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REVIEW ARTICLE

Osteocalcin and Metabolic Syndrome

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Abstract

This mini-review examines the multifaceted roles of osteocalcin, a bone-derived protein that functions as a critical mediator between skeletal biology and systemic metabolism. We explore osteocalcin's dual functions: its canonical role in bone mineralisation and structural integrity and its emerging significance as an endocrine regulator of energy homeostasis. The review synthesises current evidence regarding the distinct biological activities of carboxylated and undercarboxylated osteocalcin forms, their relationship with metabolic syndrome parameters and interactions with the autonomic nervous system. Additionally, we evaluate therapeutic interventions that modulate osteocalcin levels, potentially offering novel approaches for addressing metabolic disorders. By integrating findings from molecular, animal and clinical studies, this review aims to provide a comprehensive understanding of osteocalcin's physiological significance and its potential applications in metabolic health management, highlighting the bone-energy metabolism axis as an important frontier in endocrine research.

Key words: Metabolic syndrome; Osteocalcin; Bone and bones; Autonomic nervous system.

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Osteocalcin and its role in bone structure and energy metabolism

Osteocalcin is a protein produced by bone cells. It is a non-collagenous, vitamin K-dependent protein secreted by osteoblasts during the late stages of their differentiation. It is encoded by the bone γ-carboxyglutamate gene and its transcription is regulated by the Runx2/Cbfa1 regulatory element and stimulated by vitamin D3.[1]

In bone homeostasis, osteocalcin performs crucial functions that extend beyond mere structural composition. This protein significantly contributes to skeletal metabolism through two primary mechanisms: modulating mineralisation processes and exerting determinant influence on the qualitative aspects of bone matrix. As the most abundant non-collagenous component secreted by osteoblasts, osteocalcin interacts with the mineral structure of bone, actively participating in the dynamics of tissue remodelling. Osteocalcin binds to hydroxyapatite, a major component of bone and is involved in the nucleation of new calcium phosphate during bone remodelling. This process proves crucial for the proper mineralisation of bone, which affects bone strength and quality.[1-3] Additionally, research demonstrates that osteocalcin influences the alignment of biological apatite crystals parallel to collagen fibrils, which is important for bone

strength and the ability to withstand mechanical loading. This alignment contributes to the overall quality of bone, rather than its quantity, thus highlighting osteocalcin's role in optimising the structural integrity of bone tissue. While osteocalcin also functions as an endocrine regulator, such as in glucose metabolism, its primary physiological role in bone metabolism centres on these mineralisation processes and the enhancement of bone quality.[4]

Osteocalcin exists in two forms: carboxylated and undercarboxylated. These two forms of osteocalcin have distinct roles in bone metabolism, primarily due to differences in their structure and calcium-binding capabilities. Carboxylated osteocalcin, which contains γ-carboxyglutamic acid residues, has a high affinity for calcium ions, enhancing its ability to bind to hydroxyapatite in the bone matrix. This binding is crucial for bone mineralisation and contributes to the mechanical properties of bone by stabilising the bone matrix.[5-7] In contrast, the undercarboxylated form of osteocalcin, which lacks these γ-carboxyglutamic acid residues, has a reduced affinity for calcium and is less involved in bone mineralisation. Instead, undercarboxylated osteocalcin (ucOC) exhibits greater active in its endocrine functions, influencing energy metabolism by acting as a hormone that can enhance insulin secretion and sensitivity, as well as increase energy expenditure.[1, 7] The mechanisms underlying these differences relate to the structural changes induced by carboxylation. Carboxylation increases the stability and calcium-binding capacity of osteocalcin, which is essential for its role in bone mineralisation. Meanwhile, ucOC, with its lower calcium affinity, circulates more freely and can exert systemic effects on energy metabolism.[5-7]

These distinct roles highlight the dual function of osteocalcin in both skeletal and extra-skeletal processes. The ucOC is particularly significant in energy metabolism, acting as a hormone that influences glucose and lipid metabolism.[8, 9] Osteocalcin is initially synthesised as a prohormone (pro-OCN) and undergoes maturation through the action of the proprotein convertase furin, which is crucial for its endocrine function. This maturation process occurs independently of γ-carboxylation, a modification that can inhibit its endocrine activity. The active form of osteocalcin, particularly ucOC, participates in regulating energy metabolism by enhancing insulin secretion and sensitivity, increasing energy expenditure and improving glucose tolerance.[10-12] Osteocalcin's role in energy metabolism occurs through its interaction with the G-protein-coupled receptor GPRC6A, which facilitates its effects on insulin production and glucose and fatty acid utilisation in muscle tissue. Furthermore, ucOC influences lipid metabolism by promoting the expression of adiponectin and lipolytic enzymes, thereby protecting against diet-induced triglyceride accumulation and liver injury.[13]

Overall, osteocalcin functions as a key player in the regulation of energy metabolism, with potential implications for therapeutic strategies targeting metabolic disorders such as obesity and type 2 diabetes.[12, 14] Nevertheless, while animal studies provide strong evidence for these roles, human studies have shown mixed results, necessitating further research to fully elucidate osteocalcin's impact on human energy metabolism.[14]

The link between osteocalcin and metabolic syndrome

The link between osteocalcin and metabolic syndrome (MetS) is presented in Table 1. MetS, a cluster of risk factors for cardiovascular disease, is defined by various organisations around the world as the presence of three out of five components: waist circumference, elevated blood pressure, glucose levels, triglycerides and low HDL.[15] This definition employs population- and country-specific abdominal circumference standards. Notably, waist circumference can indicate visceral adiposity syndrome, which interprets the presence of visceral fat as an initiating mechanism or trigger for the other components of MetS.[16]

The association between osteocalcin and MetS finds support in several clinical studies that highlight its role in glucose homeostasis and metabolic health. Osteocalcin, particularly ucOC, correlates with various components of MetS, including insulin resistance and type 2 diabetes. A study involving older men found that lower levels of both ucOC and carboxylated osteocalcin were associated with unfavourable metabolic parameters, such as triglycerides, glucose, lower high-density lipoprotein cholesterol and with a higher waist circumference and blood pressure. Men with lower osteocalcin levels had a higher risk of MetS,

Table 1: Summary of clinical studies correlating osteocalcin with metabolic syndrome and diabetes

Year	First author	Study population	Osteocalcin measurement method	Main outcomes/ correlations
2021	Liu	2575 older Australian men (70-89 years)	Electrochemiluminescence for total and ucOC; mean ucOC: 11.4 ± 5.1 ng/mL	ucOC inversely associated with MetS components; (≤ 5.8 vs > 13.0 ng/mL; OR = 2.4; 95 % CI, 1.8-3.2)
2011	Kanazawa	289 Subjects with T2DM (mean age 59-67 ± 13-9 years)	Electrochemiluminescence for ucOC; mean: 2.5 ± 1.6/ 4.2 ± 3.0 ng/mL	In men, ucOC negatively correlated with percent trunk fat (% trunk fat; by DXA) and visceral/subcutaneous fat ratio (by CT)
2019	Darwish	20 participants with T2DM (mean age 63.0±6.7 years)	ELISA for ucOC; mean: 2.7 ± 1.8 ng/mL	Lower unOCN was associated with HbA1c (rho = −0.516, p = 0.020)
2015	Yeap	2966 older men from HIMS cohort (mean age 77 years)	ELISA for ucOC; mean: 11 ± 5 µg/L	Higher ucOC associated with reduced diabetes risk (odds ratio [OR] per 1 SD increase 0.55, p < 0.001)
2020	Riquelme-Gallego	235 Spanish MetS patients (mean age 64 ± 5 years)	ELISA for ucOC; mean: 5.9 ng/mL	Lower ucOC associated with higher cardiovascular risk and T2DM risk
2021	Zeng	5169 subjects of East Asian (mean age 63 ± 10 years)	Electrochemiluminescence for OCN; mean: 19 ng/mL	Higher OCN exhibited significant correlations with favorable body fat distribution

MetS = metabolic syndrome; T2DM = type 2 diabetes mellitus; ucOC = undercarboxylated osteocalcin; HOMA-IR = homeostatic model assessment-insulin resistance; OR = odds ratio; CI = confidence interval; RIA = radioimmunoassay; HIMS = health in men study;

suggesting that osteocalcin levels could serve as a biomarker for metabolic risk.[17] Moreover, another study using Mendelian randomisation indicated a causal relationship between type 2 diabetes and reduced serum osteocalcin levels, further supporting the role of osteocalcin in metabolic regulation.[18] Additionally, research on patients with MetS revealed that lower circulating levels of ucOC were associated with a worse cardiometabolic profile and higher cardiovascular and type 2 diabetes risk, suggesting its potential as a risk estimator in this population.[19] Furthermore, evidence highlights the relation between osteocalcin levels and MetS outcomes. Changes in ucOC levels associate with metabolic outcomes, particularly in older men and individuals with type 2 diabetes.[20] The medical literature highlights several key populations affected by these changes:

1. Older men: Studies indicate that lower levels of ucOC associate with unfavourable metabolic parameters and an increased risk of MetS in older men. For instance, the Health in Men study found lower serum ucOC levels linked to higher waist circumference, triglycerides, glucose, blood pressure and lower HDL cholesterol, all of which are components of MetS. Also, the same study showed that higher ucOC levels associate with reduced diabetes risk in older men, suggesting a protective role against metabolic disorders.[21]

2. Individuals with type 2 diabetes: In patients with type 2 diabetes, ucOC levels inversely correlate with plasma glucose levels and fat mass. This suggests that higher ucOC levels may correlate with better glucose metabolism and lower fat accumulation, which are critical factors in managing type 2 diabetes. Moreover, lower osteocalcin concentrations, including ucOC, correlate with poorer glycaemic control and increased insulin resistance in individuals with type 2 diabetes.[19, 21, 22]

Osteocalcin interaction with the autonomic nervous system

MetS components, mainly blood pressure and glucose, undergo significant regulation by the sympathetic nervous system.[23] In previous study we found a strong trend for an independent association between MetS patients with high blood

pressure, glucose levels and higher sympathetic activity.[24]

Evidence indicates that osteocalcin interacts with the sympathetic and parasympathetic nervous systems in several ways, influencing various physiological processes. Research shows that osteocalcin has been shown to mediate the acute stress response by inhibiting parasympathetic tone, which may have implications for conditions such as acute myocardial infarction.[25] This suggests that osteocalcin can modulate autonomic nervous system activity, potentially affecting cardiovascular responses during stress. Furthermore, osteocalcin's interaction with the sympathetic nervous system emerges in its role in energy metabolism. Studies demonstrate that leptin, an adipocyte-derived hormone, can inhibit insulin secretion through the sympathetic nervous system by modulating osteocalcin bioactivity. Specifically, sympathetic tone stimulates the expression of the Esp gene in osteoblasts, which inhibits osteocalcin activity, thereby affecting insulin secretion and glucose homeostasis.[26] This interaction underscores the complex regulatory network involving osteocalcin, the sympathetic nervous system and metabolic processes.

The association between levels of ucOC and sympathetic activity primarily features a negative relationship. According to the study by Hinoi et al,[26] sympathetic tone influences the bioactivity of osteocalcin by modulating the expression of the Esp gene in osteoblasts, which inhibits osteocalcin activity. This modulation forms part of the mechanism by which leptin inhibits insulin secretion, indicating that increased sympathetic activity reduces osteocalcin bioactivity. Consequently, higher sympathetic activity is associated with decreased levels of active osteocalcin, suggesting a negative association between sympathetic activity and the levels of ucOC.

Bidirectional communication: osteocalcin and neural regulation

Our understanding of bone-autonomic nervous system crosstalk has evolved significantly in recent years, revealing intricate molecular dialogues between these seemingly disparate systems. Osteoblasts respond to sympathetic stimulation through specialised β2-adrenergic receptors that, when activated, initiate intracellular cascades involving protein kinase A signalling pathways.[26, 27] This neural input ultimately influences bone metabolism by modifying transcriptional programs—particularly those mediated by the transcription factor ATF4—which subsequently alter osteocalcin's bioavailability through modulation of the Esp gene.[28] Conversely, evidence from experimental models suggests that ucOC can influence brain function, particularly affecting vagal regulation during stress responses.[25] This effect appears mediated, at least partially, through specific G-protein coupled receptors, including GPRC6A, which are expressed in select brainstem regions associated with autonomic control.[29] Intriguingly, recent investigations point to osteocalcin's capacity to counterbalance leptin-mediated sympathetic activation via hypothalamic mechanisms, suggesting a regulatory role in energy homeostasis beyond direct metabolic effects.[30] The incretin pathway represents another intersection between these systems, where osteocalcin-stimulated gut hormone production influences pancreatic function both directly and through neural inputs.[31] Collectively, these findings reveal a sophisticated regulatory network where skeletal signals integrate with neural circuits to coordinate metabolic responses, establishing bone as an unexpected but crucial component of autonomic regulation with significant implications for cardiometabolic health.[32]

Interventions that interfere with uncarboxylated osteocalcin levels

Given the established relationship between ucOC levels and metabolic parameters, there is growing interest in therapeutic strategies that can modulate osteocalcin bioavailability and activity. Understanding these interventions is crucial not only for elucidating the mechanistic pathways through which osteocalcin influences energy metabolism but also for developing potential clinical applications for metabolic disorders such as insulin resistance and type 2 diabetes. The following section examines evidence-based approaches

that have demonstrated efficacy in increasing ucOC levels and improving metabolic outcomes, highlighting the translational potential of osteocalcin as a therapeutic target at the intersection of bone and energy homeostasis.

The scientific literature highlights several promising approaches:

Physical activity protocols: Contemporary meta-analytical evaluation of randomised controlled studies reveals that structured exercise regimens consistently elevate circulating ucOC levels. This elevation correlates with metabolic improvements characterised by diminished fasting glucose concentrations, reduced insulin levels and enhanced insulin sensitivity as measured by HOMA-IR parameters.[33]

Enteral osteocalcin supplementation: Experimental investigations demonstrate that orally administered ucOC enhances glucose regulatory mechanisms through a novel pathway involving stimulation of GLP-1 release. This cascade subsequently potentiates insulin production and facilitates pancreatic β-cell expansion. Preclinical models exhibit remarkable improvements in glycaemic profiles, including reduced fasting glucose measurements and superior glucose tolerance curves.[34]

Periodic osteocalcin injections: Murine experimental models subjected to intermittent osteocalcin administration display marked improvements in glucose homeostasis and insulin responsiveness. The underlying mechanisms encompass expansion of pancreatic β-cell populations, augmented insulin secretory capacity, metabolic rate enhancement and remarkable resistance to obesity development despite high-calorie dietary challenges.[35]

Nutritional interventions: Innovative research has identified bone-derived extracts, specifically from porcine sources containing bioactive osteocalcin, as potential metabolic modulators. When incorporated into dietary regimens, these compounds demonstrate capacity to normalise glycaemic parameters and enhance both glucose tolerance and insulin sensitivity in experimental systems.[36]

The autonomic nervous system and inflammatory reflex in metabolic syndrome: therapeutic implications

In recent decades, compelling evidence has emerged regarding autonomic nervous system-mediated control over inflammatory responses, known as the inflammatory reflex. This neural circuit, pioneered by Kevin J Tracey and colleagues, elucidates how the *vagus* nerve modulates innate immune responses and inflammation, reducing inflammatory activity in numerous animal models and clinical studies, leading to the term "cholinergic anti-inflammatory pathway".[37, 38] The efferent reflex pathway involves acetylcholine release, which interacts with α7 nicotinic acetylcholine receptors (α7nAChR) on immune cells, suppressing pro-inflammatory cytokine production.[39]

Preclinical studies have investigated the effects of *vagus* nerve stimulation (VNS) and cholinergic modulation in animal models of MetS.[40] Notably, electrical stimulation of the *vagus* nerve in diet-induced obese rats improved metabolic parameters and reduced inflammation.[41] Similar results were observed in a study that blocked TNF with pentoxifylline in a non-alcoholic hepatitis model.[42]

Pavlov and colleagues demonstrated that treatment with galantamine, an anticholinesterase drug, reduced body weight, improved insulin sensitivity, decreased inflammation and attenuated hepatic steatosis in murine models of obesity and MetS.[43] Anticholinesterases inhibit the enzyme acetylcholinesterase, responsible for acetylcholine degradation, thereby increasing this neurotransmitter's availability in the nervous system. Traditionally, these medications are used to treat neurodegenerative diseases such as Alzheimer's disease and neuromuscular disorders like myasthenia gravis.[44]

Recently, preclinical studies have explored the therapeutic potential of anticholinesterases in reducing inflammatory mediators across different scenarios, including metabolic dysfunctions. In animal models of hepatic steatosis, galantamine demonstrated reduced liver fat accumulation and

improved insulin sensitivity.[43] In diabetes models, the drug effectively reduced blood glucose and protected pancreatic β-cells.[45] Furthermore, in MetS models, galantamine exhibited beneficial effects in reducing systemic inflammation, improving lipid profiles and decreasing insulin resistance.[43]

These preclinical findings suggest promising therapeutic potential for *vagus* nerve stimulation or anticholinesterase use, particularly galantamine, in managing metabolic disorders, paving the way for more in-depth clinical investigations.[46, 47] Emerging evidence on cholinergic stimulation in MetS has significant clinical implications. Pharmacological interventions, such as acetylcholinesterase inhibitors like galantamine, have shown promise in treating inflammation and improving metabolic parameters.[48] Our group has contributed significantly to this perspective. A recently published study demonstrated that 12-week galantamine administration to MetS patients was associated with reduced serum inflammatory markers and improved insulin sensitivity, independent of patient weight reduction.[49] In a second analysis, we demonstrated that galantamine use improved the oxidative stress biomarker profile in these patients.[48]

Non-pharmacological approaches, particularly non-invasive *vagus* nerve stimulation, represent an exciting frontier in MetS management. A pilot study by Moraes et al on *transauricular vagus* nerve stimulation mobilised immune cells with an anti-inflammatory profile and slightly reduced blood pressure in MetS patients.[48]

Cholinergic stimulation and osteocalcin modulation: emerging perspectives for metabolic syndrome management

Recent advances in neuroendocrine research have revealed intriguing connections between autonomic nervous system activity, bone-derived hormones and metabolic regulation, offering novel therapeutic avenues for MetS. This intersection represents a paradigm shift in our understanding of metabolic disorders, highlighting the complex interplay between neural circuits and endocrine signalling.

The cholinergic anti-inflammatory pathway effectively suppresses pro-inflammatory cytokine production, addressing a key pathophysiological component of MetS. Both pharmacological approaches and non-pharmacological interventions have shown promising results in clinical and preclinical studies, improving insulin sensitivity, reducing inflammatory markers and enhancing oxidative stress profiles in MetS patients.

Concurrently, the identification of undercarboxylated osteocalcin (ucOC) as a bone-derived hormone with significant metabolic effects has expanded our understanding of energy homeostasis regulation. ucOC influences glucose metabolism by enhancing insulin secretion and sensitivity, while also affecting lipid metabolism through adiponectin expression and lipolytic enzyme regulation. The most compelling aspect of current research is the emerging evidence of bidirectional communication between the autonomic nervous system and osteocalcin signaling. Sympathetic activation, through β2-adrenergic receptors on osteoblasts, suppresses osteocalcin bioactivity via ATF4-dependent transcriptional regulation and Esp gene modulation. Conversely, ucOC influences parasympathetic activity through GPRC6A receptors in the brainstem, affecting vagal tone during stress responses and potentially modulating sympathetic output via hypothalamic mechanisms.

This intricate neuro-skeletal-metabolic axis presents promising therapeutic targets for MetS management. Several potential intervention strategies warrant further investigation. Combined cholinergic-osteocalcin approaches could explore whether parasympathetic stimulation through vagal nerve activation or acetylcholinesterase inhibition might enhance ucOC bioavailability, creating synergistic metabolic benefits. Structured physical activity regimens that simultaneously activate parasympathetic tone and increase circulating ucOC levels could provide multifaceted benefits for MetS patients. Developing dietary approaches that both support vagal tone and optimise osteocalcin metabolism, potentially including bioactive bone-derived extracts containing osteocalcin, represents another promising avenue. Additionally, creating targeted therapies that modulate both cholinergic signalling

and osteocalcin pathways could potentially offer more comprehensive metabolic regulation than single-target approaches.

The convergence of these two regulatory systems—cholinergic anti-inflammatory signalling and osteocalcin-mediated metabolic control—represents a frontier in metabolic research with significant translational potential. Future studies should focus on elucidating the precise molecular mechanisms linking these pathways and developing integrated therapeutic strategies that leverage this neuro-skeletal-metabolic communication to effectively address the multifaceted pathophysiology of MetS.

We acknowledge that osteocalcin measurement and interpretation carry inherent limitations that could lead to false positive results in MetS assessment. Future clinical applications should incorporate these considerations through standardised protocols, appropriate clinical context evaluation and multi-parameter assessment approaches. These limitations do not negate the potential clinical utility of osteocalcin but emphasise the need for careful, standardised implementation in clinical practice.

Conclusion

The emerging understanding of osteocalcin's dual role as both a bone matrix protein and metabolic hormone presents significant clinical opportunities for managing MetS and related disorders. Current evidence supports the potential implementation of osteocalcin-targeted therapeutic strategies across multiple domains: structured exercise protocols that consistently elevate circulating ucOC levels while improving insulin sensitivity; nutritional interventions incorporating bioactive bone-derived compounds; and innovative pharmacological approaches targeting the cholinergic anti-inflammatory pathway through acetylcholinesterase inhibitors like galantamine, which our research demonstrates can improve metabolic parameters independent of weight reduction. The bidirectional communication between the autonomic nervous system and osteocalcin signalling offers particularly promising avenues for combination therapies, where parasympathetic stimulation through non-invasive vagal nerve stimulation could synergistically enhance ucOC bioavailability.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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