

# Vitamin D and the Pathogenesis of Primary Hypothyroidism

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## Abstract:

**Background:** Vitamin D deficiency is a risk factor for neuropsychiatric disorders and autoimmune diseases.

**Objectives:** This study aimed to investigate the relationship between vitamin D and the pathogenesis of primary hypothyroidism.

**Methods:** A case-control study was conducted at the Department of Biochemistry, College of Medicine, University of Baghdad, and Endocrinology and Diabetes Clinic. The study involved 81 patients aged 29-62 years, with 24 newly diagnosed hypothyroidism, 33 had established hypothyroidism, and 24 had subclinical hypothyroidism. The control group consisted of 40 healthy individuals aged 29-62 years. The study used the MAGLUMI® 800 analyzer Chemiluminescence Immunoassay System, which uses Acridinium Ester-based Immunoassay technology for high sensitivity and specificity (True Negative Rate). Thyroid peroxidase antibodies and 25-hydroxyvitamin D were also tested using the Enzyme-Linked Immunosorbent Assay technique.

**Results:** The results revealed that the median and 1<sup>st</sup> -3<sup>rd</sup> quartile range values of serum 25 hydroxyvitamin D levels of newly diagnosed, established, and subclinical primary hypothyroidism were significantly decreased compared to controls (for all,  $p < 0.0001$ ). However, there were non-significant differences between newly diagnosed and subclinical, newly diagnosed and established, and between subclinical and established. There was a significant negative correlation between 25-hydroxyvitamin D and thyroid stimulating hormone in newly diagnosed and significant positive correlation in subclinical. Also, there were significant positive correlations between 25-hydroxyvitamin D and freeT4 in established and subclinical.

**Conclusion:** Vitamin D deficiency may play an important role in the pathogenesis of primary hypothyroidism, whether it is a newly diagnosed, established, or subclinical one.

**Keywords:** 25(OH) D; Hypothyroidism; Immunoassay; Serum TSH; Subclinical.

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## Introduction

Hypothyroidism is an endocrine condition defined by reduced blood thyroxine levels, resulting in a clinical spectrum ranging from no signs and symptoms to life-threatening problems (1,2). The main circulating thyroid hormones are thyroxine (T4) and triiodothyronine (T3), along with their free forms, free T4 (fT4) and free T3 (fT3) (3). The intricate interplay of the hypothalamus, pituitary gland, and thyroid gland meticulously governs blood levels via a sophisticated negative feedback mechanism (4). In primary overt hypothyroidism, serum levels of free thyroxine (fT4) are typically low, while thyroid stimulating hormone (TSH) levels are correspondingly elevated (5). Additionally, subclinical hypothyroidism, a hidden illness with normal total T4 levels but slightly raised TSH, is included in the disease spectrum. According to the United States Population's National Health and

Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994, the total prevalence of hypothyroidism is 4.6%, with 0.3% having overt hypothyroidism and 4.3% having subclinical hypothyroidism (6). Hypothyroidism resulting from iodine deficiency is common in areas with iodine-deficient soil, particularly in hilly and mountainous regions. Conversely, in the iodine-sufficient areas, autoimmune etiology, specifically Hashimoto's thyroiditis, is predominant (7).

Vitamin D is a fat-soluble substance that is typically transformed in vivo to the active hormone calcitriol (1,25-dihydroxycholecalciferol) by two hydroxylation processes: first in the liver (producing calcidiol or 25-hydroxy vitamin D) and subsequently in the kidneys. The serum 25-hydroxyvitaminD level measurement assesses circulating vitamin D status. Vitamin D exists in two forms. Specifically, vitamin D2 and vitamin D3. Vitamin D2 is sourced from the plant sterol ergosterol, whereas vitamin D3 (cholecalciferol) is synthesized from cholesterol in the skin(8). Vitamin D is vital for maintaining healthy physiological systems, particularly the immune

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system. Additionally, it serves as a cancer prevention tool (9). Vitamin D deficiency is common in developed and developing nations, characterized by serum 25-hydroxyvitamin D levels below 25 nmol/l (10). The prevalence rate of vitamin D insufficiency in the US was 41.6%, with the greatest rates observed among Black individuals, followed by Hispanics (1). Bone health and the balance of calcium and phosphorus depend on vitamin D (11). Vitamin D is also important in many non-skeletal diseases for example coronary artery disease (12,13). Reports indicate that vitamin D deficiency may contribute to the risk of neuropsychiatric disorders and autoimmune diseases (14). Furthermore, vitamin D is recognized as a newly identified immunomodulatory hormone that regulates the immune system (15,16). Common thyroid diseases, including Hashimoto's thyroiditis (HT) and Graves' disease (GD), frequently involve autoimmune factors in their pathogenesis (17). Previous research indicates that the vitamin D receptor (VDR) is present in immune cells, influencing their proliferation and differentiation, which can lead to thyroid damage, and vitamin D is linked to thyroid function (18,19). The study designed to investigate the relationship between vitamin D and the pathogenesis of primary hypothyroidism.

### Patients and Methods

This case-control research was conducted in the Specialized Center for Endocrinology and Diabetes, Medical City, Baghdad, Iraq, by the Department of Biochemistry, College of Medicine, University of Baghdad, from April 2024 to August 2024. This study involved 81 patients, age range (29-62 years). Twenty-four of them (Group 1) were diagnosed to have new hypothyroidism (duration of disease within a week of the study inclusion and before starting thyroxine treatment), thirty-three had established hypothyroidism (Group 2; those patients who were already on thyroxine treatment), and twenty-four had subclinical hypothyroidism (Group 3), and 40 healthy subjects as controls were free from any acute and chronic illnesses (Group 4). The diagnosis of primary hypothyroidism was established using clinical examination, radiographic assessments, and thyroid function testing, including serum TSH, free tetraiodothyronine (fT4), free triiodothyronine (fT3), and anti-thyroid peroxidase (anti-TPO) to confirm Hashimoto's thyroiditis. Subclinical hypothyroidism diagnosis was based on findings of normal serum fT4 and elevated serum TSH. The age range of the patients and controls was 29-62 years. The ethical and scientific review boards of the College of Medicine and Department of Biochemistry approved this study. Additionally, the Ministry of Health in Iraq and the Specialized Center for Endocrinology and Diabetes at Medical City in Baghdad provided their ethical clearance. Participants verbally agreed before participating in this study. The exclusion criteria involved those patients who had diabetes mellitus, alcohol abuse, smoking, pregnancy, cardiovascular diseases, renal disease, secondary hypothyroidism, tumors, liver diseases, and any other acute or chronic

illness based on history, physical examination, and laboratory results.

The body mass index (BMI) of patients and controls was calculated by international equation:  $BMI (Kg/m^2) = Weight (Kg) / height (m^2)$ . Five milliliters (ml) of blood were obtained from the peripheral vein of each patient and control group, allowed to coagulate for 15 minutes, and subsequently centrifuged for 10 minutes at 2500 rpm. The isolated serum was preserved at -45° C until the day of laboratory analysis, which encompassed assessments of TSH, fT4, fT3, anti-TPO, and 25-hydroxyvitamin D. The thyroid function tests (TSH, fT4, fT3) were assayed enzymatically on a fully automated MAGLUMI® 800 analyzer Chemiluminescence Immunoassay (CLIA) System, United Kingdom. The principle of CLIA specifically utilizes an Acridinium Ester-based Immunoassay (ABEI) technology. Its high sensitivity and specificity characterize this method, making it suitable for various diagnostic tests (20). Measurements of 25 hydroxyvitamin D and Anti-TPO were achieved by using enzyme-linked immunosorbent assay (ELISA) Sandwich methods (Elabscience, USA). The principle of sandwich ELISA (Enzyme-Linked Immunosorbent Assay) involves using two antibodies that bind to distinct epitopes on the same antigen (21).

### Statistical Analysis

The obtained data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26 software, employing mean, standard deviation, median, and the interquartile range (Q1-Q3) for description. ANOVA is used to determine the difference in mean values of numerical data. Regarding the data that did not match the normality requirements necessary for parametric testing, the Kruskal-Wallis test, a non-parametric alternative to one-way ANOVA, was employed to compare the medians of the three. In cases where statistically significant differences were noted, the groups that differed were identified using a post hoc analysis test corrected for Bonferroni. The parameters' cutoff value, sensitivity, and specificity were determined for distinguishing between the three, hypothyroidism and control, groups. The receiver operator characteristic (ROC) and area under the curve (AUC) were also examined. It assessed the correlation between numeric data using Pearson correlation regression (r). The significance level was chosen at a (P) value less than 0.05.

### Results:

Table 1 showed the mean ( $\pm$ SD) values of age and body mass index (BMI) of the three studied groups (newly diagnosed primary HT, established primary HT, subclinical primary HT, and controls). The mean age and body mass index values did not differ significantly among and between these groups. We involved age and BMI in order to exclude the effects of them on vitamin D results in comparison among and between studied groups and therefore we matched them in group

**Table 1. Mean ( $\pm$ SD) values of age and body mass index in newly diagnosed primary hypothyroidism, established primary hypothyroidism and control groups**

Parameter	Control (n=40)	Newly diagnosed primary HT (n=24)	Established primary HT (n=33)	Subclinical primary HT (n=24)
Age (years) <sup>NS</sup>	41.93 $\pm$ 8.39	42.46 $\pm$ 11.03	45.79 $\pm$ 14.26	42.88 $\pm$ 13.19
Body mass index (Kg/m <sup>2</sup> )	27.61 $\pm$ 2.95	30.6 $\pm$ 4.29	30.23 $\pm$ 5.48 <sup>NS</sup>	29.62 $\pm$ 5.02 <sup>NS</sup>

ANOVA and *t*-tests were revealed. NS: non-significant difference among groups and between groups,

Table 2 showed the median and 1<sup>st</sup> -3<sup>rd</sup> quartile range (Q1-Q3) values of the four studied groups' serum TSH, fT4, fT3, and anti-TPO levels. The median value of serum TSH was significantly increased in newly diagnosed, established, and subclinical primary HT groups compared to controls ( $p < 0.001$ ). Also, the median serum TSH of newly diagnosed primary HT was significantly higher than that of established and subclinical primary HT ( $P < 0.0001$ ). Meanwhile, the median values of fT3 levels did not differ significantly among or between the four groups. However, the median values of fT4 were

significantly decreased in newly diagnosed primary HT compared to controls, established, and subclinical primary HT (for all,  $P = 0.001$ ), with a non-significant difference between controls and established primary HT. The median value of anti-TPO levels was significantly higher in established and subclinical primary HT than in controls ( $P = 0.019$ ) but without significant difference between newly diagnosed primary HT and controls as well as among and between newly diagnosed, established and subclinical primary HT.

**Table (2): Median (1<sup>st</sup> -3<sup>rd</sup> quartile range) values of TSH, fT3, fT4, and anti-TPO levels in newly diagnosed primary hypothyroidism, established primary hypothyroidism, subclinical primary hypothyroidism and control groups**

Control (n=40)	Newly diagnosed primary HT (n=24)	Established primary HT (n=33)	Subclinical primary HT (n=24)
2.21 (1.41-2.67)	22.07*** (18.4-63.01)	6.00* (3.18-14.6)	6.59* (5.7-6.96)
2.79 (2.4-3)	2.66 (2.38-2.82)	2.85 (2.67-3.08)	2.86 (2.63-3.13)
1.08 (1.05-1.15)	0.6* (0.54-0.64)	1.07 <sup>NS</sup> (1.05-1.13)	1.08 <sup>NS</sup> (1.06-1.21)
17.33 (15.73-18.02)	18.75 <sup>NS</sup> (17.15-23.71)	19.03* (16.01-21.21)	19.63* (16.09-26.33)

Kruskal-Wallis and Bonferroni-adjusted Mann-Whitney post-hoc analysis test revealed ●significant increase in TSH in newly diagnosed, subclinical, and established HT than in controls (for all,  $P = 0.001$ ), ●●● significant increase in TSH in newly diagnosed than in established and subclinical HT ( $P = 0.001$ ), ◆significant decrease in fT4 in newly diagnosed than in controls, subclinical and established HT ( $P = 0.001$ ), ◆significant increase in anti-TPO in established and subclinical HT than in controls ( $P = 0.019$ ), NS: non-significant differences in fT3 among and between groups, in fT4 between established HT and controls and between subclinical HT and controls, in anti-TPO between newly diagnosed HT and each of controls, established and subclinical HT.

Table 3 reveals the median and (Q1-Q3) values of serum vitamin D3 of the four studied groups. The median values of vitamin D3 levels of newly diagnosed, established, and subclinical primary HT were significantly decreased compared to controls

(for all,  $P < 0.0001$ ). However, there were non-significant differences between newly diagnosed primary HT and subclinical HT, newly diagnosed HT and established HT, and between subclinical HT and established HT.

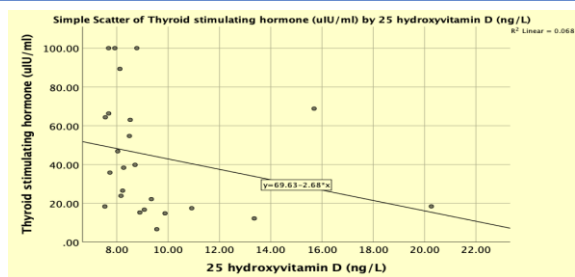
**Table (3): Median (1<sup>st</sup> -3<sup>rd</sup> quartile range) values 25 hydroxyvitamin D3 in newly diagnosed primary hypothyroidism, established primary hypothyroidism, subclinical primary hypothyroidism, and control groups**

Parameter	Control (n=40)	Newly diagnosed primary HT (n=24)	Established primary HT (n=33)	subclinical primary HT (n=24)
25 hydroxyvitamin D (ng/L)	15.41 (13.44-18.29)	8.51* <sup>NS</sup> (8.12-9.07)	8.79* (8.2-10.18)	8.52* (8.28-8.97)

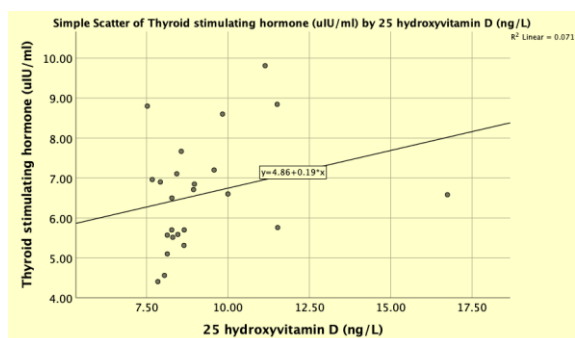
Kruskal-Wallis and Bonferroni-adjusted Mann-Whitney post hoc analysis test revealed ◆significant decrease in 25 hydroxyvitamin D3 in newly diagnosed, established, and subclinical HT than in controls (for all,  $p = 0.001$ ). NS: non-significant differences among and between HT groups in 25 hydroxyvitamin D.

There was a significant negative correlation between 25-hydroxyvitamin D and TSH in newly diagnosed primary HT ( $r = -0.507$ ,  $P = 0.012$ , Figure 1) and significant positive correlation in subclinical primary HT ( $r = 0.416$ ,  $P = 0.039$ , Figure 2). Also, there were significant positive correlations between 25-hydroxyvitamin D and fT4 in established primary HT

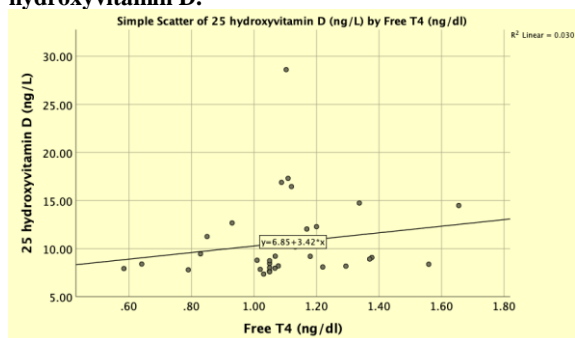
( $r = 0.384$ ,  $P = 0.027$ , Figure 3) and subclinical primary HT ( $r = 0.488$ ,  $P = 0.013$ ).



**Figure (1): Scatter plot illustrating the association between thyroid-stimulating hormone and 25-hydroxyvitamin D.**



**Figure (2): scatter plot illustrating the association between thyroid-stimulating hormone and 25-hydroxyvitamin D.**



**Figure (3): scatter blot demonstrating a relationship between 25 hydroxyvitamin D and Free T4**

The results revealed that receiver operating characteristic (ROC) and area under the curve (AUC=0.934) for 25-hydroxyvitamin D levels between newly diagnosed primary HT and controls with confidence interval 0.86-1.0 (sensitivity=87.5, specificity=85) at cutoff value (12 ng/L). Also, the AUC = 0.88 for 25-hydroxyvitamin D levels between established primary HT and controls with confidence interval 0.799 -0.964 (sensitivity= 72.7, specificity=87.5) at cutoff value (12 ng/L). Similarly, the AUC= 0.969 for 25-hydroxyvitamin D levels between subclinical primary HT and controls with a confidence interval of 0.921- 1.00(sensitivity= 95.8, specificity=87.5) at cutoff value (12 ng/ L unit), as shown in Table 4.

**Table (4): Statistical analysis of area receiver operating curve of 25-hydroxyvitamin D between hypothyroidism groups and healthy control**

	Area	Sensitivity	Specificity	cutoff	Asymptotic 95% Confidence Interval		
					Lower Bound	Upper Bound	Bound
Newly diagnosed primary HT and controls	0.934	87.5	85	12	0.860	1.00	
Established primary HT and controls	0.88	72.7	87.5	12	0.799	0.964	
subclinical primary HT and controls	0.969	95.8	87.5	12	0.921	1.00	

## Discussion

There was no significant difference in age and BMI among the studied groups: established HT, subclinical HT, newly diagnosed HT, and control groups. Thus, the effect of these two demographic parameters was excluded on the 25OHVD results. The results of thyroid gland hormones, including TSH, T3, T4, and anti-TPO (table 2), were aligned with diagnosing each subtype of primary hypothyroidism (22). The present study found a significant decrease in serum 25OHVD in all studied groups (established, newly diagnosed, and subclinical) of primary hypothyroidism. The results of the current study agreed with Fang *et al.* (23) Shaji *et al.* (24), and Sulejmanovic *et al.* (25). Vitamin D plays a crucial role in maintaining bone and mineral balance. Recent studies indicate that a deficiency in this vitamin is linked to a range of health issues, including cardiovascular disease, cancer, infections, obesity, and osteoporosis (19). Limited research has been undertaken to establish a substantial correlation between 25OHVD levels and hypothyroidism, as well as to ascertain if 25OHVD insufficiency contributes to the etiology of hypothyroidism or is only a result of the condition. Interpretation of the low levels of 25OHVD in patients with hypothyroidism by two mechanisms. First, 25OHVD is critical in modulating the immune system, particularly in suppressing autoimmune responses. In autoimmune hypothyroidism (e.g., Hashimoto's thyroiditis), low 25OHVD levels may impair immune tolerance, leading to increased production of thyroid autoantibodies(1,26). Secondly, it may result from inadequate absorption of 25OHVD in the gut (27). Also, Thyroid hormones are required to activate hepatic 25-hydroxylase, which converts vitamin D3 to 25OHVD. Dysregulated thyroid function could thus impede this process (24). The present findings revealed a substantial negative connection between 25OHVD and TSH in newly diagnosed primary Hypothyroidism and subclinical primary Hypothyroidism. This increase in TSH levels with a



fall in 25OHVD observed in the present study agreed with a study done by Zhang et al (28) on Chinese population where they found that high 25OHVD status was associated with low levels of TSH irrespective of thyroid hormones status. Also, there were significant positive correlations between 25OHVD and fT4 in established primary HT ( $r=0.384$ ,  $0.027$ ), and subclinical primary HT ( $r=0.488$ ,  $p=0.013$ ). The result of this study agreed with Chao et al (29), Fang et al. (21), and Donayeva et al (30). Thyroid hormones exert biological effects by binding to thyroid receptors, including vitamin D receptors (VDR). Vitamin D regulates thyroid hormone levels in the body (31).

### Conclusions

Vitamin D deficiency may play an important role in the pathogenesis of primary hypothyroidism, whether it was a newly diagnosed, established, or subclinical one.

### Authors' declaration

We confirm that all Figures and Tables in the manuscript are pertinent to the present study. Authors confirm the approval of ethical considerations - Ethical Clearance: The local ethical committee approved the project in the location where the research was conducted or samples were collected, as indicated by the code number (448) on (29/ 1/ 2025).

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### Authors' contributions

Study conception & design: (Basil O. Saleh, Omar F. Al-Azzawi & Abbas S. Jebur). Literature search: (Abbas S. Jebur). Data acquisition: (Abbas S. Jebur, Omar F. Al-Azzawi). Data analysis & interpretation: (Basil O. Saleh, Abbas S. Jebur, Omar F. Al-Azzawi). Manuscript preparation: (Abbas S. Jebur, Basil O. Saleh, Omar F. Al-Azzawi). Manuscript editing & review: (Basil O. Saleh, Omar F. Al-Azzawi, Abbas S. Jebur).

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## العلاقة بين فيتامين د وتكوين مرض قصور الغدة الدرقية الأولي

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### الخلاصة:

**خلفية البحث:** نقص فيتامين د هو عامل خطر للاضطرابات العصبية والنفسية وأمراض المناعة الذاتية.

**الاهداف:** صُممت هذه الدراسة لدراسة العلاقة بين فيتامين د ومرض قصور الغدة الدرقية الأولي.

**المرضى وطرائق العمل:** أجريت دراسة الحالات والشواهد في قسم الكيمياء الحيوية بكلية الطب بجامعة بغداد وعيادة الغدد الصماء والسكري. شملت الدراسة 81 مريضاً تتراوح أعمارهم بين 29 و 62 عاماً، منهم 24 مصاباً بقصور الغدة الدرقية حديث التشخيص، و 33 مصاباً بقصور الغدة الدرقية الصريح، و 24 مصاباً بقصور الغدة الدرقية دون السريري. تتكون المجموعة الضابطة من 40 فرداً سليماً تتراوح أعمارهم بين 29 و 62 عاماً. استخدمت الدراسة نظام التحليل المناعي الكيميائي الضوئي (CLIA) MAGLUMI® 800، والذي يستخدم تقنية التحليل المناعي القائم على إستر الأكرينيوم (ABEI) للحساسية العالية والخصوصية.

**النتائج:** وجدت الدراسة أن مستويات فيتامين د3 انخفضت بشكل ملحوظ في مرضى قصور الغدة الدرقية الأولي الذين تم تشخيصهم حديثاً والمثبت وغير السريري مقارنةً بالأصحاء. كان هناك ارتباط سلبي كبير بين 25-هيدروكسي فيتامين د TSH في قصور الغدة الدرقية الأولي المكتشف حديثاً وقصور الغدة الدرقية الأولي دون السريري. أيضاً، كانت هناك ارتباطات إيجابية كبيرة بين 25-هيدروكسي فيتامين د و fT4 في قصور الغدة الدرقية الأولي المثبت وقصور الغدة الدرقية الأولي دون السريري.

**الاستنتاجات:** تم توثيق مستويات فيتامين د المنخفضة بشكل ملحوظ في المرضى الذين يعانون من قصور الغدة الدرقية الأولي. ترافقت الأجسام المضادة للغدة الدرقية ووظائف الغدة الدرقية غير الطبيعية مع نقص فيتامين د.

**الكلمات المفتاحية:** (OH) D25، التحليل المناعي، تحت سريري، قصور الغدة الدرقية، هرمون تحفيز الغدة الدرقية في المصل.