REVIEW

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Lipocalin-2 and Bone Loss: A Brief Review

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Background: **Recent research has redefined bone as an active endocrine organ with diverse physiological functions beyond structural support. Among the hormones secreted by osteoblasts, lipocalin 2 (LCN2) has gained attention for its dual roles in regulating bone metabolism and systemic energy balance.**
Materials: **A comprehensive review of the literature was conducted, focusing on experimental and clinical studies that investigate LCN2 secretion by osteoblasts, its impact on bone remodeling, and its systemic effects on appetite regulation and energy homeostasis.**
Results: **LCN2 acts as a context-dependent regulator of bone metabolism. Evidence indicates that it promotes bone formation under certain conditions while also stimulating bone resorption in others. Beyond the skeleton, LCN2 serves as a potent anorexigenic hormone, linking bone-derived signals to appetite control and systemic energy regulation.**
Conclusion: **LCN2 represents a key mediator at the intersection of skeletal health and systemic metabolism. Its dual effects on bone remodeling and its ability to regulate appetite highlight its potential as a therapeutic target for managing skeletal diseases and metabolic disorders.**

Keywords: Lipocalin-2, Osteoblast, Osteoclast, Bone Loss, Anorexigenic Signal.

INTRODUCTION

Bone homeostasis is maintained through a tightly regulated balance between bone formation by osteoblasts and bone resorption by osteoclasts. Disruption of this balance under pathological or physiological stress such as inflammation, metabolic dysfunction, aging, or hormonal changes can lead to osteopenia, osteoporosis, and other forms of bone loss. In recent years, attention has shifted toward understanding how systemic factors and immune-derived mediators influence skeletal integrity. Among these emerging regulators, lipocalin-2 (LCN2) has gained significant interest.

While it is important to acknowledge that other osteokines (such as osteocalcin and FGF23) also play major roles in bone-endocrine crosstalk, lipocalin-2 is a secreted glycoprotein traditionally recognized for its role in innate immunity, iron trafficking, and inflammatory responses. However, accumulating evidence suggests that LCN2 also acts as an important mediator at the interface of metabolism, inflammation, and bone biology. Elevated LCN2 expression has been observed in metabolic syndrome, obesity, infections, and chronic inflammatory diseases, conditions frequently associated with reduced bone mass. Mechanistically, LCN2 appears to influence bone loss through several pathways, including modulation of osteoclast differentiation, alteration of osteoblast function, and regulation of systemic energy metabolism that indirectly affects skeletal remodeling.

Understanding the multifaceted roles of lipocalin-2 in bone turnover is crucial for identifying new therapeutic targets and biomarkers for skeletal diseases. As research continues to elucidate the molecular mechanisms connecting LCN2 to bone pathology, it offers promising insights into how immune and metabolic cues converge to regulate bone health.

In contrast to previous reviews that primarily examine LCN2 from molecular, metabolic, or immunological perspectives, the present brief narrative review focuses specifically on the orthopaedic relevance of LCN2. Most existing summaries emphasize LCN2's roles in obesity, diabetes, and inflammation, with limited integration of how these systemic pathways intersect

with clinically important orthopedic conditions such as osteoporosis, fracture healing, implant-associated infections, and degenerative joint disease.

By synthesizing emerging experimental and clinical findings, this review aims to clarify how LCN2 signaling may influence musculoskeletal pathology, treatment response, and postoperative outcomes, areas that remain underrepresented in current literature. Its added value for orthopedic clinicians and researchers lies in highlighting LCN2 as a potential biomarker and therapeutic target within bone and joint disorders, thereby bridging basic endocrine insights with practical orthopedic implications.

THE LITERATURE SEARCH STRATEGY

A comprehensive search was conducted through online databases, including PubMed, MEDLINE, Scopus, Web of Science, Google Scholar, Embase, and the Cochrane Library. Keywords in the search included "Lipocalin-2" and its synonyms, "Orthopedic & Bone Conditions" such as bone, skeleton, osteoporosis, osteopenia, bone resorption, bone density, fracture healing, bone remodeling, osteomyelitis, degenerative joint disease, osteoarthritis, bone cancer, cartilage, chondrocyte, osteoblast, and osteoclast. No language restrictions were applied. In addition, the reference lists of relevant articles were reviewed to ensure a complete assessment and to identify any potentially missing publications. Finally, all data were imported into EndNote software to manually remove duplicate studies.

LIPOCALIN-2, STRUCTURE AND FUNCTION

Lipocalin-2 (LCN2), also known as oncogene 24p3, siderocalin, uterocalin and neutrophil gelatinase-associated lipocalin (NGAL)[1], is a 25 kDa secreted glycoprotein originally considered an inflammatory cytokine and adipokine[2]. However, it is now known that it is primarily produced by osteoblasts, not adipocytes. In fact, its expression in osteoblasts is 10-fold higher; about two-thirds (⅔) of LCN2 in circulation is derived from bone[3]. LCN2 is a 198-amino acid glycoprotein encoded by a gene on chromosome 9 (9q34.11), producing multiple functional transcripts. Two receptors located on the cell surface have been suggested for this protein: megalin/glycoprotein GP330, which interacts with human LCN2 and SLC22A17 or 24p3R, which connects to the LCN2 protein found in mice[4,5]. It can be found in many types of cells, such as neutrophils, hepatocytes, lung cells, bone marrow, adipose tissue, macrophages, thymus, non-cancerous breast duct, prostate, and renal cells.

LCN2 is a multifunctional protein involved in immunity, tissue remodeling, and metabolism, with emerging links to obesity, diabetes, and cancer progression. It was first extracted from neutrophil granules that are released at infection and inflammation sites in humans[6]. LCN2 exhibits bacteriostatic characteristics that play a crucial part in iron removal during the antibacterial innate immune response by binding to bacterial ferric siderophores such as enterobactin (Ent)[5]. In addition to its significant function in innate immunity, this capability also provides protection during infection, injury, inflammation[7], and various forms of cellular stress. Furthermore, it also plays a role in matrix remodeling and tumor progression by forming a complex with matrix metalloproteinase 9 (MMP-9), preventing its auto-degradation and enhancing activity, which may promote tumor progression and metastasis[8]. In recent years, the metabolic function of LCN2 as an anorexigenic signal has been identified in mice, monkeys, and humans. Additionally, LCN2 functions as an osteoblast-derived endocrine factor regulating appetite via hypothalamic pathways and acts as an anorexigenic (appetite-suppressing) signal in mice, monkeys, and humans[9].

Other functions of LCN2 include its role as a critical regulator of bone metabolism. It acts as a dual-function hormone, both promoting bone formation and stimulating bone resorption, with its overall effect being highly context-dependent. Its most significant role is as a powerful anorexigenic (appetite-suppressing) signal from the bone that influences whole-body energy metabolism, creating a direct link between the skeleton and other organs[10,11].

LCN2 ON THE STIMULATION OF OSTEOCLAST FORMATION AND ACTIVITY

Osteoclasts are highly specialized multinucleated cells that play a crucial role in the breakdown of bone matrix and are essential for the ongoing processes of bone remodeling and maintaining mineral balance. These cells arise from the proliferation, fusion, and maturation of hematopoietic precursors that belong to the monocyte/macrophage lineage. Two key molecules, receptor activator of nuclear factor-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF), are both necessary and sufficient for the formation of osteoclasts. M-CSF begins cellular responses by interacting with its receptor, c-Fms. The

engagement of M-CSF causes the receptor to dimerize and undergo tyrosine autophosphorylation, which subsequently activates various signaling pathways, including the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3 kinase (PI3K)/Akt pathways. These cellular processes deliver the necessary signals for the proliferation and survival of osteoclast precursor cells.

Previous studies have shown that LCN2 and its receptors, megalin and 24p3 receptor (24p3R), are expressed in osteoclast lineage cells[11]. Furthermore, ectopic expression or recombinant LCN2 treatment has been shown to suppress the proliferation and differentiation of osteoclast lineage cells, thereby inhibiting osteoclast formation[11]. Kim and colleagues also showed that LCN2 deficiency increased macrophage proliferation and osteoclast differentiation in vitro. LCN2 deficiency also increased M-CSF-induced proliferation of bone marrow macrophages (BMMs), the precursors of osteoclasts, without altering their survival. The rapid proliferation of LCN2-deficient precursors is associated with increased expression and activation of the M-CSF receptor, c-Fms. Furthermore, LCN2 deficiency stimulates the induction of c-Fos and nuclear factor of activated T cells c1 (NFATc1), key transcription factors for osteoclastogenesis, and enhances RANKL-induced inhibitor of kappa B (IκBα) phosphorylation. They showed that LCN2 deficiency did not affect basal osteoclast formation in vivo (LCN2-deficient mouse model)[12]. Lu et al. reported that LCN2 suppresses the production of osteoprotegerin (OPG), a decoy receptor that inhibits RANKL. This further tilts the RANKL/OPG ratio in favor of bone breakdown. Therefore LCN2 does not directly act on osteoclast precursors. Instead, it binds to its receptor on osteoblasts and stimulates osteoblasts to dramatically increase their production of RANKL[13]. Since RANKL is the main cytokine required for the formation, activation, and survival of osteoclasts, by increasing RANKL expression, LCN2 creates a pro-osteoclastogenic environment, leading to increased bone resorption[14]. A summary is provided in Table I.

LCN2 ON THE INHIBITION OF OSTEOBLAST FUNCTION AND OSTEOGENIC DIFFERENTIATION

LCN2 directly interferes with the cells that are crucial for bone formation, inhibiting the functionality of osteoblasts and contributing to the loss of bone density. Several mechanisms have been suggested in this context. Studies have revealed several pathways, such as the induction of osteoblast apoptosis, impairment of osteoblast differentiation and promotion of a pro-inflammatory environment, through which LCN2 can reduce osteoblast activity. High levels of LCN2, especially under cellular stress, can activate pro-apoptotic pathways within osteoblasts. The binding of LCN2 to 24p3R can trigger the internalization of iron-bound LCN2. This sudden influx of iron in to the cell leads to the production of reactive oxygen species (ROS), causing oxidative stress that inhibits osteoblast proliferation and differentiation while increasing osteoclast activity[15,16]. Additionally, LCN2 can disrupt critical signaling pathways necessary for a mesenchymal stem cell to become a functional osteoblast. Studies have shown that LCN2 can suppress the Wnt/β-catenin signaling pathway, apro-osteogenic signal. By inhibiting Wnt signaling, LCN2

Table I. — Summary of the effect of Lipocalin-2 on stimulating osteoclast formation and activity.

Mechanism of Action	Effect on Osteoclasts & Precursors	Outcome on Bone Resorption
Direct Inhibition of Precursors	Recombinant LCN2 treatment or ectopic expression suppresses proliferation and differentiation of osteoclast lineage cells.	Inhibits osteoclast formation.
LCN2 Deficiency Effect (in vitro)	LCN2 deficiency increases M-CSF-induced proliferation of BMMs (precursors) and enhances RANKL-induced signaling (IκBα phosphorylation) and key transcription factors (c-Fos, NFATc1).	Promotes osteoclast differentiation.
LCN2 Deficiency Effect (in vivo)	LCN2 deficiency shows no effect on basal osteoclast formation in a mouse model.	No significant change in basal bone resorption.
Indirect Stimulation via Osteocytes	Under hypoxia, LCN2 is upregulated in osteocytes and promotes osteoclastogenesis by increasing RANKL expression.	Promotes osteoclast formation and bone resorption.
Indirect Stimulation via Osteoblasts	LCN2 binds to receptors on osteoblasts, stimulating them to increase RANKL production and suppress OPG production.	Alters RANKL/OPG ratio to dramatically promote osteoclast formation, activation, and survival.

prevents the expression of master regulators like runt-related transcription factor 2 (Runx2) and Osterix, effectively halting the differentiation process[17]. Furthermore, LCN2 is strongly upregulated by inflammatory cytokines such as TNF-α, IL-1β, and IL-6, further amplifying the inflammatory response[18,19]. Because inflammatory cytokines are potent inhibitors of osteoblast function and survival, LCN2 creates an environment that is inherently hostile to osteoblasts by maintaining an inflammatory state and stimulating the production of inflammatory cytokines, leading to suppression of bone formation and increased bone resorption[18,20].

A novel mechanism by which the cytokine LCN2 promotes osteoporosis by regulating iron metabolism in osteocytes, the most common bone cells[16].

Yu Xia et al. identified REPIN1, an origin-specific DNA-binding protein, as a critical upstream regulator of this process. Mechanistically, REPIN1 drives bone loss by promoting LCN2 expression, which in turn exacerbates intracellular iron accumulation. Elevated LCN2 enhances iron uptake and retention in osteocytes and osteoblasts, leading to mitochondrial dysfunction, increased oxidative stress, and activation of apoptosis pathways. These findings highlight a novel pathogenic pathway in which REPIN1 activates LCN2, LCN2 disrupts iron homeostasis in osteocytes and osteoblasts, and iron overload triggers mitochondrial apoptosis, ultimately leading to osteoporosis[16].

Chen et al. investigated the role of LCN2 in bone development and age-related osteoporosis. They found that LCN2 protein levels were significantly higher in both the cancellous bone and serum of aged (16-month-old) mice compared to young (3-month-old) mice. Thet also, found that treating mesenchymal stem cells (MSCs) with recombinant LCN2 protein significantly decreased the expression of key osteogenic markers (osterix, alkaline phosphatase and osteocalcin), demonstrating its inhibitory effect on osteogenic differentiation[21]. Ponzetti et al. demonstrated that LCN2 contributes to the bone loss and muscle pathology in Duchenne Muscular Dystrophy (DMD). Blocking LCN2, either genetically or with an antibody, alleviates these symptoms, suggesting LCN2 is a promising therapeutic target for treating DMD-induced bone loss[22]. A summary is provided in Table II.

LCN2 AS A MEDIATOR OF HORMONAL AND INFLAMMATORY BONE LOSS

Hormonal changes such as estrogen loss, and inflammation from condition like arthritis and aging, are major contributors to bone loss. despite having different triggers, they both lead to the upregulation of LCN2, which causes bone-destructive effects[20]. The link between estrogen deficiency and bone loss is a classic exemplifies LCN2's role. Estrogen typically inhibits LCN2 production, but its loss in menopause or ovariectomy results in increased LCN2 production, mainly from osteocytes[23,24]. Elevated LCN2 affects osteoblasts and osteocytes, prompting more RLNKL, which in turn increases bonr-resorbing osteoclasts. This imbalance between bone-resorption and formation leads to bone loss, higher fracture risk, and osteoporosis. Studies in animal models have shown that removing of the Lcn2 gene protects mice from

Table II. — Summary of the effect of Lipocalin-2 on the inhibition of osteoblast function and osteogenic differentiation.

Outcome on Bone Metabolism	Effect on Bone Cells	Mechanism of Action
Triggers osteoblast apoptosis, inhibits proliferation and differentiation, and augments osteoclast activity.	Binds to 24p3R receptor on osteoblasts, causing iron influx and ROS production.	Induction of Oxidative Stress & Apoptosis
Prevents expression of Runx2 and Osterix, halting osteoblast differentiation from MSCs.	Suppresses a critical pro-osteogenic pathway.	Inhibition of Wnt/β-catenin Signaling
Creates a hostile environment that suppresses osteoblast function and survival, promoting bone resorption.	Upregulated by and amplifies inflammatory cytokines (TNF-α, IL-1β, IL-6).	Amplification of Inflammation
Increases intracellular iron accumulation and regulates mitochondrial apoptotic pathway.	Iron overload induces oxidative stress and mitochondrial dysfunction.	REPIN1–LCN2 axis accelerates bone loss in iron-overload conditions.
Significantly decreases key osteogenic markers (Osterix, ALP, OCN), blocking the formation of new osteoblasts.	Direct treatment of MSCs with LCN2.	Inhibition of Osteogenic Differentiation
Promotes muscle and bone pathology; its blockade improves bone volume, strength, and reduces fibrosis.	Elevated in and contributes to pathology in DMD and aging.	Contribution to Disease-Specific Bone Loss

severe bone loss following ovariectomy[25,26].

Chronic inflammation is another significant factor in bone destruction, with playing a crucial role. Conditions like rheumatoid arthritis (RA) and periodontitis create an inflammatory environment with high levels of pro-inflammatory cytokines like Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and IL-6Which induce LCN2 gene expression[27]. This leads to increased LCN2 production by neutrophils, synovial cells, and bone cells[28]. Studies indicate that LCN2 levels are significantly elevated in the serum and synovial fluid of RA patients, correlating with disease severity and joint damage[29,30]. See Table III for a summary.

LCN2 AS AN ANOREXIGENIC SIGNAL

Research indicates that LCN2 is produced by osteoblasts, with levels in these cells being at least ten times greater than in white adipose tissue or other organs. Its synthesis is enhanced by insulin and various postprandial hormones. LCN2, originating from osteoblasts, has the ability to cross the blood-brain barrier and reduces appetite by binding to the melanocortin 4 receptor (MC4R) found on neurons in the hypothalamus, which is the brain's key area for appetite management[3]. When MC4R is activated, it initiates the anorexigenic pathway, promoting the release of hormones that induce feelings of fullness (such as α-MSH) while inhibiting hunger signals (like AgRP), leading to decreased food consumption and heightened sensations of satiety[3]. In studies involving animals, the introduction of LCN2 to mice resulted in less food intake and weight reduction, whereas mice that were genetically modified to lack the LCN2 gene (LCN2 knockout mice) became obese and exhibited hyperphagia (excessive eating). These findings reveal an intriguing physiological feedback loop where, upon eating, the bones detect this (likely through insulin) and subsequently communicate with the brain to signal the cessation of eating once energy requirements are satisfied. This establishes the skeleton as a vital player in the regulation of energy balance[31].

CONCLUSION

Lipocalin-2 is a versatile protein that has evolved beyond its original classification as an immune molecule. It plays a crucial role in regulating bone remodeling, impacting both formation and resorption, and acts as a key hormonal signal from bone to the brain to regulate energy metabolism. Its actions very depending on the context, making it a challenging but highly promising target for developing new therapies for metabolic bone diseases like osteoporosis.

In certain bone diseases, such as rheumatoid arthritis, elevated levels of LCN2 in the blood or synovial fluid can serve as biomarkers to predict the risk of bone loss or monitor the severity of bone destruction. Changes in lipocalin levels can also be utilized for therapeutic purposes. Developing drugs that inhibit LCN2 (such as neutralizing antibodies or small molecule inhibitors that prevent it from binding to the RANK receptor) could be a promising new therapeutic approach for the treating osteoporosis and inflammatory bone diseases.

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Table III. — Summary of the effect of Lipocalin-2 on hormonal and inflammatory bone loss.

Aspect	Hormonal Bone Loss (e.g., Menopause)	Inflammatory Bone Loss (e.g., Rheumatoid Arthritis)
Primary Trigger	Loss of estrogen (e.g., menopause, ovariectomy)	Chronic inflammation (e.g., from arthritis, periodontitis, aging)
Key Initiating Event	Removal of estrogen's suppressive effect on LCN2 production.	Pro-inflammatory cytokine storm (TNF-α, IL-1β, IL-6).
Main Source of LCN2	Osteocytes (bone cells)	Neutrophils, synovial fibroblasts, and bone cells.
LCN2 Induction	Dramatic increase due to loss of hormonal "brake."	Powerful induction by pro-inflammatory cytokines.
Primary Mechanism	LCN2 stimulates osteoblasts/osteocytes to produce RANKL.	LCN2 stimulates osteoblasts/osteocytes to produce RANKL.
Final Effect	Increased osteoclast formation/activity → Excessive bone resorption.	Increased osteoclast formation/activity → Excessive bone resorption.

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