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# Parathyroid-leptin axis as an intricate network of hormonal interactions; an updated review

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## Abstract

The parathyroid-leptin axis represents a network of hormonal interactions that play a critical role in regulating calcium homeostasis, energy balance, and metabolic health. The parathyroid hormone, primarily responsible for maintaining calcium and phosphate balance, interacts intricately with leptin, a hormone secreted by adipose tissue that regulates appetite, energy expenditure, and bone metabolism. This interplay involves both direct and indirect mechanisms, including leptin's influence on parathormone (PTH) secretion and PTH's modulation of leptin signaling in adipose tissue. Calcium and vitamin D further fine-tune this axis, creating a feedback loop that integrates bone, adipose, and metabolic functions. Dysregulation of the parathyroid-leptin axis has been implicated in various pathological conditions, such as osteoporosis, obesity, and metabolic disorders, highlighting its significance in maintaining physiological homeostasis. This review explores the mechanisms underlying the parathyroid-leptin axis, its physiological and pathological implications, and its potential as a therapeutic target for metabolic and bone-related diseases.

**Keywords:** Parathyroid hormone, Leptin, Calcium homeostasis, Parathormone

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## Introduction

The parathyroid glands are indispensable endocrine organs consisting of four small glands embedded within the posterior aspect of the thyroid gland (1). The glands contain two primary cell types; chief cells, which are responsible for parathyroid hormone (parathormone; PTH) synthesis and secretion, and oxyphil cells, whose function remains not fully understood (2). The chief cells respond to changes in blood calcium levels through specialized calcium-sensing receptors, allowing precise regulation of PTH secretion to maintain optimal calcium homeostasis (1,2). PTH plays a central role in regulating serum calcium levels. In reaction to low blood calcium concentrations, PTH acts on various target organs including the bones, kidneys, and intestines to increase calcium levels (3). PTH stimulates the release of calcium from bones, enhances renal reabsorption of calcium, and stimulates the production of calcitriol from the kidneys, which in turn increases intestinal absorption of calcium (3,4). This orchestration is crucial for maintaining calcium homeostasis, protecting the body from the detrimental effects of hypocalcemia (3,4).

Leptin is an adipocyte-derived hormone primarily

recognized for its role in regulating energy balance and body weight by inhibiting hunger (5). It conveys the status of energy reserves by serving as an afferent signal in a negative feedback loop within the brain, which regulates adipose tissue mass through the control of appetite and metabolism (5). Beyond its primary production site in adipose tissue, leptin is also synthesized by other tissues, including the stomach, placenta, and mammary glands (5). Elevated levels of leptin correlate with increased fat mass, while conditions of energy deficit are associated with lower leptin levels (6). In addition of its central effects, leptin also influences peripheral actions, including impact on bone metabolism and immune function (6).

Recent findings have elucidated the association amongst leptin and PTH, suggesting that elevated leptin levels can stimulate the release of PTH (7). This relationship appears particularly pronounced in cases of obesity, where patients with primary hyperparathyroidism display significantly higher leptin levels than healthy individuals (7,8). It is possible that leptin enhances PTH secretion through direct actions on the parathyroid glands, revealing a novel endocrine function of leptin beyond its classic metabolic roles (7,8). Furthermore, leptin has been noticed to

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### ■ Implication for health policy/practice/research/medical education

The parathyroid-leptin axis represents a network of hormonal interactions that play a critical role in regulating calcium homeostasis, energy balance, and metabolic health. The parathyroid hormone, primarily responsible for maintaining calcium and phosphate balance, interacts intricately with leptin, a hormone secreted by adipose tissue that regulates appetite, energy expenditure, and bone metabolism. This interplay involves both direct and indirect mechanisms, including leptin's influence on parathormone (PTH) secretion and PTH's modulation of leptin signaling in adipose tissue. Calcium and vitamin D further fine-tune this axis, creating a feedback loop that integrates bone, adipose, and metabolic functions. Dysregulation of the parathyroid-leptin axis has been implicated in various pathological conditions, such as osteoporosis, obesity, and metabolic disorders, highlighting its significance in maintaining physiological homeostasis. This review explores the mechanisms underlying the parathyroid-leptin axis, its physiological and pathological implications, and its potential as a therapeutic target for metabolic and bone-related diseases.

influence calcium metabolism by interacting with PTH. It seems that leptin can both elevate PTH levels and enhance its effects in stimulating bone resorption (7,8). Recent studies have demonstrated that leptin is involved in regulating calcium-regulating hormones, including PTH, 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub>, and fibroblast growth factor 23 (9). This interaction suggests a feedback loop where leptin not only responds to energy balance but also modifies the activity of calcium-regulating hormones, thereby integrating energy and mineral homeostasis (9). This axis also has significant effect on several body systems, predominantly obesity, hyperparathyroidism, and osteoporosis (10). Dysregulation of either hormone can contribute to metabolic disorders (10). Previous investigations detected that elevated leptin levels in obesity can lead to increased PTH levels, that may enhance bone resorption, potentially increasing the risk of osteoporosis and fractures (11,12). This narrative review investigates the complex interplay between PTH and leptin, discovering their individual functions, how they influence each other, and the broader implications for metabolic health and bone metabolism.

### Search strategy

For this narrative review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords like; parathyroid hormone, leptin, calcium homeostasis and parathormone.

### The parathyroid-leptin axis

The parathyroid-leptin axis represents a network of endocrine interactions that integrate calcium homeostasis with energy metabolism (7). The interaction between PTH and leptin occurs through multiple pathways, both direct and indirect (7). Recently it was shown the presence

of leptin and leptin receptor mRNA in parathyroid chief cells from patients with hyperparathyroidism, as well as in normal parathyroid tissue (7,13). This discovery provides evidence for direct molecular communication between these hormonal systems (14). Studies have shown that PTH secretion increases in response to leptin exposure and decreases with leptin receptor inhibition, suggesting a direct regulatory mechanism (14). Furthermore, experiments using wild-type mice and leptin receptor-deficient mice have confirmed a direct effect of leptin on PTH secretion, independent of changes in ionized calcium, phosphate, or other metabolic factors (13).

Indeed, the leptin's influence on PTH secretion comprises several mechanisms that highlight the complexity of this hormonal interaction (8,15). More recent studies have discovered that PTH secretion in parathyroid explants increases in response to leptin and decreases with leptin receptor signaling inhibition through the JAK2/STAT3 pathway which appears to be functionally significant, as demonstrated by experiments showing that ob/ob mice injected with leptin exhibited increased PTH levels from baseline (15). The relationship between these hormones is further evidenced by clinical observations showing that patients with primary hyperparathyroidism have significantly higher leptin levels than healthy controls, though this finding varies across studies (8,16). Correspondingly, PTH exerts significant effects on adipose tissue metabolism and leptin signaling pathways (17-19). Recent preclinical studies have documented PTH's ability to stimulate lipolysis in both adipocytes and liver cells, while also promoting the browning of adipose tissues (17,19). This process involves PTH/PTHrP-activation of protein kinase A and affects the ubiquitin proteasome proteolytic system. The pathway demonstrates how PTH can influence energy metabolism through direct effects on adipose tissue, creating a feedback loop with leptin production (17). Additionally, PTH has been shown to increase cytosolic calcium in adipocytes through receptor-mediated mechanisms, suggesting another pathway through which PTH influences adipose tissue function (17). Moreover, interaction between PTH and leptin is significantly influenced by calcium and vitamin D levels, creating a complex regulatory network (8,20,21). On the other hand, vitamin D status appears to modify the relationship between leptin and PTH, as demonstrated by studies showing that the association between vitamin D deficiency and hyperparathyroidism is primarily observed in individuals with elevated leptin levels. This phenomenon suggests that leptin may be an important modifier of vitamin D's effects on PTH secretion (22). The relationship becomes more complex when considering that leptin is known to inhibit 1,25(OH)<sub>2</sub>D<sub>3</sub> secretion, which can affect PTH concentrations (8,15). Furthermore, multiple regression analysis has shown that approximately 44% of the variance in plasma PTH can be explained by a model involving plasma leptin and 25-OH-vitamin D,

with leptin providing the most significant contribution (18).

### Dysregulation of the parathyroid-leptin axis

The complex interplay between PTH and leptin extends beyond their individual roles in calcium homeostasis and energy metabolism. This correlation has profound implications for various physiological systems, particularly in bone metabolism, metabolic disorders, and cardiovascular health and dysregulation of this axis can lead to several hazards and complications (23, 24). The parathyroid-leptin axis plays a fundamental role in bone metabolism through multiple mechanisms, with leptin exerting both direct and indirect effects on bone health (25). The presence of leptin receptors in adult primary osteoblasts and chondrocytes indicates that leptin directly influences bone growth and metabolism (25). Additionally, leptin impacts bone metabolism through activating fibroblast growth factor 23 and regulating osteocalcin, both of which influences bone metabolism and insulin sensitivity (26). The significance of the leptin-bone relationship becomes particularly clear in cases of leptin deficiency, where studies have shown reduced bone mass in both axial and appendicular skeletal sites (11,27). Importantly, the administration of leptin has been found to increase bone mineral density, bone mineral content, and the mineral apposition rate in both skeletal regions (11). Dysregulation of this axis is characterized by elevated plasma leptin levels alongside increased PTH concentrations, leading to enhanced bone turnover, resorption, and ultimately osteoporosis (28). Prior studies have indicated that higher plasma PTH correlates with decreased bone mineral density, particularly in obese individuals where the increased leptin contributes to elevated PTH levels (11,29). The consequences of osteoporosis include a heightened risk of fractures, which can lead to significant morbidity in elderly population (30). In cases with obesity, increased fat stores lead to elevated leptin levels; nevertheless, this condition results in a state of leptin resistance, where the brain fails to respond to high plasma leptin concentration (31). This dysregulation can exacerbate the risk of developing obesity-related comorbidities such as insulin resistance, type 2 diabetes, and metabolic syndrome (32). Furthermore, obesity is intrinsically linked with chronic inflammation, which can further disturb leptin and PTH signaling, creating a negative feedback loop that worsens the body condition (31). Like leptin, PTH shows a direct relationship with obesity, with significantly higher levels observed in morbidly obese individuals. This relationship becomes particularly evident as PTH concentrations decrease following bariatric surgery (33). The complex interaction between these hormones contributes to metabolic dysfunction, as both leptin and PTH have been linked with complications arising from obesity, including hypertension and cardiovascular disease (34).

The association between PTH and metabolic syndrome is particularly noteworthy, demonstrating a positive correlation with blood pressure and waist circumference, independent of vitamin D levels (35,36).

The disruption of the parathyroid-leptin axis manifests distinctly in various parathyroid disorders. In primary hyperparathyroidism, experimental studies indicate a positive feedback loop between leptin and PTH (8). Clinical studies have consistently shown higher leptin levels in patients with primary hyperparathyroidism compared to healthy controls, although the relationship between PTH and leptin levels remains complex (37). Interestingly, in secondary hyperparathyroidism, particularly in patients with chronic kidney disease, the relationship appears to be inverse, suggesting different regulatory mechanisms in various pathological contexts (8). Recent studies also discuss on a strong association between leptin levels and cardiovascular system, indicating that elevated leptin is linked to various cardiovascular diseases, including hypertension and atherosclerosis (38). In addition, the role of PTH in calcium metabolism and its ability to affect vascular smooth muscle contraction can further complicate cardiovascular function when the parathyroid-leptin axis is dysregulated (39). Numerous investigations showed that, elevated PTH levels can lead to vascular calcification and impaired endothelial function, contributing to cardiovascular morbidity connected with high leptin levels (40). Accordingly, cases with axis dysregulation may demonstrate increasing risks of cardiac events, such as heart attacks and strokes too (40). The parathyroid-leptin axis also plays a central role in the metabolic syndrome, which encompasses a cluster of conditions including hypertension, dyslipidemia, insulin resistance, and abdominal obesity (7). Leptin dysregulation can impair insulin sensitivity while increased levels of PTH can affect glucose metabolism (41). The relationship between these hormones creates an environment conducive to metabolic syndrome, further increasing the risk of cardiovascular diseases, type 2 diabetes, and chronic kidney disease. These overlapping health issues suggest a multifaceted approach to the treatment and management of patients exhibiting dysregulation in the parathyroid-leptin axis (8,42).

### Parathyroid-leptin axis in weight loss

The parathyroid-leptin axis demonstrates a feedback mechanism where elevated leptin may stimulate PTH release, which in turn can affect body weight regulation. Studies suggest that effective weight loss interventions may need to modulate this axis to overcome leptin resistance and improve metabolic outcomes. Weight loss itself has been shown to decrease PTH levels, suggesting a potential for reduced caloric intake and increased physical activity to concomitantly lower both leptin and PTH levels. It should remember that, behavioral interventions, such as structured diet and exercise regimens, can

lead to significant fat loss and subsequent reductions in both leptin and PTH levels. As an example, dietary interventions reducing caloric intake, particularly those emphasizing low glycemic index foods, can lower leptin levels and promote hormonal balance, thus facilitating weight reduction. Finally, targeted nutritional strategies that ensure adequate calcium and vitamin D intake are important for maintaining healthy PTH levels during weight loss.

## Conclusion

The parathyroid-leptin axis demonstrates a complex network of hormonal interactions that bridges bone metabolism, energy homeostasis, and overall metabolic health which processes in the human body. This axis highlights the interconnectedness of endocrine systems, demonstrating how PTH and leptin collaboratively regulate calcium balance, adipose tissue function, and bone remodeling. Dysregulation of this axis has profound implications for a range of conditions, including osteoporosis, obesity, and metabolic disorders, emphasizing its importance in both physiological and pathological contexts. Advances in understanding the mechanisms underlying this axis offer promising avenues for targeted therapies and personalized medicine.

## Authors' contribution

**Conceptualization:** Parisa Tajdini, Majid Foroutan.

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**Validation:** Parisa Tajdini.

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**Writing-review and editing:** Parisa Tajdini, Majid Foroutan.

## Conflicts of interest

The authors declare that they have no competing interests.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

## Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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