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Review Article

Lipid Dysregulation and Bone Fragility: Emerging Mechanisms in Osteoporosis Development

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Abstract

Osteoporosis is a common and serious metabolic bone disorder that significantly impacts millions of individuals worldwide and places a growing burden on healthcare systems. It is primarily characterized by a progressive decline in bone mineral density, which increases the risk of fragility fractures and leads to a substantial reduction in quality of life. Traditional treatment approaches focus mainly on stimulating bone formation and preventing bone loss. However, a deeper understanding of the cellular and molecular mechanisms underlying osteoporosis is essential for the development of more effective therapies. Osteoblasts, the cells responsible for bone formation, originate from bone marrow mesenchymal stem cells (BM-MSCs), and their differentiation competes directly with adipocyte formation. This balance between osteogenesis and adipogenesis is regulated by several signaling pathways, most notably the Wnt/β-catenin pathway and the peroxisome proliferator-activated receptor gamma (PPARγ) pathway. Recent research highlights the crucial role of lipid metabolism in the progression of osteoporosis. Lipids influence bone remodeling by modulating immune cell function, especially macrophages, which secrete pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. These cytokines enhance osteoclastogenesis, shifting the bone remodeling process toward resorption. Furthermore, oxidative stress associated with obesity reduces antioxidant enzyme activity and impairs osteoblast function, worsening bone loss. This review emphasizes the interconnected roles of lipid metabolism, chronic inflammation, and oxidative stress in osteoporosis and suggests that managing these factors may offer promising strategies for improving bone health and developing more targeted treatments for osteoporosis.

Key words: Osteoporosis (OP), Obesity, Lipid metabolism.
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Introduction

Osteoporosis is a progressive and systemic skeletal disorder characterized by a significant reduction in bone mass and deterioration in bone microarchitecture, ultimately compromising bone strength and increasing vulnerability to fractures. [1,2]

Clinically, it is classified into two primary categoryies: primary osteoporosis which includes postmenopausal osteoporosis associated with estrogen deficiency and senile osteoporosis related to advanced age and secondary osteoporosis, which results from other underlying medical conditions. These may include chronic illnesses such as diabetes mellitus, chronic kidney disease, gastrointestinal malabsorption syndromes, and the long-term use of certain medications like glucocorticoids.[3, 4]

Populations most at risk include postmenopausal women due to hormonal changes, elderly men owing to age-related bone loss, and patients with metabolic disturbances, particularly those suffering from type 2 diabetes or insulin resistance. Although various pharmacological interventions have been developed, targeting either bone resorption or bone formation pathways, many fail to fully regenerate the lost bone tissue or reverse the structural deficits.[5] Even though extensive research has sought to unravel the intricate pathophysiological processes of osteoporosis, a universally agreed-upon mechanism that explains all forms of the disease is still lacking. [6,7] A clearer identification of converging molecular pathways across diverse types of osteoporosis may significantly contribute to more effective and targeted therapies.

Recent studies have increasingly highlighted that insufficient osteoblast activity rather than merely excessive osteoplastic bone resorption plays a more decisive role in disease progression. While osteoclasts are indispensable for maintaining bone turnover through the breakdown of old or damaged bone, [8] Therapeutic strategies that exclusively inhibit their activity have shown limited success in rebuilding skeletal integrity.[9]

Consequently, current research emphasizes the critical importance of osteoblasts, particularly their differentiation and function, which are primarily regulated by bone marrow-derived mesenchymal stem cells (BM-MSCs).

Enhancing osteoblastogenesis and ensuring the proper lineage commitment of BM-MSCs toward bone-forming cells may open new avenues for the prevention and treatment of various osteoporosis subtypes. [10]

Obesity-induced osteoporosis

Osteoporosis is widely recognized as a progressive and systemic skeletal disorder that results in the deterioration of bone tissue and a significant reduction in bone strength, thereby increasing the likelihood of fractures. [1,2] This condition is generally classified into two main categories: primary osteoporosis, which includes postmenopausal and senile (age-related) forms, and secondary osteoporosis, which occurs because of underlying medical conditions such as chronic kidney disease, endocrine disorders like diabetes, or malabsorption syndromes affecting the gastrointestinal tract. [3,4]

Certain population groups are particularly vulnerable to developing osteoporosis. These include postmenopausal women, due to estrogen deficiency, elderly men who experience age-related declines in bone density, and individuals with metabolic diseases, notably diabetes mellitus, which disrupts bone metabolism through several mechanisms. Although several pharmacological interventions have been developed with the goal of promoting bone formation and inhibiting the activity of osteoclasts, these treatments frequently fail to fully restore optimal bone mass and structure.[5]

Despite considerable advancements in understanding the cellular and molecular mechanisms underpinning the disease, researchers have yet to reach consensus on a unified pathophysiological model that can explain all subtypes of osteoporosis.[6,7] Therefore, identifying common biological pathways shared across different forms of osteoporosis may offer promising avenues for more effective and universal treatment strategies.

Among the various factors contributing to osteoporosis, a growing body of evidence suggests that reduced osteoblast activity rather than merely heightened osteoclast activity plays a pivotal role in the pathogenesis of the disease. While osteoclasts are indispensable for normal bone remodeling by resorbing old or damaged bone tissue, [8] their inhibition alone is insufficient for regener-

ating new, healthy bones, especially in cases of advanced bone loss. [9]

Thus, a more comprehensive understanding of osteoblast biology, particularly their differentiation from bone marrow-derived mesenchymal stem cells (BM-MSCs), is essential for advancing therapeutic approaches that target bone formation directly. [10] Enhancing the function and survival of osteoblasts holds promise for reversing the progression of osteoporosis and achieving better clinical outcomes.

Balance of osteogenesis and adipogenesis

Bone marrow derived mesenchymal stem cells (BM- MSCs) represent a vital population of multipotent progenitor cells endowed with the abilities of self- renewal and differentiation into multiple specialized cell types, most notably osteoblasts and adipocytes.[11] The precise regulation of the differentiation balance between osteogenesis (bone formation) and adipogenesis (fat formation) is essential for maintaining the structural integrity and functional competence of the skeletal system. A disruption in this finely tuned balance, particularly a shift that favors adipogenic over osteogenic differentiation, has been strongly implicated in the etiology of bone loss and the progression of osteoporosis, especially under pathological conditions such as obesity and aging. [11]

A complex network of molecular signaling pathways orchestrates the fate decisions of BM-MSCs. Among the most pivotal pathways are the Wnt/β-catenin signaling pathway and the peroxisome proliferator-activated receptor gamma (PPARγ) pathway. Activation of Wnt/β-catenin signaling fosters osteogenic differentiation by enhancing the expression of bone morphogenetic proteins (BMPs) and promoting the transcriptional activation of osteoblast-specific genes. In contrast, activation of PPARγ drives BM-MSCs toward adipogenic differrentiation while simultaneously inhibiting osteoblastogenesis.

This inhibitory effect is mediated through the upregulation of Wnt signaling antagonists, such as members of the Dickkopf (DKK) protein family, and through direct suppression of β-catenin-dependent transcriptional activities within the nucleus. [12, 13]

In addition to these canonical signaling pathways, epigenetic mechanisms have emerged as crucial modulators of BM-MSC differentiation. Modifications such as DNA methylation and histone tail modifications play key roles in dictating the lineage commitment of these progenitor cells. For instance, the di-methylation of histone H3 at lysine 9 (H3K9me2) at the promoter region of runt-related transcription factor 2 (Runx2) a master gene essential for osteoblast differentiation significantly influences the osteogenic potential and mineralization ability of BM-MSCs. [14]

Furthermore, comprehensive DNA methylation profiling studies have identified the participation of zinc-finger E-box-binding homeobox (ZEB) transcription factors in regulating both osteogenic and adipogenic pathways. Notably, the expression levels of ZEB transcription factors exhibit a correlation with body mass index (BMI) and PPARγ activity, highlighting a possible link between systemic metabolic status and local epigenetic control of cell fate. [15]

Moreover, the non-canonical Wnt signaling pathway has been shown to exert additional regulatory effects by suppressing PPARγ-mediated adipogenesis. This is achieved through the activation of SET domain bifurcated 1 (SETDB1), a histone methyltransferase responsible for inducing H3K9 methylation, which in turn silences adipogenic gene expression programs. [16]

Collectively, these molecular and epigenetic insights underscore the intricate mechanisms by which obesity-induced alterations in lipid metabolism and intracellular signaling pathways can skew BM-MSC differentiation toward adipogenesis, thereby impairing bone formation and contributing to the development and exacerbation of osteoporosis. [15]

Given the significant impact of obesity on the adipogenic -osteogenic balance in BM-MSCs, recent research has focused on identifying potential therapeutic strategies that can restore this balance and improve skeletal outcomes. Pharmacological agents that stimulate Wnt/β-catenin signaling or inhibit PPARγ activity have demonstrated promise in preclinical models. For instance, Wnt agonists

and DKK1 inhibitors have been shown to enhance osteoblastogenesis and bone mineral density by counteracting the adipogenic shift**.** [13]

Similarly, selective PPARγ modulators (SPPARMs) can attenuate adipocyte formation without severely impairing systemic lipid metabolism. These agents offer a dual benefit reducing bone marrow adiposity and enhancing bone strength. Additionally, natural compounds such as resveratrol and curcumin have shown potential to modulate these signaling pathways and favor osteogenic differentiation under metabolic stress. [17]

Beyond direct modulation of signaling cascades, recent approaches are exploring epigenetic reprogramming strategies. Small molecules that inhibit histone deacetylases (HDACs) or DNA methyltransferases (DNMTs) can potentially reverse repressive epigenetic marks on osteogenic genes like Runx2 and Osterix, reactivating osteoblast-specific transcription in BM-MSCs.[14] These approaches could prove particularly effective in obese individuals, in whom the pro-adipogenic epigenetic landscape contributes to long-term skeletal deterioration. However, these therapies remain largely experimental, and future research is needed to validate their safety and efficacy in human populations. [17]

Nutritional and Lifestyle Interventions to Preserve Osteogenic Potential in Obese Individuals

While molecular therapies are gaining traction, nutritional and lifestyle interventions remain indispensable for preserving the osteogenic capacity of BM- MSCs in obese individuals. Adequate intake of calcium, vitamin D, and omega-3 fatty acids is crucial not only for supporting bone mineralization but also for modulating inflammatory and metabolic pathways that influence BM-MSC fate. [18, 19]

Vitamin D, in particular, plays a dual role by enhancing calcium absorption and regulating PPARγ-mediated adipogenesis. Its deficiency—common in obese populations—has been associated with increased bone marrow adiposity and decreased trabecular bone volume. [20]

In parallel, moderate weight-bearing exercise and resistance training have been shown to enhance osteogenic signaling through mechanical loading, which activates Wnt/β-catenin pathways and suppresses adipogenic differentiation of BM-MSCs**.**[21] Moreover, physical activity contributes to systemic metabolic improvements, including insulin sensitivity and reduced inflammatory cytokine levels, which indirectly benefit skeletal homeostasis. Therefore, a combined strategy that incorporates targeted pharmacological modulation, epigenetic interventions, and lifestyle optimization holds the greatest potential to counteract obesity-associated osteoporosis by restoring the osteogenic capacity of BM-MSCs and promoting bone regeneration. [21]

Hyperlipemia-induced pathological changes and osteoporosis

In parallel with chronic inflammation, oxidative stress plays a pivotal role in the pathophysiology of obesity-induced osteoporosis. The excessive accumulation of reactive oxygen species (ROS) disrupts redox balance, damages cellular components, and impairs the function of osteoblasts while enhancing osteoclastogenesis. In osteoblasts, ROS interferes with Wnt/β-catenin signaling and downregulates critical transcription factors such as Runx2 and Osterix, thereby suppressing bone formation.[13] Conversely, osteoclast differentiation is promoted by ROS through the activation of NF-κB and c-Fos/NF-ATc1 pathways, like cytokine-induced mechanisms. The vulnerability of bone tissue to oxidative stress is particularly heightened in metabolic conditions like obesity, where mitochondrial dysfunction and lipid peroxidation amplify ROS production. [22]

Furthermore, antioxidant defense mechanisms such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) are often compromised in obese individuals, exacerbating oxidative damage.[23]

Experimental studies using high- fat diet (HFD) models have demonstrated that antioxidant supplementation, such as with N-acetylcysteine or resveratrol, can restore osteoblast function and mitigate bone loss by reducing ROS levels**.** [17] This highlights the therapeutic potential of targeting oxidative stress alongside inflammatory pathways in the treatment of osteoporosis associated with metabolic syndrome.

Cross-Talk Between Lipid Metabolism and Bone Cell Regulation

Emerging evidence suggests that lipid metabolism disorders are not only risk factors for cardiovascular and metabolic diseases but also critical determinants of skeletal health. In the context of hyperlipidemia, elevated circulating levels of free fatty acids (FFAs), particularly saturated fatty acids like palmitate, induce lipotoxicity in bone-forming cells.[24] Palmitate has been shown to inhibit osteoblast proliferation and differentiation by activating ER stress pathways and promoting apoptosis, while simultaneously enhancing osteoclastogenesis via inflammatory signaling cascades. Moreover, oxidized low-density lipoproteins (oxLDL) contribute to osteoclast activation and bone resorption by engaging scavenger receptors on macrophage-lineage cells. [24,25]

The dysregulation of lipid handling within the bone marrow microenvironment also favors adipog-enic over osteogenic lineage commitment in BM-MSCs, as noted earlier. This shift contributes to marrow adiposity, a hallmark of osteoporotic bone in obese individuals.[15] Therapeutic strategies aimed at improving systemic lipid profiles such as statins or dietary lipid modulation have shown potential in enhancing bone formation and reducing fracture risk. [26] Thus, maintaining lipid homeostasis emerges as a key target not only for metabolic health but also for preserving bone mass and structural integrity. obesity-related hyperlipidemia promotes chronic inflammation that disrupts bone homeostasis through complex interactions between adipocytes, immune cells, and osteoblast/osteoclast regulatory pathways. Targeting inflammatory pathways and modulating macrophage activity may represent effective strategies for mitigating lipid-induced bone loss and preserving skeletal integrity. [27]

The Impact of Lipotoxicity on Bone Metabolism

In individuals affected by obesity and dyslipidemia, the excessive levels of circulating lipids frequently accumulate in tissues not specialized for fat storage,such as the bone marrow. This abnormal lipid deposition results in a pathological condition known as lipotoxicity, which significantly impairs skeletal health. Within the bone marrow microenvironment, this lipid overload has detrimental effects on osteoblasts the bone-forming cells compromising both their survival and functional capacity. Notably, saturated fatty acids like palmitic acid have been implicated in triggering apoptosis and promoting oxidative stress in osteoblasts, thereby hindering the synthesis of bone matrix components and impairing mineral deposition processes essential for bone strength and integrity. [28]

In addition to promoting oxidative injury, lipid accumulation in bone marrow induces endoplasmic reticulum (ER) stress and disrupts mitochondrial function, both of which contribute to a hostile intracellular environment that is unfavorable for osteoblast lineage commitment. These metabolic disturbances not only attenuate osteoblastogenesis but also encourage the expression of genes associated with adipocyte differentiation. Consequently, bone marrow-derived mesenchymal stem cells (BM-MSCs) are more likely to differentiate into adipocytes rather than osteoblasts, shifting the cellular balance away from bone formation and toward fat accumulation**.** [23, 26]

This lipotoxic milieu does not affect osteoblasts. It also exerts indirect effects on osteoclasts the bone-resorbing cells by fostering a microenvironment that facilitates their activity. Enhanced osteoclast function, when combined with suppressed osteoblastogenesis, results in accelerated bone resorption and compromised skeletal structure. Altogether, these lipid-induced cellular alterations create a profound imbalance in bone remodeling, contributing to the progression and severity of osteoporosis in obese individuals. [29]

Adipokines and Their Dual Role in Bone Remodeling

Adipose tissue is no longer viewed merely as a passive energy reservoir; rather, it is now widely recognized as an active endocrine organ that produces and secretes numerous bioactive signaling molecules collectively known as adipokines. Among the most studied adipokines are leptin, adiponectin, resistin, and visfatin, each of which plays a distinct role in regulating systemic physiology, including bone metabolism. These adipokines can influence bone cells both directly at the local tissue level and indirectly through

systemic pathways. [30]

One of the most complex and debated adipokines is leptin. Centrally, leptin interacts with the hypothalamus, where it activates the sympathetic nervous system, leading to an inhibition of bone formation. However, this central effect contrasts with leptin's peripheral action, where it has been shown to stimulate the proliferation and activity of osteoblasts, thereby potentially enhancing bone formation under certain physiological conditions. This duality reflects the context- dependent nature of leptin's function in bone homeostasis. [31]

On the other hand, adiponectin generally exerts favorable effects on the skeletal system. It has been associated with anti-inflammatory actions, and it supports bone health by promoting osteoblast differentiation while simultaneously suppressing osteoclastogenesis. Thus, under normal conditions, adiponectin contributes to the maintenance of bone formation and remodeling equilibrium**.** [30]

However, the situation changes drastically in the context of obesity. The dysregulation of adipokine secretion, which is a hallmark of excess adiposity, results in a disrupted hormonal environment. Specifically, obesity is characterized by elevated levels of pro-inflammatory adipokines like resistin and visfatin, alongside a marked reduction in protective adipokines such as adiponectin. This altered adipokine profile contributes to the establishment of a catabolic bone environment that favors bone resorption over formation.[12; 13] As a result, individuals with obesity are at increased risk of developing bone fragility and osteoporosis, driven in part by the endocrine imbalance originating in adipose tissue. [31]

Oxidative Stress and Bone Resorption in Obesity

Oxidative stress has emerged as a critical pathological mediator linking obesity to compromised bone health. In individuals with obesity, the excessive production of reactive oxygen species (ROS) is primarily a consequence of adipocyte hypertrophy, chronic low-grade inflammation, and mitochondrial dysfunction. These factors together contribute to an environment of cellular stress, where ROS levels rise beyond the body's capacity to neutralize them. Elevated ROS levels have been shown to significantly damage osteoblasts, the bone-forming cells, thus impairing their differentiation and functionality. This disruption in osteoblast activity is accompanied by an increase in osteoclastogenesis, the process through which bone-resorbing cells, osteoclasts, are formed. The activation of redox-sensitive transcription factors, such as NF-κB and AP-1, plays a central role in this process, as these factors are integral to the inflammatory response and bone resorption. [32]

Moreover, oxidative stress amplifies the inflammatory environment within bone tissue, further perpetuating the cycle of bone degradation. ROS also promote the release of pro-inflammatory cytokines, which collectively contribute to a vicious cycle in which bone regeneration is continuously impaired, and the delicate balance between osteogenesis and bone resorption is disturbed. In obese individuals, the body's antioxidant defenses, which normally help to neutralize ROS, are often found to be compromised. Enzymes such as superoxide dismutase (SOD) and catalase, which are key players in protecting cells from oxidative damage, are frequently present in lower levels in the context of obesity. [15]

Notably, immune cells such as macrophages and T-cells also infiltrate adipose tissue in obese individuals, enhancing the secretion of pro-inflammatory mediators. These cells not only contribute to local inflammation but also directly affect the bone microenvironment by promoting osteoclast activity and inhibiting osteoblast function. Furthermore, studies have demonstrated that increased levels of inflammatory cytokines like IL-1 and TNF-α promote bone resorption by increasing the expression of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), a key molecule involved in osteoclast activation. The dysregulation of adipokine secretion in obesity creates a catabolic bone state that favors resorption over formation, thereby increasing the risk of fractures in obese individuals. [32]

As a result, targeting inflammation, particularly by modulating cytokine production and immune cell activity, may offer promising therapeutic approaches for treating osteoporosis associated with obesity. Reducing inflammation could not

only help to preserve bone density but also restore the balance between osteoclast and osteoblast activity, thus preventing further skeletal damage. **(27)**

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