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Review Article

Obesity Significantly Modifies Signaling Pathways Associated with Bone Remodeling and Metabolism

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Abstract

It is obvious that obesity-related diseases are increasing in parallel with the prevalence of obesity, which has reached epidemic proportions worldwide. Cardiovascular disease, multiple cancers, stroke, type 2 diabetes and many other non-communicable diseases are more likely to develop in people living with obesity compared to those living at a healthy weight. In recent years, deeper investigation of the role of multi-organ interaction mechanisms in obesity and related chronic diseases has contributed to the development of new treatment and prevention strategies for obesity and its related-diseases. Bone tissue is also one of those target tissues in obesity. In this sense, the involvement of adipokines derived from adipose tissue in bone metabolism through hormonal and inflammatory factors suggests that obesity may be metabolically associated with bone loss. Moreover, recent epidemiologic and clinical studies have shown that obesity might be a risk factor for osteoporosis and fragility fractures. In obesity, various mechanisms affect bone remodeling and may be involved in the development of osteoporosis by triggering or modifying signaling pathways through the release of adipokines from adipose tissue and osteokines from bone. This review aims to elucidate the relationship between obesity and osteoporosis by focusing on the complex and reciprocal interaction between adipose tissue and bone tissue, discussing the changes in signaling pathways.

Keywords: Obesity, Adipokines, Signaling pathways, Osteokines, Bone remodelling, Osteoporosis

Introduction

Obesity, defined simply as a body mass index (BMI) ≥ 30 kg/m^2, is a complex, chronic disease characterized by excessive accumulation of fat or adipose tissue (AT) in the body [1]. Obesity is a major risk factor for many diseases such as type 2 diabetes (T2D), cardiovascular diseases and stroke worldwide [2]. This global health epidemic has also traditionally been associated with increased load on the skeletal system, leading to the assumption of a positive effect on bone health [3,4]. However, recent evidence challenges this simplistic view and reveals a complex and multifaceted relationship between obesity and bone tissue (BT) [5,6]. In other words, obesity is also recognized as a complex factor influencing BT through various signaling pathways beyond mere mechanical loading [7]. Bone tissue has numerous vital functions and is closely linked to the biochemical, homeostatic and pathophysiological functions of many important tissues and organs. Because of this critical link, obesity, like some diseases, is associated with musculoskeletal diseases. Therefore, interdisciplinary research on the relationship between bone health and obesity may provide new insights into both bone-related and obesity-

related diseases [8]. This review aims to summarize current data on obesity-related modifications in signaling pathways involved in bone remodeling and metabolism and their mechanisms.

Traditional Views and Emerging Realities

Although there is a widespread view that increased mechanical load due to obesity provides a protective effect on bone health, recent research shows that the effect of obesity on BT goes beyond the effects of weight-bearing alone [6].

Adipose tissue as an endocrine organ

The realization that AT functions as an endocrine organ has transformed our understanding of obesity's systemic effects. Adipocytes secrete a myriad of hormones and cytokines collectively termed adipokines, which play a crucial role in metabolic regulation and inflammation [9]. For example, the rapid expansion of AT in obesity could provide intrinsic signals including adipocyte death, hypoxia, and mechanical stress arising from interactions between the cells and the extracellular matrix that might trigger an inflammatory response [10]. As these adipokines circulate throughout the body, they can modulate various signaling pathways in bone cells, influencing bone remodeling dynamics [11]. Beyond body weight balance, adipokines participate in bone homeostasis through their effects on bone formation and resorption (**Table 1**).

Inflammatory milieu and bone remodeling

Chronic low-grade inflammation is a hallmark of obesity, with AT acting as a significant source of pro-inflammatory cytokines. Adipose tissue inflammation is initiated and sustained over time by dysfunctional adipocytes secreting inflammatory adipokines and an infiltration of bone marrow-derived immune cells signaling through the production of cytokines and chemokines [12]. The pro-inflammatory cytokines; tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1 cause a significant increase in osteoclasts and suppression of osteoblast activity when RANKL (receptor activator of nuclear factor-kappa B ligand) is present. In particular, TNF-α and IL-6, disrupt the delicate balance of bone remodeling by affecting osteoblast and osteoclast activity [13]. IL-17 is another pro-inflammatory cytokine that promotes bone resorption via upregulating RANKL [14]. The interaction between the inflammatory environment and bone cells suggests potential alterations in the complex signalling pathways mediating the impact of obesity on bone health and homeostasis [7,15]. Furthermore, it has been also shown that osteoblasts and osteoclasts can communicate with each other through direct cell-cell contact, cytokines, and extracellular matrix interaction [16].

Adipokines and Their Influence on Bone Cells

Adipose tissue is an active endocrine organ and a source of various signaling molecules and metabolic mediators known as adipokines. Adipokines are involved in the regulation of numerous metabolic processes, including satiety, energy metabolism and inter-organ crosstalk. Adipokines also have effects on the musculoskeletal and cardiovascular systems [11,17].

Leptin: a double-edged sword

Leptin, often referred to as the "satiety hormone," is predominantly secreted by adipocytes [18]. It has been suggested that leptin may be an important mediator of the effects of subcutaneous adipose tissue (SAT) on the skeleton [19]. Leptin plays an important role in bone metabolism through both direct and indirect effects via peripheral and central (hypothalamic) pathways [20]. Although *in vivo* studies have reported inconsistent results, leptin has direct effects on bone metabolism and contributes to the positive relationship between adiposity and bone density [21]. Leptin stimulates the differentiation of stromal cells into osteoblasts [22], increases osteoblast proliferation and inhibits osteoclastogenesis without affecting mature osteoclasts [23]. In addition, it has been suggested that leptin, which has angiogenic properties, promotes bone formation through down-regulation of

Table 1. Adipose tissue-derived main adipokines with relevance in bone metabolism.

Secretory cells of adipose tissue	Adipocytokines	Effect on bone health and metabolism
Precursors / preadipocytes, Adipocytes, Endothelial cells, M1 and M2 macrophages, Dendritic cells Eosinophils, T and B cells	- Leptin - Adiponectin - Resistin - Visfatin - IL-6 - TNF-α - Chemerin, Omentin, Nesfatin-1, RBP-4, Vaspin, etc.	- Induce either bone formation/resorption - Negative effect on bone formation - Stimulates osteoclastogenesis/proliferation of osteoblasts - Production of type I collagen in osteoblasts - Associated with lower bone mass bone-resorptive factor - Stimulator of bone resorption (osteoclastogenesis)

nuclear factor kappa-B ligand (RANKL) receptor activator [24] and that the response of bone to leptin signaling may differ between different skeletal regions and bone structures [25]. However, suggested that high leptin levels, acting as a proinflammatory adipokine, may activate inflammatory pathways in osteoblasts causing poorer bone health [26]. On the other hand, unhealthy (such as high-fat or -calorie) diets may impair bone metabolism by inducing inflammation through proinflammatory cytokines (TNF-α, IL-6) and leptin [27]. Ultimately, the dual impact of leptin emphasizes its complex role in the obesity-bone relationship.

As a balancing factor in bone homeostasis, adiponectin

Adiponectin, which has been shown to be expressed in human osteoblasts, is known to promote proliferation, differentiation, and mineralization [28]. Accumulating evidence also suggests that adiponectin promotes osteoblastogenesis, while simultaneously inhibiting osteoclastogenesis [29,30]. Adiponectin indirectly inhibits RANKL expression and increases FoxO1 activity, which results in osteoblast proliferation and increased bone formation, bone mass, and circulating osteocalcin levels [31]. Under healthy conditions, adiponectin promotes the survival of osteoblasts, reduces osteoclastogenesis and resorption and ultimately protecting to bone homeostasis. By contrast, in bones these traits are broadly dysregulated by aging and obesity [32]. However, changes in environmental cues, such as an increase in estrogen affecting downstream signaling pathways (e.g. MAPK and AMPK) triggered by increased adiponectin levels, may pathologically shift this balance in favor of bone resorption and damage [33]. On the other hand, although its negative association with bone mineral density (BMD) has been demonstrated, targeting low levels of adiponectin is controversial, as it is protective for metabolic conditions such as insulin resistance (IR) and T2D [34]. Both leptin and adiponectin have dual effects on bone metabolism. Leptin has some positive effects on bone metabolism, but adiponectin shows a negative relationship with BMD [35]. Moreover, since the overall metabolic effects of these two adipokines are opposite, their effects on the relationship between obesity and bone health have not yet been fully elucidated.

Resistin and visfatin: emerging players

Resistin and visfatin are adipocyte-derived hormones that have been proposed to link obesity and IR. Clinical and experimental studies have shown that the expression and secretion of resistin and visfatin are increased during inflammation and in response to pro-inflammatory cytokines [36]. Both AT and BT are highly metabolically active endocrine organs that play a critical role in energy homeostasis [37]. Although what is known about the effect of resistin and visfatin on bone health is still unclear, resistin has been shown to play a role in promoting osteoclastogenesis and inhibiting osteoblast differentiation, potentially contributing to bone loss in obesity [38,39]. Resistin has been implicated in promoting osteoclastogenesis and inhibiting osteoblast differentiation, potentially contributing to bone loss in obesity [34]. Visfatin, also known as adipokine nicotinamide phosphoribosyltransferase (NAMPT) or insulin-mimetic hormone, inhibits the early stages of osteoclastogenesis by down-regulating early RANKL-dependent signaling pathways [40]. It is thought that peroxisome proliferator-activated receptor-gamma (PPARγ) inhibition or activation in combination with adipocyte-derived adipokines may alter or disrupt the communication between osteoblasts and osteoclasts. Adipokines such as visfatin and resistin increase osteoblast differentiation and inhibit osteoclast formation, whereas leptin and adiponectin abolish osteoblast formation and thus cause changes in bone homeostasis [34,37]. Briefly, Leptin, adiponectin, resistin, and visfatin secreted by adipocytes show complex and sometimes opposing effects on bone metabolism, suggesting that adipokines play an effective role in obesity-related bone changes.

Insulin Resistance and Bone Metabolism

The insulin-bone axis

In insulin-resistant states, impaired insulin signaling can disrupt bone homeostasis, affecting both bone formation and resorption [41]. Obesity, in particular central obesity (visceral adiposity) is often associated with IR, a condition where cells become less responsive to the effects of insulin. Adipose tissue releases adipokines and inflammatory cytokines, contributing to a chronic low-grade inflammatory state that inhibits insulin signaling [42]. Insulin, beyond its role in glucose metabolism, influences bone cells. Insulin receptors are present on osteoblasts, and insulin signaling is crucial for osteoblast function [43]. In insulin-resistant states, impaired insulin signaling may disrupt bone homeostasis, influencing both bone formation and resorption [44]. Although insulin is an anabolic agent for bone formation, more and more studies have shown a negative association between IR and bone mineral density [45,46]. Interestingly, it has been suggested that the higher the degree of IR in female patients, the higher the risk of osteoporosis [47]. However, according to another view, hyperinsulinaemia may negatively affect sex hormone binding globulin, increasing free sex hormone levels and preventing bone loss [48]. Additionally, in obesity-related IR, high blood glucose levels contribute to the formation of advanced glycation end products [49]. These end-products can also accumulate in BT and may adversely affect the biomechanical properties of bone [50].

Substantially, visceral adipose tissue (VAT) is more strongly associated with poor bone health than SAT in obese patients: Firstly, VAT is associated with lower trabecular bone volume, lower bone formation rate, and lower stiffness. Secondly,

VAT releases proinflammatory cytokines, such as TNF-α and IL-6, which increase bone resorption [6,51]. Moreover, obese postmenopausal women with more VAT have lower osteocalcin levels, a bone turnover marker. However, some studies suggest that the effects of VAT on bone health become less apparent after correcting for body weight. Others suggest that VAT is not associated with a detrimental effect on bone microarchitecture after adjusting for BMI or weight [51,52]. In fact, long-term obesity causes ectopic fat accumulation in different organs, leading to organelle dysfunctions. Consequently, organelle dysfunctions increase systemic inflammation, leading to IR [53]. Insulin resistance, in turn, negatively affects both energy metabolism and bone metabolism directly or indirectly [54].

Sex Hormones and Obesity-Induced Bone Changes

Sex hormones, particularly estrogen and testosterone, play pivotal roles in maintaining bone density and preventing bone loss. Accumulating evidence suggests that a wide range of reproductive hormones beyond estrogens and androgens are essential components of the physiological endocrine inventory regulating skeletal homeostasis [55]. Testosterone plays an important role in both increasing bone mass and maintaining musculoskeletal mass. In contrast, the role of estrogen, which has important effects on the regulation of osteoporotic processes, is complex and is a highly active factor in postmenopausal women [56]. In obesity, changes in sex hormone levels are common, with increased conversion of androgens to oestrogen in AT playing an inductive role in the onset of obesity [57]. However, the net effect on BT is complex because the relationship between sex hormones and bone metabolism is multifaceted and influenced by several factors, including obesity. For example, obesity may affect bone health differently in men and women because sex hormones regulate bone metabolism [58]. In postmenopausal women, the decline in estrogen levels associated with obesity can accelerate bone loss, contributing to an increased risk of osteoporosis and fractures [59].

Inflammation and Bone Remodeling Dynamics

NF-κB Signaling: Orchestrating Inflammation

The nuclear factor-kappa B (NF-κB) pathway, which plays a central role in inflammation, plays important roles in immune homeostasis and chronic inflammation, particularly in chronic inflammatory diseases and ageing [60]. There is a bidirectional relationship between NF-κB signaling, metabolic diseases such as obesity, T2D, and inflammation. These diseases, which also lead to IR, can cause over-activation of NF-κB signaling and inflammation through oxidative stress and regulation of macrophage function [61]. AT-derived inflammatory signals, including TNF-α, activate NF-κB, influencing the transcription of genes involved in bone remodeling [62]. Genetic evidence suggests that the MyD88-dependent TLR pathway is crucial for M1 macrophage polarization and inducible expression of pro-inflammatory cytokines [63]. Remarkably, the osteoclast differentiation factor NF-κB receptor activator ligand (RANKL) of osteoclast differentiation has an active role in osteoclastogenesis and is responsible for the involvement of the activated immune system in bone loss [61]. Low-grade systemic inflammation is detrimental to bone, and increased adipogenesis in the bone marrow is associated with decreased bone mass in obese individuals [64]. Specific to bone, persistent activation of innate NF-κB signaling produces several negative effects on bone mass preservation, including inhibition of osteoblast differentiation and mineralization and abnormal activation of osteoclastic activities [65]. NF-κB-mediated inflammation disrupts the delicate balance between osteoblasts and osteoclasts, favoring bone resorption over formation. Inflammatory cytokines can not only promote bone resorption alone, but their mutual activation can enhance the activation of the TNF-α/NF-κB signaling pathway, activate osteoclast-related genes, and enhance bone resorption, which can be seriously detrimental to osteoporotic patients [66].

RANKL-RANK-OPG axis: a key regulator

Bone homeostasis is a process cycle that depends on the formation of bones by the osteoblasts and the resorption by osteoclasts. RANKL/RANK signaling regulates osteoclast formation, activation, and survival in normal bone modeling and remodeling and various pathological conditions characterized by increased bone remodeling [67]. RANKL and its trap receptor osteoprotegerin (OPG) form a critical axis of three key signaling molecules in bone remodeling; the RANKL and the soluble decoy receptor OPG. OPG protects bone from excessive resorption by binding to RANKL and preventing it from binding to RANK [67,68]. There is some evidence for a potential contribution of the OPG-RANKL-RANK axis to the pathogenesis of metabolic diseases such as obesity, T2DM, and NAFLD. Furthermore, the dysregulated RANKL-RANK-OPG axis provides a molecular link between inflammation and the altered bone dynamics observed in obesity [69]. In obesity-induced inflammation, an imbalance in the RANKL/OPG ratio can occur, promoting osteoclastogenesis and bone resorption [70]. Indeed, obesity leads to a proinflammatory state that affects metabolic function in insulin-sensitive tissues, including bone and its immune compartment bone marrow. The obesogenic condition may also induce bone marrow hyperplasia, defined by an increased number of immune cells migrating into the circulation [15].

Wnt/β-Catenin Signaling: Balancing Act Disturbed

Wnt signaling in bone homeostasis

The activation/inhibition of the Wnt signaling pathway leads to different effects in obesity pathogenesis, which is determined by the specific pathways of action. Wnt proteins enter the nucleus as a transcription coactivator of TCF to regulate the

transcription of target genes. The activation of the Wnt/β-catenin pathway leads to the supersession of adipogenesis, the inhibition of brown AT-related thermogenesis, and the increase of insulin sensitivity. The canonical Wnt signaling can be stimulated by factors including leptin, OSBPL2, and miRNAs. These factors are all involved in the pathogenesis of obesity by regulating the Wnt/β-catenin signaling pathway. Additionally, Wnt5a, a part of the non-canonical Wnt pathway, induces obesity-associated inflammation in white AT in a JNK-dependent manner, which further contributes to the occurrence of IR in AT [7]. Mouse genetic studies have confirmed the importance of the canonical Wnt signaling pathway in the regulation of bone homeostasis, while numerous genome-wide association studies have revealed the importance of the WNT signaling pathway for bone in the general population [71]. The Wnt/β-catenin signaling pathway is fundamental for bone development and maintenance. Activation of this pathway promotes osteoblast differentiation and bone formation while inhibiting osteoclastogenesis. Therefore, this pathway has also been considered as a therapeutic target for osteoporosis treatment and fracture healing [72]. In obesity, it has been suggested that the Wnt/β-catenin signaling pathway may direct BMSC towards inhibited osteoblast differentiation [73]. In other words, secreted frizzled-associated protein 1, an inhibitor of Wnt/β-catenin signaling, is reported to be increased in mild obesity and leads to increased bone marrow AT formation, but is decreased in severe obesity, possibly limiting further adipocyte formation [74]. The mice lacking β-catenin, in osteoblasts, show decreased fat accumulation and increased energy expenditure [75]. Compared to lean controls, Wnt/β-catenin signaling in exosomes derived from obese VAT emerges as one of the top canonical pathways [76]. However, adipokines and inflammatory signals can interfere with Wnt signaling, tipping the delicate balance in favor of bone resorption [27]. Activation of the Wnt/β-catenin pathway not only stimulates osteoblast formation but also inhibits adipocyte differentiation. Adipokines and inflammatory signals can interfere with Wnt signaling, tipping the delicate balance in favor of bone resorption [7]. To sum up, the Wnt/β-catenin pathway may be disrupted in obesity and contribute to impaired bone health.

Sclerostin and DKK1: Antagonists in action

Sclerostin and Dickkopf-1 (DKK1) are key regulators of Wnt signaling and act as antagonists that inhibit osteoblast activity [77]. In particular, DKK1, a well-known inhibitor of Wnt signaling, has been shown to be overexpressed in various metabolic disorders, including obesity [78] and osteoporosis [79], which may negatively affect bone health. DKK1 inhibits bone formation and stimulates bone resorption by increasing the receptor activator of RANKL/OPG in osteogenic cells. On the other hand, results from a recent experimental high-fat diet (HFD) study showed that adipogenic DKK1 does not contribute to HFD-induced bone loss. However, the authors suggested that DKK1 may play a transient role in the regulation of bone mass during adolescence [80]. Similarly, another mouse study showing that DKK1 derived from osteogenic cells had no effect on metabolic parameters suggests that DKK1 may contribute to the expansion of bone marrow fat in obesity [81]. Consequently, the studies showing that DKK1 and sclerostin are elevated in obese individuals provide new insights into the interaction between Wnt/β-catenin signaling and its regulators and the molecular basis of obesity-related bone changes [81-83].

AMP-Activated Protein Kinase (AMPK) and Energy Sensing

The AMP-activated protein kinase (AMPK) regulates cellular metabolic balance through direct or indirect activation pathways. The AMPK pathway, known for its role in cellular energy sensing, is also associated with bone metabolism [84]. Obesity is associated with decreased AMPK activation with alterations in glycolysis, insulin sensitivity, hepatic lipid metabolism and inflammation [85]. Since it is characterized as a state of energy surplus, obesity may dysregulate AMPK signaling in bone cells. Li and colleagues found that AdipoRon, an adiponectin receptor type1/type2 activator activated AMPK, and downstream AMPK signaling enhanced osteoblast differentiation [86]. Another study demonstrated that AMPK activation may stimulate osteoblast differentiation and mineralization through the induction of autophagy [87]. Although AMPK activation has been associated with the inhibition of osteoclast formation, studies of the effects of AMPK on osteoclasts or their precursors have revealed conflicted conclusions [88,89]. However, the potential for the use of pharmacological therapies against AMPK signaling pathway disorders in metabolic diseases is a remarkable development. Indeed, two recent studies have shown that tartaric acid administration leads to improvement in experimental NAFLD by activating the AMPK signaling pathway [90] and similarly, XZF regulates hepatocyte lipid metabolism and protects against NAFLD progression by activating AMPK and PPAR signaling pathways [91].

The AMPK signaling, which also intersects with insulin signaling pathways, forms a nexus where metabolic and bone regulatory pathways converge [92,93]. In conditions of obesity, impaired insulin signaling and dysregulated AMPK activity may synergistically influence bone metabolism [54]. Dysfunction of insulin signaling in obesity is a consequence of impaired binding of IGF-1 to insulin receptors on osteoblasts, which may adversely affect bone remodeling. Indeed, increased IGF-1 secretion in response to low AMPK in mouse hepatocytes suggests an inverse relationship between AMPK and IGF-1 [94]. Given recent data, understanding the cross-talk between energy-sensing pathways and their effects on bone cells provides a comprehensive view of how systemic metabolic changes in obesity translate into altered BT dynamics [95,96].

On the other hand, gut microbiota and related dysbiotic changes are a critical player not only associated with obesity [97] but also influencing the development of osteoporosis through BT loss [98]. Regarding the recent data, it is also considered that specific mediators or metabolites formed due to dysbiosis as well as changes in signaling pathways (NF-κB, Wnt/β-catenin pathways) play a role in the development of obesity and osteoporosis [98,99].

Conclusion and Future Perspective

Obesity and osteoporosis are two important public health problems prevalent worldwide. Recent studies have shown that both diseases share several common genetic and environmental factors. There are complex interactions between metabolic factors and regulatory pathways influencing both obesity and osteoporosis [100]. The common precursor stem cell that leads to the differentiation of both adipocytes and osteoblasts, as well as the secretion of adipocyte-derived hormones that affect bone development, may partially explain epidemiologic and physiologic associations between fat and bone. Current data and findings show that the response of the skeleton to obesity is complex and depends on diversified factors, such as mechanical loading, obesity type, the location of AT, gender, age, bone sites, and secreted adipokines and osteokines (**Figure 1**) [5].

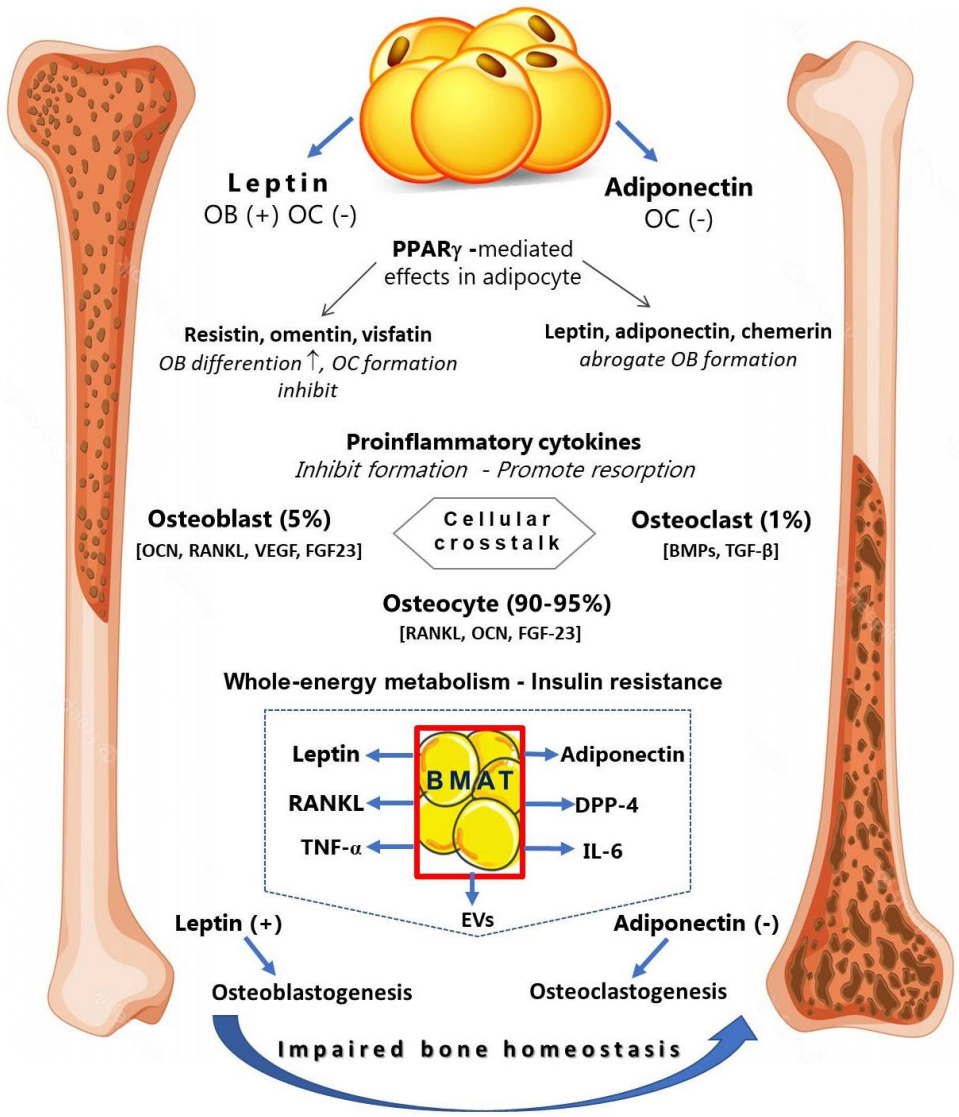

Figure 1. The interaction between adipose and bone tissue; Examples of bone tissue pathophysiological changes associated with obese fat tissue. OB: Osteoblast; OC: Osteoclast; OCN: Osteocalcin; VEGF: Vascular Endothelial Growth Factor; FGF23: Fibroblast Growth Factor 23; BMPs: Bone Morphogenetic Proteins; TGF-β: Transforming Growth Factor Beta; BMAT: Bone Marrow Adipose Tissue; DPP-4: Dipeptidyl Peptidase 4; EVs: Extracellular Vesicles.

Indeed, bone remodeling requires communication between osteoclasts, osteoblasts, osteocytes, and bone lining cells, and is a complex process that involves several hormones, cytokines, and signaling pathways [101]. In addition to genetic and epigenetic factors, inflammation, oxidative stress, cellular aging, and estrogen deficiency are the main factors affecting the number and activity of bone cells. Moreover, both systemic (PTH, vitamin D, leptin, irisin, estrogens) and local factors (RANKL, sclerostin, DKK1, FGF23) affect osteocyte function [102]. Obesity, which affects bone homeostasis and metabolism through signaling mechanisms as well as systemic and local factors, may cause bone loss and osteoporosis development in the long term. Obesity may also associate with bone dysfunction that alters osteokine secretion [70] and it may lead to increased circulating levels of osteokines, as in T2D [103]. Nonetheless, it has been reported sclerostin deletion [104] and overexpressed PTHrP [105] protect against high-fat diet-induced obesity and IR. Therefore, changes in some osteokine concentrations suggest that these factors have a protective effect against obesity.

Indeed, there is a wide repertoire of hormone-like "osteokines" secreted by bone cells including RANKL, sclerostin, osteocalcin, FGF23, PGE2, TGF-β, BMPs, IGF-1, and PTHrP (**Table 2**) [103]. Given the normal or better-than-normal BMD, the skeletal fragility of these patients seems to be a problem of bone quality rather than quantity. Recent developments therefore suggest that skeletal fractures are not only a complication of obesity, but like T2D, obesity is now recognized as a cause of secondary osteoporosis [106,107]. Therefore, it can be concluded that long-term prevention of skeletal damage is, to some extent, related to the prevention of the development of T2D in obese individuals and the management of the disease.

Notably, pharmacological treatment methods are also being discussed today to prevent obesity-related bone loss and fractures. An example of these treatment approaches that also target obesity is leptin [108,109]. Leptin, which is useful in the treatment of obesity due to congenital leptin deficiency, is also used in the treatment of lipodystrophy, a typical obesity model [108]. However, although it is not effective for typical obesity, a study found that recombinant human leptin can help with bone formation and may protect bones in obese people [109]. Leptin can also regulate vitamin D metabolism, which is important for bone health [21]. Interestingly, Piezo ion channels may be an important target for new drugs that can help obesity and bone diseases [110]. For example, activating Piezo1 with Yoda1 accelerates fracture healing in mice. Piezo1 is a mechanically activated ion channel that senses physical forces such as tension, osmotic pressure and shear force [111]. It plays a role in maintaining bone homeostasis and may be a potential treatment for osteoporosis. Similarly, this molecule triggered when the stomach is stretched may help fight obesity. By boosting the activity of these molecules, the brain can be tricked into thinking it is full earlier and the feeling mimicking satiety [112].

Meanwhile, liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, shows different effects on bone health. In humans, liraglutide treatment has been shown to prevent bone loss associated with weight loss and patients treated with liraglutide had increased serum P1NP (N-terminal propeptide of type 1) procollagen levels [113]. Interestingly, a recent study in a Danish population reported that liraglutide was an effective weight loss strategy that also preserved bone health during weight loss in women with obesity [114].

Table 2. Bone and bone marrow-derived osteokines and paracrine factors with relevance in bone health and metabolism.

Secretory cells of bone tissue	Osteokines	Effect on bone health and metabolism
Osteoblasts, Osteocytes, and Osteoclasts	- Osteocalcin	- Bone formation and resorption
	- RANKL	- Bone resorption
	- Sclerostin	- Inhibition of bone formation
	- FGF23	- Regulation of serum phosphate level
	- TGF-β	- Bone remodeling
	- PGE2	- Bone remodeling
	- IGF-1	- Bone growth, bone homeostasis
	- PTHrP	- Calcium release from bone during lactation, bone resorption
Paracrine factors originating from osteoblasts, osteocytes and osteoclasts		
- *Osteoblasts* activate osteoclast formation by expressing M-CSF, RANKL, and WNT5A. They also inhibit osteoclast activity via OPG, the trap receptor of RANKL, SEMA3A, and WNT16		
- *Osteocyte*-derived SOST inhibits osteoblast differentiation but stimulates osteoclastogenesis		
- *Osteoclasts* act on osteoblasts and osteocytes by secreting binding factors such as BMP6, CTHRC1, EFNB2, S1P, WNT10B, SEMA4D, and CT-1; thus, influence bone formation		

In conclusion, obesity, characterized by chronic inflammation, changes in adipokine profile, and disturbances in metabolic signaling pathways, may have profound effects on bone remodeling dynamics. Various adipokines, including leptin, adiponectin, resistin, and visfatin, act as molecular messengers that modulate the delicate balance between bone formation and resorption. Insulin resistance associated with obesity impairs insulin signaling in bone cells, affecting both osteoblasts and osteoclasts. Sex hormones, which are vital for maintaining bone density, change in the context of obesity and affect both sexes, especially postmenopausal women. Inflammation as a major player in obesity occupies a central position, with NF-κB signaling and the RANKL-RANK-OPG axis acting as the main mediators of obesity-induced BT changes. The Wnt/β-catenin pathway, vital for osteoblast function, is impaired in obesity, whereas antagonists such as sclerostin and DKK1 contribute to impaired bone formation. The AMPK signaling pathway, a central player in cellular energy sensing and involved in insulin signaling, is dysregulated in chronic diseases such as obesity. Understanding this complex interplay of signaling pathways opens avenues for targeted therapeutic interventions that could reduce the negative effects of obesity on bone health. For example, precision medicine approaches that take into account individual epigenetic differences may be key to developing effective strategies to prevent and manage obesity-related bone complications.

This review underlines the need for a holistic approach that considers the complex signaling network governing obesity-mediated effects on BT. The quest for knowledge in this area holds promise for improving clinical outcomes, developing preventive strategies, and addressing the growing health challenges posed by the intersection of obesity and bone health. However, more research is needed to elucidate adipokine and osteokine-dependent signaling mechanisms in a tissue-specific manner.

Declarations

Conflict of interest

All authors declare that they have no conflict of interest.

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