vitamin D levels are higher because of the reservoir in the fat tissue, which maintains a sufficient supply in vitamin D.

11β-hydroxysteroid dehydrogenase type 1

11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) is an enzyme converting the inactive cortisone to active cortisol. Active glucocorticoids have a negative impact on bone health. Local expression of the 11β-HSD1 can determine the skeletal response to different types of glucocorticoids[102]. The enzyme is expressed in both the adipocytes and osteoblasts[103], and it appears that pro-inflammatory cytokines (TNF-α, IL-6) can up-regulate the expression of 11β-HSD1 and, therefore, induce bone damage via fat accumulation[104].

An attractive hypothesis described recently is that the visceral adipose tissue is metabolically more active compared with the subcutaneous one. This, together with the above-mentioned actions of 11β-HSD1, may explain why visceral adipose tissue seems to have a worse skeletal phenotype than subcutaneous adipose tissue. However, this hypothesis is still under review, and some studies have not supported the negative association between bone density and subcutaneous adipose tissue.

Obesity, osteoporosis and fracture risk: the "obesity paradox"

The historical belief was that obesity acted protectively against fractures[105]. This unusual association was thought to be one of the many aspects of the "obesity paradox"[106]. However, accumulating evidence has challenged this notion and, as far as bone metabolism goes, the view that obesity is protective is probably over-simplistic[107].

The initial belief about the favourable role of obesity in bone metabolism was mainly supported by the positive correlation between BMD and BMI[78,84] and the lower incidence of hip fractures in obese adults[108]. However, a UK study in 2011 reported, for the first time, a high prevalence of obesity (27%) in post-menopausal women presenting with fragility fractures[109].

The fracture risk in obese adults is not the same for all skeletal sites, and it seems to be site-dependent: the risk for some non-vertebral fractures, such as proximal humerus, upper leg and ankle, is higher compared with normal weight[110,111], whereas the risk is lower at vertebral sites and proximal femur in obese adults[112].

The results of a study demonstrated a surprisingly high prevalence of obesity in postmenopausal women presenting to the fracture liaison service with low-trauma fracture. Interestingly, most of these women had normal BMD, as measured by DXA[112,113]. These results again support the opinion that obesity is not protective against fractures.

The observation that BMI is positively associated with BMD was challenged in the past. The argument was that the BMD measured in obese individuals might be an overestimate due to the overlying subcutaneous tissue. However, this observation has been confirmed by precise quantitative methods, such as high-resolution pQCT and ultrasound[114]. These measurements are not affected by the overlying soft tissue, giving a more reliable way to assess bone density in obese individuals. An additional advantage of these methods is that they can reliably assess the cortical and trabecular compartment of the bone. In a cross-sectional case-control study, obese women had higher volumetric BMD (vBMD) at the lumbar spine, and both obese men and women had higher vBMD at the distal radius and distal tibia compared with normal-weight individuals[14]. However, although BMD is higher in obesity, it may not be sufficiently increased to

compensate for the negative factors in terms of bone health, including biomedical and biomechanical factors.

The findings are consistent in children and younger adults. Early-onset obesity is associated with a lower radius cross-sectional area[115]. The likely mechanism is that when obesity occurs during skeletal growth, the expected skeletal adaption to mechanical loading and pressure is impaired.

The data are not consistent with regards to central obesity. Some studies have shown that visceral adiposity (assessed by waist-to-hip ratio) is associated with lower bone mass. However, other reports have demonstrated that obese subjects with larger waist circumference are less likely to have osteoporosis [defined by dual-energy X-ray absorptiometry (DXA)]. The association is highly complex. Several hormonal and mechanical factors are involved.

The outcomes from various studies are conflicting. In one study, the researchers measured visceral adipose tissue (VAT) CT scans and skeletal strength using HR-pQCT: individuals with higher visceral adiposity showed higher BMD and improved bone micro-architecture except for distal radius. However, once these results were corrected for BMI, they were no longer significant[116]. This indicates that the effect might be related to obesity in general rather than visceral adiposity. However, in a study using a similar methodology, VAT had an inverse correlation with vBMD at the spine even when adjusted for sex, age and BMI[117].

A recent biomechanical study showed that increased waist circumference at the same body weight leads to increased pressure on the spine with a higher risk for low-trauma and compression fracture[118].

In summary, differences in the distribution of adipose tissue seem to be important for skeletal health. It is speculated that mechanical factors, as well as the propensity of visceral fat to systemic inflammation, might be the critical factor for these findings.

Conclusions

The association between the bone and adipose tissue is complex. The two tissues, both highly active metabolically, interplay through adipokines, oestrogens and bone-derived metabolic factors. The cross-talk between them is complicated with feedback mechanisms, which affect bone remodelling, body weight control, adipogenesis, glucose homeostasis and muscle adjustment.

Mechanical loading, as expected, has positive effects on bone health, but this may not suffice in obese individuals. Accumulating data suggest that obesity has a negative impact on bone health. Low-grade systemic inflammation is probably harmful to the bone due to up-regulation of pro-inflammatory cytokines and/or increased leptin production, observed in obesity. Another plausible mechanism is that the increased bone marrow adipogenesis may lead to decreased bone mass in obese individuals, due to aberrant commitment of the common progenitor stem cell into adipocytes rather than osteoblasts, again observed in obesity. Finally, visceral abdominal fat may exert different actions to the bone tissue compared with the subcutaneous abdominal fat.

The effects of obesity on skeletal health seem to differ depending on the age. Obese children and adolescents may have a higher likelyhood to experience adverse effects on bone health. The mechanisms underlying these events are not fully understood. Achieving a better understanding of the association between adipose and bone tissue may help to identify new targets for molecular therapy that will promote osteoblastic activity and/or inhibit adipogenesis and osteoclastic activity.

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