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Impact of Vitamin D Supplementation on Lipid Profile and Vascular Stiffness Patients with Hypothyroidism: A Prospective Randomized Controlled Study

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ABSTRACT

Background: Hypothyroidism has been connected with dyslipidemia and elevated cardiovascular risk through underlying metabolic abnormalities and impairment of function of the endothelium. In this context, vitamin D insufficiency is common and linked to with adverse cardiometabolic profiles, but its therapeutic effects remain contested. **Aim of Study:** The aim of this research was to evaluate how vitamin D supplementation affected the lipid profiles and vascular stiffness in hypothyroidism. **Materials and Methods:** This is an interventional prospective randomized controlled clinical trial (RCT) enrolled 120 adults with primary hypothyroidism who were allocated in a 1:1 ratio to either the vitamin D supplementation group (G1, n = 60) or the control group (G2, n = 60). A computer-generated random sequence was used to allocate groups. Participants in the intervention group received standard levothyroxine therapy plus oral cholecalciferol (2,000 IU/day) for six months, whereas those in the control group received standard levothyroxine therapy alone. Clinical, biochemical, lipid profile, and vascular stiffness assessments, including augmentation index (AIx) and pulse wave velocity (PWV), were performed at baseline before initiation of treatment and repeated after the 6-month intervention period. Treatment effects were evaluated using both within-group and between-group comparisons, and effect sizes (Cohen's d) with corresponding 95% confidence intervals (CIs) were calculated to quantify the magnitude of observed differences. **Results:** Vitamin D treatment significantly improved the lipid parameters and vascular stiffness versus controls Conclusion. Total cholesterol and LDL-C declined by −26.2 mg/dL (95% CI: $-31.4\ to\ -21.0$; $\beta = 0.95$) and −24.2 mg/dL (95% CI: $-28.7\ to\ -19.7$; $\beta = 1.08$), respectively, and triglycerides by −23.1 mg/dL (95% CI: −28.5 to −17.6; $\beta = 0.85$) and HDL-C increased by +3.5 mg/dL (95% CI: $1.2\ to\ 5.8$; $\beta = 0.56$). Results showed reductions in PWV (−1.3 m/s [95% CI: $-1.6\ to\ -1.0$; $\beta = 1.12$]) and AIx (−4.8% [95% CI: $-6.0\ to\ -3.6$; $\beta = 1.04$]). The control group is non-demonstrates any marked changes. Lower levels of LDL-C, PWV, and AIx were linked to higher serum 25(OH)D levels (all $p < 0.01$). **Conclusion:** In individuals with hypothyroidism, vitamin D treatment improved arterial stiffness and lipid profiles. Nevertheless, because of the limited sample size, short follow-up, and absence of objective clinical results, the results do not permit causal inference and probably generalizability. These results both replicated some prior evidence and failed to reconcile important inconsistencies between studies. These associations need to be validated in larger well-powered randomized trials with prolonged follow-up and mechanistic end points.

1. INTRODUCTION

Hypothyroidism is the most prevalent endocrine disorder caused by insufficient synthesis of hormones that are critical for metabolic dysregulation and cardiovascular function [1]. It generally leads to a higher risk of cardiovascular disease and an atherogenic package. It is often linked to triglycerides, low-density lipoprotein

cholesterol (LDL-C), dyslipidemia, high total cholesterol, and reduced HDL-C [2]. Apart from metabolic complications (as mentioned above), hypothyroidism is associated with vascular dysfunction, such as decreased endothelial function and increased vascular stiffness which are recognized independent risk factors for cardiovascular events [3]. The augmentation index (AIx) and pulse wave velocity (PWV) are non-invasive methods of measuring arterial stiffness caused by these structural alterations [4]. Such pleiotropic pathways include oxidative damage, inflammation, dyslipidemia, and endothelial dysfunction [5] The fat-soluble secosteroid hormone vitamin D is widely recognized for its involvement in bone metabolism, but its significance in cardiometabolic control is just recently being recognized [6] Its receptors are found on Vascular endothelium and smooth muscle cells, suggesting a possible role in vascular homeostasis [7]. Endocrine disease vitamin D deficiency and dyslipidemia and vascular disruption [8] Vitamin D may thereby improve vascular function through proposed mechanisms, including modulation of the renin–angiotensin–aldosterone system (RAAS), increased endothelial nitric oxide (NO) bioavailability from $eNOS$, and decreased oxidative stress [9] In addition, the interplay of vitamin D and thyroid hormone signaling through immune modulation, receptor regulation, and peripheral hormone metabolism may also modulate cardiometabolic effects in hypothyroidism [10] However, clinical evidence for vitamin D supplementation is mixed, including in hypothyroid populations, despite such biological associations. Significantly, previous studies have primarily assessed lipid parameters or vascular stiffness independently, with little data on their coordinated response within the same cohort, despite sharing common pathophysiology. We postulated that correction of vitamin D deficiency by means of supplementation gives concurrent benefit to its direct effect by ameliorating the vascular stiffness and indirect effect through lipid profile in patients of hypothyroidism. Hence, this controlled clinical study was done to assess prospective, randomized association of vitamin D supplementation on change in lipids parameters and vascular stiffness indices (PWV and AIx). The current study is a novel integrated assessment of both metabolic and vascular outcomes in the same cohort.

2. MATERIALS AND METHODS

Research Design and Environment

This prospective, randomized, controlled clinical experiment was executed over a six-month duration in endocrinology outpatient clinics and associated clinical labs in Iraq. Eligible adults with primary hypothyroidism were randomly allocated in a 1:1 ratio to either the intervention group (G1), which received oral vitamin D_3 (cholecalciferol) supplementation alongside standard levothyroxine therapy, or the control group (G2), which received standard levothyroxine therapy exclusively. Randomization was executed with a computer-generated random sequence with allocation concealment. Participants were monitored for six months, during which clinical, biochemical, lipid profile, and vascular stiffness measures, including augmentation index (AIx) and pulse wave velocity (PWV), were evaluated at baseline and at the conclusion of the intervention period. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

ETHICAL APPROVAL

The research was carried out in accordance with the Declaration of Helsinki and was officially authorised by the Institutional Review Board (IRB) of the College of Science, University of Al-Qadisiyah (Reference No. 412 dated 7/10/2025). Participants gave their informed permission before their data was published.

PARTICIPANTS

Eligibility criteria included clinically and biochemically proven hypothyroidism in adults between 25–60 years. Low levels of thyroid hormones in the blood and elevated thyroid-stimulating hormone (TSH) identified the diagnosis Prior to enrolment, all patients had to have low or very low blood 25-hydroxyvitamin D levels and be stable on thyroid hormone replacement treatment for at least three months. Methodology: In this cross-sectional study, sequential participants were recruited from endocrinology outpatient clinics at Diwaniyah Teaching Hospital during October 2024 to March 2025. Trained clinicians determined eligibility based on predetermined inclusion and exclusion standards. Eligible individuals were a prior completed screening who signed written informed consent and the enrolment with the assignment into the study groups. We excluded participants with a history or clinical evidence of cardiovascular disease, or other conditions which could independently influence lipid metabolism or vascular function (chronic kidney or liver disease, autoimmune inflammatory disorders, uncontrolled hypertension, severe obesity and acute or chronic insulin-dependent diabetes mellitus). Further outlying factors involved; the use of vitamin D supplements, use of lipid-lowering agents, or use of corticosteroids being pregnant or nursing throughout the previous three months. A pure power analysis based on expected differences in LDL-C and PWV, conceived from earlier studies was done a priori to determine sample size. Based on an expected small-to-medium effect size (Cohen's d ~ 0.7–0.8), power of 80%, and two-sided α level of 0.05, it concluded that each group would need at least 50 people. To compensate for potential attrition, 60 participants were recruited to each group (total n = 120).

INTERVENTION

The intervention group was given additional standard thyroid hormone replacement therapy (replacement therapy) in the form of 2000 IU/day oral cholecalciferol (vitamin D_3) for 6 months, while the control group received standard therapy alone. The dose of oral vitamin D was chosen according to clinical recommendations in the literature and previous studies that have shown that daily doses of 1500–2000 IU are appropriate to correct vitamin D insufficiency and to maintain optimal serum 25-hydroxyvitamin D concentrations while remaining safe for long-term use. Monthly pill counts and patient interviews were used to assess adherence. To limit behavioral variability, participants were asked to continue with their

normal diet and physical activity during the entire duration of the study.

CONTROL OF CONFOUNDING VARIABLES

Although randomization was implemented to minimize baseline imbalances between the study groups, a number of possible confounding variables, such as food consumption and physical activity, sunlight exposure, and seasonal variation, were not quantitatively assessed or adjusted for in the statistical analyses. These variables are known to influence both vitamin D status and lipid metabolism. To minimize their potential impact, participants in both groups were recruited during the same study period from the same geographic region and were instructed to maintain their usual dietary habits, physical activity, and lifestyle throughout the six-month intervention. Consequently, any seasonal or environmental influences were expected to affect both groups similarly. Nevertheless, because these factors were not objectively measured, when assessing the research results, residual confounding should be taken into account since it cannot be totally ruled out.

SAMPLE COLLECTION

During the period from 17/10/2025 to 28/3/2026, 120 subjects (60 males and 60 females) were randomly recruited from Diwaniyah Teaching Hospital, Iraq. A total of 120 subjects, aged 25–55 years, were divided equally into an intervention group (G1; n = 60) and control group ($G2;\ n = 60$), stratified by gender (30 males and 30 females in each group). Following a 10–12-hour overnight fast, 5 mL of fasting venous blood were extracted using the conventional aseptic method. The antecubital vein was used to draw blood samples, which were then centrifuged for ten minutes at 3000 rpm after being allowed to clot for twenty to thirty minutes at room temperature. After being separated, the serum was aliquoted into microtubes with labels and stored at $-20\ °C$ until analysis.

LABORATORY AND VASCULAR ASSESSMENTS

Total cholesterol (TC), triglycerides (TG), and HDL-C were measured in the blood using an automated analyser (Beckman Coulter AU480, USA) as directed by the manufacturer. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Fried Ewald formula wherever feasible. Blood levels of 25-hydroxyvitamin D [25(OH)D] were measured using the Abbott Architect i2000SR system's enzyme-linked immunosorbent assay (ELISA). A Roche Eleusis analyzer was used to measure thyroid-stimulating hormone (TSH) using electrochemiluminescence immunoassay (ECLIA). All assays were standardized against reference materials with internal quality controls. Measurement bias was reduced by blinding laboratory personnel to group allocation. PWV and AIx were assessed as markers of vascular stiffness with the Sphygmic system (Actor Medical) by means of carotid–femoral pulse wave analysis and applanation tonometry. Evaluations were done in a climate-controlled room with the subject resting supine for 10 minutes or more. Three measurements of each parameter were made, and the study was done using the mean value. Operators were blinded to treatment and trained.

STATISTICAL ANALYSIS

The analysis was conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categories are represented by frequency and percentage, whereas fixed variables are expressed as mean ± standard deviation (SD) for regularly distributed data or median (interquartile range) for non-normally distributed data. Q-Q plot analysis and the Shapiro-Wilk test were used to determine normality. Categorical data was analysed using chi-square tests, and baseline comparisons were conducted using either independent samples t-tests or Mann-Whitney U tests, depending on the situation. Wilcoxon signed-rank tests or paired t-tests were used to measure changes within groups. Statistical comparison between groups was performed by analysis of covariance ($ANCOVA$), adjusting for baseline values for post-intervention results. In order to account for multiple comparisons, P values were shown and adjusted using the Bonferroni correction. Multivariable linear regression analysis was used to evaluate the relationship between blood 25-hydroxyvitamin D and cardiometabolic characteristics (LDL-C, PWV, and AIx). Age, sex, body mass index (BMI), and baseline values of the corresponding outcomes were all considered while adjusting for relevant confounders. The 95% confidence interval (CI), p-value, and standardized regression coefficients (β) were shown. Variance inflation factors were used to assess the model's assumptions (linearity, residual normality, homoscedasticity, and lack of multicollinearity) prior to interpretation. A corrected p-value of less than 0.05 for every two-tailed significance test was considered statistically significant.

3. RESULTS

Baseline Characteristics of the Randomized Cohort

Among those, 146 subjects were screened for eligibility, with 120 meeting inclusion criteria and subsequently assigned to either the vitamin D (G1, n = 60) or control groups (G2, $n = 60$). Five participants (8.5%) were lost during follow-up in G1, and 6 in G2 (9.2%) (one non-adherent, three withdrew consent, and two lost to follow-up). Fifty-five participants in G1 and 54 in G2 completed the study, which were included in per-protocol analysis. The two groups had similar baseline characteristics, as seen by the lack of statistically significant differences in age, sex distribution, BMI, TSH, and blood 25(OH)D levels ($p > 0.05$ for all) (Table 1).

Table 1: *Baseline features of research participants.*

Parameter	Vitamin D Group (G1) (n = 60)	Control Group (G2) (n = 60)	p-value
Age (years)	44.3 ± 8.7	45.1 ± 9.1	0.63
Gender (M/F)	22/38	20/40	0.68
BMI (kg/m²)	28.5 ± 3.6	28.9 ± 3.9	0.54
TSH (μIU/mL)	7.8 ± 2.1	7.6 ± 2.3	0.72
Serum 25(OH)D (ng/mL)	18.6 ± 4.2	19.1 ± 4.5	0.48

EFFECTS ON LIPID PROFILE

Total cholesterol, LDL-C, and the triglycerides significantly decreased in the intervention group, along with a slight increase in HDL-C (Table 2). No major changes were seen in the control group. Using ANCOVA to adjust for baseline values, age, sex, and BMI, between-group differences remained significant for total cholesterol, LDL-C, and triglycerides (all adjusted $p < 0.01$) and the

increase in HDL-C was still modest but significant ($p < 0.05$).

Table 2: *Modifications to the lipid profile before and after the intervention*

Parameter	Vitamin D Group (G1) Baseline	Vitamin D Group (G1) Post	Control Group (G2) Baseline	Control Group (G2) Post
Total Cholesterol (mg/dL)	224.5 ± 28.7	198.3 ± 25.6 **	222.8 ± 27.5	221.5 ± 26.8
LDL-C (mg/dL)	142.7 ± 22.4	118.5 ± 20.3 **	140.9 ± 21.9	139.7 ± 22.1
HDL-C (mg/dL)	42.6 ± 5.7	46.1 ± 6.3 *	43.0 ± 5.5	43.2 ± 5.8
Triglycerides (mg/dL)	168.3 ± 30.6	145.2 ± 28.1 **	165.7 ± 29.4	164.5 ± 30.1

*$P < 0.05$ and **$p < 0.001$ in comparison to baseline indicate significance

Figure 1 shows bar graphs showing the total cholesterol, LDL-C, HDL-C, and triglyceride readings for the vitamin D group and the control group at baseline and after the intervention. While total cholesterol, LDL-C, and triglycerides showed significant decreases, HDL-C showed a little increase in the vitamin D group.

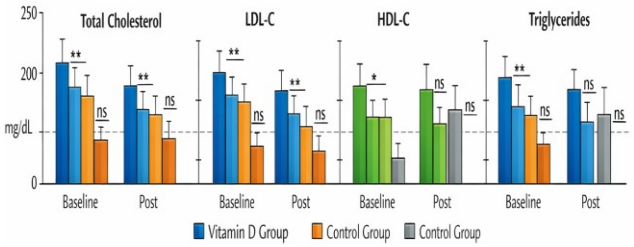

Figure 1: *Changes in lipid profile parameters following vitamin D supplementation.*

Effects on Vascular Stiffness

Table 3 shows that the effect of vitamin D supplementation led to significant decrease in PWV and AIx values in G1, but no significant change was highlighted in G2. Although differences adjusted for age, sex, BMI and baseline values were less pronounced, they remained significant (both adjusted $p < 001$).

Table 3*: Changes in Vascular Stiffness Parameters*

Parameter	Vitamin D Group (G1) Baseline	Vitamin D Group (G1) Post	Control Group (G2) Baseline	Control Group (G2) Post
Pulse Wave Velocity (m/s)	10.4 ± 1.2	9.1 ± 1.0 **	10.2 ± 1.1	10.1 ± 1.0
Augmentation Index (%)	28.5 ± 4.6	23.7 ± 3.9 **	27.9 ± 4.4	27.7 ± 4.2

**$p < 0.001$ compared to baseline.

Before and after the intervention, both study groups' PWV and AIx changed. Significant decreases were seen in the vitamin D treatment group, indicating improved artery flexibility (Figure 2).

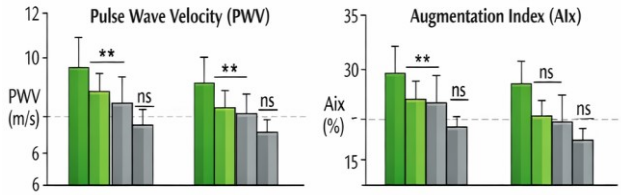

Figure 2: *Vascular stiffness measures are affected by vitamin D administration.*

Association Between Vitamin D Levels and Cardiometabolic Parameters

Table 4 summarizes the correlations between blood levels of 25-hydroxyvitamin D [25(OH)D] and cardiometabolic indicators. Low-density lipoprotein cholesterol (LDL-C) ($r = -0.52$, $p < 0.001$), pulse wave velocity (PWV) ($r = -0.48$, $p < 0.001$), and augmentation index (AIx) ($r = -0.41$, $p = 0.002$) were shown to be substantially negatively linked with serum 25(OH)D levels. Additionally, it was shown that serum 25(OH)D concentration was an independent predictor of LDL-C (standardized $\beta = -0.38$; 95% CI, −0.55 to −0.21; $p < 0.001$), PWV (standardized $\beta = -0.35$; 95% CI, −0.52 to −0.18; $p < 0.001$), and AIx (standardized $\beta = -0.29$; 95% CI, −0.46 to −0.12; $p = 0.002$). These findings demonstrate that higher serum 25(OH)D concentrations were independently associated with reduced LDL-C levels and improved arterial stiffness after adjusting for potential confounding variables.

Table 4: *Relationship between vitamin D levels and cardiometabolic indicators.*

Parameter	Correlation with 25(OH)D (r)	standardized regression coefficients (β)	95% CI for β	p-value
LDL-C (mg/dL)	−0.52	0.38	−0.55 to −0.21	<0.001
PWV (m/s)	−0.48	−0.35	−0.52 to −0.18	<0.001
AIx (%)	−0.41	−0.29	−0.46 to −0.12	0.002

The levels of serum 25(OH)D are inversely correlated with LDL-C, PWV, and AIx, according to scatter plots (Figure 3).

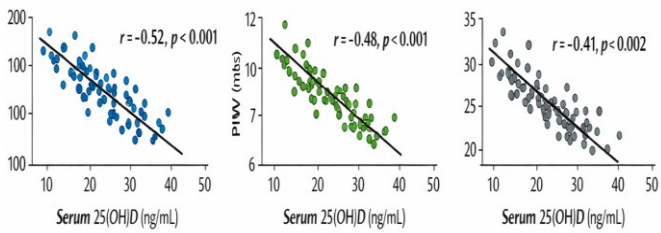

Figure 3: *Correlation between cardiovascular risk factors and blood vitamin D levels.*

Integrated Effects on Metabolic and Vascular Outcomes

In an analysis combining lipid and vascular outcomes (Table 5), vitamin D supplementation was linked to simultaneous reductions in both LDL-C and triglycerides as well as PWV and AIx, with a modest increase in HDL-C.

These associations held even after controlling for confounders. The control group did not exhibit these alterations. The results demonstrate a repeatable pattern of improvements in vitamin D effects upon metabolic and vascular indices with variable small to medium effect sizes across the six outcomes.

Table 5: *Effects of vitamin D supplementation on lipid profile and vascular stiffness in hypothyroid patients*

Parameter	Vitamin D Group (G1) Baseline	Vitamin D Group (G1) Post	Control Group (G2) Baseline	Control Group (G2) Post	p-value (Post vs Baseline, Vit D)
Total Cholesterol (mg/dL)	224.5 ± 28.7	198.3 ± 25.6 **	222.8 ± 27.5	221.5 ± 26.8	<0.001
LDL-C (mg/dL)	142.7 ± 22.4	118.5 ± 20.3 **	140.9 ± 21.9	139.7 ± 22.1	<0.001
HDL-C (mg/dL)	42.6 ± 5.7	46.1 ± 6.3 *	43.0 ± 5.5	43.2 ± 5.8	0.02
Triglycerides (mg/dL)	168.3 ± 30.6	145.2 ± 28.1 **	165.7 ± 29.4	164.5 ± 30.1	<0.001
Pulse Wave Velocity (m/s)	10.4 ± 1.2	9.1 ± 1.0 **	10.2 ± 1.1	10.1 ± 1.0	<0.001
Augmentation Index (%)	28.5 ± 4.6	23.7 ± 3.9 **	27.9 ± 4.4	27.7 ± 4.2	<0.001

*Significance: $*p < 0.05$, $**p < 0.001$ compared to baseline in Vitamin D group.

As shown in figure 4, vitamin D supplementation reduced atherogenic lipids compared with controls and vascular stiffness (PWV, AIx). Improvements were modest and inconsistent for HDL-C. Cardiometabolic effects are coordinated, although mechanistic interpretability is limited.

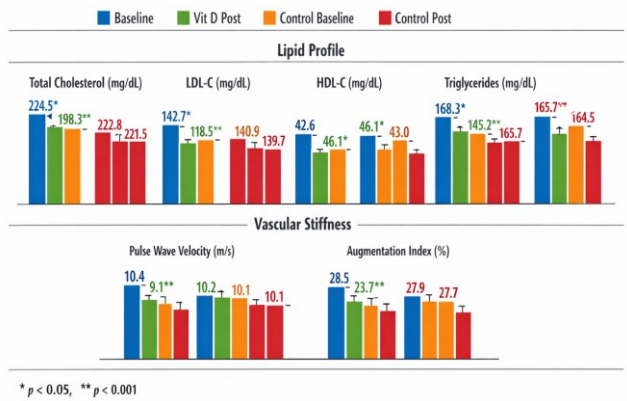

Figure 4: *Effects of vitamin D supplementation on lipid profiles and vascular consequences in hypothyroidism.*

4. Discussion

Baseline equivalency and internal validity were supported since baseline variables such as age, gender distribution, BMI, TSH, and serum 25(OH)D levels were similar across groups, as Table 1 and Figure 1 demonstrate. This balance ensures that the observed differences are less likely to arise from baseline differences. However, the randomized design, together with the observation that some lifestyle-related factors (e.g. diet, sun exposure, physical activity) were not controlled for, encourages the possibility of residual confounding [11]. Furthermore, the limited sample size probably restricts design sensitivity and power for more subtle effects. This means that results should be interpreted correlatively not causatively [12] Despite conflicting results from meta-analyses and randomized trials but several show only small or no effects on lipids our observed significant decreases of 0.486 SD of total cholesterol and LDL cholesterol (Table 2 and figure 1) agree with several but not all prior studies, however, the decreases in total cholesterol and LDL-C after vitamin D. Part of this heterogeneity probably represents differences in baseline vitamin D status; dosing regimens; duration of supplementation; and the characteristics of the populations (e.g. metabolic and endocrine disease) [13]. Vitamin D could, in this way, affect hepatic lipid metabolism via VDR-mediated transcriptionally. It is then suggested that VDR activation affects the expression of genes which regulate cholesterol homeostasis, and the increased expression of LDL receptor and possible reduction of HMG-CoA reductase expression activity would result in a more decreased secretion of LDL in the plasma [14]. Other indirect effects, that are accomplished by improved insulin sensitivity and system-wide inflammation, can also modify lipids. This is reflected in the different clinical responses available in the various studies, as in some cases a change in mechanism does not result in a concordant decrease in lipids [15]. While this small increase in HDL-C aligns with previous observational associations between cardioprotective HDL characteristics and high 25(OH)D status, evidence relating to a causal association for this effect have been inconsistent regarding interventional analyses. Some studies show supplementation results in increment of HDL-C while other studies show no significant difference. Differences in research populations and baseline deficient status might be the cause of this possible disparity [16]. At a mechanism level, vitamin D potentially modulates HDL metabolism via direct effect on apolipoprotein expression, reverse cholesterol transport enhancement and anti-inflammatory effects to stabilize HDL. Despite this, the HDL function, which is more closely related with gastroprotection than is HDL concentration itself, was not evaluated in this study, thus limiting interpretation of this finding of potential clinical relevance. Therefore, the increase in HDL-C must be considered with caution [17]. The large decrease in triglycerides after the administration of vitamin D could represent an improvement in excretion of hepatic lipids and acute systemic inflammation. Insulin sensitivity and triglyceride metabolism are closely linked, and it has been shown that vitamin D affects some inflammatory pathways and insulin signaling associated with peripheral clearance and hepatic very-low-density lipoprotein (VLDL) synthesis. The observed reduction in triglycerides in the study, however, was stabilized from previous results but is inconsistent with evidence in the literature. Vitamin D may indirectly affect triglyceride metabolism by improving insulin sensitivity, suppressing pro-inflammatory singalongs, and altering hepatic very-low-density lipoprotein (VLDL) synthesis [18]. Each of these pathways may operate together to facilitate lipid removal and to reduce plasma triglycerides. However, as between-study heterogeneity indicates the triglyceride response is contingent on baseline metabolic status, severity of deficiency and genotypic differences. Thus, the entire observed response is likely context-specific

metabolism leading to changes that mimic physiological actions of different supplementation [19]. This indicates that vitamin D supplementation restores PWV to a level that statistically implies healthy arterial compliance in hypothyroid patients (Table 3 and Figure 2). Reduction of pulse wave velocity (PWV) indicates an increased vascular compliance. Background: Adverse cardiovascular morbidity and mortality are independently associated with arterial stiffness. Such properties include anti-oxidative, anti-inflammatory, enhanced bioavailability of endothelial nitric oxide (NO) and downregulated Renin-angiotensin-aldosterone system (RAAS) activity [20]. These actions may enhance endothelial function and decrease vascular smooth muscle tone. On the other hand, randomized clinical studies evaluating the effect of vitamin D on PWV has yielded inconsistent results with some showing beneficial effects while others showing no effect. Likely discrepancies are due to a difference in baseline vitamin D status, supplantation protocols, populations studied and length of study. This may represent biological plausibility as the lower PWV cannot be proved by mere association which is limited modelling [21]. Furthermore, in females with lower AIx, there is functional improvement in wave reflection and vascular tone. AIx actually loads depending on arterial stiffness and peripheral resistance and on ventricular–arterial coupling. Alternatively, vitamin D may achieve such effects on the endothelial modulatory and vascular smooth muscle regulatory effects of AIx. Observational studies of 25(OH)D levels and AIx have shown inverse relationships perhaps offer temporal prioritization between vitamin D technical status and mechanical vascular effects [22] Intervention studies, by comparison, have shown inconsistent results, with a number failing to find an effect at all. This heterogeneity indicates that the benefit to the vasculature may be obscured in healthy populations but apparent in deficiency or in those with prior dysfunction. Therefore, in light of contradicting data, the present findings should be regarded cautiously [23] In accordance with earlier findings examining the connections between changes in unfavorable patterns of cardiometabolic illness and vitamin D levels undertaken in population-based studies (Table 4, Figure 3) both LDL-C and both PWV and AIx were inversely related to serum 25(OH)D. These associations have biological plausibility, possibly representing common pathways (endoluminal distension or inflammatory or neurohormonal mediators [eg, RAAS]). Nevertheless, such an association does not prove causation and may be vulnerable to unmeasured confounding or reverse causation. Thus, although these results are consistent with an association they should not be taken as evidence of a mechanistic effect [24]. In conclusion, those on vitamin D supplementation had improved lipid parameters and several vascular stiffness measures, while a negative connection existed between serum 25(OH)D and cardiometabolic markers. These results are biologically plausible and corroborate some of the literature; however, there are major inconsistencies between studies, and methodological challenges hinder a strong conclusion. However, these results require replication by larger, well planned randomized controlled studies with extended follow-up periods, standardized treatments, and mechanistic outcomes to determine if vitamin D is causally relevant and provides clinically meaningful benefits in the modulation of risk for cardiometabolic disease in hypothyroid patients.

5. Clinical Implications

Nevertheless, some studies reported unexplained higher cardiovascular risk in hypothyroid patients despite well-controlled thyroid hormone replacement, which might be linked, at least in part, to persistent dyslipidemia and vascular dysfunction. Vitamin D supplementation seems to improve lipid parameters and arterial stiffness indices as evidenced by the study; however, because of the study's methodology, these findings should be regarded cautiously. A routine testing of vitamin D status could be indicated as benefit to such a low-risk intervention could outweigh risks especially in case of deficiency within this population group. However, the use of vitamin D as a harmony supplement is not supported by enough data approach in other to reduce the probability of cardiovascular risk and of mean cardiovascular effect, should remain exploratory until proven otherwise by traffic randomized controlled trial.

Research Highlights

Total cholesterol, LDL-C, and triglycerides all dropped with vitamin D therapy, while HDL-C substantially (albeit marginally) rose, suggesting changes in lipid profile characteristics. Two indicators of vascular stiffness, PWV and AIx, also exhibited reduced values after the surgery. Vitamin D status was connected to cardiometabolic risk, as reflected by the inverse correlations of the serum 25-hydroxyvitamin D with the LDL-C and vascular stiffness markers. However, due to the nature of the associations being observational and conflicting results reported previously, our findings should be considered exploratory and need the confirmation from future controlled large-scale trials.

6. CONCLUSIONS

Vitamin D replacement in hypothyroid patients not only improved vitamin D status, but also significantly improved lipid profile and also vascular stiffness parameters, that is significant decreases in total cholesterol, LDL-C, triglycerides and PWV and AIx with a slightly higher increase in HDL-C. These results indicate a potentially clinically relevant cardiometabolic action in hypothyroid patients who continue to have an elevated risk of cardiovascular disease despite standard therapy with thyroid hormone replacement. These associations are consistent with hypothesized mechanisms of action involving modulation of the renin–angiotensin–aldosterone system, reduction of asymmetric dimethylarginine induced nitric oxide deficiency, and potential interactions with thyroid hormone–regulating metabolic pathways, although direct assessment of these mechanisms was not performed. Large randomized studies and meta-analyses have shown conflicting results, these results should be considered associative rather than confirmatory. Causal inference is additionally hampered by methodological limitations

including sample size, potential residual confounding and design reporting issues. In conclusion, vitamin D may be a complementary role in cardiometabolic risk, but further randomized studies are needed before firm conclusions can be made regarding the clinical benefit of vitamin D in these situations.

LIMITATIONS

There were several limitations to take into consideration when interpreting these findings. First, although a randomized design was used, allocation procedures and potential adherence to the protocol were reported poorly, leading to uncertainty on the strength of randomization and potential residual bias due to selection. This does however constitute a potential limitation of differential bias, but this issue is at least partly mitigated by similar baseline characteristics between the cohorts. Second, the evaluation of the observed lipid and vascular alterations' long-term stability and clinical importance is constrained by the short-term follow-up. Third, potential effect modifiers, for example diet, physical activity and sunlight exposure were not systematically measured or controlled for, which could incorporate the exposure effect to both vitamin D status and cardiometabolic outcomes. Fourth, the statistical analysis, albeit involve fairly simple adjusted models, could not account for other possible residual confounding because other unobserved factors may explain this relationship. Finally, because of their single-center design, these findings may not be as applicable to a wider population in more varied environmental and demographic circumstances. These constraints together indicate that the findings should be regarded as exploratory and conducive to hypothesis generation. Conclusion To validate these results and more accurately evaluate their clinical significance, larger, methodologically sound randomized controlled trials with thorough confounder evaluation and extended follow-up are needed.

NOVELTY STATEMENT

This study gives new insight to the literature by integrating lipid metabolism and vascular stiffness, together with vitamin D supplementation's antihyperlipidemic benefits in vitamin D-deficient euthyroid adult hypothyroid patients which has not been previously reported in literature separately in two groups. Strengths of this study include the assessment of multiple biochemical endpoints (lipid profile) and hemodynamic endpoints (PWV and AIx) in the same subjects, which leads to a comprehensive characterization of cardiometabolic status of the same high-risk population. Previous studies and meta-analyses have compiled a heterogeneous and often contradictory literature, whereas this work offers context-specific evidence of relevance for hypothyroid patients who receive standard thyroid hormone therapy. Although exploratory, these findings will help to propose a potential complement to thyroid replacement by vitamin D to act on cardiometabolic risk. However, because of the methodological weaknesses and heterogeneity within the current high-quality evidence, these findings require confirmation in high-quality, adequately powered RCTs with standardized treatments and mechanistic outcomes.

FUTURE DIRECTIONS

Longer duration and duplication in subsequent studies from single center designs to sufficiently powered multicenter randomized controlled trials that can ascertain interim benefits in lipid and related vascular factors equate to a decrease in cardiovascular events with prolonged follow-up are necessary. This implies that a mechanistic integration of RAAS activity, endothelial function, and inflammatory biomarkers is warranted, which may resolve inconsistencies across prior trials. In addition, dose–response and stratum analyses by baseline vitamin D status are important for targeting real patients and identifying effective supplements.

AUTHORS' DECLARATION

We certify that all of the manuscript's figures and tables are included in the present investigation.

CONFLICT OF INTEREST

Regarding the publishing of this paper, the authors state that they have no conflicts of interest.

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