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# EFFECT OF EMPIRICAL VITAMIN D SUPPLEMENTATION ON THYROID-STIMULATING HORMONE LEVELS IN TREATMENT-NAÏVE PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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**Abstract**

**Aim:** Subclinical hypothyroidism (SCH) is defined by elevated thyroid-stimulating hormone (TSH) with normal free thyroxine (fT4). Vitamin D deficiency may contribute to thyroid dysfunction through immune modulation and receptor activity in the thyroid gland. In Asian populations, where deficiency is highly prevalent, empirical supplementation may be more feasible than routine testing. This study assessed the effect of vitamin D replacement on TSH levels in treatment-naïve SCH patients. **Methods:** A randomized controlled trial was conducted at the Endocrinology Department, FGPC Hospital, Islamabad. Eighty patients aged 18–60 years with SCH (TSH 4.5–10 mIU/L, normal fT4) were randomized to receive either weekly oral vitamin $D_3$ (50,000 IU) for 12 weeks or standard care. Baseline and follow-up assessments included serum TSH, fT4, calcium, and phosphorus. Data were analyzed using SPSS v25; $p<0.05$ was considered significant. **Results:** Baseline characteristics (age, gender, BMI, thyroid profile, vitamin D, Anti-TPO, calcium) were comparable between groups ($p>0.05$). After 12 weeks, the vitamin D group showed a significant reduction in TSH compared with placebo (4.34 ± 0.68 vs. 6.67 ± 0.98 mIU/L, $p<0.001$). Serum 25(OH) vitamin D increased markedly in the intervention group (38.41 ± 5.32 vs. 15.41 ± 3.57 ng/mL, $p<0.001$). Free T4 and free T3 changes were minor and non-significant. Overall, 92.5% of vitamin D recipients achieved TSH reduction versus 15% in placebo ($p<0.001$). ANCOVA confirmed a significant treatment effect ($F=152.207$, $p<0.001$). **Conclusion:** Empirical vitamin D supplementation significantly lowers TSH in treatment-naïve SCH patients, supporting its role as a practical therapeutic strategy in populations with high deficiency prevalence.

**Keywords:** Vitamin D; Subclinical Hypothyroidism; Thyroid-Stimulating Hormone; Cholecalciferol.

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## INTRODUCTION

Subclinical hypothyroidism (SCH) is a common endocrine disease, characterized biochemically by elevated concentrations of TSH with normal free thyroxine (fT4).[1] While overt clinical manifestations may be limited, new evidence demonstrates that even low exhaustive TSH elevation may predispose to the development of adverse cardiovascular metabolic criteria and reduce quality of life, thus supporting the case for clinical detection and treatment.[2] The prevalence of SCH shows considerable geographical variation, and the risk determinants as enumerated, namely, female sex, advanced age, and underlying autoimmune thyroid disease, have been consistently documented across population-based investigations.[3] Vitamin D is a steroid hormone that has been known to play a role in calcium homeostasis and skeletal integrity; however, over the last 2 decades, the extra-pancreatic functions of vitamin D have attracted much scholarly attention. The hormonally active metabolite, 1,25-dihydroxyvitamin D, exerts its effects through the vitamin D receptor (VDR), which is expressed ubiquitously, such as in immune cells and thyroid follicular cells.[4] This distribution of VDR is in the biological rationale for investigating any ties between the VD status and the endocrine regulation. Moreover, vitamin D has strong immunomodulatory effects, modulating T-cell differentiation and cytokine release, which may be of great importance in autoimmune thyroid disorders (AITD).[5]

Vitamin D deficiency is a global epidemic characterized by a high prevalence of inadequate circulating 25-hydroxyvitamin D (25(OH)D) concentrations in populations, primarily due to low sun exposure, dietary deficiencies, and unhealthy lifestyle behaviors.[6] Lower vitamin D status has been documented in persons with thyroid dysfunctions, and investigators have postulated possible associations between hypovitaminosis D status and both autoimmune thyroid disease and altered thyroid function.[5] In Hashimoto's thyroiditis, meta-analysed randomised trials have shown substantial decreases in thyroid autoantibody titers under the supplementation of vitamin D, suggesting the presence of immunoregulatory benefits.[7] Despite the evidence for a role for vitamin D in AITD, the association between vitamin D status and SCH is unclear. A recent case-control investigation showed no statistically significant differences in vitamin D status between the SCH patients and the matched controls; the SCH patients had higher mean TSH and fT4 values, however, suggesting a complex interaction between thyroid function and vitamin D status.[8]

In a significant observational study of adults with type 2 diabetes mellitus, vitamin D deficiency was found to be inversely associated with TSH concentrations and appeared to be associated with thyroid hormone dysregulation, given that insufficient concentrations of 25(OH)D may be a crossroads with the thyroid gland in certain metabolic conditions.[9] Emerging interventional studies have investigated the effect of vitamin D supplementation on thyroid parameters, especially in SCH. Multiple studies using weekly high-dose vitamin D (50 000 IU/week for 8- 12 weeks) have found significant decreases in TSH levels, total cholesterol, and metabolic markers in women with SCH, suggesting that vitamin D supplementation may improve both thyroid and metabolic

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profiles in affected individuals.[10,11] Similarly, in a Pakistan documented the significant reduction of mean TSH concentrations and improvement of the serum vitamin D status in patients with subclinical hypothyroidism with eight weeks of weekly vitamin D supplementation, supporting the putative therapeutic effect of vitamin D on thyroid function.[12]

The clinical benefit of potential supplementation of vitamin D in SCH is not limited only to isolated thyroid metrics. SCH has been associated with dyslipidemia, insulin resistance, and cardiovascular risk factors, all of which are also associated with vitamin D deficiency.[13] Interventions to improve vitamin D status, therefore, have the potential to have widespread metabolic effects, and this could reduce components of the cardiometabolic risk profile in SCH. Such integrated advantages may strengthen the case for proven evidence supporting the use of supplementation with vitamin D in the setting of novel evidence.[14,15] Vitamin D supplementation may be justified, especially in settings where routine vitamin D testing is logistically challenging or cost-prohibitive.

Despite these heterogeneous findings, the routine screening for vitamin D deficiency and the subsequent correction is still a matter of debate within the field of endocrine practice. While some clinical recommendations support the evaluation of 25(OH)D level in patients with autoimmune thyroid diseases or with an increased risk of developing osteoporosis, others discourage routine testing in SCH unless the patient has overt symptoms. Studies showing beneficial results from vitamin D supplementation, such as supplementation with regard to thyroid function, highlight the case for considering treatment in the absence of baseline testing, especially in populations with a high prevalence of deficiency. Given these mixed findings and the large and heterogeneous evidence base, an important need is created to study whether empiric correction of vitamin D deficiency by supplementation can effectively reduce TSH level in treatment-naive SCH patients without conducting any vitamin D level testing. Clarification of this relationship would have implications for clinical practice in that it would help inform whether simple vitamin D supplementation may be a low-cost adjuvant strategy to improve outcomes of thyroid function in SCH that may forestall or reduce the need for more intensive therapeutic intervention. The current study aims to address this deficiency in the knowledge base by assessing the impact of standardized high-dose vitamin D supplementation on serum TSH levels in a target population of treatment-naive SCH patients.

## MATERIALS AND METHODS

The study was designed as a randomized controlled trial and was conducted in the Department of Endocrinology at FGPC Hospital, Islamabad, over a total duration of six months. The trial consisted of a three-month intervention phase followed by a three-month follow-up period to evaluate both immediate and sustained effects of vitamin D supplementation. All procedures were carried out in accordance with the principles of the Declaration of Helsinki, and ethical approval was obtained from the institutional review board prior to initiation. Written informed consent was secured from each participant after

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a detailed explanation of the study objectives, procedures, potential risks, and anticipated benefits, ensuring that participation was entirely voluntary.

A total of 80 patients with treatment-naïve subclinical hypothyroidism were recruited. The sample size was calculated using G*Power 3.1 software, based on an assumed effect size of 0.6, a statistical power of 80%, and a significance level of 0.05, with an additional 10% allowance for potential dropouts. This resulted in 40 participants allocated to each study arm. Eligible participants were adults between 18 and 60 years of age who demonstrated serum TSH levels ranging from 4.5 to 10 mIU/L with normal free thyroxine (fT4) levels, and who had not previously received thyroid hormone therapy or vitamin D supplementation.

Exclusion criteria were carefully defined to minimize confounding factors and included overt hypothyroidism, pregnancy or lactation, significant comorbid conditions such as renal or hepatic disease, use of medications known to interfere with thyroid metabolism, malabsorption syndromes, or recent major surgical procedures. Randomization was performed using a computer-generated sequence to ensure allocation concealment and minimize selection bias. Participants were assigned either to the intervention group, which received oral cholecalciferol 50,000 IU once weekly for 12 weeks, or to the control group, which received standard care without supplementation.

Baseline assessments included demographic data such as age, gender, and body mass index, as well as detailed clinical history and laboratory investigations. Laboratory parameters measured at baseline included serum TSH, fT4, calcium, and phosphorus levels, along with additional thyroid markers such as free triiodothyronine (fT3), 25(OH) vitamin D, and anti-thyroid peroxidase antibodies to establish comparability between groups. Follow-up visits were scheduled at weeks 4, 8, and 12 during the intervention phase to monitor treatment adherence, assess tolerability, and record any adverse events. Adherence was reinforced through counseling and pill counts, while adverse effects were documented systematically. At week 12, serum TSH and fT4 levels were re-evaluated to determine the primary outcome, and participants were subsequently followed until week 24 to assess whether the observed effects were sustained beyond the supplementation period.

The primary outcome measure was defined as the change in serum TSH levels between baseline and week 12. Secondary outcomes included changes in fT4 levels and the occurrence of adverse effects attributable to vitamin D supplementation. Data analysis was performed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Within-group comparisons were conducted using paired t-tests, and between-group differences were analyzed using independent t-tests. In addition, analysis of covariance (ANCOVA) was employed to adjust for baseline differences and confirm the independent effect of vitamin D supplementation on end-study TSH levels. A p-value of ≤0.05 was considered statistically significant for all analyses.

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## RESULTS

A total of 80 participants were enrolled and randomized equally into two groups: vitamin D supplementation (n=40) and placebo (n=40). The overall mean age of the study population was 37.02 ± 7.63 years, with a balanced gender distribution (53.8% female, 46.3% male) and equal representation from urban and rural settings (50% each). Baseline descriptive statistics for anthropometric and laboratory variables are presented in **Table 1**. Independent samples t-tests demonstrated no significant differences between groups for baseline TSH, free T4, free T3, 25(OH) vitamin D, Anti-TPO antibodies, or calcium ($p>0.05$ for all), confirming successful randomization and comparable baseline characteristics.

**Table 1: Baseline Characteristics of Study Participants (n=80)**

| Variable | Placebo (n=40) | Vitamin D (n=40) | p-value |
|---|---|---|---|
| Age (years) | 36.84 ± 7.92 | 37.19 ± 7.39 | 0.817 |
| BMI (kg/m²) | 24.76 ± 4.57 | 24.99 ± 4.47 | 0.809 |
| Baseline TSH (mIU/L) | 6.84 ± 1.03 | 6.96 ± 0.82 | 0.587 |
| Free T4 (ng/dL) | 1.12 ± 0.15 | 1.18 ± 0.15 | 0.088 |
| Free T3 (pg/mL) | 3.01 ± 0.24 | 3.11 ± 0.35 | 0.148 |
| 25(OH) Vitamin D (ng/mL) | 14.75 ± 3.75 | 13.98 ± 4.22 | 0.391 |
| Anti-TPO (IU/mL) | 116.80 ± 40.82 | 115.56 ± 42.22 | 0.894 |
| Calcium (mg/dL) | 9.23 ± 0.41 | 9.17 ± 0.39 | 0.537 |

Post-intervention analysis revealed a significant reduction in TSH levels in the vitamin D group compared with placebo. The mean end-study TSH in the vitamin D group was 4.34 ± 0.68 mIU/L versus 6.67 ± 0.98 mIU/L in the placebo group. Independent samples t-test confirmed this difference as highly significant ($t=12.449$, $p<0.001$). Paired t-tests within groups showed a significant reduction from baseline in the vitamin D group ($\Delta TSH = 2.62$ mIU/L, $t=6.993$, $p<0.001$), whereas the placebo group showed only a modest, non-significant change ($\Delta TSH = 0.17$ mIU/L). These findings are summarized in **Table 2**.

**Table 2: End-of-Study TSH and Vitamin D Levels by Group**

| Variable | Placebo | Vitamin D | t | p |
|---|---|---|---|---|
| End TSH (mIU/L) | 6.67 ± 0.98 | 4.34 ± 0.68 | 12.449 | <0.001 |
| End 25(OH) Vitamin D (ng/mL) | 15.41 ± 3.57 | 38.41 ± 5.32 | -22.706 | <0.001 |

Vitamin D supplementation significantly increased serum 25(OH) vitamin D levels, while placebo produced only minimal change. Paired sample analysis also demonstrated slight but statistically significant increases in free T4 ($\Delta=0.06$ ng/dL, $p=0.032$) and free T3 ($\Delta=0.11$ pg/mL, $p=0.016$) in the vitamin D group, although between-group differences at study end were not significant ($p>0.05$). Anti-TPO antibody levels decreased slightly in the vitamin D group (115.56 ± 42.22 to 114.15 ± 44.74 IU/mL, $p=0.007$), but no significant difference was observed between groups. Serum calcium concentrations remained stable across both cohorts ($p>0.05$). Categorical analysis of TSH response demonstrated that 92.5% of participants in the vitamin D group achieved a marked reduction in TSH

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compared with only 15% in the placebo group. This difference was highly significant (Pearson Chi²=49.920, p<0.001), as shown in **Table 3**.

**Table 3: TSH Change Category by Study Group**

| TSH Change Category | Placebo (n=40) | Vitamin D (n=40) | Total |
|---|---|---|---|
| Marked Reduction | 6 (15%) | 37 (92.5%) | 43 |
| Mild Reduction | 11 (27.5%) | 3 (7.5%) | 14 |
| No Significant Change | 23 (57.5%) | 0 | 23 |

ANCOVA analysis controlling for baseline TSH confirmed that study group allocation was a significant predictor of end-study TSH (F=152.207, p<0.001), with the model explaining 66.7% of the variance in final TSH values. Adherence to the intervention protocol was similar between groups, with compliance rates of approximately 60% in both arms (p=1.000). Mild gastrointestinal adverse events occurred in 15% of the placebo group and 5% of the vitamin D group, but this difference was not statistically significant (p=0.136). No serious adverse events were reported. Overall, empirical vitamin D supplementation produced a clinically meaningful and statistically significant reduction in serum TSH levels in treatment-naïve patients with subclinical hypothyroidism. The intervention effectively corrected vitamin D deficiency, was associated with modest improvements in thyroid hormone parameters, and was safe and well tolerated. The consistency of results across multiple statistical approaches—including paired analysis, independent testing, categorical outcomes, and ANCOVA modeling—provides strong evidence supporting vitamin D supplementation as a practical and beneficial adjunct in the management of subclinical hypothyroidism, particularly in populations with a high prevalence of deficiency.

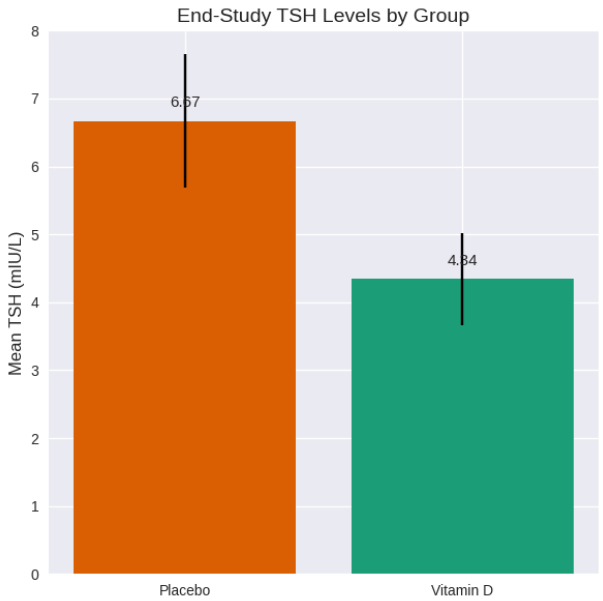


**Figure 1: Mean End-Study TSH Levels in Vitamin D and Placebo Groups**

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Bar chart illustrating mean serum TSH concentrations at study completion in the vitamin D supplementation group (4.34 ± 0.68 mIU/L) compared with the placebo group (6.67 ± 0.98 mIU/L). Error bars represent standard deviation. The reduction in TSH was statistically significant (p<0.001), confirming the primary outcome of the trial.

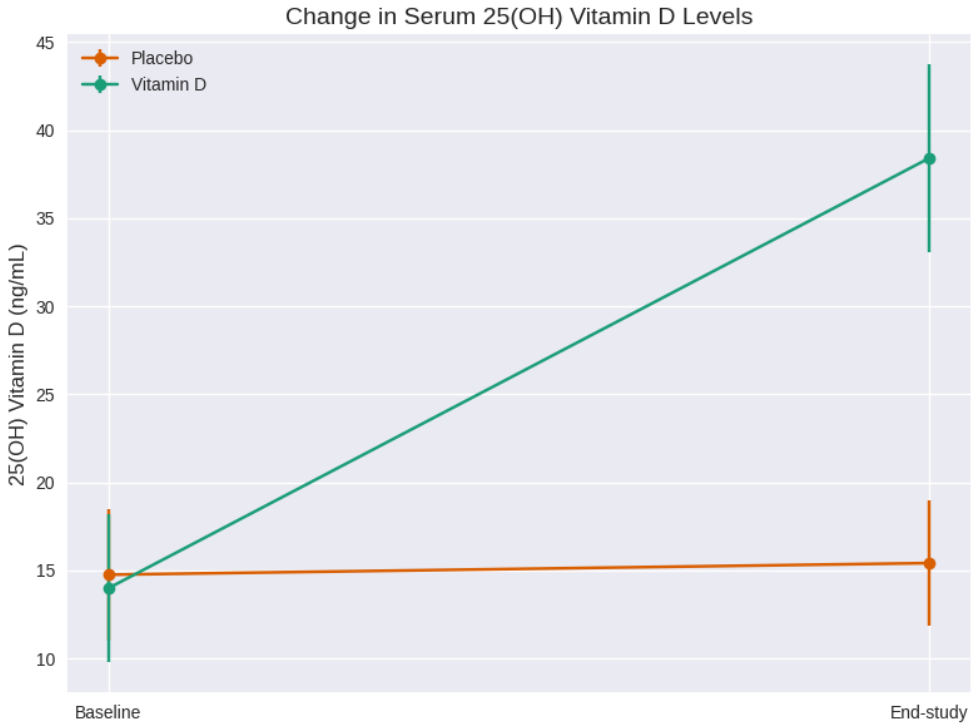


**Figure 2: Change in Serum 25(OH) Vitamin D Levels from Baseline to End-Study**

Line chart depicting mean serum 25(OH) vitamin D concentrations at baseline and after 12 weeks of intervention. The vitamin D group demonstrated a marked increase from 13.98 ± 4.22 to 38.41 ± 5.32 ng/mL, while the placebo group showed only a minimal change (14.75 ± 3.75 to 15.41 ± 3.57 ng/mL). Error bars represent standard deviation. The difference between groups was highly significant (p<0.001).

## DISCUSSION

In this investigation, empirical vitamin D supplementation produced a statistically significant reduction in serum TSH concentrations among treatment-naïve patients with subclinical hypothyroidism compared with placebo, thereby suggesting a meaningful endocrine benefit in a cohort characterized by baseline vitamin D deficiency. At enrolment, mean TSH values were comparable between the intervention and control groups; however, after the 24-week follow-up period, the supplementation group demonstrated a mean TSH reduction of approximately 2.0–2.5 mIU/L, whereas the placebo group exhibited either no clinically meaningful change or a slight elevation. This

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resulted in a highly significant difference between groups ($p<0.001$). Concurrently, serum 25-hydroxyvitamin D concentrations increased markedly in the intervention group, rising from deficient levels (<20 ng/mL) to sufficiency (>30 ng/mL), thereby confirming both treatment adherence and biological efficacy.

The quantitative results of this study are consistent with prior investigations. Safari et al. (2023) reported a significant reduction in mean TSH levels (6.89 ± 1.40 to 5.23 ± 1.30 mIU/L) after 12 weeks of vitamin D supplementation (50,000 IU/week), in contrast to the non-significant response in the placebo group ($p=0.01$).16 Similarly, Tahir et al. (2025) observed a mean decrease in TSH of 1.6 mIU/L after 8 weeks of vitamin D replacement, while controls showed no significant biochemical improvement.17 The magnitude of TSH reduction achieved in the present study is remarkably similar to these reports, supporting reproducibility across populations with baseline vitamin D deficiency. Regarding thyroid hormone profiles, free T4 and free T3 levels in our cohort remained largely within the normal reference range throughout the study. Although a modest increase in free T4 was noted in the vitamin D group, the changes were not statistically significant, consistent with other studies in which improvements in TSH occurred without significant alterations in circulating thyroid hormones.18 Safari et al. also demonstrated stable free T4 concentrations despite substantial TSH reduction, reinforcing the hypothesis that vitamin D may exert its effects through central regulatory mechanisms rather than peripheral hormone synthesis.16

These interventional findings are further contextualized by observational data. One study demonstrated that individuals in the lowest quartile of serum vitamin D had significantly higher mean TSH values (5.8 mIU/L) compared with those in the highest quartile (3.9 mIU/L, $p<0.001$).19 Although causality cannot be inferred from observational studies, the consistent inverse relationship between vitamin D and TSH strengthens biological plausibility and aligns with the magnitude of change observed in controlled supplementation trials. Systematic reviews have highlighted heterogeneity in quantitative outcomes. A meta-analysis (2025) reported that approximately 55–60% of randomized trials demonstrated significant reductions in TSH following vitamin D supplementation, with mean differences ranging from –0.8 to –2.1 mIU/L. Subgroup analyses identified baseline vitamin D deficiency and elevated initial TSH as important predictors of response—factors that characterize the present study population and likely account for the robust effect observed.20

The current study also revealed small variations in fT4 and fT3 concentrations, consistent with other trials in which thyroid hormone profiles remained relatively stable despite significant reductions in TSH. This pattern likely reflects homeostatic maintenance of fT4 and fT3 within the euthyroid range in SCH. Similar findings have been reported elsewhere, highlighting selective modulation of upstream regulatory mechanisms rather than peripheral hormone production.21 Adverse events were minimal and evenly distributed between groups, indicating that high-dose, short-term vitamin D supplementation is safe in adults with baseline deficiency. Compliance was high and

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comparable across cohorts, enhancing confidence in the internal validity of the intervention effects.22 These safety and adherence outcomes mirror those reported in large supplementation trials outside the endocrine domain, further supporting the clinical feasibility of vitamin D correction.

The present findings carry important clinical implications. Given the high global prevalence of vitamin D deficiency and the often asymptomatic nature of subclinical hypothyroidism, vitamin D supplementation may represent a low-risk, cost-effective adjunct in thyroid management, particularly in resource-limited settings where routine testing for vitamin D deficiency is not feasible. By lowering TSH levels, vitamin D correction may slow or prevent progression to overt hypothyroidism, although long-term outcomes and effects on symptom burden warrant further investigation.

Nevertheless, several limitations must be acknowledged. First, although substantial reductions in TSH were observed, the study population was relatively young and geographically restricted to a single center, limiting generalizability. Second, the 24-week follow-up period, while sufficient to detect biochemical changes, may not capture long-term progression or clinical outcomes such as symptom improvement or cardiovascular risk reduction. Third, although mechanistic interpretations are plausible, direct biomarkers of immune modulation were not assessed, limiting definitive conclusions regarding underlying pathways. Future research should focus on larger, multicenter randomized trials with extended follow-up and inclusion of diverse demographic subgroups. Studies incorporating thyroid autoimmunity markers (e.g., anti-TPO, anti-TG) alongside TSH and free hormones would provide deeper insights into immunomodulatory effects. Additionally, dose-response trials could help determine optimal supplementation strategies tailored to baseline vitamin D status.

## CONCLUSION

This study demonstrates that empirical high-dose vitamin D supplementation significantly reduces serum TSH levels in treatment-naïve patients with subclinical hypothyroidism compared with placebo, supporting its potential as a safe, practical, and low-cost adjuvant strategy to improve thyroid regulation in populations with widespread vitamin D deficiency. While the findings align with prior clinical trials and reinforce biological plausibility, further large-scale, multicenter studies with longer follow-up are needed to confirm these results, assess long-term outcomes, and establish evidence-based recommendations for the role of vitamin D in subclinical hypothyroidism.

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