Association Between Vitamin D Status and Peripheral Thyroid Hormone Activation: Insights from FT3/FT4 Ratio Analysis

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ABSTRACT

Background: Vitamin D deficiency has been increasingly recognized as a potential factor influencing endocrine regulation beyond calcium metabolism. However, its relationship with peripheral thyroid hormone activation remains insufficiently clarified, particularly in populations with high rates of thyroid dysfunction.

Objective: This study aimed to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D], intact parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), and the FT3/FT4 ratio as an indicator of peripheral thyroid hormone conversion.

Methods: A retrospective cross-sectional study was conducted at the in-vitro division of Institute of Nuclear Medicine and Allied Sciences (INMAS), Mohakhali, Dhaka. A total of 138 participants were included. Serum levels of TSH, Free triiodothyronine (FT3), Free thyroxine (FT4), 25(OH)D, PTH, and calcium were measured using chemiluminescence immunoassay (CLIA). Due to non-normal distribution, TSH values were log-transformed prior to analysis. Correlations were assessed using Pearson's coefficient, and linear regression was performed to determine explanatory power.

Results: The study population demonstrated marked thyroid dysfunction and widespread vitamin D deficiency. Serum 25(OH)D levels showed a strong positive correlation with the FT3/FT4 ratio ($r = +0.69$, $p < 0.001$). Log-transformed TSH exhibited a significant inverse correlation with the FT3/FT4 ratio ($r = -0.64$, $p < 0.001$), explaining 40.5% of its variability. Intact PTH showed a weaker but statistically significant inverse association with the FT3/FT4 ratio ($r = -0.23$, $p = 0.027$), accounting for 5.5% of the variation.

Conclusion: Higher vitamin D levels are linked to enhanced peripheral thyroid hormone conversion, while greater stimulation of the thyroid axis correlates with a decreased FT3/FT4 ratio. Vitamin D status shows a stronger relationship with thyroid hormone activation compared to PTH. These results suggest the importance of vitamin D in thyroid hormone metabolism and its potential role in endocrine evaluation, indicating the need for further prospective studies to explore the mechanisms involved.

Keywords: Vitamin D deficiency, FT3/FT4 ratio, Log TSH, Thyroid hormone conversion, Parathyroid hormone, Endocrine correlation.

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INTRODUCTION

The thyroid and parathyroid hormones are essential regulators of metabolic and mineral homeostasis in the human body (1). Thyroid gland primarily controls energy metabolism, growth, and thermogenesis, whereas the parathyroid glands maintain calcium and phosphate balance. Although these endocrine systems were traditionally examined independently, growing evidence suggests that they may interact through shared regulatory mechanisms, particularly those involving vitamin D and calcium metabolism (2). Within this broader endocrine context, vitamin D has emerged as an important modulator of several physiological processes beyond its classical role in skeletal health (3). The widespread presence of vitamin D receptors in multiple tissues suggests potential involvement in gene expression, immune regulation, and hormonal signaling. Several studies have explored the relationship between vitamin D status and thyroid function; however, findings remain inconsistent across different populations, indicating that this interaction requires further clarification. Understanding this relationship requires consideration of peripheral thyroid hormone metabolism. Circulating thyroid hormone activity depends not only on glandular secretion but also on tissue-level conversion of thyroxine (T4) into the biologically active triiodothyronine (T3). This conversion is mediated by iodothyronine deiodinase enzymes, primarily DIO1 and DIO2 (4). Because this process reflects peripheral thyroid hormone activation, the FT3/FT4 ratio has been proposed as a practical indicator of metabolic efficiency and deiodination

activity (5). A reduced FT3/FT4 ratio may therefore indicate impaired peripheral hormone conversion and altered metabolic status, even when serum thyroid-stimulating hormone (TSH) concentrations remain within conventional reference ranges (6). Molecular studies have also suggested potential interactions between vitamin D receptor (VDR) and thyroid hormone receptor pathways, particularly through their shared association with the retinoid X receptor (RXR), which participates in transcriptional regulation (7). These observations indicate a possible biological link between vitamin D status and thyroid hormone signaling. In South Asia, including Bangladesh, vitamin D deficiency has become highly prevalent, largely due to limited sunlight exposure, lifestyle changes, and rapid urbanization (8). Such widespread hypovitaminosis D may influence endocrine balance and metabolic regulation, and in individuals receiving standard thyroid therapy, inadequate vitamin D levels may contribute to persistent metabolic alterations despite biochemical control of conventional thyroid parameters (9). Vitamin D deficiency is frequently accompanied by a compensatory increase in parathyroid hormone (PTH), which helps maintain calcium homeostasis (10). Although this response primarily regulates mineral metabolism, disturbances in vitamin D status may also coincide with broader endocrine alterations. However, whether elevated PTH independently influences peripheral thyroid hormone conversion remains unclear. The present study was designed to examine the relationships between serum 25-hydroxyvitamin D [25(OH)D], intact PTH, TSH (including log-transformed values), and the FT3/FT4 ratio in a clinical cohort.

METHODS

This retrospective cross-sectional study was conducted in the In Vitro Division of INMAS, Mohakhali, Dhaka. A total of 138 participants were included using a non-probability purposive sampling approach. Individuals attending the laboratory for routine endocrine evaluation or suspected thyroid dysfunction were considered eligible. To minimize potential confounding, patients receiving vitamin D supplementation, those with chronic kidney disease (CKD), and individuals on thyroid hormone replacement therapy were excluded from the primary analysis. Venous blood samples (5 mL) were collected under aseptic conditions using disposable syringes. After collection, samples were allowed to clot at room temperature for 15–20 minutes and were subsequently centrifuged at 4000 RPM for 20 minutes to obtain serum. Biochemical parameters were measured using automated chemiluminescence immunoassay (CLIA) on the ADVIA Centaur XPT Immunoassay System (Siemens Healthcare AG, Germany). Serum TSH, FT3, FT4, 25-hydroxyvitamin D [25(OH)D], and intact PTH levels were quantified using the same platform to ensure analytical consistency. Total serum calcium was measured by the Arsenazo III colorimetric method using an automated clinical chemistry analyzer. Vitamin D status was classified according to established clinical criteria as deficient (<20 ng/mL), insufficient (21–29 ng/mL), and sufficient (≥30 ng/mL). The FT3/FT4 ratio was calculated for each participant as an indicator of peripheral thyroid hormone conversion and was considered a surrogate marker of deiodinase activity. Prior to statistical analysis, data distribution was assessed for normality. Variables showing skewed distribution, including TSH and vitamin D levels, were summarized using the median and interquartile range (IQR) in addition to the mean ± standard deviation (SD). Because serum TSH demonstrated significant skewness, logarithmic transformation (log TSH) was performed before correlation and regression analyses to stabilize variance and satisfy parametric assumptions. Statistical analyses were conducted using SPSS version 26.0 and R statistical software. Relationships between the FT3/FT4 ratio and metabolic variables (vitamin D, log TSH, and PTH) were evaluated using the Pearson correlation coefficient (r). Simple linear regression analysis was performed to determine the coefficient of determination (R^2) and to assess the proportion of variance explained by each independent variable. A p-value of less than 0.05 was considered statistically significant. Graphical representations were generated using Origin 2018.

RESULT

A total of 138 participants were included in this study to explore the relationship between thyroid function and vitamin D status. The baseline demographic and biochemical characteristics of the study population are summarized in Table 1.

Because several biochemical parameters exhibited substantial variability, results are presented as mean ± standard deviation as well as median with interquartile range (IQR) to better reflect the distribution of the data.

Table 1: Baseline Clinical and Biochemical Profile of the Study Population

Parameters	Mean ± SD	Median	IQR (25^{th}-75^{th})	Reference Range
Age (Years)	39.40 ± 14.20	37.50	28.00-51.00	
Serum TSH (mIU/L)	70.34 ± 52.17	75.72	17.56-114.96	0.55-4.78
Serum FT3 (pmol/L)	2.58 ± 1.32	2.42	1.85-3.20	2.80-9.50
Serum FT4 (pmol/L)	7.92 ± 5.14	7.15	4.80-10.40	9.50-25.50
Serum 25(OH)D (ng/mL)	15.03 ± 7.19	13.91	9.12-19.18	30.00-100.00
Intact PTH (pg/mL)	46.56 ± 42.94	36.00	16.10-63.00	18.80-88.00
Calcium (mg/dL)	8.92 ± 1.08	9.10	8.40-9.60	8.50-10.50

The biochemical profile indicates a high prevalence of thyroid dysfunction accompanied by widespread vitamin D deficiency within the cohort. Serum TSH levels were markedly elevated with a mean of 70.34 ± 52.17 mIU/L and a median of 75.72 mIU/L, indicating severe thyroid axis stress in a substantial proportion of participants. The wide interquartile range (17.56–114.96 mIU/L) further reflects considerable heterogeneity in the degree of thyroid dysfunction within the cohort. Vitamin D concentrations were consistently low. The mean serum 25(OH)D level was 15.03 ± 7.19 ng/mL, well below the accepted sufficiency threshold of 30 ng/mL. The median value of 13.91 ng/mL with an IQR of 9.12–19.18 ng/mL indicates that vitamin D deficiency was prevalent across most participants. Serum calcium values remained largely within the lower physiological range (8.92 ± 1.08 mg/dL), while intact PTH levels showed moderate variability with a mean value of 46.56 ± 42.94 pg/mL and a median of 36.00 pg/mL. The interquartile range (16.10–63.00 pg/mL) suggests heterogeneous parathyroid responses, likely reflecting varying degrees of compensatory endocrine adjustment to vitamin D deficiency. To evaluate peripheral thyroid hormone activation, the FT3/FT4 ratio was correlated with vitamin D, TSH, and PTH. Because serum TSH values displayed substantial variability and skewness, logarithmic transformation of TSH (log TSH) was performed before correlation analysis to stabilize variance and better capture the relationship between thyroid axis stimulation and hormone conversion efficiency. The statistical associations are detailed in Table 2.

Table 2: Correlation Matrix of FT3/FT4 Ratio and Metabolic Markers

Sl. No.	Variable Pair	Number (n)	Pearson(r)	Regression(R^2)	p-Value
1.	FT3/FT4 vs Vit D	117	+0.69	0.471	<0.001
2.	FT3/FT4 vs Log TSH	117	-0.64	0.405	<0.001
3.	FT3/FT4 vs PTH	89	-0.23	0.056	0.027

A strong positive relationship was observed between vitamin D levels and the FT3/FT4 ratio ($r = +0.69$, $p < 0.001$), suggesting that higher vitamin D status is associated with improved peripheral thyroid hormone activation. (Figure 1).

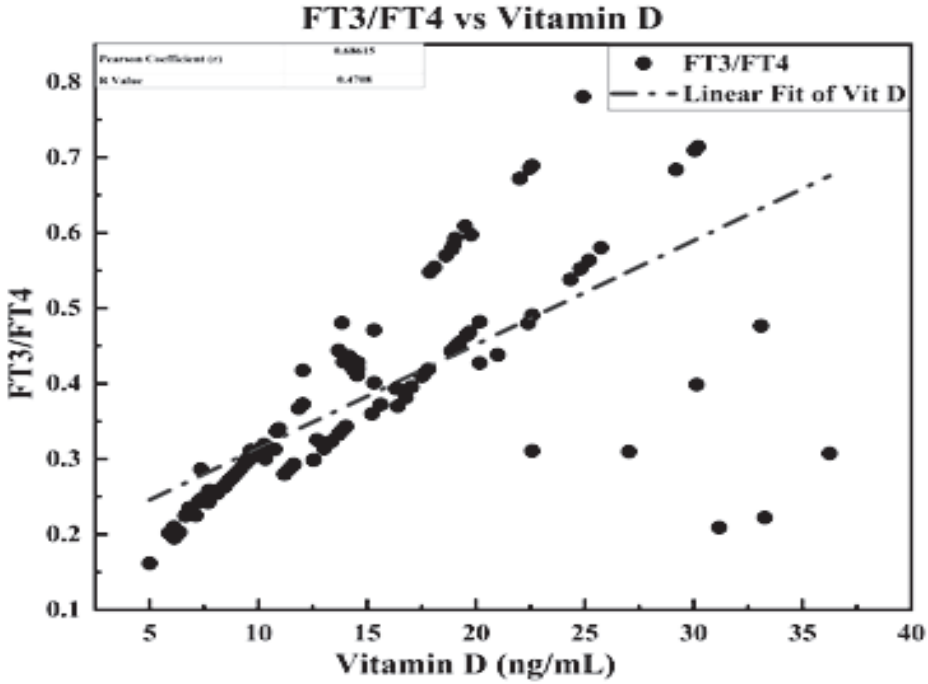

Figure 1: Scatter plot showing the positive association between serum vitamin D [25(OH)D] and FT3/FT4 ratio with linear regression fit

approximately 40.5% of the variability in FT3/FT4 ratio (R^2 = 0.405), highlighting a substantial relationship between thyroid axis stress and peripheral hormone conversion. (Figure 2).

When log-transformed TSH was analyzed, a significant inverse correlation with the FT3/FT4 ratio was identified (r = −0.64, p < 0.001). Linear regression analysis further indicated that log TSH accounted for

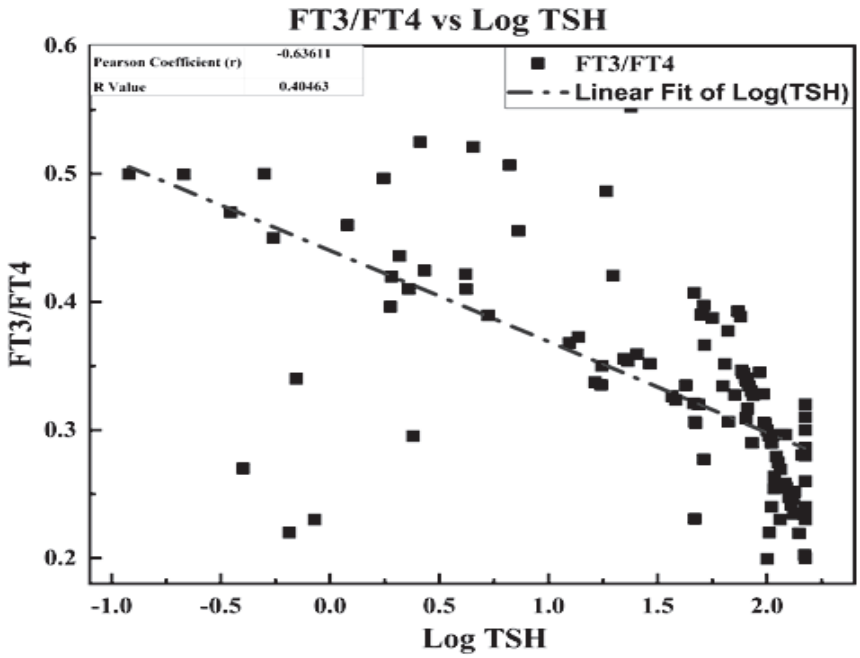

Figure 2: Inverse relationship between log-transformed TSH and FT3/FT4 ratio indicating reduced peripheral thyroid hormone activation with increasing thyroid axis stimulation

In contrast, PTH showed a weaker but statistically significant inverse correlation with the FT3/FT4 ratio ($r = -0.23$, $p = 0.027$). Regression analysis indicated that PTH accounted for only 5.5% of the variability in peripheral thyroid hormone conversion (Figure- 3).

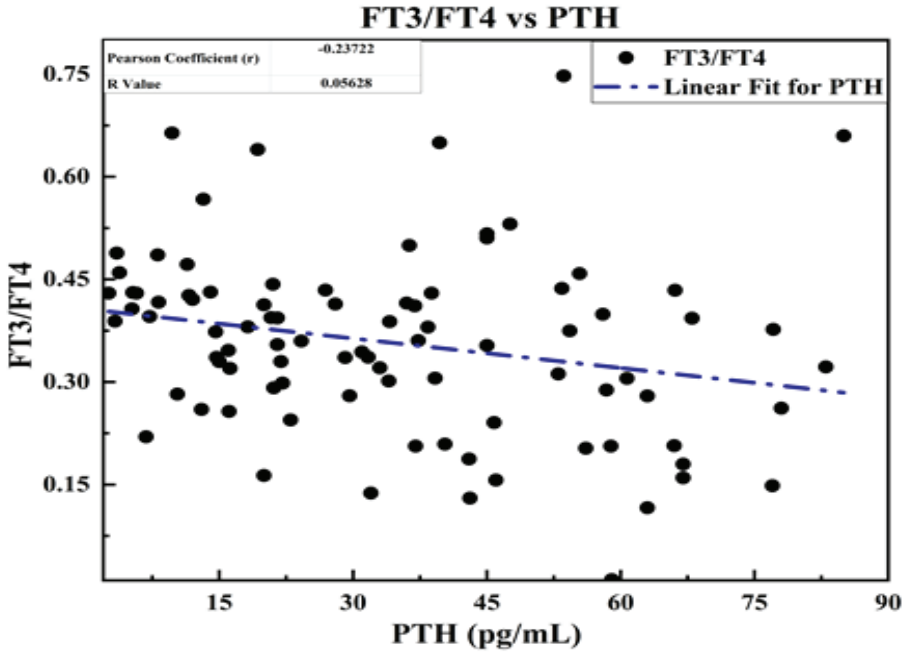

Figure 3: Relationship between FT3/FT4 ratio and parathyroid hormone (PTH) levels, showing a weak negative association

DISCUSSION

Present study highlighted a meaningful metabolic interaction between vitamin D status and the thyroid–parathyroid endocrine network. The most prominent observation was the strong positive association between serum 25(OH)D levels and the FT3/FT4 ratio ($r = +0.69$, $p < 0.001$). This finding supports the growing view that vitamin D may play an active role in regulating peripheral thyroid hormone activation rather than acting solely as a supportive micronutrient. Physiologically, the biologically active thyroid hormone T3 is primarily generated through enzymatic deiodination of T4 by iodothyronine deiodinases (11). Experimental evidence suggests that vitamin D may influence the expression and activity of these enzymes through genomic regulatory pathways (12). Within the context of our cohort, where the median vitamin D level was only 13.91 ng/mL, vitamin D deficiency appears to represent a metabolic constraint on this conversion process. The relatively high regression coefficient ($R^2 = 0.471$) indicates that vitamin D status alone accounted for nearly half of the variability in peripheral thyroid hormone activation in this population. Previous endocrine research has indicated that the interaction between vitamin D status and thyroid regulation may not always be strictly linear (13), with both severe deficiency and excessive levels potentially altering endocrine feedback dynamics. In the present study, however, a clear linear relationship was observed between serum 25(OH)D concentrations and the FT3/FT4 ratio. One possible explanation lies in the biochemical profile of the study population, where vitamin D deficiency was highly prevalent. Under such conditions, the data likely captures the rising phase of the physiological response curve rather than its full spectrum. Within this deficient range, gradual increases in vitamin D were consistently associated with improved peripheral conversion of T4 to T3, as reflected by the strong positive correlation identified in our analysis ($r = +0.69$, $p < 0.001$). These findings suggest that although a metabolic plateau may eventually occur once optimal vitamin D levels are reached, the predominant biological

response in a deficient population is the progressive restoration of thyroid hormone activation. The relationship between thyroid-stimulating hormone and hormone conversion efficiency also revealed important insights. Because serum TSH values showed wide dispersion and strong skewness, logarithmic transformation was applied prior to correlation analysis, a standard approach when evaluating endocrine relationships involving TSH. Following transformation, log TSH demonstrated a strong inverse correlation with FT3/FT4 ratio ($r = -0.64$, $p < 0.001$). This suggests that increasing thyroid axis stimulation is associated with progressively reduced peripheral activation of T4. The extremely broad distribution of TSH in this study (median 75.72 mIU/L; IQR 17.56–114.96 mIU/L) indicates that many participants were experiencing advanced thyroid dysfunction. In such states, the physiological buffering capacity of the thyroid axis may become overwhelmed, leading to a more direct and proportional decline in peripheral hormone activation as thyroid stress increases. In endocrine physiology, the relationship between TSH and circulating thyroid hormones is often described as non-linear (14) or logarithmic, reflecting the tight homeostatic regulation of the hypothalamic–pituitary–thyroid axis. In the present study, however, a significant inverse relationship was observed between log-transformed TSH and the FT3/FT4 ratio ($r = -0.64$, $p < 0.001$). One possible explanation for this finding may be related to the biochemical characteristics of the study population. The participants in this cohort exhibited markedly elevated TSH concentrations, with a median value of 75.72 mIU/L, indicating a substantial burden of overt thyroid dysfunction. Under such circumstances, the normal buffering capacity of the thyroid axis may become less effective, allowing a clearer association between increasing thyroid stimulation and reduced peripheral hormone activation to emerge. Another factor that may contribute to this observation is the potential influence of micronutrient status on thyroid hormone metabolism. Experimental and clinical studies have suggested that vitamin D may affect the expression of enzymes involved in thyroid hormone conversion. In the context of widespread vitamin D deficiency observed in this cohort, reduced efficiency of T4-to-T3 conversion may therefore contribute to the inverse association between log TSH and the FT3/FT4 ratio. In contrast to vitamin D and TSH, PTH demonstrated only a modest inverse relationship with FT3/FT4 ratio ($r = -0.23$, $p = 0.027$). Although statistically significant, the relatively low regression coefficient ($R^2 = 0.056$) suggests that PTH contributes only a limited proportion of the variability in thyroid hormone conversion. This finding indicates that while secondary hyperparathyroidism may accompany vitamin D deficiency, its direct influence on thyroid hormone activation is likely secondary compared with the effect of vitamin D itself. Taking together, these observations suggest that vitamin D deficiency may initiate a cascade of endocrine adjustments involving both the thyroid and parathyroid systems. However, the data indicates that the primary metabolic driver of impaired T4-to-T3 conversion appears to be vitamin D deficiency rather than PTH elevation alone.

CONCLUSION

This study found a significant association between vitamin D status and peripheral thyroid hormone activation in a cohort with marked thyroid dysfunction and widespread vitamin D deficiency. Serum 25(OH)D levels correlated positively with the FT3/FT4 ratio, indicating that lower vitamin D levels are related to less efficient T4-to-T3 conversion. Additionally, TSH levels had an inverse relationship with the FT3/FT4 ratio, suggesting that higher thyroid axis stimulation corresponds with reduced peripheral hormone activation. Although intact PTH levels were inversely correlated with the FT3/FT4 ratio, this relationship was modest, indicating a secondary role for PTH in this metabolic interaction. The findings support the notion that vitamin D status is important in thyroid hormone metabolism, particularly under combined endocrine stress, and suggest the value of assessing vitamin D alongside thyroid function in clinical evaluations. Future studies should explore causality and the effects of vitamin D supplementation on thyroid hormone conversion through longitudinal and interventional designs, as well as investigate deiodinase activity and VDR pathways to clarify mechanisms.

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