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Emerging Roles of Adipokines in Bone Homeostasis and Osteoimmunology: Narrative Review

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ABSTRACT

Aims: This review aims to examine the role of adipokines as key mediators linking obesity, inflammation, bone metabolism, and immune regulation. It seeks to elucidate how dysregulated adipokine secretion from white adipose tissue and bone marrow adipose tissue influences bone remodeling and osteoimmune interactions, thereby contributing to obesity-related skeletal disorders.

Method and Materials: A narrative review of current scientific literature was conducted, focusing on experimental, clinical, and translational studies that investigate the effects of adipokines on bone cells and immune pathways. Relevant publications were analyzed to synthesize existing knowledge on adipokine signaling, osteoblast and osteoclast regulation, bone marrow microenvironment dynamics, and the intersection between metabolic inflammation and osteoimmunology.

Findings: The reviewed evidences indicated that adipokines act as critical regulators of bone homeostasis through endocrine, paracrine, and autocrine mechanisms. Key adipokines, including leptin, adiponectin, resistin, and visfatin, significantly influence osteoblast differentiation, osteoclastogenesis, and immune cell activity. In obesity, altered adipokine profiles promote a chronic inflammatory state that disrupts the balance between bone formation and resorption, leading to impaired skeletal integrity and increased fracture risk. Additionally, adipokines play an important role in osteoimmunology by mediating crosstalk between adipose tissue, immune cells, and skeletal cells within the bone microenvironment.

Conclusion: Adipokines represent a crucial link between metabolic dysfunction, immune regulation, and bone health. Dysregulation of adipokine signaling in obesity contributes to chronic inflammation, altered osteoimmune interactions, and compromised bone remodeling. Improved understanding of these complex mechanisms may facilitate the development of targeted therapeutic strategies for preventing and managing obesity-related bone disorders and enhancing skeletal health.

Keywords: Obesity, Osteoimmunology, Adipokine, Adipose tissue, Bone Homeostasis

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Introduction

Bone homeostasis refers to the dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts. This process, known as bone homeostasis, is tightly regulated by systemic hormones, local growth factors, and the cellular components of the bone marrow microenvironment[1]. Over the past two decades, a growing body of evidence has highlighted that bone remodeling is not only a mechanical and endocrine process but also profoundly influenced by the immune system, a concept that has given rise to the field of osteoimmunology[2]. Within this context, metabolic and inflammatory mediators serve as critical links connecting energy metabolism, immunity, and skeletal biology. Among these mediators, adipokines, bioactive cytokines secreted predominantly by adipose tissue, have emerged as key regulators of bone metabolism. Initially recognized for their roles in energy homeostasis and insulin sensitivity, adipokines such as leptin, adiponectin, resistin, visfatin, chemerin, and lipocalin-2 are now understood to influence bone formation and resorption both directly and indirectly. They act directly on bone cells by modulating osteoblast differentiation, osteoclastogenesis, and the activity of mesenchymal Stem Cells (MSCs)[3] and indirectly, they influence bone turnover through immune-mediated

mechanisms by altering cytokine production, macrophage polarization, and T-cell differentiation. The Bone Marrow Adipose Tissue (BMAT) compartment serves as a unique source of local adipokine production, creating a paracrine environment that affects neighboring osteogenic and immune cells. This adipocyte-bone–immune axis becomes particularly significant in metabolic disorders such as obesity, diabetes, and osteoporosis, where alterations in adipokine profiles contribute to dysregulated bone remodeling [4].

Understanding the dual and sometimes paradoxical actions of adipocytes is therefore crucial for unraveling the complex interplay between metabolism, immunity, and skeletal health. Elucidating these pathways not only provides insight into the pathophysiology of bone loss in metabolic and inflammatory diseases but also opens avenues for novel therapeutic interventions that target adipokine signaling to restore bone homeostasis.

Method and Materials

This review is based on a comprehensive evaluation of published literature examining the role of adipokines in bone metabolism and osteoimmunology, particularly in the context of obesity and chronic inflammation. Scientific articles were identified through systematic searches of major electronic databases, including PubMed, Scopus, and Web of Science. Keywords used in the search strategy included combinations of adipokines, obesity, bone metabolism, osteoblasts, osteoclasts, bone marrow adipose tissue, white adipose tissue, inflammation, and osteoimmunology.

Original research articles, review papers, and relevant clinical studies published in peer-reviewed journals were considered. Studies addressing the endocrine, paracrine, and autocrine actions of adipokines on skeletal cells, immune cell interactions within the bone microenvironment, and mechanisms linking metabolic disorders to bone fragility were prioritized. Reference lists of selected articles were also screened to identify additional relevant publications.

The collected literature was critically assessed and synthesized to provide an integrated overview of current knowledge regarding adipokine-mediated regulation of bone remodeling and immune–skeletal crosstalk. Emphasis was placed on key adipokines, including leptin, adiponectin, resistin, and visfatin, and their effects on osteoblast differentiation, osteoclastogenesis, immune signaling pathways, and bone homeostasis. This narrative approach was employed to highlight emerging concepts, unresolved questions, and potential therapeutic implications related to obesity-associated bone disorders.

Data were compiled and stored in Microsoft Excel (Excel 2016, version 16.0). Descriptive statistics were generated to determine frequency distributions. Further analysis was performed using SPSS software (version 11.0; SPSS Inc., Chicago, IL, USA). Comparisons between categorical variables were made using the Chi-square test, while correlations were assessed using Pearson's correlation coefficient (r) and Spearman's rank correlation. A p-value of less than 0.05 was considered statistically significant. For correlation analyses, variables with r values between 0 and +1 were interpreted as having a positive correlation, whereas those with values between 0 and –1 indicated a negative correlation.

Findings

Major Adipokines and Mechanisms

Major adipokines, including resistin, chemerin, leptin, adiponectin and Lipocalin-2, play key regulatory roles in bone homeostasis and osteoimmunology by influencing the balance between osteoblast-mediated bone formation and osteoclast-directed bone resorption. Each of them is mentioned below and summarized in Table 1.

ResistinResistin is a cysteine-rich peptide hormone originally identified as an adipokine secreted by adipose tissue, but later found to be expressed in various other cells, including macrophages, monocytes, gastric cells, and bone-related cells [5, 6]. In humans, resistin is encoded by the RETN gene and acts primarily as a pro-inflammatory cytokine. It plays a significant role in linking metabolic and

inflammatory pathways, contributing to conditions such as insulin resistance, obesity, and chronic inflammation. Beyond its metabolic effects, resistin has emerged as an important regulator in bone biology and osteoimmunology [7]. Several studies have shown that resistin promotes osteoclast differentiation and activity, often by stimulating pro-inflammatory pathways such as NF-κB and MAPK. These signaling cascades lead to increased expression of receptor activator of nuclear factor κB ligand (RANKL), a key mediator of osteoclastogenesis [8, 9]. Consequently, elevated resistin levels are often associated with enhanced bone resorption and decreased bone mass, linking it to conditions like osteoporosis and rheumatoid arthritis [10, 11]. On the other hand, resistin can also affect osteoblasts by inhibiting their differentiation and mineralization, further disrupting skeletal integrity. In the context of osteoimmunology, resistin acts as an immune-modulatory molecule that connects inflammation and bone remodeling. It is secreted by immune cells within inflamed tissues, where it amplifies the production of cytokines such as TNF-α, IL-6, and IL-1β as key mediators of both inflammation and osteoclast activation[12]. Through these actions, resistin contributes to the inflammatory microenvironment that drives pathological bone loss in diseases like rheumatoid arthritis, periodontitis, and ankylosing spondylitis. Moreover, resistin has been shown to interact with Toll-Like Receptor 4 (TLR4), triggering innate immune responses that can alter osteoclastogenesis and osteoblast function, reinforcing its role as a molecular bridge between immune and skeletal systems [13].

Chemerin

Chemerin, also known as retinoic acid receptor responder protein 2 (RARRES2), is an adipokine originally identified as a chemoattractant involved in immune cell trafficking. It is secreted as an inactive precursor (prochemerin) and activated by proteolytic cleavage during inflammatory processes [14]. Chemerin primarily signals through the ChemR23 receptor (also known as CMKLR1), as well as through GPR1 and CCRL2, which are expressed in a variety of tissues, including adipose tissue, bone marrow, and immune cells [15, 16]. Chemerin and its receptors are expressed in osteoblasts, osteoclasts, mesenchymal stem cells (MSCs), and bone marrow adipocytes, indicating both systemic and local roles in bone homeostasis [17]. In recent years, chemerin has emerged as a significant mediator at the intersection of metabolism, immunity, and skeletal biology. Chemerin directly regulates bone cell function. In vitro studies demonstrate that chemerin promotes osteoblast differentiation and mineralization via CMKLR1-mediated activation of the ERK1/2 and PI3K/Akt pathways [18]. Conversely, high concentrations of chemerin or dysregulated signaling, often seen in obesity and chronic inflammation, can impair osteoblast maturation and reduce the expression of osteogenic markers such as Runx2, osteocalcin, and Alkaline Phosphatase (ALP)[19]. Chemerin also influences osteoclastogenesis. It can stimulate osteoclast differentiation either directly through receptor-mediated effects on precursor cells or indirectly by enhancing RANKL expression in osteoblasts and stromal cells [20]. This dual regulation suggests that chemerin may act as both a pro-osteogenic and pro-resorptive factor depending on the microenvironmental context and local cytokine milieu. Beyond its effects on bone cells, chemerin plays a pivotal role in immune bone crosstalk. It functions as a chemoattractant for macrophages, dendritic cells, and NK cells, linking adipose tissue inflammation with bone metabolism [21]. In inflammatory states, elevated chemerin levels promote macrophage recruitment and M1 polarization[22], enhancing pro-inflammatory cytokine production (IL-1β, IL-6, TNF-α), which in turn drives osteoclastogenesis and bone resorption[23].

Leptin

Leptin is a 16-kDa peptide hormone primarily secreted by adipocytes, encoded by the ob gene[24]. It was first identified in 1994 as a key regulator of energy balance and body weight, functioning mainly through the hypothalamus

to suppress appetite and increase energy expenditure. Beyond its classical metabolic role, leptin acts as a multifunctional hormone that affects various physiological systems, including bone metabolism and the immune system [25]. The effects of leptin on bone are complex and depend on whether it acts centrally (via the brain) or peripherally (directly on bone cell) [26]. Centrally, leptin acts on hypothalamic neurons to regulate bone mass via the sympathetic nervous system. Activation of β2-adrenergic receptors on osteoblasts by sympathetic neurotransmitters generally leads to reduced bone formation and increased bone resorption, suggesting that central leptin signaling exerts a catabolic effect on the skeleton. In contrast, peripheral leptin directly binds to leptin receptors on osteoblasts, stimulating their proliferation, differentiation, and production of bone matrix proteins. It also enhances osteoprotegerin (OPG) expression and suppresses receptor activator of nuclear factor κB ligand (RANKL), thereby inhibiting osteoclastogenesis [27, 28].

Leptin also plays an important role in shared molecular pathways and cellular interactions between the immune and skeletal systems by acting as an immunomodulatory hormone with cytokine-like properties. It promotes the proliferation and activation of T lymphocytes, particularly enhancing pro-inflammatory Th1 and Th17 cell responses, while inhibiting regulatory T cells (Tregs) that suppress inflammation [29]. Leptin also stimulates macrophages, dendritic cells, and other immune cells to secrete cytokines such as Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), which are known to induce osteoclast differentiation through the RANK/RANKL pathway[30]. Therefore, leptin indirectly enhances bone resorption under inflammatory conditions, linking immune activation to skeletal degradation. This mechanism is particularly relevant in chronic inflammatory diseases such as rheumatoid arthritis and obesity-associated bone loss.

Adiponectin

Adiponectin, which is also known as GBP-28, apM1, AdipoQ, and Acrp30, is a protein hormone predominantly secreted by adipocytes and is one of the most abundant adipokines in circulation. It plays a critical role in regulating glucose metabolism, lipid oxidation, and overall energy homeostasis. In human beings, it is encoded by the ADIPOQ gene and is mainly synthesized in adipose tissue, though it can also be found in muscle tissue and even the brain [31].

Unlike many other adipokines, adiponectin exhibits anti-inflammatory and insulin-sensitizing properties[32]. Beyond its metabolic effects, adiponectin has gained significant attention in recent years for its involvement in bone physiology and. Its functions in bone homeostasis are complex and context-dependent, influenced by factors such as receptor distribution, local inflammatory environment, and metabolic status[33]. Adiponectin influences Bone homeostasis, though its effects can vary depending on tissue context and experimental models. Generally, adiponectin enhances osteoblast differentiation and mineralization by activating signaling pathways such as AMP-activated protein kinase (AMPK), p38 MAPK, and peroxisome proliferator-activated receptor gamma (PPARγ) [18]. These pathways promote the expression of osteogenic markers like Runx2, osteocalcin, and alkaline phosphatase. Conversely, adiponectin can suppress osteoclastogenesis by inhibiting RANKL-mediated differentiation through decreasing expression levels of osteoclastogenic regulators, NFAT2 and TRAF6, as well as another two osteoclastic differentiation markers, TRACP and cathepsin K [34]. However, some studies report that adiponectin may have indirect effects that can increase bone resorption, particularly under conditions of low energy availability or chronic inflammation [35-37]. Thus, adiponectin's role in bone homeostasis is bidirectional but generally favors bone formation and maintenance of skeletal integrity.

In osteoimmunology, adiponectin functions as an immunomodulatory factor that bridges metabolic and immune regulation of bone. Adiponectin promotes the anti-inflammatory

M2 phenotype while inhibiting the pro-inflammatory M1 phenotype [38, 39]. It suppresses secretion of TNF-α, IL-1β, and IL-6, cytokines known to enhance osteoclast differentiation and bone resorption [40, 41]. Through this mechanism, adiponectin indirectly reduces osteoclast activity and bone loss under inflammatory conditions. In addition, adiponectin influences T cell differentiation. It Enhances regulatory T cell (Treg) development and IL-10 production, promotes immune tolerance and bone preservation [42]. Also, adiponectin inhibits Th1 and Th17 responses, decreases production of IFN-γ and IL-17, which are associated with osteoclast activation [43, 44]. On the other hand, adiponectin modulates dendritic cell maturation and antigen presentation, reducing their capacity to activate inflammatory T cells [45]. This can help dampen chronic inflammation in bone microenvironments such as those found in rheumatoid arthritis and periodontitis. These effects position adiponectin as an immunomodulatory molecule protecting bone from inflammation-driven resorption. Serum adiponectin levels are inversely correlated with obesity and metabolic syndrome but have complex relationships with bone mineral density (BMD). While higher adiponectin levels are generally protective in inflammatory contexts, some studies have found an association between elevated adiponectin and lower BMD, especially in postmenopausal women, possibly due to indirect metabolic effects [46]. Nevertheless, adiponectin's anti-inflammatory and pro-osteogenic functions make it a promising therapeutic target for bone and joint diseases characterized by chronic inflammation and bone destruction.

Lipocalin-2 (LCN2)

Lipocalin-2 (LCN2) or neutrophil gelatinase-associated lipocalin (NGAL) is a secreted glycoprotein belonging to the lipocalin family, which is involved in the transport of small hydrophobic molecules such as lipids, steroids, and iron-binding siderophores. It is encoded by the LCN2 gene [47]. Initially identified as a component of neutrophil granules, lipocalin-2 is now known to be expressed in a variety of tissues, including adipose tissue, liver, kidney, and bone. It functions as both an adipokine and an acute-phase protein, playing critical roles in metabolism, immune regulation, and inflammation. In recent years, increasing evidence has revealed that lipocalin-2 also exerts significant influence on bone homeostasis and osteoimmunology, serving as a molecular bridge between energy metabolism, immune responses, and skeletal remodeling. Lipocalin-2 has been shown to affect bone homeostasis through several mechanisms. On one hand, LCN2 negatively regulates osteoblast differentiation and bone formation by inhibiting key osteogenic transcription factors such as Runx2 and osterix [48]. It can also impair osteoblast proliferation and mineralization by reducing Wnt/β-catenin signaling, a pathway essential for bone formation [49]. Consequently, elevated lipocalin-2 levels have been associated with decreased bone mass and delayed fracture healing in both experimental and clinical settings. On the other hand, lipocalin-2 can modulate osteoclast differentiation. Some studies suggest that LCN2 inhibits osteoclastogenesis by suppressing RANKL-induced signaling and reactive oxygen species (ROS) generation, thereby restraining bone resorption [50]. However, under inflammatory conditions, LCN2 may indirectly promote osteoclast activation through its pro-inflammatory actions, suggesting a dual and context-dependent role in bone remodeling[51].

As a pro-inflammatory mediator, LCN2 is upregulated in response to cytokines such as IL-1β, TNF-α, and IL-6, and in turn, it enhances the production of these cytokines, creating a feedback loop that amplifies inflammation [52]. This inflammatory milieu affects bone turnover, often leading to pathological bone loss, as seen in diseases like rheumatoid arthritis, osteoporosis, and periodontitis[53]. Moreover, lipocalin-2 regulates iron metabolism by sequestering bacterial siderophores, thereby limiting microbial growth; however, this iron-regulatory function can also influence bone

cell metabolism and differentiation, since iron is a critical cofactor for osteoblast and osteoclast function [54].

In clinical contexts, elevated serum lipocalin-2 levels are associated with metabolic and inflammatory bone disorders. For example, patients with rheumatoid arthritis, obesity-related bone loss, or chronic kidney disease often exhibit increased LCN2 levels correlated with inflammation and impaired bone quality[55, 56]. This makes lipocalin-2 a potential biomarker for inflammation-induced bone turnover and a possible therapeutic target for preventing inflammatory osteopathies. Modulating LCN2 expression or blocking its signaling pathways may help restores bone homeostasis, especially in metabolic and immune-mediated skeletal diseases.

Signaling Pathways Associated with Adipokines and Bone Remodeling.

RANKL/RANK signaling pathway

The regulation of bone homeostasis relies on the continuous process of bone formation by osteoblasts and bone resorption by osteoclasts. The RANKL/RANK signaling pathway is essential for the formation, activation, and survival of osteoclasts during normal bone development and remodeling, as well as in various diseases marked by increased bone remodeling[9]. RANKL and OsteoProteGerin (OPG), its soluble decoy receptor, are crucial components of a significant axis of three key signaling molecules involved in bone remodeling. OPG serves to shield bone from excessive resorption by attaching to RANKL, thus stopping it from associating with RANK [9, 57]. There is emerging evidence suggesting that the OPG-RANKL-RANK axis may play a role in the development of metabolic disorders like obesity, Type 2 Diabetes Mellitus (T2DM), and Non-Alcoholic Fatty Liver Disease (NAFLD). Moreover, the unregulated RANKL-RANK-OPG axis establishes a molecular connection between inflammation and the altered bone dynamics seen in obesity [58]. Inflammation related to obesity can disrupt the balance of the RANKL/OPG ratio, which encourages osteoclast development and bone resorption[59]. Indeed, obesity creates a state of chronic inflammation that impacts metabolic processes in insulin-sensitive tissues, including bone and its immune tissues in the bone marrow. The condition associated with obesity may also lead to hyperplasia in the bone marrow, characterized by an increased influx of immune cells into the circulation [60].

NF-κB signaling pathway

The NF-κB signaling pathway is vital in regulating inflammation and plays a significant role in both immune balance and chronic inflammatory processes [61]. The overactivation of NF-κB signaling, alongside inflammation driven by oxidative stress and dysfunctional macrophage activity, is observed in bone-related conditions such as rheumatoid arthritis [62]. Inflammatory signals derived from adipose tissue, like TNF-α, trigger NF-κB activation, which in turn affects the expression of genes that regulate bone remodeling [63]. Genetic studies indicate that the MyD88-dependent TLR pathway is essential for the polarization of M1 macrophages and the production of pro-inflammatory cytokines [64]. Notably, the NF-κB receptor activator ligand (RANKL) is a key factor in osteoclast differentiation, significantly contributing to the immune system's role in bone loss. Persistent low-grade systemic inflammation negatively impacts bone health, and increased adiposity in bone marrow correlates with a reduction in bone mass among obese individuals [65]. Especially relating to bone, ongoing activation of innate NF-κB signaling leads to several adverse effects on the preservation of bone mass, including the suppression of osteoblast differentiation and mineralization, as well as the inappropriate stimulation of osteoclastic activity [66]. Inflammation mediated by NF-κB disturbs the fragile equilibrium between osteoblasts and osteoclasts, promoting more bone resorption than formation. Inflammatory cytokines not only encourage bone resorption independently but can also enhance the activation of the TNF-α/NF-κB signaling pathway, stimulate osteoclast-related genes, and further increase bone resorption, posing

serious risks to individuals with osteoporosis[67].

AMP-Activated Protein Kinase (AMPK) signaling pathway

The AMP-Activated Protein Kinase (AMPK) is responsible for managing cellular metabolic balance through various direct and indirect activation pathways. Recognized for its function in cellular energy detection, the AMPK pathway is also linked to bone metabolism[68]. Obesity leads to reduced AMPK activation, causing changes in glycolysis, insulin sensitivity, liver fat metabolism, and inflammation[69]. As obesity represents a condition of excess energy, it may disrupt AMPK signaling in bone cells. Research by Li and colleagues demonstrated that AdipoRon, a modulator of adiponectin receptor types 1 and 2, promotes AMPK activation, which in turn enhances the differentiation of osteoblasts[70]. Tanaka et al. showed that activating AMPK might encourage osteoblast differentiation and mineralization through the promotion of autophagy[71]. While AMPK activation has been noted to inhibit osteoclast formation, studies examining its effects on osteoclasts or their precursors have yielded mixed results [72, 73]. Nonetheless, the prospect of employing pharmacological treatments to address disorders in the AMPK signaling pathway related to metabolic diseases represents a significant advancement. In fact, two recent studies indicated that administering tartaric acid improves experimental NAFLD by activating the AMPK signaling pathway, and similarly, XZF influences liver fat metabolism and safeguards against NAFLD progression by engaging the AMPK and PPAR signaling pathways[74]. The AMPK signaling pathway also intersects with insulin signaling pathways, establishing a connection where metabolic and bone regulatory pathways come together[75]. In instances of obesity, the dysfunction in insulin signaling coupled with impaired AMPK activity may jointly affect bone metabolism. The disruption of insulin signaling in obesity occurs due to reduced binding of IGF-1 to insulin receptors on osteoblasts, potentially compromising bone remodeling. Notably, increased IGF-1 secretion in response to decreased AMPK in mouse liver cells implies an inverse correlation between AMPK and IGF-1[76]. Considering recent findings, comprehending the interactions between energy-sensing pathways and their impact on bone cells offers a broader understanding of how systemic metabolic shifts in obesity affect bone turnover dynamics[77]. Conversely, gut microbiota and related dysbiotic alterations play a significant role not only in obesity but also in the development of osteoporosis through bone turnover loss[78]. It is proposed based on recent evidence that specific mediators or metabolites resulting from dysbiosis, along with alterations in signaling pathways (like NF-κB and Wnt/β-catenin), contribute to the onset of obesity and osteoporosis [79].

Wnt signaling pathway

The activation or inhibition of the Wnt signaling pathway results in varying effects on the development of obesity, influenced by the specific mechanisms involved. Wnt proteins function as transcription coactivators of TCF within the nucleus, controlling the expression of target genes. When the Wnt/β-catenin pathway is activated, it suppresses adipogenesis, inhibits thermogenesis related to brown adipose tissue, and enhances insulin sensitivity. Several factors, such as leptin, Oxysterol-Binding Protein Ligand 2 (OSBPL2), and miRNAs, can stimulate canonical Wnt signaling. These factors play a role in the development of obesity by influencing the Wnt/β-catenin signaling pathway. Moreover, Wnt5a, part of the non-canonical Wnt pathway, triggers inflammation associated with obesity in white adipose tissue through a JNK-dependent mechanism, which further contributes to insulin resistance in adipose tissue[80]. Genetic studies in mice have validated the significance of the canonical Wnt signaling pathway in maintaining bone health, and numerous genome-wide association studies have highlighted the relevance of the WNT signaling pathway for bone in the broader population[81]. The Wnt/β-catenin signaling pathway is crucial for bone growth

and preservation. Activating this pathway facilitates the differentiation of osteoblasts and the formation of bone, while simultaneously inhibiting the formation of osteoclasts. Consequently, this pathway is also regarded as a potential target for treating osteoporosis and promoting fracture healing [82]. In cases of obesity, it is suggested that the Wnt/β-catenin signaling pathway may lead to a reduction in osteoblast differentiation of bone marrow stromal cells. In other terms, secreted frizzled-associated protein 1, which inhibits Wnt/β-catenin signaling, has been found to be elevated in mild obesity, leading to greater formation of bone marrow adipose tissue, yet its levels decrease in severe obesity, perhaps limiting further stem cell differentiation into adipocytes[83]. Mice that lack β-catenin specifically in osteoblasts exhibit less fat accumulation and increased energy expenditure[84]. In comparison to lean controls, Wnt/β-catenin signaling in exosomes sourced from visceral adipose tissue of obese individuals is identified as one of the most prominent canonical pathways[85]. However, adipokines and inflammatory factors may disrupt Wnt signaling, causing a shift that favors bone resorption. The activation of the Wnt/β-catenin pathway not only promotes the formation of osteoblasts but also inhibits the differentiation of adipocytes. Adipokines and inflammatory signals have the potential to disrupt Wnt signaling, tipping the fragile balance towards increased bone resorption [86]. In conclusion, the Wnt/β-catenin pathway may become altered in obesity, leading to compromised bone health.

Discussion

Adipose tissue is not merely a fat storage site but an active endocrine organ that secretes bioactive molecules known as adipokines, which influence both inflammation and bone physiology. In obesity, the expansion of adipose tissue leads to an altered adipokine profile, favoring pro-inflammatory signaling. Adipokines such as leptin, resistin, and visfatin promote the release of inflammatory mediators that enhance osteoclastogenesis and suppress bone formation. In contrast, adiponectin, which has anti-inflammatory and bone-protective effects, is often reduced in obesity, further exacerbating inflammation-induced bone deterioration.

The interplay between inflammation and adipokines establishes a vicious cycle in which inflammation alters adipokine secretion, and adipokines, in turn, perpetuate inflammatory signaling in bone tissue. This relationship highlights the metabolic-immune connection underlying skeletal fragility in obesity and related disorders. Therapeutic strategies that modulate adipokine activity or reduce inflammation—such as lifestyle modification, anti-inflammatory agents, and insulin-sensitizing drugs—hold promise in preserving bone health. Understanding how adipokines mediate the crosstalk between adipose tissue and bone may open new avenues for preventing and treating inflammation-associated bone loss.

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Authors Contribution

MM was the principal investigator and collected the data, analyzed it, and wrote the initial draft. AJ and MM supervised the study. All authors approved the study.

Conflict of interest

The authors declared there is no conflict of interest for this study.

Ethical Permission

This manuscripy does not require ethical permission.

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