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Review Article

# Multifactorial Regulation and Limitation of the PTH-Vitamin D Axis

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## Abstract

Parathyroid hormone (PTH) and vitamin D (Vit D) play a central role in the regulation of calcium-phosphate metabolism through a complex feedback system involving calcitriol, FGF23-Klotho signaling, renal function, and adipocyte-derived leptin.

While maximal suppression of PTH at serum 25-hydroxyvitamin D [25(OH)D] concentrations around 30 ng/mL has been widely adopted as a marker of Vit D sufficiency in adults, growing evidence indicates substantial interindividual variability influenced by age, genetic background, renal function, adiposity, and calcium intake. In children and adolescents, the relationship between PTH and 25(OH)D appears linear and lacks a clear inflection point, questioning the applicability of adult thresholds.

Moreover, leptin and declining renal function further modulate PTH secretion independently of vitamin D status. This review highlights the multifactorial regulation of the PTH/Vit D axis and underscores the limitations of defining universal thresholds for Vit D sufficiency based solely on PTH suppression.

***Keywords:*** *Parathyroid Hormone; Vitamin D; Leptin; Homeostasis; BMI*

## Introduction

Parathyroid hormone (PTH) and Vit D are the two principal regulators of mineral metabolism and of calcium and phosphate homeostasis through a finely tuned feedback system. PTH stimulates the synthesis of the biologically active form of Vit D, calcitriol, whereas calcitriol exerts an inhibitory effect on PTH synthesis. The activity of these two hormones is further modulated by the FGF23-Klotho complex, which interferes with the same metabolic pathway, as well as by adipocyte-derived leptin.

PTH is secreted by the parathyroid glands either from preformed granules located near the plasma membrane or from vesicles adjacent to the Golgi apparatus, and also through de novo synthesis in response to variations in serum calcium concentration or to the influence of epinephrine, calcitonin, vitamin D, phosphate, and magnesium [1].

This regulatory algorithm aimed at maintaining mineral homeostasis may undergo substantial variation depending on individual genetic, hormonal, and dietary factors, as well as on age-related changes and alterations in the function of specific target organs. These variables often require adaptive adjustments in the interactions among the hormones involved.

PTH secretion is typically pulsatile and follows a circadian rhythm, with a nocturnal peak that coincides with increased bone resorption. However, PTH-similarly to Vit D-exhibits pleiotropic activity and exerts effects on multiple organs beyond its role in calcium-phosphate homeostasis. For this reason, and given the importance of maintaining circulating PTH concentrations appropriate to physiological conditions, considerable attention has long been focused on the PTH/Vit D axis in endocrine bone disorders and in conditions arising from alterations in their serum concentrations.

Despite its major pathophysiological relevance, a definitive interpretation of this axis has not yet been achieved, and it is likely that no single answer exists, as the system depends on numerous variables, some of which are difficult to predict.

Evidence from multiple experimental and clinical studies suggests that, in adults, an appropriate functional state is associated with a serum 25-hydroxyvitamin D [25(OH)D] concentration of approximately 30 ng/mL, a level at which PTH suppression appears to be maximal. This concept is based on the fact that the primary stimulus for PTH secretion is a reduction in serum ionized calcium. In adults, several cross-sectional studies evaluating the relationship between serum PTH and 25(OH)D have demonstrated a plateau in PTH suppression when 25(OH)D levels reach around 30 ng/mL. This observation has provided the rationale for selecting 30 ng/mL as the threshold defining optimal Vit D status [2,3].

Nevertheless, this value represents a population average and conceals considerable interindividual variability. Differences in age, sex, ethnicity, body mass index (BMI), fat mass, genetic background, dietary calcium intake, and renal function may all influence the relationship between 25(OH)D and PTH. Consequently, a given serum 25(OH)D concentration may be sufficient for some individuals but not for others. Indeed, many subjects exhibit very low 25(OH)D levels without a compensatory increase in PTH, while in other cases 25(OH)D concentrations above 30 ng/mL fail to fully suppress PTH secretion.

Progressive decline in renal function is associated with reduced activity of Vit D-metabolizing enzymes, including CYP27A1, and with impaired hydroxylation of 25(OH)D, resulting in decreased production of calcitriol [$1,25(OH)_2D$]. Calcitriol deficiency indirectly contributes to elevated PTH levels, while a reduction in glomerular filtration rate (GFR) independently promotes secondary hyperparathyroidism. Together, these alterations predispose to the development of mineral and skeletal disorders [4].

Additional uncertainty arises from observations that some patients display low PTH levels despite markedly reduced 25(OH)D concentrations. Moreover, the biological effect of 25(OH)D depends not only on its circulating concentration but also on its uptake by target cells and on the efficiency of its conversion to $1,25(OH)_2D$. The interpretation of the Vit D/PTH relationship is further complicated in pediatric populations, in whom elevated PTH levels do not necessarily indicate Vit D inadequacy and may be associated with enhanced calcium absorption.

During puberty, PTH concentrations physiologically increase and may promote periosteal bone formation and skeletal accrual. Preliminary evidence suggests that, in the presence of adequate calcium intake, high-normal PTH levels combined with low-normal 25(OH)D concentrations may be associated with greater bone mass and bone size during pubertal development.

It is therefore evident that the serum concentrations of 25(OH)D and PTH associated with clinical outcomes vary considerably according to multiple factors, including genetic determinants that influence Vit D metabolism and account for a significant portion of interindividual variability. Relevant polymorphisms involve enzymes such as 7-dehydrocholesterol reductase in the skin, hepatic cytochrome CYP3A4,

and the Vit D-binding protein in the circulation. Ultimately, the functional impact of a given 25(OH)D concentration depends on cellular uptake and on the efficiency of renal 1α-hydroxylation leading to the production of $1,25(OH)_2D$.

## Clinical data

A study by Kang JI., *et al*. (2017) evaluated the relationship between PTH and 25(OH)D in young subjects. The results indicated that 25(OH)D concentrations above 18 - 22 ng/mL were sufficient to induce minimal and stable PTH levels in the majority of individuals, although some subjects with values below 18 ng/mL still exhibited low PTH concentrations. With respect to calcium metabolism, hypocalcemia was observed only when 25(OH)D levels were below 18 ng/mL, although an equivalent number of subjects maintained normal calcium values [5].

The prevalence of hyperparathyroidism (PTH > 65 ng/L) was significantly higher in children with 25(OH)D < 18.0 ng/mL compared with those with 25(OH)D ≥ 18.0 ng/mL (49.2% vs. 6.1%, P < 0.0001). Similarly, hypocalcemia (calcium < 8.8 mg/dL) was more frequent in the group with lower 25(OH)D levels (39.3% vs. 11.4%, P < 0.0001).

Other studies [6,7] have reported different inflection points for PTH suppression, ranging from 20 to 36 ng/mL, depending on age and sex. While maximal PTH suppression has often been used as an indicator of adequate Vit D status in adults, the relationship between PTH and 25(OH)D in children and adolescents remains unclear and highly variable. A large study by Hill MK., *et al*. (2010) [8] involving subjects aged 7 - 18 years demonstrated a linear relationship between 25(OH)D and PTH after appropriate adjustments. The Authors concluded that the absence of a true inflection point precludes the identification of an optimal serum 25(OH)D concentration in this age group.

Even in adults, several studies have failed to identify a single, well-defined inflection point, leaving the classification of Vit D deficiency and insufficiency partly unresolved. Mukhopadhyay., *et al*. (2019) [9] identified two inflection points in the PTH-25(OH)D relationship: a less pronounced one at approximately 32 ng/mL and a steeper one at 16.5 ng/mL. The latter is commonly considered indicative of Vit D deficiency, whereas 32 ng/mL falls within the range of sufficiency. Across studies, reported inflection points range widely, from 15 ng/mL to 44 ng/mL, and some investigations have failed to demonstrate any clear association [10].

These discrepancies likely reflect heterogeneity in the populations studied. Furthermore, it should be emphasized that PTH secretion is primarily regulated by ionized calcium via calcium-sensing receptors (CaSRs), rather than directly by circulating 25(OH)D. Nevertheless, calcitriol may exert a direct effect on parathyroid activity by increasing CaSR expression on parathyroid cells.

Renal function represents another major determinant of PTH reference intervals, particularly with regard to the upper limits of normal. In addition, substantial evidence indicates that adipocyte-derived leptin influences the relationship among 25(OH)D, PTH, and GFR. Clinical observations have shown that patients with hyperparathyroidism often exhibit elevated leptin levels [11-13], while parathyroidectomy is associated with reductions in circulating leptin. Elevated PTH concentrations are also frequently observed in obese individuals.

Leptin may further affect PTH indirectly by increasing FGF23 levels, thereby inhibiting renal CYP27B1 activity. Moreover, experimental data indicate that Leptin is a biologically active product of the Parathyroid glands and directly stimulates PTH synthesis [14]. A recent experimental study in mice demonstrated that leptin directly enhances PTH secretion by modulating CaSR signaling in parathyroid tissue [15].

Additional insights into the interaction between 25(OH)D, PTH, and Leptin were provided by Maetani., *et al*. (2015) [16]. Based on the hypothesis that leptin may partially mediate the increase in PTH associated with Vit D deficiency, the authors observed that the rise in PTH linked to low 25(OH)D levels was significantly greater in subjects with Leptin concentrations exceeding 10 ng/mL. In contrast,

individuals with leptin levels above this threshold showed no significant association between 25(OH)D and PTH concentrations. These findings suggest that adiposity may be a stronger determinant of circulating PTH levels, whereas only 25(OH)D concentrations above 40 ng/mL appear capable of influencing leptin levels across a broad BMI range. Overall, the proposed model identifies adiposity (BMI) and 25(OH)D as the principal determinants of circulating leptin and PTH concentrations.

## Conclusion

The regulation of mineral metabolism by the PTH/Vit D axis represents a highly complex and dynamic system influenced by numerous physiological and pathological variables. Although in adults a serum 25(OH)D concentration of approximately 30 ng/mL is commonly associated with maximal suppression of PTH and has been adopted as a practical threshold for Vit D sufficiency, this value reflects a population average rather than an individual optimum.

Interindividual variability driven by genetic polymorphisms, renal function, adiposity, calcium intake, and hormonal interactions, particularly involving leptin and the FGF23-Klotho system, significantly modifies the relationship between 25(OH)D and PTH. In children and adolescents, the absence of a clear PTH suppression plateau and the physiological role of higher PTH levels during growth further challenge the applicability of adult-based criteria.

Overall, current evidence suggests that no single 25(OH)D threshold can universally define Vit D sufficiency or predict PTH behavior across all populations. A more individualized interpretation of Vit D and PTH levels, taking into account age, renal function, body composition, and genetic background, appears necessary for accurate clinical assessment and management.

## Bibliography

1. Syed Jalal Khundmiri., *et al*. "PTH and vitamin D". *Comprehensive Physiology* 6.2 (2016): 561-601.

2. Hawkins Carranza F., *et al*. "Association of low serum 25OHD levels with abnormal bone microarchitecture in well-differentiated thyroid cancer". *Medical Sciences (Basel)* 8.4 (2020): 49.

3. Holick MF., *et al*. "Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline". *Journal of Clinical Endocrinology and Metabolism* 96.7 (2011): 1911-1930.

4. Dusso AS and Tokumoto M. "Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: a downward spiral in kidney disease". *Kidney International* 79.7 (2011): 715-729.

5. Jung In Kang., *et al*. "The serum level of 25-hydroxyvitamin D for maximal suppression of parathyroid hormone in children: the relationship between 25-hydroxyvitamin D and parathyroid hormone". *Korean Journal of Pediatrics* 60.2 (2017): 45-49.

6. Prerna Patel., *et al*. "Dietary calcium intake influences the relationship between serum 25-hydroxyvitamin D3 (25OHD) concentration and parathyroid hormone (PTH) concentration". *Archives of Disease in Childhood* 101.4 (2016): 316-319.

7. Ashley Lotito., *et al*. "Serum parathyroid hormone responses to vitamin D supplementation in overweight/obese adults: a systematic review and meta-analysis of randomized clinical trials". *Nutrients* 9.3 (2017): 241.

8. Hill KM., *et al*. "An inflection point of serum 25-hydroxyvitamin D for maximal suppression of parathyroid hormone is not evident from multi-site pooled data in children and adolescents". *Journal of Nutrition* 140.11 (2010): 1983-1988.

9. Pradip Mukhopadhyay., *et al*. "Inverse relationship between 25 hydroxy vitamin D and parathormone: are there two inflection points?" *Indian Journal of Endocrinology and Metabolism* 23.4 (2019): 422-427.

10. Thomas MK., *et al*. "Hypovitaminosis D in medical inpatients". *New England Journal of Medicine* 338.12 (1998): 777-783.

11. de Luis DA., *et al*. "Relation of leptin and adiponectin with cardiovascular risk factors, intact parathormone, and vitamin D levels in patients with primary hyperparathyroidism". *Journal of Clinical Laboratory Analysis* 26.5 (2012): 398-402.

12. Kamycheva E., *et al*. "Serum parathyroid hormone level is associated with body mass index. The 5th Tromsø Study". *European Journal of Endocrinology* 151.2 (2004): 167-172.

13. Hoang D., *et al*. "Leptin signaling and hyperparathyroidism: clinical and genetic associations". *Journal of the American College of Surgeons* 218.6 (2014): 1239-1250.

14. Hoang D., *et al*. "Leptin is produced by parathyroid glands and stimulates parathyroid hormone secretion". *Annals of Surgery* 266.6 (2017): 1075-1083.

15. Rachel Kilav-Levin., *et al*. "Leptin regulates parathyroid hormone secretion through CaSR-ERK1/2 signaling". *FASEB Journal* 39.8 (2025): e70506.

16. Micah Maetani., *et al*. "Association of leptin, 25-hydroxyvitamin D, and parathyroid hormone in women". *Nutrition and Cancer* 61.2 (2009): 225-231.

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