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Calcium Homeostasis: Physiological Regulation by Parathyroid Hormone and Vitamin D

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Abstract

Calcium homeostasis is essential for the maintenance of numerous physiological processes, including neuromuscular function, bone remodeling, enzymatic activity, and blood coagulation. The human body regulates serum calcium levels within a narrow range through an intricate feedback system primarily involving the parathyroid hormone (PTH), vitamin D, and to a lesser extent, calcitonin. This review outlines the physiological mechanisms through which PTH and vitamin D maintain calcium balance, emphasizing their synergistic roles in intestinal absorption, renal reabsorption, and skeletal mobilization of calcium.

Keywords: calcium, parathyroid hormone, vitamin D, metabolism

1. Introduction

Calcium is a vital mineral involved in a wide range of cellular and systemic physiological functions. Despite its high abundance in the body—approximately 99% stored in bones—the extracellular calcium concentration is tightly regulated between 8.5–10.5 mg/dL [1]. Disruption of calcium homeostasis can lead to severe clinical consequences, such as tetany, cardiac arrhythmias, and bone disorders. The endocrine system achieves calcium regulation through a finely-tuned network centered on parathyroid hormone (PTH) and the hormonally active form of vitamin D—calcitriol (1,25-dihydroxyvitamin D_3) [2].

2. Parathyroid Hormone (PTH): Secretion and Actions.

Parathyroid hormone (PTH) is a key regulator of calcium homeostasis and is synthesized and secreted by the chief cells of the parathyroid glands in direct response to declining serum calcium levels, a condition known as hypocalcemia. The secretion of PTH is tightly controlled by the calcium-sensing receptor (CaSR), a G-protein-coupled receptor located on the surface of parathyroid cells, which detects even minute fluctuations in extracellular calcium concentration and adjusts hormone release accordingly [3].

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Once secreted, PTH exerts its physiological effects through multiple pathways, targeting primarily the bones and kidneys, while also playing an indirect yet critical role in the activation of vitamin D. In the skeletal system, PTH does not directly stimulate osteoclasts; instead, it binds to receptors on osteoblasts, leading to the upregulation of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), a membrane-bound protein that binds to RANK receptors on osteoclast precursors. This interaction promotes the differentiation and activation of osteoclasts, which are responsible for bone resorption. As a result of increased osteoclastic activity, calcium and phosphate are mobilized from the mineralized bone matrix into the circulation, thereby elevating serum calcium levels [4].

In the kidneys, PTH contributes to the conservation of calcium by enhancing its reabsorption in the distal convoluted tubules of the nephron. This action reduces the amount of calcium lost in the urine and is crucial for maintaining calcium balance, especially during times of dietary insufficiency or increased physiological demand [5]. Concurrently, PTH acts to lower serum phosphate levels by inhibiting its reabsorption in the proximal tubules. This phosphaturic effect facilitates the excretion of phosphate in the urine, which is important for preventing the supersaturation and potential precipitation of calcium-phosphate complexes in soft tissues [6]. This coordinated regulation of both calcium and phosphate levels ensures that the serum remains within a safe physiological window and that pathological calcification is avoided.

In addition to its effects on bone and renal physiology, PTH plays a central role in the regulation of vitamin D metabolism. It stimulates the activity of 1-α-hydroxylase, an enzyme located in the proximal tubular cells of the kidney, which catalyzes the conversion of 25-hydroxyvitamin D (the inactive circulating form) to 1,25-dihydroxyvitamin D, also known as calcitriol, the hormonally active form of vitamin D [7]. Calcitriol subsequently enhances calcium absorption in the intestine, amplifying the calcium-conserving effects of PTH and reinforcing the systemic effort to correct hypocalcemia.

Through these interrelated mechanisms—stimulating bone resorption, enhancing renal calcium reabsorption, promoting phosphate excretion, and activating vitamin D—PTH functions as a master hormone in the maintenance of calcium homeostasis. Its actions are rapid, adaptive, and precisely modulated, enabling the body to respond effectively to both acute and chronic changes in calcium availability.

3. Vitamin D: Synthesis and Role in Calcium Homeostasis

Vitamin D plays an indispensable role in calcium and phosphate homeostasis and exerts significant effects on bone metabolism. It can be synthesized endogenously in the skin from 7-dehydrocholesterol when exposed to ultraviolet B (UVB) radiation from sunlight, or it can be acquired through dietary intake in the form of either vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol). Regardless of the source, vitamin D is biologically inactive and must undergo two sequential hydroxylation steps to become fully active. The first hydroxylation occurs in the liver, where vitamin D is converted to 25-hydroxyvitamin D [25(OH)D], the major circulating

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form and clinical marker used to assess vitamin D status. The second hydroxylation takes place primarily in the proximal tubular cells of the kidney and is catalyzed by the enzyme 1-α-hydroxylase, which converts 25(OH)D to 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], also known as calcitriol. The activity of this renal enzyme is tightly regulated by several factors, most notably by parathyroid hormone (PTH), which strongly stimulates its expression in response to hypocalcemia [8].

Once formed, calcitriol functions as a hormone by binding to the vitamin D receptor (VDR), a nuclear receptor expressed in various target tissues, including the intestines, bones, kidneys, and parathyroid glands. In the gastrointestinal tract, particularly in the small intestine, calcitriol significantly enhances the absorption of calcium and phosphate from dietary sources. It achieves this by upregulating the expression of calcium transport proteins such as calbindin-D and epithelial calcium channels, thereby facilitating the transcellular transport of calcium across the enterocytes and into the bloodstream [9]. This action plays a critical role in maintaining adequate serum calcium levels, especially during periods of dietary insufficiency or increased physiological demand.

In addition to its effects on intestinal absorption, calcitriol also influences bone remodeling. Under normal physiological conditions, calcitriol promotes bone mineralization by ensuring an adequate supply of calcium and phosphate ions for the formation of hydroxyapatite crystals. However, in conditions of calcium deficiency, calcitriol, in conjunction with PTH, may also contribute to bone resorption by indirectly promoting osteoclastogenesis through increased RANKL expression in osteoblasts, thereby facilitating the release of calcium from the skeletal reservoir into the circulation [10]. This dual action allows vitamin D to support both the construction and deconstruction of bone, depending on the calcium needs of the organism.

Moreover, calcitriol plays an important role in endocrine feedback regulation. It acts directly on the parathyroid glands to inhibit the transcription of the PTH gene and suppress PTH synthesis and secretion. By doing so, calcitriol completes a classic negative feedback loop that prevents excessive PTH activity and helps protect against hypercalcemia [11]. This regulatory mechanism ensures that once calcium levels are restored to the physiological range, the stimulatory signals driving PTH secretion are appropriately dampened, maintaining calcium balance and preventing pathological bone loss or ectopic calcification.

Altogether, the synthesis and action of vitamin D represent an essential component of the hormonal control system that governs calcium homeostasis. Through its effects on the intestine, bone, and parathyroid glands, vitamin D ensures that calcium availability is maintained, contributing to skeletal integrity, neuromuscular stability, and overall metabolic health.

4. Integration and Feedback Mechanisms

The interaction between parathyroid hormone and vitamin D represents a well-established example of an endocrine feedback loop that ensures the maintenance of calcium homeostasis.

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When serum calcium concentrations fall below the physiological threshold, the parathyroid glands respond by increasing the secretion of parathyroid hormone. This initial response triggers a cascade of physiological mechanisms aimed at restoring calcium balance. Elevated PTH levels lead to increased bone resorption through the activation of osteoclasts, enhanced renal reabsorption of calcium in the distal tubules, and stimulation of the renal enzyme 1-α-hydroxylase, which catalyzes the production of the active form of vitamin D, calcitriol.

Calcitriol, once synthesized, exerts its effects primarily on the gastrointestinal tract, where it enhances the absorption of dietary calcium and phosphate by increasing the expression of calcium-binding and transport proteins in the intestinal mucosa. This augmentation of intestinal calcium uptake serves to further elevate serum calcium levels. Simultaneously, calcitriol acts directly on the parathyroid glands to suppress PTH gene transcription and hormone secretion, thus completing a negative feedback loop. This feedback ensures that the stimulatory effects of PTH are self-limiting and that calcium levels do not exceed the optimal physiological range.

When serum calcium returns to normal or rises above the homeostatic set point, the secretion of PTH decreases accordingly. As PTH levels fall, the stimulation of 1-α-hydroxylase in the kidney diminishes, leading to a reduction in calcitriol synthesis. Consequently, calcium absorption in the intestine decreases, bone resorption is attenuated, and urinary calcium excretion may increase slightly, all contributing to the re-establishment of calcium equilibrium in the bloodstream [12]. This tightly regulated hormonal axis allows for rapid and effective adaptation to fluctuations in calcium availability, thereby safeguarding cellular function and skeletal integrity.

5. Clinical Implications

Disruptions in the tightly regulated parathyroid hormone–vitamin D (PTH–vitamin D) axis can result in several clinically significant pathologies, each characterized by imbalances in calcium and phosphate metabolism. One of the most common disorders associated with this axis is primary hyperparathyroidism, a condition characterized by the autonomous overproduction of PTH, often due to a parathyroid adenoma or hyperplasia. The persistent elevation of PTH leads to excessive bone resorption, hypercalcemia, and increased renal calcium reabsorption. However, despite increased renal reabsorption, the high filtered load of calcium can result in hypercalciuria and the formation of kidney stones (nephrolithiasis). Over time, the continual mobilization of calcium from bone may contribute to osteopenia or osteoporosis [13].

In contrast, hypoparathyroidism is marked by insufficient secretion of PTH, which may occur as a result of autoimmune destruction of the parathyroid glands, surgical removal during thyroid or neck surgery, or genetic mutations affecting gland development or hormone secretion. The deficiency of PTH impairs bone resorption and reduces calcium reabsorption in the kidneys and calcium absorption in the intestines due to decreased calcitriol synthesis. Consequently, serum calcium levels drop, leading to hypocalcemia, which manifests clinically as neuromuscular irritability, muscle cramps, carpopedal spasms, and in severe cases, tetany or life-threatening cardiac arrhythmias [14].

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Another widespread and clinically relevant condition is vitamin D deficiency, which can result from inadequate sunlight exposure, poor dietary intake, malabsorption syndromes, or chronic kidney disease impairing 1-α-hydroxylation. The resulting reduction in active calcitriol levels leads to diminished intestinal calcium absorption, prompting a compensatory rise in PTH secretion—a condition known as secondary hyperparathyroidism. Prolonged vitamin D deficiency during childhood impairs normal bone mineralization, resulting in rickets, a disorder characterized by skeletal deformities and growth retardation. In adults, insufficient vitamin D leads to osteomalacia, which is marked by bone pain, muscle weakness, and increased fracture risk due to defective bone mineralization [15].

These clinical conditions underscore the physiological importance of the PTH–vitamin D axis and highlight the necessity of maintaining optimal levels of both PTH and vitamin D to preserve bone health, neuromuscular function, and overall calcium balance in the body.

6. Conclusion

Parathyroid hormone (PTH) and vitamin D function as the primary hormonal regulators of calcium homeostasis through a network of finely tuned, interdependent mechanisms that involve the skeletal system, renal function, and the gastrointestinal tract. Their coordinated actions ensure that extracellular calcium concentrations remain within a narrow physiological range, which is essential for the proper functioning of neuromuscular transmission, cardiac excitability, blood coagulation, and bone integrity.

PTH acts as the first-line responder to acute decreases in serum calcium, exerting rapid effects to restore balance by stimulating bone resorption, enhancing renal calcium reabsorption, promoting phosphate excretion, and increasing the synthesis of the active form of vitamin D—calcitriol. In turn, calcitriol primarily facilitates the intestinal absorption of calcium and phosphate, while also contributing to bone remodeling and inhibiting further PTH secretion via negative feedback. Together, these hormones maintain a dynamic equilibrium between calcium intake, storage, mobilization, and excretion.

This hormonal interplay exemplifies a classical endocrine feedback system with both acute and long-term regulatory capacity. The system allows the body to adapt efficiently to varying physiological demands such as growth, pregnancy, aging, and dietary insufficiency. Moreover, the integration of signals from PTH and vitamin D not only preserves serum calcium levels but also prevents pathological calcification of soft tissues by carefully regulating serum phosphate levels.

A comprehensive understanding of this regulatory axis is essential for clinicians and researchers alike, as disturbances in the PTH–vitamin D pathway underpin a wide array of clinical disorders, including hyperparathyroidism, hypoparathyroidism, osteoporosis, rickets, and vitamin D deficiency-related bone diseases. Effective diagnosis, monitoring, and therapeutic intervention in

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these conditions depend heavily on an in-depth appreciation of the molecular and physiological roles played by PTH and vitamin D in calcium metabolism.

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