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Vitamin D cannot be used as a global predictor of post-thyroidectomy hypocalcaemia

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Main Article

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Abstract

Objective. To assess the relationship between vitamin D and post-operative hypocalcaemia in patients undergoing total thyroidectomy in our population.
Methods. A prospective cohort of 210 patients meeting inclusion criteria from March 2020 to September 2023 at Sultan Qaboos University Hospital was analysed. Pre-operative serum 25-hydroxy vitamin D was measured, with calcium and parathyroid hormone assessed post-operatively, and symptoms recorded.
Results. Univariate and logistic regression analyses showed no significant association between pre-operative vitamin D levels and post-operative hypocalcaemia ($p = 0.254$ and 0.52, respectively). Receiver operating characteristic analysis showed an area under the curve of 0.6 ($p = 0.012$), indicating limited predictive ability.
Conclusion. In our population, pre-operative vitamin D level was not a reliable predictor of post-thyroidectomy hypocalcaemia. Because of population-based differences in vitamin D metabolism and assay variability, universal cut-off values remain impractical. These findings highlight the need for further research to establish population-specific thresholds for vitamin D in predicting hypocalcaemia risk.

Introduction

Over the past several decades there has been a noted increase in the incidence of thyroid cancer, which can be partly explained by the advancement in diagnostic technology and laboratory investigations. This has led to a substantial increase in the number of total thyroidectomies performed. A population-based analysis in the USA revealed that the number of total thyroidectomies rose 39 per cent from 1996 to 2006 and this is expected to rise even further.[1,2] This has led to an interest in daycare surgery to reduce cost, but a major obstacle in fully implementing this is the development of transient hypocalcaemia post thyroidectomy, which usually occurs in the first 48 hours.

Several methods to predict the development of hypocalcaemia have been investigated in the literature, including intact parathyroid hormone, corrected calcium and vitamin D. Currently, there is still a significant paucity in the published literature regarding the utility of vitamin D in predicting hypocalcaemia post total thyroidectomy.

Vitamin D is a fat-soluble vitamin that affects a wide range of health problems, either acutely or chronically. It has been linked to immune function and cancer prevention through various observational studies that showed a reduced risk of such health problems in patients with vitamin D levels in the range of 28–32 ng/ml.[3] It plays a crucial role in calcium haemostasis because it increases the efficiency of calcium absorption from the small intestine and regulates the secretion of parathyroid hormone. Vitamin D deficiency is a worldwide health problem, with prevalence reaching up to 50 per cent in women of childbearing age in some populations. In Oman, multiple studies have concluded that vitamin D deficiency prevalence, although subclinical, is high.[4,5]

Numerous studies have examined whether low peri-operative vitamin D levels constitute an independent risk factor for post-operative hypocalcaemia, but this issue remains a topic of ongoing debate.[6–15]

The current proposed mechanism, although speculative, is that patients with vitamin D deficiency have an elevated parathyroid hormone level, leading to secondary hyperparathyroidism and potentially parathyroid gland hyperplasia. This serves as a compensatory mechanism to regulate calcium haemostasis by increasing bone resorption and renal absorption to offset the reduced intestinal absorption caused by vitamin D deficiency. During surgery, intra-operative parathyroid damage is thought to greatly impact this compensatory mechanism and hence lead to post-operative hypocalcaemia.[6,9]

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This study aimed to determine the predictive value of pre-operative vitamin D levels for post-operative hypocalcaemia following total thyroidectomy in our population.

Materials and methods

This was a prospective cohort study that took place in the ENT unit of the Department of Surgery at Sultan Qaboos University Hospital. We enrolled all consecutive patients who were scheduled to undergo total or completion thyroidectomy with and without central neck dissection between January 2021 and August 2023. Exclusion criteria included lateral neck dissection at the same setting, history of calcium or vitamin D supplementation for other medical issues and pre-existing calcaemic disorders. Ethical approval was obtained from the Research Ethics Committee in the hospital and informed consent was obtained from all participants.

Demographic data were collected, including age and sex. Data regarding the performance of central neck dissection, presence of Graves' disease, thyrotoxicosis or hypothyroidism, and pre-operative fine needle aspiration (FNA) results were obtained. FNA results were interpreted using the Bethesda system and grouped into two groups: group 1 included patients with Bethesda category 1 to 3 and group 2 included patients with Bethesda category 4 to 6.

Vitamin D status was recorded as a continuous variable and a categorical variable with a cut-off of 50 nmol/l (20 ng/ml). Vitamin D deficiency was defined as a serum 25-hydroxy vitamin D level less than 50 nmol/l (20 ng/ml) based on the current Endocrine Society consensus guideline. Vitamin D was measured using the Architect I2000 Immunoassay System (Abbott Park, Illinois, in the United States). The Architect 25-hydroxy vitamin D assay is a chemiluminescent microparticle immunoassay for the quantitative determination of 25-hydroxy vitamin D in human serum and plasma.

Corrected calcium and intact parathyroid hormone were measured the day before surgery, 6 hours post operatively, 12 hours post operatively and twice daily after that depending on the hospital stay. Transient hypocalcaemia was defined as either corrected calcium of less than 2.05 mmol/l (8.22 mg/dl) or symptomatic hypocalcaemia. Severe hypocalcaemia was defined as a corrected calcium level less than 1.9 mmol/l (7.62 mg/dl). Post-operative data, including the final histopathology and presence of parathyroid glands in the final specimen, were also included in the analysis. All patients who developed hypocalcaemia were given oral calcium and vitamin D supplements, and those who developed severe hypocalcaemia were given intravenous calcium as per the institutional protocol.

Data were summarised using descriptive statistics. Categorical variables were summarised using frequency and percentages. Continuous variables were summarised using mean and standard deviation. Univariate analysis involved the use of a two-sample *t*-test for continuous variables and either a chi-square test (when $n = 5$) or Fisher's exact test (when $n < 5$). Meanwhile, multivariate analysis was conducted through logistic regression analysis. Receiver operating characteristic curve analysis was employed to assess the discriminatory capacity of pre-operative vitamin D in predicting post-operative hypocalcaemia and the area under the curve was reported with a standard error. A p value less than 0.05 was considered to be statistically significant. All statistical analysis was performed using IBM SPSS ver. 29.0 (SPSS Inc., Chicago, IL, USA).

Results and analysis

A total of 210 patients were included in this analysis, of which 166 (79.1 per cent) were female. A total of 76 patients (36.2 per cent) had transient hypocalcaemia and 16 patients (7.6 per cent) developed severe hypocalcaemia requiring intravenous calcium supplementation. The baseline demographic and clinical characteristics of patients in both groups are shown in Table 1.

Univariate and logistic regression analyses were performed to assess the relationship between various risk factors, particularly vitamin D status, and transient hypocalcaemia following total thyroidectomy. The univariate analysis showed that out of several factors, including female sex, thyroid hormone status, pre-operative FNA, central neck dissection, vitamin D status, malignant histopathology and parathyroid tissue presence, only the presence of parathyroid tissue was significantly associated with transient hypocalcaemia ($p = 0.022$)

Importantly, vitamin D status ($p = 0.254$) did not show a significant association with post-operative hypocalcaemia (Table 1). The logistic regression analysis further confirmed that pre-operative vitamin D status was not a significant predictor of transient hypocalcaemia ($p = 0.52$). The analysis identified central neck dissection as a significant predictor ($p = 0.027$, odds ratio = 3.305, 95 per cent confidence interval (CI) = 1.142–9.565), while thyrotoxicosis and pre-operative FNA approached significance with p values of 0.064 and 0.058, respectively. These findings suggest that while central neck dissection is a significant predictor, vitamin D levels do not have a significant predictive value for transient hypocalcaemia post thyroidectomy (Table 2).

To further evaluate the predictive value of pre-operative vitamin D levels for transient hypocalcaemia, a receiver operating characteristic curve analysis was performed. This analysis yielded an area under the curve of 0.6, indicating a poor to fair level of discrimination. The area under the curve result, with a p value of 0.012, suggests that pre-operative vitamin D levels have a statistically significant but limited ability to predict transient hypocalcaemia post thyroidectomy (Figure 1).

A subgroup analysis was conducted to assess the association between pre-operative vitamin D deficiency and post-operative hypocalcaemia based on the surgical procedure. The results demonstrated no significant association in any of the subgroups. In the total thyroidectomy group ($n = 160$), hypocalcaemia occurred in 6 of 14 patients (42.9 per cent) with vitamin D deficiency, compared with 50 of 146 non-deficient patients (34.2 per cent) ($p = 0.519$). Similarly, in the completion thyroidectomy group ($n = 28$), hypocalcaemia was present in 1 of 2 patients (50.0 per cent) with vitamin D deficiency and 5 of 26 non-deficient patients (19.2 per cent) ($p = 0.307$). In the central neck dissection group ($n = 22$), the sole patient with vitamin D deficiency developed hypocalcaemia, compared with 13 of 21 non-deficient patients (61.9 per cent) ($p = 0.439$).

Given the absence of an association with any hypocalcaemia, a secondary analysis was performed to assess the relationship between vitamin D deficiency and severe hypocalcaemia (serum calcium <1.9 mmol/l). Univariate analysis demonstrated a non-significant association ($p = 0.625$) and logistic regression confirmed the lack of statistical significance ($p = 0.536$; odds ratio, 1.622; 95 per cent CI = 0.315–8.348). Receiver operating characteristic curve analysis yielded an area under the curve of 0.598 ($p = 0.191$; 95 per cent CI = 0.473–0.724), indicating poor discriminatory ability.

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Table 1. Univariate analysis of risk factors for post-operative hypocalcaemia in total thyroidectomy patients

Risk factor	Normocalcemia (*n* (%))	Transient hypocalcaemia (*n* (%))	Total (***n***)	*p* value*
Female (*n* (%))	102 (61.4)	64 (38.6)	166	0.159
Thyrotoxicosis	12 (57.1)	9 (42.9)	21	0.507
Hypothyroidism	11 (52.4)	10 (47.6)	21	0.258
Non-benign pre-operative FNA	90 (66.7)	45 (33.3)	135	0.249
Central neck dissection	8 36.4)	14 (63.6)	22	0.06
Vitamin D				0.254
– Deficiency	9 (52.9)	8 (47.1)	17	
– Insufficiency	59 (60.2)	39 (39.8)	98	
– Sufficiency	66 (69.5)	29 (30.5)	95	
Malignant final histopathology	99 (65.1)	53 (34.9)	152	0.520
Parathyroid tissue in final histopathology	25 (50)	25 (50)	50	0.022#
Graves' disease	18 (72)	7 (28)	25	0.365

*Chi-square test. #$p < 0.05$. FNA = fine needle aspiration

Table 2. Multivariate logistic regression analysis of risk factors for post-operative hypocalcaemia in total thyroidectomy patients

			95% confidence interval	
Risk factor	*P* value	Odds ratio	Lower	Upper
Sex	0.364	0.698	0.321	1.518
Graves' disease	0.738	0.846	0.318	3.250
Thyrotoxicosis	0.430	1.470	0.564	3.830
Hypothyroidism	0.321	1.613	0.628	4.142
Pre-operative vitamin D	0.379	0.629	0.224	1.767
Operation time	0.685	1.002	0.992	1.012
Central neck dissection	0.008	3.543	1.392	9.014

Discussion

Our results show that vitamin D levels do not have a significant predictive value for transient hypocalcaemia post thyroidectomy in our population. The receiver operating characteristic curve analysis yielded an area under the curve of 0.6, indicating a poor to fair level of discrimination. The area under the curve result, with a *p* value of 0.012, suggests that pre-operative vitamin D levels have a statistically significant but limited ability to predict transient hypocalcaemia post thyroidectomy.

There are several studies that had similar conclusion to ours. Erlem *et al.* included 246 patients in a retrospective analysis and concluded that serum 25-hydroxy vitamin D did not appear to have any impact on post-operative serum calcium in patients undergoing total thyroidectomy for benign goitre.[15] In addition, Cherian *et al.* included 150 patients in a retrospective analysis and found that vitamin D deficiency did not increase the risk of post-thyroidectomy hypocalcaemia.[14]

In contrast, several larger-scale studies have reported a significant association between vitamin D deficiency and post-thyroidectomy hypocalcaemia. Rubin *et al.* included 517 subjects in a retrospective analysis and demonstrated that 25-hydroxy vitamin D level is a significant predictor of post-operative hypocalcaemia after thyroidectomy.[16] However, it is imperative to understand that 25-hydroxy vitamin D levels were recorded within the range of 42 days prior to surgery or 1 day after surgery. In addition, the study included subjects who were already taking ergocalciferol supplementation and this was not elaborated on or taken into account in the analysis, but is mentioned in the limitations.

Another prospective study, by Bove *et al.*, included 177 patients who underwent total thyroidectomy and concluded that post-operative hypocalcaemia is significantly associated with low pre-operative levels of serum 25-hydroxy vitamin D. In their cohort, the risk of hypocalcaemia increased 15-fold in patients with a pre-operative vitamin D level less than 25 ng/ml.[17] This study only looked at patients undergoing total thyroidectomy and excluded patients with central neck dissection. They also excluded patients either affected by other diseases or using drugs that could interfere with the metabolism of calcium.

Vitamin D status has been linked to many diseases, including cancer, cardiovascular disease and autoimmune disorders.[3,18,19] There is no uniformly accepted definition or cut-off for vitamin D levels, leading to substantial variability in reported deficiency rates, ranging from 2 to 90 per cent across different populations.[20,21] When considering vitamin D deficiency in the context of thyroidectomy, one might initially attribute the variations in its reported predictivity to more apparent factors, such as differing cut-off levels used to define vitamin D deficiency or hypocalcaemia. Additionally, some authors have suggested reasons such as the retrospective nature of the studies or the specific type of

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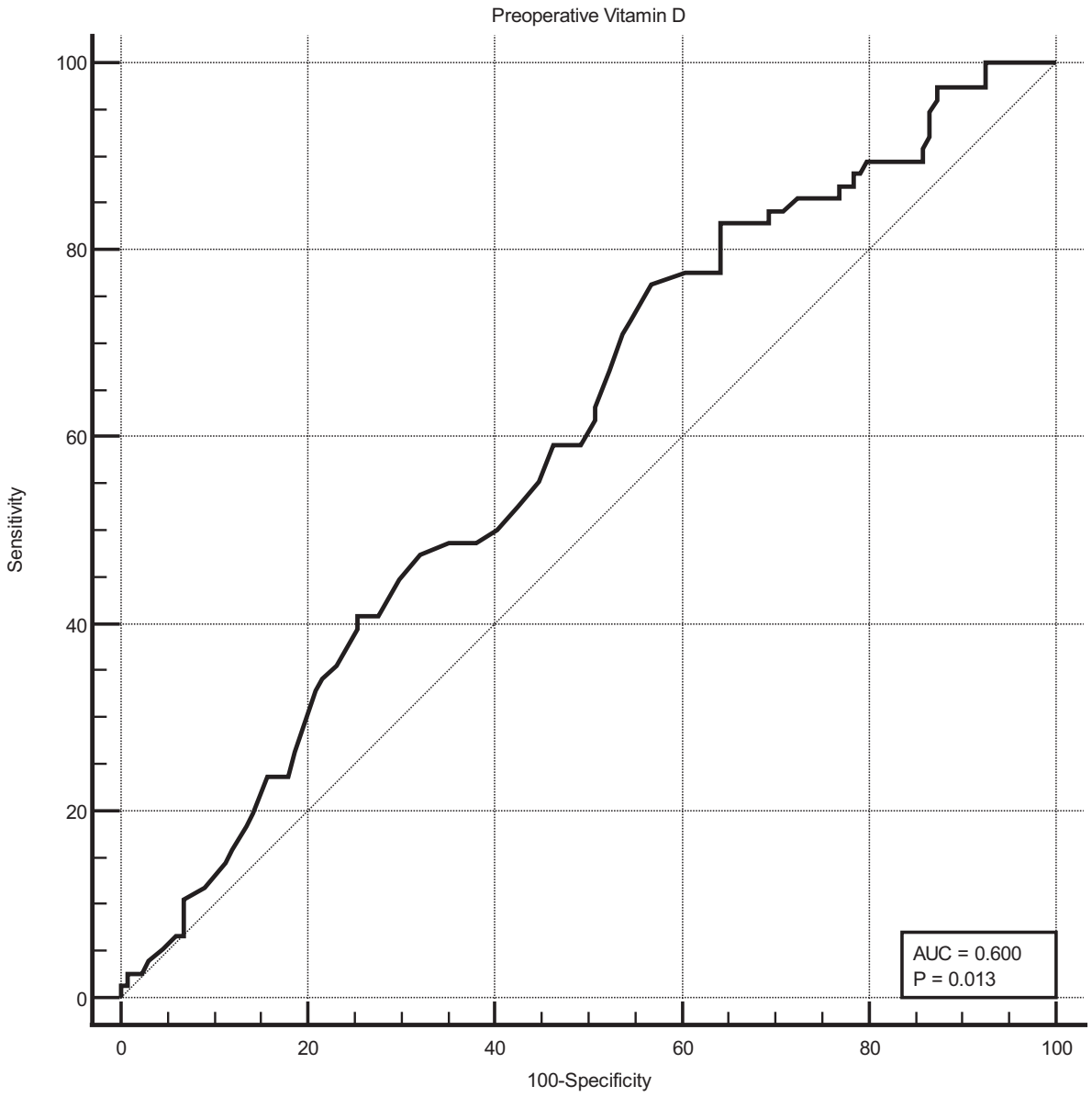


Figure 1. Receiver operating characteristic curve for vitamin D as a predictor of post-operative hypocalcaemia. AUC = area under the curve.

thyroid surgery performed as the primary contributors to this variability. However, the issue is considerably more complex. A deeper examination of the broader literature on vitamin D reveals that this substantial heterogeneity is driven by several factors that continue to pose challenges in current research.[19,21,22]

Yoon *et al.* carried out an analysis to look for genetic causes of vitamin D concentration differences among people from different ethnic groups and ancestry. They collected 320 single-nucleotide polymorphisms associated with vitamin D concentrations from a genome-wide association studies catalogue. They showed that single-nucleotide polymorphisms related to vitamin D metabolism significantly influence vitamin D concentrations among different ethnic groups. For instance, populations of European, East Asian and African descent exhibit distinct patterns in the frequency of vitamin D-related single-nucleotide polymorphisms, which correlate with their ancestral ultraviolet B exposure environments.[23]

Genetic predisposition, such as variations in the CYP2R1 and Vitamin D Binding Protein genes, also contributes to the differences observed in vitamin D levels across these populations.[24] A systematic review of 195 studies involving 168 000 participants from 44 countries showed that mean vitamin D levels varied significantly, ranging from 4.9 to 136.2 nmol/l. Over 30 per cent of studies reported mean values below 50 nmol/l, with age-related differences observed only in Asia/Pacific and Middle East/Africa regions, suggesting that definitions of deficiency may differ across populations.[25]

An important point that is often overlooked in studies examining the predictive value of vitamin D for hypocalcaemia is the pre-analytical and analytical variability in vitamin D measurements. It is crucial to recognise that, because of the biosynthetic pathway of vitamin D, its concentration is significantly influenced by ultraviolet B radiation exposure and exhibits seasonal variation, particularly at latitudes distant from the equator. This variation

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means that vitamin D levels during the summer and autumn can differ from those in winter and spring. Several studies have demonstrated that vitamin D concentrations fluctuate by an average of 40 nmol/l throughout the year, with peak changes reaching up to 105 nmol/l.[22,26,27] Consequently, a single measurement may not accurately reflect the true vitamin D status. Considering that thyroidectomies are performed year-round and blood samples are collected at varying times, this variability can lead to incorrect conclusions regarding the actual vitamin D status and its predictive ability.

Additionally, variations in the measurement of vitamin D concentrations are influenced by significant differences between the assays used. Currently, two primary methods are employed in laboratories: the more expensive and accurate liquid chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry, and the less costly antibody or protein-binding methods, such as immunoassays.[22] Despite substantial efforts to enhance the accuracy and precision of 25-hydroxy vitamin D measurements, two studies have identified considerable within-assay and between-assay variability among different commercially available instruments. These studies compared liquid chromatography-mass spectrometry results with five automated chemiluminescent immunoassays from various manufacturers, revealing that mass spectrometry instruments demonstrated superior performance with a bias of less than 10 per cent, even at concentrations as low as 5.2 nmol/l, whereas most immunoassays exhibited biases greater than ±15 per cent, with some reaching up to 30 per cent.[28,29]

Online Supplementary Table S1 shows the methods of vitamin D measurement in studies evaluating pre-operative vitamin D as a predictor of post-operative hypocalcaemia. The table highlights significant variability in the methods used to measure vitamin D across different studies evaluating its role as a predictor of post-operative hypocalcaemia in total thyroidectomy patients[6–17,30–32]. The use of diverse assays, ranging from highly accurate methods like liquid chromatography-tandem mass spectrometry to less precise immunoassays, suggests that differences in assay sensitivity and accuracy may contribute to inconsistent findings across studies. The fact that many studies did not mention the specific assay used further complicates the interpretation of results, emphasising the need for standardised measurement techniques to improve the reliability and comparability of future research in this area.

- Hypocalcaemia is the most common complication following total thyroidectomy and remains the primary barrier to early hospital discharge
- There is still significant paucity in the published literature regarding the utility of vitamin D in predicting hypocalcaemia post total thyroidectomy
- This study assessed the value of vitamin D as a predictor of hypocalcaemia
- Our results suggest that pre-operative vitamin D levels do not serve as reliable predictors of post-operative hypocalcaemia following thyroidectomy in our population
- Vitamin D cut-off values lack universal applicability because of variations in ethnicity, genetics, geography and assay methodology
- The predictive value of vitamin D cut-off values for post-operative hypocalcaemia is population-dependent, rendering a global standard unfeasible and necessitating further research to establish population-specific thresholds

Conclusion

In our population, pre-operative vitamin D deficiency was not a reliable predictor of post-operative hypocalcaemia following thyroidectomy. Currently, vitamin D cut-off values are not universally applicable because of differences in race, ethnicity, genetics, geographical location and analytical variations in vitamin D measurement. Consequently, caution should be exercised when considering vitamin D as a global predictor for post-operative hypocalcaemia because its predictive capacity may differ across diverse populations. Establishing a universal standard for vitamin D levels is presently impractical, highlighting the need for further research to identify specific cut-off values tailored to individual populations.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0022215125104003.

Competing interests. None declared

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