

Adipokines: Do They Affect the Osteochondral Unit?

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Abstract

Obesity, characterized by excessive or abnormal accumulation of body fat, is associated with a range of metabolic and inflammatory diseases, including osteoarthritis (OA). In obese individuals, adipose tissue expansion—via adipocyte hypertrophy or hyperplasia—is accompanied by altered secretion of adipokines such as leptin and adiponectin, which play significant roles in immune modulation, metabolism, and skeletal homeostasis. Leptin, acting through the hypothalamus, regulates the sympathetic nervous system and modulates hormonal axes, influencing bone metabolism and cartilage integrity. Elevated leptin concentrations in the synovial fluid, and the presence of its receptors on cartilage surfaces, suggest its direct role in cartilage degradation and OA progression. Conversely, adiponectin exerts anti-inflammatory effects, modulates osteoblast and macrophage activity, and appears to have a protective function in joint metabolism. These findings underscore the complex interplay between the adipose tissue, adipokines, and the osteochondral unit, highlighting the importance of their balance in maintaining joint health.

Keywords: obesity; osteoarthritis; leptin; adiponectin; bone metabolism; cartilage; inflammation



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1. Introduction

Osteoarthritis (OA) is now recognized as a multifactorial disease extending beyond mechanical joint damage or habitual overuse. It involves a complex interplay of inflammatory, metabolic, and biochemical mechanisms contributing to its pathogenesis [1]. Among its risk factors, obesity plays a prominent role. Defined as excessive accumulation or abnormal distribution of body fat, obesity is associated with numerous comorbidities. The expansion of the adipose tissue in obesity occurs through adipocyte hypertrophy (cell enlargement) or hyperplasia (an increased cell number), modulated by genetic and environmental factors, though the molecular pathways governing these processes remain partially understood.

In addition to their metabolic functions, adipocytes act as immunologically active cells, secreting a broad range of pro- and anti-inflammatory cytokines and hormones collectively known as adipokines. Two of the most studied adipokines, leptin and adiponectin, influence both local and systemic inflammatory responses, as well as bone and cartilage metabolism [2]. Understanding their roles in the osteochondral unit may shed light on the pathophysiology of obesity-related OA and identify potential therapeutic targets.

2. Leptin Physiopathology

Leptin (LEP) is a peptide hormone primarily secreted by the adipocytes, with circulating levels that reflect the amount of body fat and respond dynamically to acute caloric changes. LEP levels decrease during fasting and increase with energy surplus. Genetic and environmental factors contribute to the inter-individual variability in leptin concentrations, even among subjects with a similar body mass index (BMI) [3,4].

Leptin influences various physiological systems, including the skeletal system. It exerts both central and peripheral effects, with complex, sometimes opposing, outcomes. Centrally, leptin acts on the hypothalamus, regulating appetite and energy expenditure through the activation of pro-opiomelanocortin (POMC) and cocaine–amphetamine-regulated transcript (CART) neurons and the inhibition of orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) [5]. Leptin also modulates the sympathetic nervous system (SNS), influencing thermogenesis in brown adipose tissue and regulating hormonal axes that affect thyroid hormones, growth hormone, cortisol, and sex steroids—all of which have implications for bone metabolism [6].

Although the brain is protected by the blood–brain barrier, certain hypothalamic regions are permeable, allowing leptin to bind to receptors (LEPRs) expressed in the central nervous system. Peripheral leptin receptors are also found in the osteoblasts, bone marrow adipocytes, and chondrocytes, indicating local effects on bone remodeling and cartilage metabolism.

The dual role of leptin—anabolic through direct stimulation of osteoblast activity and anti-osteogenic via central SNS-mediated mechanisms—suggests that its overall impact on bone is context-dependent. Factors such as leptin concentrations, receptor sensitivity, nutritional status, and systemic inflammation may influence its ultimate physiological effect.

3. Leptin and Bone Mineral Density (BMD)

Numerous studies have demonstrated that bone mineral density (BMD) is positively associated with body mass index (BMI), as well as with both fat and lean mass, under the influence of factors such as age, sex, gonadal status, and physical activity levels [7–9]. Mechanistically, bone and fat tissues are interconnected through several mediators that ensure the skeletal mass is adequate to support body weight. Among these are adipokines like adiponectin, insulin/amylin/preptin, leptin, and adipose-derived estrogens, as well as transcription factors and signaling molecules involved in the crosstalk between bone physiology and energy metabolism [10].

Although the clinical literature suggests that adiposity exerts a protective effect against fractures, recent studies indicate that this protection may vary by fracture site. In fact, fractures of the upper arm and lower leg appear to be more frequent in individuals with a higher body weight, likely due to site-specific loading patterns or increased fall risks for these areas.

A preliminary study by Ducy et al. [11] showed that intracerebroventricular (ICV) leptin infusions in ob/ob (leptin-deficient) and wild-type mice reduced vertebral trabecular bone volume. Both their femoral and vertebral cancellous bone volumes were diminished, while their femur lengths and total femur bone volume increased to the wild-type levels. These findings suggest that ICV leptin exerts anti-osteogenic effects on trabecular bone but also promotes anabolic effects on cortical bone. Similarly, Bartell et al. demonstrated that ICV leptin increased the mineral apposition rate in both vertebrae and tibiae, comparable to the effects of subcutaneous leptin administration [12].

Several lines of evidence indicate that ICV leptin reduces the trabecular bone volume in the spine and other regions, though the underlying mechanism—reduced bone formation or increased resorption—remains unclear. In contrast, its effects on cortical bone are mixed.

More definitive insights come from the study by Takeda et al. [13], which demonstrated that leptin's primary mechanism involves the suppression of serotonin synthesis in the hypothalamus, leading to activation of the sympathetic nervous system (SNS). This activation increases norepinephrine release, which then binds to β 2-adrenergic receptors on the osteoblasts, ultimately inhibiting bone formation. It is important to note that serotonin does not cross the blood–brain barrier, highlighting the central origin of this regulatory pathway.

Further evidence supporting the role of leptin in SNS-mediated bone remodeling was provided by Elefteriou et al. [14,15], who demonstrated that β -adrenergic stimulation of osteoblast precursors increases RANKL expression and osteoclastogenesis. These findings collectively suggest that it is leptin signaling—rather than body weight per se—that regulates bone mass. This supports the hypothesis by Ahima and Flier that obese individuals, who are generally protected against osteoporosis, may be resistant to leptin's central action [16].

The impact of leptin on the SNS has prompted clinical trials investigating the effects of β -blockers on the bone structure, although the results have been inconsistent and inconclusive regarding its clear benefit.

In addition to its central effects, leptin also exerts direct actions on bone cells via its receptors on osteoblasts, with generally anabolic outcomes. Several studies have shown that leptin promotes the differentiation of human marrow stromal cells into osteoblast-like cells and stimulates osteoblast proliferation at physiological concentrations [17,18]. In an in vitro osteoblast model, Zhang et al. reported that leptin enhanced ossification through various mechanisms, including bone mineralization, remodeling, resorption, and osteoblast differentiation [19].

Studies using ob/ob mice have also shown that leptin plays a role in fracture healing, influencing callus formation and maturation [20]. Furthermore, numerous in vitro studies have demonstrated that leptin stimulates the osteoprotegerin (OPG) production by the osteoblasts and inhibits osteoclastogenesis. Collectively, the current evidence supports the notion that leptin has an anabolic effect on bone, although excessive levels may reverse this effect [21,22].

Unfortunately, human studies have yielded inconsistent and often inconclusive results regarding leptin's impact on bone. These discrepancies likely reflect differences in the study designs and subject characteristics. While some studies have reported no significant change in BMD, others have observed modest increases. Bone turnover markers were mostly unchanged or elevated, with the exception of one study that noted a reduction in the bone resorption marker CTX [23].

4. Leptin Therapy

Systemic leptin (LEP) administration in both animals and humans typically exerts a positive effect on bone mass. While the sympathetic nervous system (SNS) mediates leptin's central catabolic actions in bone, the overall balance between its central and peripheral effects remains controversial. This variability is influenced by several factors, including underlying pathologies, leptin concentrations, nutritional and hormonal status, and the presence of inflammatory conditions—all of which can modulate leptin's effects on bone metabolism.

Nonetheless, several studies suggest that leptin's direct effects on bone may be dominant. This could be attributed to the fact that leptin is primarily produced outside the central nervous system and is found in circulation at concentrations several times higher than those in cerebrospinal fluid. Furthermore, leptin is locally produced by bone marrow adipocytes, chondrocytes, and cells of the osteoblast lineage, leading to locally elevated concentrations near bone cells [24].

Leptin replacement therapy has demonstrated notable improvements in lumbar spine bone mineral density (BMD), raising the possibility of its use in metabolic bone diseases, including osteoporosis—particularly in leptin-deficient individuals. In a pilot study, Sienkiewicz et al. [25] showed that long-term metreleptin administration in young women with hypothalamic amenorrhea (HA) and hypoleptinemia resulted in an increased lumbar spine BMD and bone mineral content (BMC), alongside a shift in bone remodeling markers toward bone accrual. Similarly, Chow et al. [26] conducted a randomized, double-blind, placebo-controlled trial in women with HA using replacement doses of recombinant human leptin (metreleptin) for 36 weeks. This therapy restored menstruation and normalized the gonadal, thyroid, growth hormone, and adrenal axes. Although the changes in the bone metabolism markers suggested enhanced bone formation, no significant changes in BMD were detected during the short study period.

A well-documented phenomenon in leptin therapy is the lack of expected leptin activity despite high circulating levels. This is commonly attributed to leptin resistance, which frequently accompanies states of energy excess. Contributing mechanisms include impaired transport across the blood–brain barrier, defective LepRb trafficking from the trans-Golgi network to the cell membrane, obesity-induced endoplasmic reticulum (ER) stress, and chronic low-grade inflammation—all of which impair leptin signaling [27,28]. These should be distinguished from genetic forms of leptin resistance, where mutations in LepRb or downstream pathways block leptin response altogether [29].

The specific contribution of each mechanism to leptin resistance remains incompletely understood [30]. Similarly, the overall impact of leptin on bone metabolism across different experimental models is still under investigation. Preliminary clinical studies showing limited effects of β -blockers on bone health may suggest the predominance of leptin's peripheral actions. However, the multifaceted physiology of the human body often complicates the interpretation of both endogenous hormone function and pharmacologic interventions. Leptin's complex and context-dependent effects on bone structure exemplify this challenge.

Recent studies emphasize the interconnectedness of energy metabolism and bone physiology, suggesting novel therapeutic targets for conditions like osteoporosis. In addition to leptin, other regulatory molecules—including insulin, adiponectin, irisin, osteoglycin, lipocalin 2, osteocalcin, and calcitriol—are now recognized as active players in bone homeostasis.

Interestingly, while early animal studies suggested a potential detrimental effect of β -blockers on bone, subsequent investigations using low-dose β -blockers have shown increased osteoblast activity and reduced osteoclast surfaces. In contrast, higher doses yielded differing results [13,31,32]. This apparent contradiction may be explained by the dual expression of β 1- and β 2-adrenergic receptors (Adr β 1 and Adr β 2) on the osteoblasts. Low doses of β -blockers selectively antagonize the Adr β 2 receptors, favorably impacting bone mass without affecting cardiovascular parameters. However, higher doses that also block Adr β 1 fail to provide additional skeletal benefits and may impact heart rate and respiration [31].

Several observational studies have attempted to clarify the effects of β -blockers on bone mass and fracture risk. A comprehensive meta-analysis by Toulis et al. evaluated the efficacy of β 1-selective versus non-selective β -blockers. Across 16 studies involving 1,644,570 subjects, β -blocker use was associated with a significantly reduced risk of fractures, particularly vertebral and forearm fractures, though not all of the results reached statistical significance. Interestingly, the reduction in fracture risk was not dose-dependent. Notably, β 1-selective agents were significantly more effective than non-selective β -blockers (pooled effect size: 0.82; 95% CI: 0.69–0.97) [33].

Regardless of the precise efficacy of β -blockers or the optimal dosing strategies and receptor targets, what remains consistently supported is the pivotal role of leptin in modulating bone metabolism.

5. Leptin and Cartilage

A key question remains: can leptin (LEP) influence chondrocyte activity, and what are the consequences? The answer is supported by growing evidence. Chondrocytes are known to produce adipokines, and joint-associated fat pads—such as the infrapatellar fat pad—are located near the meniscus, bone, cartilage, synovium, and tendons, facilitating paracrine interactions. Notably, chondrocytes express the long isoform of the leptin receptor (OB-Rb), indicating that LEP may directly regulate their activity [34].

Otero et al. showed that leptin, in synergy with interferon gamma (IFN- γ), can induce inducible nitric oxide synthase (iNOS) in the chondrocytes, leading to nitric oxide (NO) release. This process interferes with collagen and proteoglycan synthesis and promotes chondrocyte apoptosis [35]. Additionally, high leptin concentrations in the synovial fluid and the presence of leptin receptors on the cartilage suggest a role of LEP in cartilage metabolism [36].

Local effects of leptin on the articular cartilage are supported by its elevated levels in the synovial fluid, which correlate with the radiographic severity of osteoarthritis (OA) [37]. These findings also suggest that leptin may stimulate the production of inflammatory cytokines such as IL-6, thereby exacerbating joint inflammation.

It is worth noting that glucocorticoids and insulin can increase leptin mRNA expression in human and rat adipocytes. Similarly, hyperinsulinemia, various cytokines, environmental toxins, and sex steroids are all associated with increased leptin production [38]. Recent studies also demonstrate that leptin, alone or in combination with pro-inflammatory cytokines (e.g., IL-6, TNF- α), enhances collagen degradation and upregulates the expression of matrix metalloproteinases (MMP-1 and MMP-13) in the chondrocytes [39].

Both clinical and experimental models confirm a strong association between obesity, inflammation, and joint disease. The adipose tissue serves as a key source of cytokines, chemokines, and metabolically active adipokines—including leptin and adiponectin—which modulate immune responses and contribute to cartilage degradation. Obese individuals and animal models typically exhibit elevated circulating levels of TNF- α , IL-1 β , and IL-6, all secreted by adipose-tissue-derived macrophages [40].

6. Leptin and Osteoarthritis (OA)

Osteoarthritis is a degenerative and inflammatory joint disorder that affects the entire joint structure, including the cartilage, subchondral bone, synovium, and ligaments [41]. Clinical studies have shown that leptin levels correlate with the structural progression of OA and with the severity of cartilage degradation, fibrillation, and matrix loss. A longitudinal and cross-sectional study by Stannus et al. confirmed that leptin concentrations consistently correlate with cartilage thinning [42,43].

These findings have led to the hypothesis that leptin serves as a critical link between inflammation, metabolism, and immunity in joint diseases. However, how to modulate leptin's detrimental effects on cell viability and prevent leptin-induced cartilage senescence remains an open question.

Zhao et al. recently highlighted the role of mTOR (mechanistic Target of Rapamycin), a serine/threonine protein kinase involved in cell growth, metabolism, survival, and lifespan regulation. Cartilage-specific mTOR deletion was found to enhance autophagy and protect mice from OA [44,45]. Autophagy is essential for cellular homeostasis by

clearing dysfunctional organelles and proteins. Impaired autophagy leads to oxidative stress, mitochondrial dysfunction, and eventually cell death.

Additional evidence shows that the mTOR signaling pathway is essential for joint tissue metabolism but also contributes to cartilage degradation, subchondral bone alterations, and synovial inflammation [46]. Emerging research suggests a complex interplay between mTOR and leptin signaling: in the hypothalamus, mTOR modulates food intake; in the peripheral tissues, it regulates lipid metabolism and inflammation.

Leptin has been shown to inhibit chondrocyte autophagy via mTOR activation, and mTOR inhibition can partially reverse leptin-induced cellular senescence. Zhao's study demonstrated that mTOR deficiency in the cartilage increased autophagy, reduced MMP-13 expression, decreased chondrocyte apoptosis, and conferred significant protection against OA. These findings support the therapeutic potential of mTOR inhibition in rebalancing catabolic and anabolic factors in OA.

Nonetheless, the complexity of mTOR signaling makes it challenging to fully characterize its impact on OA, especially in relation to leptin. Many questions remain unanswered.

In conclusion, LEP exerts diverse effects on bone and cartilage, modulated by its local and systemic concentrations and influenced by the hormonal and inflammatory contexts. While leptin is implicated in joint pathologies and bone metabolism, adiponectin (APN)—another adipocyte-derived hormone—often exhibits opposing effects, particularly in OA.

Recently, four clinical OA phenotypes have been proposed: biomechanical OA, osteoporotic OA, metabolic (obesity-related) OA, and inflammatory OA [47,48]. In obese patients, OA's pathogenesis involves both mechanical overload and metabolic/inflammatory disturbances, including increased M1 macrophage activity and the secretion of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- α , which contribute to chondrocyte dysfunction and cartilage matrix degradation.

7. Adiponectin: Biological Functions and Implications for Bone and Inflammatory Metabolism

Adiponectin is an adipokine, i.e., a protein primarily secreted by adipocytes from white adipose tissue, with significant metabolic, anti-inflammatory, and cardiovascular effects. Unlike many other inflammatory cytokines secreted by the adipose tissue (such as TNF- α or IL-6), adiponectin levels are inversely proportional to fat mass: they decrease in obese individuals and increase with weight loss.

Despite the wide presence of adiponectin in the circulation, in vitro studies and gene-targeted animal models have not consistently clarified its effects on bone tissue. This is likely due to the existence of multimeric forms of adiponectin and the heterogeneity of its binding to bone receptors. Although adiponectin (AD) is produced by various cells and tissues [49], the adipose tissue remains its main source, with serum concentrations ranging from 2 to 26 $\mu\text{g/mL}$, depending on the combination of oligomeric forms [50,51].

At the cardiovascular level, adiponectin exerts a protective role on the vascular endothelium by reducing monocyte adhesion and smooth muscle cell proliferation, as well as preventing atherosclerotic plaque formation through the inhibition of LDL oxidation and the downregulation of adhesion molecules.

Adiponectin also regulates glucose and lipid metabolism via activation of the AMP-activated protein kinase (AMPK) pathway in hepatic and muscle tissues. This activation promotes glucose utilization and fatty acid oxidation and enhances glucose uptake in the skeletal muscle, thereby improving glucose tolerance.

Beyond its metabolic effects, adiponectin's anti-inflammatory activity is of particular interest. Adiponectin deficiency has been associated with several metabolic disorders such

as type 2 diabetes, obesity, and atherosclerosis. Nevertheless, while the anti-inflammatory role of adiponectin is well documented, several studies have reported a dual function, including pro-inflammatory roles in autoimmune diseases [52]. Elevated serum levels of adiponectin have been associated with the severity of rheumatoid arthritis and chronic kidney disease. This paradoxical activity is likely linked to the different circulating isoforms of adiponectin, which appear to be responsible for distinct pathophysiological outcomes [53–55].

Despite these contradictory aspects, it has been shown that certain adiponectin isoforms binding to adipoR1 receptors on the osteoblasts stimulates oxidative phosphorylation, promoting osteoblast differentiation likely through the suppression of sclerostin, a WNT inhibitor sclerostin. Moreover, adiponectin signaling modulates inflammation by reducing the RANKL (Receptor Activator of Nuclear factor κ B Ligand)-to-OPG (Osteoprotegerin) ratio in the osteoblasts, thereby suppressing osteoclastic activity [49].

However, not all studies report consistent results. A recent longitudinal study on postmenopausal women [56] found that increased serum adiponectin levels were associated with a decrease in the BMD of the proximal femur, though not a decrease in the BMD of the lumbar spine, even after adjusting for confounding factors including BMI. Partially different findings emerged from other longitudinal studies [57,58], where baseline adiponectin levels, along with specific body composition parameters, predicted bone mineral content (BMC) loss and the reduction in the BMD of the lumbar spine.

The variability in these outcomes has also been attributed to the influence of pro- or anti-inflammatory cytokines, particularly the balance between adiponectin and leptin. Indeed, adiponectin exerts its anti-inflammatory effects by inhibiting the polarization of the macrophages towards the M1 phenotype, reducing TNF- α and IFN- γ expression while promoting the production of IL-10 and IL-1RA [59]. This is in contrast to the pro-inflammatory effects generally associated with leptin [60]. Moreover, some studies have reported an increased fracture risk associated with higher adiponectin levels in women [61], as well as in elderly men in the U.S. [62].

8. Osteoarthritis

Differently from LEP, numerous animal and human studies have shown that adiponectin (APN) delays the progression of OA through anti-inflammatory factors [63]. A paper by Honsawek et al. reported that the concentration of adiponectin in the blood and synovial fluid was significantly negatively correlated with the grade of OA [64].

Moreover, Yusuf et al. reported that patients with higher serum adiponectin levels had a 70% reduced risk of developing hand OA over 6 years compared with that in patients with the lowest serum adiponectin [65].

Several scientific works have reported that adiponectin inhibits the proliferation of bone marrow monocyte progenitor cells by inducing apoptosis and inhibits the functions of mature macrophages, including phagocytosis and the release of TNF- α and IL-6, a biological effect partly mediated by inhibition of the NF- κ B signaling pathway. In addition, adiponectin also mediates the differentiation of monocyte macrophages into M2 macrophages. Chen et al. reported that adiponectin can upregulate tissue inhibitor of matrix metalloproteinases-2 (TIMP-2) and downregulate IL-1 β -induced MMP-13 in human chondrocytes [66].

Although the role of adiponectin in OA has not been fully elucidated, it seems to be effective in decreasing inflammatory factors and promoting the metabolism of FA and triglyceride. Therefore, adiponectin may be one of the important factors involved in the molecular events that prevent OA development.

9. Conclusions

Although it is well known how fat mass can affect bone metabolism, somewhat less known is the influence of adiponectin on both the bone and cartilage and how LEP can also influence cartilage metabolism. The properties exhibited by adipokines make it possible to say that these two hormones, with their pleiotropic influence on numerous other organs, are also able to modulate the metabolism of the osteochondral system, and only their physiological and optimal ratios can enable homeostasis of the system to be achieved.

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