Vitamin D Deficiency Reduces Postthyroidectomy Protracted Hypoparathyroidism Risk. Is Gland Preconditioning Possible?

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Abstract

Context: Hypoparathyroidism is the most frequent complication after total thyroidectomy (PT-hypoPTH). After 1 year, most patients recover parathyroid function; however, the implicated physiologic dynamics remain unknown. Vitamin D deficiency (VDD) is the main cause of secondary hyperparathyroidism. Whether this compensatory hyperparathyroidism could influence parathyroid function recovery (PFR) in the setting of PT-hypoPTH has not been studied.

Objective: This work aimed to evaluate the effect of preoperative VDD on PFR.

Methods: A retrospective study was conducted with a prospectively maintained database including patients undergoing a total thyroidectomy between May 2014 and June 2019. Preoperative vitamin D (25(OH)D) less than 20 mg/mL was defined as VDD. Intact PTH less than 14 pg/mL on postoperative day 1 was defined as PT-hypoPTH. Transient PT-hypoPTH displayed PFR within the first year (early recovery: < 30 days; protracted recovery: > 30 days) whereas definite PT-hypoPTH did not. Survival analysis evaluated the effect of preoperative VDD on PFR, and a binary logistic regression model identified associated factors.

Results: A total of 397 patients were identified. The observed rates of transient, protracted, and definite PT-hypoPTH were 32.9%, 15.1%, and 5.2%, respectively. Rates of VDD were higher in the early-recovery PT-hypoPTH group (55.2% vs 31.5%; P = .01). Preoperative VDD was associated with faster PFR (19 vs 35 days; P = .03) and behaved as a protective factor for protracted PT-hypoPTH (odds ratio 0.47; 95% CI, 0.25-0.88; P = .016) in the multivariable analysis.

Conclusion: Preoperative VDD could act as a preconditioning factor of the parathyroid glands prior to the surgical aggression exerted against them during surgery aiding PFR. Basic research studies and prospective clinical trials are needed to explain the underlying physiological mechanisms and to provide further evidence to improve clinical management.

Key Words: postthyroidectomy hypocalcemia, vitamin D deficiency, organ preconditioning

Abbreviations: 25(OH)D, vitamin D; BMI, body mass index; Ca, calcium; ICG, indocyanine green; IO, intraoperative; iPTH, intact parathyroid hormone; IQR, interquartile range; LT, lymphadenectomy; NIFI, near-infrared fluorescence imaging; OR, odds ratio; PFR, parathyroid function recovery; PGs, parathyroid glands; POD, postoperative day; PTH, parathyroid hormone; PT-hypoPTH, postthyroidectomy hypoparathyroidism; TT, total thyroidectomy; VDD, vitamin D deficiency.

Hypoparathyroidism is the most frequent complication after total thyroidectomy, with an overall prevalence of 7% to 51% [1, 2]. The wide range in the rate of postthyroidectomy hypoparathyroidism (PT-hypoPTH) results from differences in the technical difficulties of the procedure and expertise of the operating surgeon and is further complicated by the lack of a universal language used to identify and define this complication [3]. A multicenter study in our country found its prevalence to be 22.9% at 3 to 6 months after surgery, 16.7% at 12 months after surgery, and 14.5% at last outpatient visit [4]. The mechanisms involved in the development of PT-hypoPTH have been defined throughout the literature. These include confusion or inadvertent extraction of the parathyroid glands (PGs), transient vascular spasm, or damage to their vascular supply [5]. Therefore, there exists a correlation between the levels of intact parathyroid hormone (iPTH) and the risk of PT-hypoPTH [6]. Most study groups have focused on identifying risk factors of PT-hypoPTH and on analyzing the efficacy of new surgical
advances such as near-infrared fluorescence imaging (NIFI) and indocyanine green (ICG) angiography [7, 8]. The latter aims to reduce PT-hypoPTH through better intraoperative PG detection and sparing. Most patients recover parathyroid function during the first year. However, the underlying physiologic mechanisms and whether these could be implemented into clinical practice are yet to be evaluated.

Following this investigation line, the influence of preoperative vitamin D (25(OH)D) levels in the development of PT-hypoPTH is undetermined [9]. Many study groups have found an association between preoperative vitamin D deficiency (VDD) and postoperative hypocalcemia conditioned by reduced 1,25(OH)2D3 formation necessary for calcium (Ca) uptake in the gastrointestinal tract and renal tubules [8]. 25(OH)D is a key integer in Ca homeostasis, and VDD is one of the most frequent causes of secondary hyperparathyroidism resulting from PG hyperplasia in response to lower Ca absorption [10]. Research investigating whether this PG hyperplasia could interfere with parathyroid function restoration (PFR) once the surgical aggression has taken place is scarce. The aforementioned situation resembles the foundations behind organ preconditioning, in which a transient precursor event confers an organ a temporary tolerance to similar stressors [11]. Its application in protecting against ischemia/reperfusion injuries in several organ sites alongside its direct clinical translation has been widely studied [12]. We hypothesized whether the PG hyperplasia conditioned by VDD could condition a faster PFR in PT-hypoPTH and whether this could be transferred to clinical practice.

The principal aim of our study was to investigate the influence of preoperative VDD on the evolution or recovery times and risk of PT-hypoPTH. Secondary aims included the identification of other risk factors associated with PT-hypoPTH.

Materials and Methods

This study was approved by the ethics committee of our center and took place following the criteria established by the Declaration of Helsinki.

A retrospective study was conducted over a prospectively maintained database including consecutive patients treated at the Endocrine and Metabolic Surgery Unit in our center. Patients undergoing total thyroidectomy (TT) surgery (1- or 2-stage, ie, complete thyroidectomy) regardless of etiology and with or without any associated degree of lymphadenectomy between May 2014 and June 2019 were identified. Patients had to meet the following criteria to be included: age older than 18 years at the time of TT; final histological report available confirming or ruling out malignancy; and have at least 365 days of follow-up at our center. Patients with conditions known to disturb Ca and phosphate metabolism other than VDD (ie, chronic renal failure, regular lithium or thiazide medication, Paget disease, or primary hyperparathyroidism) were excluded. Patients with definitive PT-hypoPTH (see definition discussed later) were excluded from the comparative analysis for the purpose of this study.

Data on patient demographics, thyroid pathology, and extent of surgical procedure were collected. Preoperative iPTH, Ca, and 25(OH)D levels alongside intraoperative and postoperative day 1 (POD1) iPTH and Ca levels were registered. Follow-up information focused on the development of hypoPTH-TT and time to parathyroid function recovery (PFR).

Laboratory Testing

Plasma iPTH levels were measured using a second-generation immunoassay ADVIA Centaur system (normal values: 14-72 pg/mL). Quantitative plasma 25(OH)D levels were processed using Alinity-i-automated-analyzer (Abbott Laboratories). Values were obtained in a one-step delayed-action immunoassay using chemiluminescent microparticle technology (normal values: 15.0-70.0 ng/mL).

Clinical Management and Surgical Procedure

Complete bone and renal profile blood tests with iPTH were routinely performed. The measurements of intraoperative iPTH (iPTHio) during skin incision and closure (ΔiPTH) [13] and POD1 iPTH levels [14-16] were used to define PT-hypoPTH and guide replacement therapy. Patients with ΔiPTHio less than 70% and final iPTH greater than 14 pg/mL were discharged without any supplementation. Patients in any other situation received oral supplementation with Ca carbonate 1 g thrice daily and 1,25(OH)2D (dose adjusted to risk of PT-hypoPTH) if total and ionized Ca levels were within normal range. Discharge was delayed in patients developing symptomatic PT-hypoPTH or with abnormal total and ionized blood Ca levels. Treatment consisted of oral 1,25(OH)2D alongside oral and intravenous Ca replacement as required per patient. Serum magnesium was monitored if hypocalcemia was severe or resistant to treatment; intravenous magnesium sulphate was administered if hypomagnesemia was present. At discharge, patients were flagged about signs of hypocalcemia, and Ca and iPTH levels were monitored on a weekly basis during the first postoperative month and then periodically. Ca and 1,25(OH)2D supplementation were suspended when Ca and iPTH levels were within normal limits.

Surgery at our unit was performed by 3 experienced endocrine surgeons (E.M.C., I.A.P., and J.L.E.C.). Neuromonitorization was set up for each case. Care was taken to identify and preserve all PGs. If a PG was inadvertently resected or devascularized, it was cut into fragments and autotransplanted into the ipsilateral sternocleidomastoid muscle following the technique described by Wells et al [17]. Skin closure took place with iPTHio levels still pending.

Definitions

The definitions of the different conditions are summarized in Table 1.

An iPTH reading below the lower threshold in our laboratory (< 14 pg/mL) on POD1 [14-16], and/or the need for treatment with Ca and calcitriol at discharge [18, 19], were the parameters considered to define PT-hypoPTH. Transient PT-hypoPTH was reserved for cases in which PFR occurred within the year [20]. Within this group, we distinguished between early-recovery PT-hypoPTH (PT-hypoPTH < 30 d), where PFR took place in less than 30 days, and, transient protracted PT-hypoPTH (PT-hypoPTH > 30 d), where PFR was after 30 days. This 30-day PFR cutoff is clinically relevant as protracted PT-hypoPTH patients are at a higher risk of developing definitive PT-hypoPTH [21].

Cases were categorized as definite PT-hypoPTH when no PFR was observed 1 year after TT [6, 20]. The term late recovery was employed to define the small group of cases for which PFR took place after 1 year [6, 20].
agression to PGs). Missing data were handled by means of deletion methods, hence models including variables with missing data (eg, 25(OH)D levels, VDD) were based on fewer observations. Statistical significance was defined as P less than .05.

**Results**

A total of 397 patients meeting the inclusion criteria underwent TT at the Endocrine Surgery Unit of our center between May 2014 and June 2019. Most patients were women (324, 81.8%), with a mean age of 55.6 years (±14.4 SD). The vast majority of procedures performed were a one-stage TT (393, 99%) whereas 4 (1%) consisted of complete TT. Histopathological diagnoses revealed benign thyroid disease (nodular goiter, Graves-Basedow disease) in 244 (61.5%) and malignancy in 153 (38.5%). Ninety (22.7%) patients had an associated lymphadenectomy. The degree of lymphadenectomy performed was as follows: unilateral central neck dissection in 37 (9.5%), bilateral central neck dissection in 29 (7.3%), unilateral modified radical neck dissection in 19 (4.8%) and bilateral modified radical neck dissection in 5 (1.3%). Preoperative 25(OH)D levels were available for 374 patients, of whom 170 (42.5%) had VDD. VDD patients had higher median preoperative iPTH values (60 pg/mL [IQR, 46-80 pg/mL] vs 48 pg/mL [IQR, 38-64 pg/mL]; P < .001).

The rate of PT-hypoPTH was 38.2% (152 patients out of 397). Of these 152 patients, PFR took place within the year in 131 (32.9%) (transient PT-hypoPTH); 70 (53.4%) within the first 30 days (early-recovery transient PT-hypoPTH or PT-hypoPTH < 30 d), and 61 (46.6%) after 30 days (transient protracted PT-hypoPTH or PT-hypoPTH > 30 d). Twenty-one (5.2%) patients had not recovered parathyroid function at 365 days (definitive PT-hypoPTH). However, only 5 patients out of the total 397 remained hypoparathyroid at the last follow-up (1.26%) as a late recovery was observed in the remaining 16. If only patients with one-stage TT and without associated lymphadenectomy were considered, the rate of definitive PT-hypoPTH decreased to 3.6% (11/303); see Fig. 1.

After the exclusion of the 21 patients with definitive PT-hypoPTH, comparisons were performed between patients with parathyroid normofunction at discharge and those with transient PT-hypoPTH (Table 2) and between PT-hypoPTH < 30 d and PT-hypoPTH > 30 d (Table 3). Patients developing transient PT-hypoPTH had statistically significantly higher rates of thyroid malignancy on histology (45% vs 33.1%; P = .002) and associated lymphadenectomy (30.5% vs 16.3%; P = .002) than patients with normal parathyroid function at discharge (see Table 2). No differences were found in preoperative iPTH, Ca, or 25(OH)D levels. When patients developing transient PT-hypoPTH (N = 131) were divided into transient PT-hypoPTH < 30 d (n = 70) and transient PT-hypoPTH > 30 d (n = 61), significant differences were found only in 25(OH)D and ΔiPTH/POD1 iPTH parameters. Median preoperative 25(OH)D levels were significantly lower in patients in PT-hypoPTH < 30 d (19.7 vs 23.9; P = .001), while the percentage of VDD was significantly higher (55.2% vs 31.5%; P = .01). PT-hypoPTH > 30 d had a significantly higher ΔiPTH (median 94.6% vs 89.6%; P = .02) and lower POD1 iPTH levels (median 3 ng/mL vs 7 ng/mL; P = .029) (see Table 3).

Survival analysis was performed including the 120 out of the 131 transient PT-hypoPTH patients for whom preoperative 25(OH)D and iPTH recovery times were available (Fig. 2A). This revealed that VDD patients had an earlier

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**Table 1. Definitions and criteria of different conditions**

| PT-hypoPTH | Presence of low iPTH levels (< 14 pg/mL, below lower threshold in our laboratory) in POD1 [14-16] independently of ΔiPTH and/or need for treatment with Ca and calcitriol at discharge [18, 19] |
| Transient PT-hypoPTH | Low iPTH levels (< 14 pg/mL) or need for treatment with Ca and/or calcitriol < 365 d after surgery [6, 20] |
| Transient protracted PT-hypoPTH (hypoPTH-TT > 30 d) | Low iPTH levels (< 14 pg/mL) or need for treatment with Ca and/or calcitriol 30 to 365 days after surgery |
| Early-recovery PT-hypoPTH (hypoPTH-TT < 30 d) | Low iPTH levels (< 14 pg/mL) or need for treatment with Ca and/or calcitriol < 30 d after surgery. 30-day PFR cutoff is clinically relevant as protracted PT-hypoPTH patients are at a higher risk of developing definitive PT-hypoPTH [21] |
| Definitive PT-hypoPTH | Low iPTH levels (< 14 pg/mL) or need for treatment with Ca and/or calcitriol > 365 days after surgery |
| Late-recovery PT-hypoPTH | Patients who have required treatment with Ca and/or calcitriol beyond 365 days after surgery but PFR has taken place at last visit [6, 20] |
| VDD | 25(OH)D levels < 20 ng/mL (50 nmol/L) [22] |
| Severe VDD | 25(OH)D levels < 10 ng/mL [22] |

Abbreviations: 25(OH)D, vitamin D; Ca, calcium; iPTH, intact parathyroid hormone; PFR, parathyroid function recovery; POD1, postoperative day 1, PT-hypoPTH, postthyroidectom hypoparathyroidism; VDD, vitamin D deficiency.

The threshold used to designate VDD was 25(OH)D levels less than 20 ng/mL (50 nmol/L) as per the American Endocrine Society’s clinical practice guidelines [22]. A subgroup of severe VDD was identified if 25(OH)D was less than 10 ng/mL [22]. In case of preoperative VDD, routine supplementation is not a standardized practice at our center.

**Statistical Analysis**

Statistical analysis and data management were conducted using SPSS version 23.0 (IBM) and R software. Normal distribution was evaluated via visual methods (frequency distribution histogram) and the Kolmogorov-Smirnov test. Means of continuous variables with normal distributions were compared using the t test and nonparametric tests (Mann-Whitney U test) were used for those without normal distributions. Categorical data were analyzed using Pearson chi-square and Fisher exact test. In patients developing PT-HypoPTH, time to PFR was calculated from the day of TT surgery to the day of iPTH level normalization and suspension of Ca and 1,25(OH)2D supplementation. Survival analysis was performed using the Kaplan-Meier method and the log-rank test. Multivariable analysis was performed using a logistic binary regression studying intervariable relationships and allowing us to identify possible confounding variables (eg, lymphadenectomy, sex, malignancy, surgical
Postoperative hypoparathyroidism is the most common complication after TT and the most frequent cause of hospital readmission [23]. A recent meta-analysis found pooled incidence rates of 24.9% and 1.96% of transient and permanent PT-hypoPTH, respectively [24]. However, the comparison of results throughout the literature is complicated by the lack of standardization in the definition of PT-hypoPTH [3]. To carry out this study, the definition of PT-hypoPTH was strictly set at iPTH levels below 14 ng/mL at 24 hours. Following this definition, the observed rate of transient PT-hypoPTH was 32.9%.

Malignancy, need for combined lymphadenectomy, and prior neck surgery [9, 24] are well-established intraoperative risk factors of PT-hypoPTH. These are closely related to the main mechanisms resulting in PG damage: contusion, inadvertent extraction, vascular injury or vascular spasm secondary to extensive dissection, and inadvertent extraction [9, 24]. In fact, previous study groups have found a linear relationship between the prevalence of PT-hypoPTH and the number of preserved PGs in situ [25]. In our series, malignancy and combined lymphadenectomy acted as risk factors for transient PT-hypoPTH with respective OR of 1.81 (95% CI, 1.04-3.2; \( P = .034 \)) and 2.31 (95% CI, 1.38-3.87; \( P = .002 \)).

Since PG damage is the main contributor to the development of PT-hypoPTH, most research groups have focused on evaluating the efficacy of surgical advances in decreasing PT-hypoPTH through better preservation of PGs and their vascular supply. The aim of NIFI is to facilitate PG identification [7], which can be complex either due to the disparity of their anatomical location [26] and their position embedded in the loose connective tissue in the posterior margin of the lateral lobe [27]. This is further complicated by the fibrous
surgical fields found in patients with prior neck surgery [27]. ICG angiography evaluates the integrity of the vascular pedicle [7, 8]. Vidal Fortuny et al [8] demonstrated in a randomized clinical trial that the preservation of at least one well-vascularized PG at the end of the surgical procedure confirmed with ICG angiography predicts normal postoperative iPTH levels. One meta-analysis observed that the use of NIFI and ICG angiography technologies reduced both short- and medium-term hypocalcemia rates when compared to traditional TT surgery, but this did not translate into significant differences in iPTH levels [7].

Regarding the postoperative period, study groups have concentrated on developing PT-hypoPTH risk prediction models to guide the need for oral supplementation and predict PFR [28].

Table 2. Demographic characteristics of patients according to whether they developed postthyroidectomy hypoparathyroidism

|                      | No PT-hypoPTH (n = 245) (%) | Transient PT-hypoPTH (n = 131) (%) | P    |
|----------------------|-----------------------------|-----------------------------------|------|
| Female sex           | 193 (78.8)                  | 113 (86.3)                        | .095*|
| Age (mean, SD), y    | 56.8 (17)                   | 55.1 (14)                         | .349b|
| BMI (mean, SD)       | 27.2 (5.7)                  | 26.1 (3.5)                        | .586b|
| Thyroid malignancy   | 81 (33.1)                   | 59 (45)                           | .025*|
| Associated LT        | 40 (16.3)                   | 40 (30.5)                         | .002*|
| Unilateral CCND      | 20 (8.2)                    | 16 (12.2)                         |      |
| Bilateral CCND       | 10 (4.1)                    | 14 (10.7)                         |      |
| CCND and unilateral RND | 8 (3.3)                  | 8 (6.1)                           |      |
| CCND and bilateral RND | 2 (0.8)                  | 2 (1.4)                           |      |
| Preoperative PTH (median-IQR) | 55 (43-75)           | 52 (39-72)                        | .356c|
| Preoperative Ca (median-IQR) | 9.3 (9.1-9.7)   | 9.5 (9.2-9.7)                      | .102c|
| Preoperative 25(OH)D (median-IQR) | 20.2 (14.6-28) | 21.6 (15.7-28.4)                   | .575c|
| Preoperative VDD (< 20 ng/mL) | 108 (42.7)          | 54 (44.6)                         | .735c|

**Abbreviations:** 25(OH)D, vitamin D; BMI, body mass index; Ca, calcium; CCND, central compartment lymph node dissection; IQR, interquartile range; LT, lymphadenectomy; PTH, parathyroid hormone; PT-hypoPTH, postthyroidectomy hypoparathyroidism; RND, radical neck dissection; VDD, vitamin D deficiency.

*Fisher exact test.

b t test.

c Mann-Whitney U test.

Table 3. Demographic characteristics of patients according to whether they developed transient (< 30 days) or protracted (> 30 days) postthyroidectomy hypoparathyroidism

|                      | Transient PT-hypoPTH < 30 d (n = 70) (%) | Transient protracted PT-hypoPTH > 30 d (n = 61) (%) | P    |
|----------------------|-----------------------------------------|-----------------------------------------------|------|
| Female sex           | 57 (81.4)                               | 56 (91.8)                                      | .126*|
| Age (mean, SD), y    | 55.5 (14)                               | 54.6 (14)                                      | .693b|
| BMI (mean, SD)       | 25.9 (4.2)                              | 26.2 (4.2)                                     | .948b|
| Thyroid malignancy   | 34 (48.6)                               | 25 (41)                                        | .482a|
| Associated LT        | 21 (30)                                 | 19 (31.1)                                      | .887a|
| Unilateral CCND      | 8 (11.4)                                | 8 (13.1)                                       |      |
| Bilateral CCND       | 9 (12.9)                                | 5 (8.2)                                        |      |
| CCND and unilateral RND | 4 (5.7)                  | 4 (6.6)                                        |      |
| CCND and bilateral RND | 0                                    | 2 (3.3)                                        |      |
| Preoperative PTH (median-IQR) | 54 (41-80)                | 51 (37-65)                                     | .222c|
| Preoperative Ca (median-IQR) | 9.5 (9.2-9.8) | 9.5 (9.2-9.7)                                  | .999c|
| Preoperative 25(OH)D (median-IQR) | 19.7 (13.8-23.8) | 23.9 (18.3-29.4)                              | .010c|
| Preoperative VDD (< 20 ng/mL) | 108 (42.7)          | 54 (44.6)                                      | .735c|

**Abbreviations:** 25(OH)D, vitamin D; BMI, body mass index; Ca, calcium; CCND, central compartment lymph node dissection; IO, intraoperative; IQR, interquartile range; LT, lymphadenectomy; POD, postoperative day; PTH, parathyroid hormone; PT-hypoPTH, postthyroidectomy hypoparathyroidism; RND, radical neck dissection; VDD, vitamin D deficiency.

*Fisher exact test.

b t test.

c Mann-Whitney U test.
Preoperative risk factors have been classically neglected. The influence of preoperative 25(OH)D levels in the development of PT-hypoPTH is uncertain. Two recently published metaanalyses [9, 24] demonstrated a significant association between preoperative VDD and postoperative hypocalcemia. When combined, a total of 10 studies evaluating the effect of preoperative VDD on postoperative hypocalcemia were identified, out of which 4 studies observed a positive association [29-32], 1 a negative one, and most were unable to obtain a significant association. Additionally, a large multicenter retrospective study found a 2.2 higher risk of postoperative hypocalcemia in preoperative VDD cases (< 10 ng/mL) compared to vitamin D deficiency group. Preoperative VDD was associated with faster PFR times (median 8 days), but only a trend toward significance in the multivariable analysis as a result of low statistical power (only 7 patients). The physiology behind this is the basis of organ preconditioning [10]. In fact, natural organs are capable of improving responses to several insults; this is the basis of organ preconditioning. The concept and mechanisms contributing to parenchymal changes in the setting of hepatic ischemia/reperfusion injuries [10]. In the setting of PGs, it is not possible to simulate a scenario similar to that taking place during surgery, but VDD by acting at another stage is the basis of organ preconditioning.

Table 4. Multivariable analysis, odds ratio with 95% CI

|                  | Transient PT-hypoPTH | P | Transient protracted PT-hypoPTH > 30 d | P |
|------------------|----------------------|---|----------------------------------------|---|
| Female sex       | 1.77 (0.95-3.2)      | .091 † | 3.3 (1.14-9.52)                        | .031† |
| Age              | 0.99 (0.97-1.01)     | .928 † | 0.99 (0.98-1.02)                       | .678* |
| Thyroid malignancy | 1.81 (1.04-3.2)    | .034 † | 0.98 (0.30-2.45)                      | .374* |
| Associated LT    | 2.31 (1.38-3.87)     | .002 † | 2.01 (1.06-3.85)                      | .049* |
| Preoperative PTH < 55 pg/mL | 0.85 (0.51-1.42) | .532 b | 0.74 (0.38-1.43) | .371 b |
| Preoperative Ca   | 1.65 (0.95-2.88)     | .059 c | 1.31 (0.68-2.90)                      | .360 c |
| Preoperative VDD (< 20 ng/mL) | 0.89 (0.56-1.40) | .609 d | 0.46 (0.25-0.86) | .016 d |
| Severe preoperative VDD (< 10 ng/mL) | 0.39 (0.14-1.04) | .059 d | 0.15 (0.02-1.13) | .065 d |
| IO PTH drop      | 1.12 (1.08-1.15)     | <.001 † | 1.08 (1.05-1.12)                      | <.001 † |
| POD1 PTH         | 0.84 (0.77-0.92)     | .031† | 3.3 (1.14-9.52)                       | .031† |

Abbreviations: 25(OH)D, vitamin D; Ca-calcium; IO, intraoperative; LT, lymphadenectomy; POD, postoperative day; PTH, parathyroid hormone; PT-hypoPTH, postthyroidectomy hypoparathyroidism; VDD, vitamin D deficiency.

Models based on 9736 cases; 283 cases; 321 cases; 350 cases; 234 cases; and 173 cases, according to missing values.
are unknown. In the setting of chronic kidney disease, PG hyperplasia derives from the metabolic pathway involving the vitamin D receptor, Ca-sensing receptor, and protein α-klotho, a coreceptor for fibroblast growth receptor 23 resulting in the activation of transforming growth factor-α and EGF receptor (TGFα/ERGF) complex [35–37]. Similar factors must be involved in PG hyperplasia in the setting of VDD although the duration and degree of VDD should also be taken into consideration [38].

The favorable effect of VDD on the speed of PFR seems to be solid and persists in all groups with transient PT-hypoPTH over time, regardless of any kind of temporary definition considered. Temporary limits are another peculiar aspect of PT-hypoPTH. Most cases of PT-hypoPTH are transient (<1 year in duration). Beyond this cutoff point, PT-hypoPTH is considered to be definite, although this definition is still under scrutiny since the timing of PFR and the factors involved in it are poorly understood, not to mention that a significant number of patients will have their parathyroid function restored after that time [39]. Our observed rate of transient and definite PT-hypoPTH, were 32.9% and 5.6% (3.6% if complete thyroidec-tomy and associated lymphadenectomy were excluded), respectively. If we consider the rate of PT-hypoPTH at last visit, we observed that it dropped to 1.26%.

PFR is to be expected in at least two-thirds of patients within the first postoperative month [6]. Early PFR could be hypothesized to be a result of milder PG damage during the surgical procedure than that caused by protracted PT-hypoPTH (>30 days). We assessed this possibility by comparing the values of ΔiPTHio and POD1 iPTH and, as expected, significantly higher ΔiPTHio and lower POD1 iPTH levels were observed in the protracted group. Although this difference in PG damage could act as a bias in PFR, VDD maintained its significant association in the binary logistic regression for protracted PT-hypoPTH with an OR of 4.7 (95% CI, 0.25–0.881). Throughout the literature, only 1 retrospective study including 139 patients suggested similar findings, as no postoperative hypocalcemia occurred in VDD patients, but occurred in 10.3% of patients with adequate 25(OH)D levels [40].

This study is subject to limitations inherent to its retrospective design (ie, degree and duration of VDD could not be evaluated) and small size, with only 120 patients with transient PT-hypoPTH and measured preoperative 25(OH)D values available, the statistical power to detect differences was reduced. Additionally, patients could not be stratified according to their PT-hypoPTH risk status, although the multivariable analysis attempts to minimize this by adjusting the association between VDD and PT-hypoPTH to potential confounders. The use of immunoassays to measure 25(OH)D values is another limitation worth discussing. Immunoassays have lower specificity, show cross-reactivity with 25(OH)D metabolites, and cannot distinguish between 25(OH)D2 and 25(OH)D3 [41]. The gold-standard method of 25(OH)D testing is tandem mass spectrometry.

No other study group has reported the effect of preoperative VDD on PFR times. Despite the limitations of this study, its results imply that preoperative 25(OH)D levels condition PFR in PT-hypoPTH patients. However, subsequent clinical trials and basic research studies are needed to provide further understanding of the physiologic mechanisms aiding PFR and to corroborate the results obtained in this series. The goal of basic research studies would be to investigate the physiological mechanisms behind this observation. Posteriorly, its translation into clinical practice should be investigated with a trial. We propose a randomized trial including patients with VDD pre TT surgery comparing the effect of 25(OH)D supplementation on PT-hypoPTH and PFR times. Patients should be stratified according to their degree of preoperative VDD, and tandem mass spectrometry should be the method used to measure 25(OH)D levels [41]. Both efficacy and safety outcomes of preoperative 25(OH)D supplementation should be evaluated. VDD is also associated with other deleterious health conditions (eg, diabetes, cardiovascular diseases, multiple sclerosis [41]). Therefore, evaluating the safety of not supplementing 25(OH)D in VDD patients is crucial and even though our results represent a dilemma, they do not provide enough evidence to preoperatively induce VDD in patients undergoing TT surgery.

In summary, preoperative VDD could act as a PG preconditioning factor through a unknown mechanism that accelerates PFR once surgical aggression has taken place. However, the evidence behind this is limited and weak, whereby both prospective clinical trials to confirm these results as well as basic research studies to delve into the underlying physiological mechanism are being designed. It is expected that these studies will enhance our knowledge of physiological pathways on how to best prepare the PGs before TT. Indirectly, further evidence of what is the best clinical practice regarding preoperative 25(OH)D testing and normalization will be provided.

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Data Availability
Original data generated and analyzed during this study are included in this published article or in the data repositories listed in “References.”

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