ECRONICON OPEN ACCESS

EC ORTHOPAEDICS
Review Article

Vitamin D in the Endocrine Circuit: Focus on Interactions Between Vitamin D, PTH and Leptin

Rosini Sergio[1], Saviola Giannantonio[2], Stefano Rosini[3], Molfetta Francesco[4] and Molfetta Luigi[5]*

[1]*Biomaterial Research Center, Livorno, Italy*

[2]*Istituti Clinici Scientifici Maugeri, IRCCS Castel Goffredo, Castel Goffredo, Italy*

[3]*Smile-Restyle, Livorno, Italy*

[4]*DINOGMI Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies, University of Genoa, Genoa, Italy*

[5]*DISC Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies, University of Genoa, Genoa, Italy*

***Corresponding Author:** Molfetta Luigi, Professor, DISC Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies, University of Genoa, Genoa, Italy.

Received: October 23, 2025; **Published:** November 28, 2025

Abstract

Vitamin D (Vit D) plays a central role in calcium-phosphate homeostasis and bone health, but its pleiotropic actions extend far beyond skeletal physiology. Increasing evidence indicates a complex interplay between Vit D status, obesity, leptin signaling, and parathyroid hormone (PTH) regulation. Low serum 25-hydroxyvitamin D (25OHD) is frequently associated with obesity, yet this relationship cannot be fully explained by sequestration of Vit D in adipose tissue. Instead, adipocyte-derived leptin and fibroblast growth factor 23 (FGF23) emerge as key mediators modulating parathyroid function and Vit D metabolism. Studies demonstrate that PTH levels in obese individuals correlate more strongly with leptin than with 25OHD, while calcium exerts only a modest influence. Leptin appears to act directly on the parathyroid glands, promoting hypertrophy and inhibiting CaSR activity, while simultaneously inducing osteocytic FGF23 expression, which suppresses renal 1α-hydroxylase (CYP27B1) and decreases calcitriol synthesis. These mechanisms contribute to secondary hyperparathyroidism in obesity, independent of Vitamin D deficiency per se. Furthermore, leptin resistance may disrupt hormonal feedback loops, altering energy metabolism and osteoblast activity. Meta-analyses suggest that approximately 1000 IU/day of Vit D supplementation is sufficient to lower PTH in most individuals, though higher doses primarily increase serum 25OHD without further suppressing PTH. However, obese patients typically require larger doses, not only due to altered Vit D distribution but also because of leptin- and FGF23-mediated inhibition of Vit D activation. Calcium intake remains a critical determinant of PTH regulation, particularly in individuals with normal BMI, whereas in obese subjects the combined effects of calcium, Vit D, and leptin must be considered.

In conclusion, the relationship between Vit D, obesity, leptin, and PTH is multifactorial and highly variable across individuals. No universal Vit D dose can be recommended. Instead, personalized supplementation strategies should be adopted, taking into account BMI, leptin levels, calcium intake, age, genetic factors, and comorbidities, to optimize skeletal and metabolic outcomes.

Keywords: *Vitamin D; Parathyroid Hormone; Leptin; FGF23; Obesity; Calcium Metabolism*

Introduction

The pleiotropic action of Vit D has, over the past decades, enabled a deeper understanding of its multiple roles. Today, Vit D is rightly regarded as a hormone ("D-hormone"). Several studies have demonstrated an association between low concentrations of 25OHD and obesity, although the causal mechanisms underlying this relationship are not yet fully elucidated. It is well established that Vit D is not only sequestered in adipose tissue but also in other tissues, particularly muscle, liver, and skin [1,2]. With respect to the complex metabolic correlations, many investigations have examined the interplay between Vit D, 25OHD, and PTH, though results remain inconsistent due to numerous experimental variables, including age, BMI, sex, ethnicity, hydroxylating enzyme genotypes (CYP2R1, CYP24A1, etc.), D-binding protein (DBP) polymorphisms, albumin, and other lifestyle-related factors (diet, smoking, sun exposure, etc.) [3,4].

Vitamin D and obesity

Several studies indicate that women with normal BMI respond more effectively to Vit D supplementation compared to obese women. It remains unclear whether 25OHD is significantly stored in fat, since the difference in serum 25OHD levels between individuals with BMI <25 and >35 is only about 7 ng/ml [5]. Hyperparathyroidism observed in obesity, however, does not appear to be explained solely by Vitamin D status. A seminal study by Grethen E., *et al*. [6] demonstrated that, in obese individuals, no significant correlation exists between PTH increases and 25OHD concentrations ranging between 7.6 and 31.1 ng/ml (with serum calcium within normal limits). Conversely, this study highlighted a significant correlation between PTH and leptin even across a wide range of 25OHD values (3.3 - 109.3 ng/ml), while calcium exerted only minimal influence on PTH. Collectively, these findings suggest that leptin exerts direct effects on both PTH and FGF23, while serum $1,25(OH)_2D$ levels are reduced, likely due to leptin-induced upregulation of FGF23 expression in bone cells, as well as direct leptin action itself [7,8].

Adipocyte-derived leptin has also been shown to directly influence parathyroid gland volume, likely acting as a paracrine mitogen [9,10], while simultaneously inhibiting calcium-sensing receptor (CaSR) activity. In obesity, inhibition of renal 1α-hydroxylase occurs as a result of elevated FGF23 levels, which override the stimulatory action of PTH. Nonetheless, PTH suppresses osteocytic sclerostin expression, thereby facilitating osteoblastic activity, a mechanism further potentiated by leptin's direct peripheral effects on osteoblasts.

This complex scenario is further aggravated by the concurrent increase in PTH and FGF23, which enhances phosphate excretion, negatively impacting bone. The resulting interplay is highly intricate and may be further modulated by leptin resistance, which disrupts hormonal interactions and impairs hypothalamic receptor signaling, with repercussions on energy metabolism and osteoblast function [11,12].

Gallagher JC., *et al*. [13] demonstrated an inverse correlation between total body fat mass and both serum 25OHD and $1,25(OH)_2D$, while serum PTH correlated positively with total fat mass. In this study, in women with initial 25OHD values < 20 ng/ml and with normal BMI or obese, the response of 25OHD after 7 different doses of VitD (400-4800 IU) is reported; results show that obese women show a diminished response to low-dose Vitamin D supplementation (400-800 IU/day) compared with normal-weight women, whereas medium-to-high doses (≥1600 IU/day) produce similar increases in 25OHD across BMI categories. Notably, lean women with BMI <25 kg/m^2 exhibited consistently greater increases in serum 25OHD at all supplementation levels compared with overweight or obese women (Figure 1).

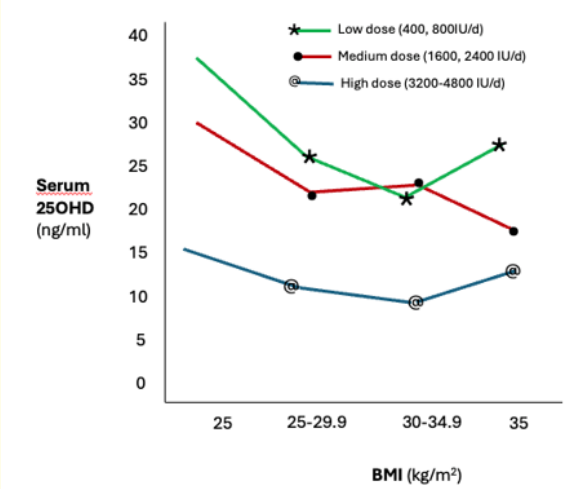

Figure 1: *Study conducted with women with initial levels of 25OHD<20 ng/ml treated with 7 doses of Vit D and placebo (+1200 mg total calcium) for 12 months [13].*

Although serum PTH is generally inversely correlated with 25OHD, numerous studies attempting to define the serum 25OHD threshold at which maximal suppression of PTH occurs have yielded inconsistent results [14,15].

A review by Sai AJ., *et al*. [16] reported large variability in these thresholds, ranging from 20 to 50 ng/ml, with some studies finding no relationship at all. In a cohort of >400 women supplemented with varying doses of Vit D, PTH concentrations decreased significantly with rising 25OHD from 6 to 60 ng/ml, without clear evidence of a plateau, although stabilization was suggested between 20 and 30 ng/ml.

Additional trials confirmed inverse correlations between 25OHD and body fat and positive correlations between PTH and fat mass [13].

Overall, these results confirm that BMI-particularly when characterized by excess adiposity-independently influences both 25OHD and PTH. Elevated leptin concentrations, reflecting fat mass, directly modulate parathyroid activity and FGF23 expression, thereby suppressing CYP27B1-mediated activation of 25OHD.

Vitamin D and PTH

Vitamin D and PTH are fundamental regulators of calcium homeostasis. PTH increases renal calcium reabsorption and stimulates the hydroxylation of 25OHD to $1,25(OH)_2D$ in the kidney. Vitamin D enhances intestinal calcium absorption efficiency (30-40%) and phosphate absorption (~80%).Inverse correlations between Vit D and PTH have been confirmed in age-stratified cohorts [17], though not always consistently across sexes. The study was conducted on groups of subjects of similar age but without distinguishing between sexes, despite the fact that other studies suggest that they behave differently. The study shows that an inverse relationship between VitD and PTH remains significant at all ages. Conversely, Grethen [6] suggested that in obese individuals, BMI exerts a dominant role in modulating PTH-25OHD dynamics.

In children and adolescents, PTH suppression was observed at serum 25OHD concentrations of ~18 ng/ml, concomitant with increases in serum calcium [18]. This finding emphasizes that calcium, rather than 25OHD per se, is the primary determinant of PTH suppression,

provided sufficient 25OHD is available to generate $1,25(OH)_2D$. It should also be noted that the efficiency of intestinal calcium absorption does not vary significantly when 25OHD concentrations increase from 20 ng/ml to 30 ng/ml.

In the same study, Kang (19) reports that the average PTH value in subjects with 25OHD<18 ng/ml is higher than the value found in subjects with 25OHD>18 ng/ml. The opposite was true for calcaemia and, albeit to a lesser extent, for phosphate. The authors suggest that a 25OHD concentration of 18.0 ng/ml is the inflection point for maximum PTH reduction, which is consistent with other criteria for Vitamin D deficiency. Other authors have reported different PTH inflection values (20-32-36 - 33 ng/ml) depending on age and gender. It should not be forgotten that PTH secretion is regulated by free calcium via CaSRs and not by 25OHD. However despite some uncertainties, it is possible that calcitriol also has a direct influence on parathyroid activity by inducing greater expression of CaSRs on the parathyroid cells themselves. The function of Vitamin D could therefore be "facilitatory", even if not indispensable, at the level of the gland itself but, obviously, extremely useful for increasing calcaemia and thus also reducing PTH.

A study by Patel P., *et al*. [19] examined the relationship between 25OHD and PTH in young individuals under different dietary calcium intakes: either below or above 520 mg/day. In the first case, PTH values were consistently higher compared with subjects consuming >520 mg/day of calcium. However, 25OHD concentration was negatively correlated with PTH at both calcium intakes, although the trend indicated a lower concentration when calcium intake exceeded 520 mg/day. It follows that calcium modifies the relationship between 25OHD and PTH.

In another recent study [20], the results of a meta-analysis on the effect of Vitamin D supplementation on PTH variation were reported. The data showed that 1000 IU of Vitamin D produced the most effective reduction in PTH, while 4000 IU resulted in the greatest increase in serum 25OHD. Interestingly, 700 IU of Vitamin D plus 500 mg of calcium produced a similar reduction in PTH. The authors concluded that 1000 IU is sufficient to reduce PTH, and higher doses merely lead to a plateau effect. However, it is noteworthy that this study did not emphasize the role of calcium, although it did recognize that obese subjects require greater amounts of Vitamin D. It is surprising that the study often neglected the work of Maetani M., *et al.* [21], which clearly demonstrated the influence of leptin on the levels of 25OHD required to suppress PTH (Figure 2).

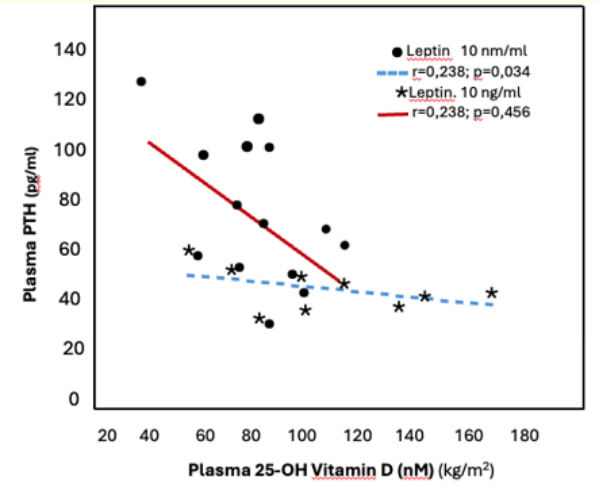

Figure 2: *Association of 25-OH-VitD with PTH and leptin in plasma. Data represent means ± SEM of the indicated analyte in plasma relative to median 25-OH-VitD stratified in quintiles (n = 57) (Modified From Maetani M., et al. 2009) [9].*

It is too often overlooked that leptin receptors are present on parathyroid cells, where leptin directly stimulates hormone release. The same study also indicated that plasma leptin levels are largely determined by two factors: positively by BMI and negatively by 25OHD.

This latter hypothesis agrees with the observation that individuals with 25OHD >40 ng/mL present relatively low leptin levels across a wide BMI range. In conclusion, the reported model suggests that an increase in adipose tissue, associated with higher BMI, leads to increased leptin production, which is partly antagonized by high 25OHD levels. In turn, leptin mediates the increase in PTH, which is also partly antagonized by 25OHD. Leptin, however, may also affect Vitamin D metabolism by down-regulating the expression of the two hydroxylases required for Vitamin D conversion, while PTH activates renal 1α-hydroxylase [22].

Additional *in vitro* data [23] indicated that Vit D exerts an important regulatory effect on leptin release from adipose tissue. An exception to the above findings was reported by Hemmingway A [24] in a study conducted on Caucasian pregnant women living in northern countries. The patients received 400 or 800 IU/day of Vitamin D, together with calcium supplementation for a total intake of 1000-1500 mg/day. The study showed that Vitamin D and PTH undergo specific adaptations during pregnancy: PTH decreases, and although its inverse relationship with 25OHD persists, it is somewhat attenuated. The study also revealed that in these particular patients, it was 25OHD and not calcium that influenced PTH concentrations. These discrepant findings are likely attributable to the physiological adaptations occurring during pregnancy.

Another critical issue concerning the 25OHD/PTH relationship lies in the definition of "normal" PTH values across different subject categories. In a large study [25], a PTH reference value of approximately 45 ng/L was reported for subjects with 25OHD >20 ng/mL, while the overall average among all subjects was about 50 ng/L (considering the wide fluctuations due to the circadian rhythm of PTH). The authors also reported that aldosterone and renin may influence PTH levels, while no significant differences were detected by sex or, interestingly, by age. However, it was correctly noted that calcium intake can interfere with PTH values. Indeed, some studies have shown that in the presence of relatively low 25OHD concentrations, calcium intake primarily regulates PTH, while at higher 25OHD concentrations, it is 25OHD itself that modulates PTH. This study also highlighted the large variability in PTH values in relation to 25OHD when not all possible patient characteristics and calcium supplementation are taken into account.

Ultimately, existing data suggest that in subjects with normal BMI, PTH is regulated by calcium, and in the absence of sufficient calcium, by Vitamin D through its role in enhancing calcium absorption. In subjects with high BMI and elevated leptin, this hormone must also be considered, requiring increased Vitamin D or calcium supplementation to maintain PTH under control.

The recommendation to provide higher doses of Vitamin D to obese individuals is not primarily due to sequestration of Vitamin D by adipose tissue, but rather to the influence of increased leptin and to the inhibition of 1α-hydroxylase caused by elevated FGF-23, resulting in reduced calcitriol synthesis [26].

Despite these considerations, it remains practically impossible to establish a single Vitamin D dosage suitable for all subjects. However, it is crucial to avoid elevations in PTH, as high PTH levels exert deleterious effects not only on bone but also on the cardiovascular and overall metabolic systems (Figure 3).

Conclusions

In summary, in individuals with normal BMI, PTH levels are primarily regulated by calcium intake, provided serum 25OHD exceeds ~15 ng/ml to allow $1,25(OH)_2D$ formation. In conditions of calcium deficiency, higher 25OHD levels are required to optimize intestinal

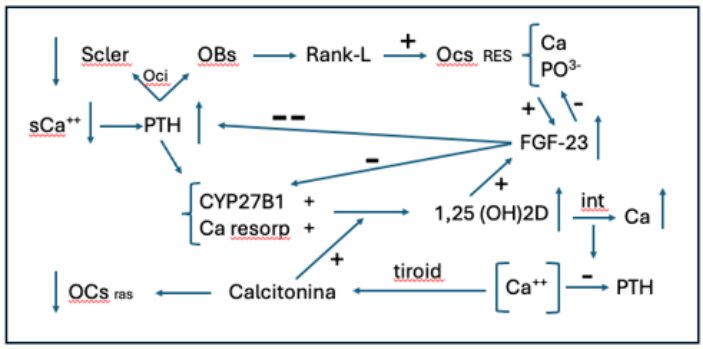

Figure 3: *Interaction between Vit D, PTH, FGF23 and calcium.*

calcium absorption and prevent bone resorption. In overweight individuals with elevated leptin and FGF23, higher Vit D doses and adequate calcium supplementation are necessary to maintain PTH within normal limits. In severe, chronic obesity, leptin resistance further complicates the regulatory network, making individualized supplementation essential. With advancing age, intestinal absorption of Vit D declines markedly, particularly in postmenopausal women and patients with inflammatory bowel diseases (e.g. celiac disease), necessitating tailored supplementation strategies.

Ultimately, no universal Vit D dosage can be established. Each patient requires individualized supplementation, considering BMI, leptin levels, age, calcium intake, pharmacological interactions with hydroxylases, DBP or albumin abnormalities, and intestinal absorption capacity.

Bibliography

1. Park CY and Han SN. "Vitamin D and obesity". *Advances in Food and Nutrition Research* 109 (2024): 221-247.
2. Bennour I., *et al*. "Vitamin D and obesity/adiposity-a brief overview of recent studies". *Nutrients* 14.10 (2022): 2049.
3. Cipriani C., *et al*. "Vitamin D and secondary hyperparathyroid states". *Frontiers of Hormone Research* 50 (2018): 138-148.
4. Ramírez Stieben LA., *et al*. "PTH levels and establishment of reference intervals: Impact of vitamin D and renal function". *Endocrinología, Diabetes y Nutrición (Engl Edition)* 72.2 (2025): 101527.
5. Almatni S., *et al*. "The correlation of 25-hydroxyvitamin D with BMI and lipid profile: A retrospective cohort study of Syrian patients". *Annals of Medicine and Surgery (London)* 76 (2022): 103457.
6. Grethen E., *et al*. "Serum leptin, parathyroid hormone, 1,25-dihydroxyvitamin D, fibroblast growth factor 23, bone alkaline phosphatase, and sclerostin relationships in obesity". *Journal of Clinical Endocrinology and Metabolism* 97.5 (2012): 1655-1662.
7. Zhou BO., *et al*. "Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow". *Cell Stem Cell* 15.2 (2014): 154-168.
8. Reid IR., *et al*. "Effects of leptin on the skeleton". *Endocrine Reviews* 39.6 (2018): 938-959.
9. Arjunan D., *et al*. "Osteoporosis and obesity". *Indian Journal of Orthopaedics* 57.1 (2023): 218-224.

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

11. Obradovic M., *et al*. "Leptin and obesity: role and clinical implication". *Frontiers in Endocrinology (Lausanne)* 12 (2021): 585887.

12. D'Amelio P., *et al*. "Energy metabolism and the skeleton: Reciprocal interplay". *World Journal of Orthopedics* 3.11 (2012): 190-198.

13. Gallagher JC., *et al*. "The effect of vitamin D supplementation on serum 25(OH)D in thin and obese women". *Journal of Steroid Biochemistry and Molecular Biology* 136 (2013): 195-200.

14. Dawson-Hughes B., *et al*. "Estimates of optimal vitamin D status". *Osteoporosis International* 16.7 (2005): 713-716.

15. Holick MF. "Vitamin D deficiency". *New England Journal of Medicine* 357.3 (2007): 266-281.

16. Sai AJ., *et al*. "Relationship between vitamin D, parathyroid hormone, and bone health". *Journal of Clinical Endocrinology and Metabolism* 96.3 (2011): 436-446.

17. Pascale AV., *et al*. "Vitamin D, parathyroid hormone and cardiovascular risk: the good, the bad and the ugly". *Journal of Cardiovascular Medicine (Hagerstown)* 19.2 (2018): 62-66.

18. 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.

19. 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.

20. Lotito A., *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.

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

22. Matsunuma A and Horiuchi N. "Leptin attenuates gene expression for renal 25-hydroxyvitamin D3-1alpha-hydroxylase in mice via the long form of the leptin receptor". *Archives of Biochemistry and Biophysics* 463.1 (2007): 118-127.

23. C Menendez., *et al*. "Retinoic acid and vitamin D(3) powerfully inhibit in vitro leptin secretion by human adipose tissue". *Journal of Endocrinology* 170.2 (2001): 425-431.

24. Hemmingway A., *et al*. "Interactions between vitamin D status, calcium intake and parathyroid hormone concentrations in healthy white-skinned pregnant women at northern latitude". *Nutrients* 10.7 (2018): 916.

25. Mathilde Touvier., *et al*. "Interpretation of plasma PTH concentrations according to 25OHD status, gender, age, weight status, and calcium intake: importance of the reference values". *Journal of Clinical Endocrinology and Metabolism* 99.4 (2014): 1196-1203.

26. Haussler MR., *et al*. "The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis". *Reviews in Endocrine and Metabolic Disorders* 13.1 (2012): 57-69.

Volume 16 Issue 7 July 2025