TSH as an Independent Determinant of Atherogenic Dyslipidemia in Hypothyroidism: An Adjusted Analysis of Non-HDL-C

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Abstract

Objectives: The association between reduced thyroid function and atherogenic dyslipidemia is well recognized. However, the independent role of Thyroid-Stimulating Hormone (TSH) versus thyroid hormones remains a matter of debate. This study investigated whether TSH is an independent determinant of Non-High-Density Lipoprotein Cholesterol (Non-HDL-C), a superior marker of atherogenic risk, in hypothyroid patients.

Methods: A case-control study enrolled 138 participants (71 hypothyroid patients, 67 euthyroid controls). Thyroid profiles, lipid panels, and anthropometrics were assessed. A hierarchical multiple linear regression analysis, adjusted for age, sex, and Body Mass Index (BMI), was performed on hypothyroid patients to determine the independent association between TSH and Non-HDL-C. Specificity was tested by analyzing TSH's association with other atherogenic indices (AIP, CRI-I, CRI-II, AC).

Results: Hypothyroid patients had significantly higher Non-HDL-C than controls (median 170.0 vs. 111.0 mg/dL, $p<0.001$). In the fully adjusted regression model, TSH was a significant, independent predictor of Non-HDL-C ($\beta=0.869$, 95% CI [0.057, 1.681], $p=0.037$), while BMI was not ($p=0.323$). This association was specific to Non-HDL-C, as TSH showed no significant relationship with any other atherogenic index (all $p>0.6$).

Conclusions: Serum TSH is an independent determinant of Non-HDL-C in hypothyroidism, an effect not mediated by BMI. The specificity of this association for Non-HDL-C suggests TSH directly influences the total burden of atherogenic lipoproteins. These findings support the potential extra-thyroidal, metabolic role of TSH and advocate for using Non-HDL-C as a primary lipid target. Future studies must include free thyroid hormones and insulin resistance markers to confirm TSH's causal role.

Keywords: Thyrotropin(TSH),Non-HDL-Cholesterol, Atherogenic Dyslipidemia, Hypothyroidism, Lipid Metabolism

Introduction

Hypothyroidism defined primarily as a condition which characterized by either insufficient of thyroid hormones (THs) production from thyroid glands, or their action on target cells is less effectiveness.[1] In the united states, the prevalence of hypothyroidism is around 4.6%. Hypothyroidism is six times more frequent in women and white people. The incidence increases with age as it is more common in people older than 60

years.[2] In hypothyroidism, progression of atherosclerosis accelerated via many mechanisms such as endothelial dysfunction, abnormal lipid metabolism, changes in blood pressure, hemostatic abnormalities and insulin resistance.[3]

Thyroid hormones regulate key hepatic genes including HMG-CoA reductase and the LDL receptor (LDL-R).[4] Consequently, hypothyroidism leads to elevated LDL-cholesterol and triglycerides,[5] resulting in a pro-atherogenic lipid profile.[6] Recent regional studies have further corroborated the link between thyroid dysfunction and elevated cholesterol profiles, emphasizing the need for early detection.

Atherogenic Dyslipidemia (AD) represents a high-risk of lipid abnormalities, extending far beyond isolated elevations in LDL-C. including high triglycerides, low HDL cholesterol, and, critically, an increase in atherogenic lipoproteins not captured by standard LDL-C measurements.[7] The studies confirmed that this risk is driven by the total of apoB-containing atherogenic particles, not just LDL-C value alone.[8] In atherogenic dyslipidemia because LDL-C value alone fails to be reflect to full risk of atherogenic lipoproteins, a more comprehensive marker is needed. Non-HDL-C uses for this purpose. Non-HDL-C, calculated simply as total cholesterol minus HDL-C, it represents the cholesterol carried by all apoB-containing atherogenic lipoproteins, including LDL, VLDL, IDL, and Lp(a) this makes it as superior marker for assessing cardiovascular risk in this context.[9]

While the link between low thyroid function and adverse lipid profiles is well-recognized; however, the precise underlying mechanism remains controversial. The traditional hypotheses attributes dyslipidemia to low thyroid hormone levels (fT4/fT3), but this fails to explain the dyslipidemia often seen in subclinical hypothyroidism where fT4 is normal. However, emerging evidence suggests TSH may exert direct extrathyroidal effects on lipid metabolism via TSH receptors in the liver and adipose tissue, potentially influencing cholesterol synthesis and clearance independently of thyroid hormone levels

The extent to which TSH contributes to atherogenic dyslipidemia independently of confounding metabolic factors like obesity remains debated. Therefore, this study aimed to investigate whether serum TSH is an independent determinant of Non-HDL-C in patients with primary hypothyroidism, adjusting for key confounders such as Body Mass Index (BMI), and to evaluate the specificity of this association compared to other atherogenic indices.

Methods

This case-control study utilized a consecutive sampling technique to enroll 138 participants between January 12, 2025, and April 29, 2025. Participants were recruited from the medical outpatient clinics at Al-Rifai Teaching Hospital, Thi-Qar Governorate, Iraq. The study protocol was approved by the Institutional Review Board (IRB) of the College of Health and Medical Technology, Al-Furat Al-Awsat Technical University (Protocol 7/37/135). The sample size was determined based on the availability of eligible participants presenting to the clinic during the study period.

This study included patients aged ≥16 years with a newly diagnosed, treatment-naive primary hypothyroidism. Diagnosis was confirmed based on elevated TSH and reduced or low thyroid hormones. Control individuals were healthy, euthyroid volunteers matched for age and sex.

Individuals were excluded from the final analysis if they presented with Any acute illness, active pregnancy or a diagnosis of familial hypercholesterolemia. In addition, presence any of renal, hepatic impairment or concurrent use of medications known to significantly affect thyroid or lipid metabolism (as, amiodarone, systemic corticosteroids, anabolic steroids).

Thyrotropin (TSH), measured via a electrochemiluminescence immunoassay (ECLIA) on MAGLUMI analyzer the established normal range this assay is (0.45–4.5 μIU/mL). Lipid Profile measurement: Total Cholesterol (TC), Triglycerides (TG), and HDL-C were measured following a mandatory minimum 10-hour overnight fast. Analyses were performed using enzymatic colorimetric methods . Atherogenic indices were subsequently calculated from the standard lipid panel: Non-HDL-C), which using the formula;

Non-HDL-C = (Total Cholesterol) – (HDL-C).

Atherogenic Index of Plasma (AIP) AIP = was proposed by Dobiasova and Frohlich in 2001.[10]

Log (Triglycerides / HDL-C).

Castelli's Risk Index (CIR): Castelli's Risk Index is based on three important lipid profile parameters i.e. TC, LDLc and HDLc and it is categorized into two; CIR-1 and CIR-11.[11] Castelli's Risk Index I (CRI-I) also known as the Cardiac Risk Ratio (CRR).

= Total Cholesterol / HDL-C.

Castelli's Risk Index II (CRI-II) = LDL-C / HDL-C.

Atherogenic Coefficient (AC) is an indirect measure of cholesterol in VLDLc, IDLc, and LDLc lipoprotein fractions in reference with HDLc fraction. Mathematically, it is expressed as; AC= {(TC-HDLc)/HDLc} or {(Non-HDLc)/HDLc} ratio

from participants we collected data on the confounders as demographics which included, Age (continuous, in years) and Sex (categorical, male/female). In addition to, Anthropometrics as Body Mass Index (BMI), calculated as kg/m² and treated as a continuous variable.

All statistical analyses were performed using Graph Pad Prism version 8.0.1. Baseline characteristics were represented by descriptive statistics where mean ± standard deviation for normally distributed data or median with interquartile range [IQR] for skewed data in case continuous variables and categorical variables were presented as counts and percentages (n, %). Group comparisons between hypothyroid patients and euthyroid controls were conducted using the Independent t-test for normally distributed continuous variables the Mann-Whitney U test for skewed continuous variables and the Chi-square (χ^2) test for categorical variables.

Results

In this study a total of 138 individuals were enrolled, comprising 71 newly diagnosed hypothyroid patients and 67 healthy euthyroid controls. The baseline demographic, thyroid, and atherogenic profiles of both groups are showed in Table 1. The sex were well matched between the two groups with a similar proportion of females in both the patient (78.9%) and control (77.6%) cohorts (p = 0.857). There was no statistically significant difference in age between the two groups (median: 43 vs. 36 years, p = 0.078). However, participants in the hypothyroid group had a significantly higher Body Mass Index (BMI) compared to healthy controls (25.95 ± 4.63 kg/m² vs. 24.20 ± 3.36 kg/m², p = 0.027).

Table 1: Baseline Demographic and Atherogenic Profile of Study Participants.

Variables	**Hypothyroid Patients (n=71)**	**Healthy Controls (n=67)**	***p*-value**
Demographics			
Age (years)	43 (35-52.5)	36(33 - 46.2)	0.078
Sex (Female, n (%))	56 (78.9%)	52 (77.6%)	0.857
BMI (kg/m²)	25.95 ± 4.63	24.20 ± 3.36	0.027
Thyroid and Lipid Profile			
TSH (μIU/mL)	46.0 [18.0 – 65.0]	1.80 [0.5 – 4.1]	< 0.001
Non-HDL-C (mg/dL)	170.0 [134.0 – 209.0]	111.0 [74.0 – 151.0]	< 0.001
AIP (log ratio)	0.81 ± 0.21	0.45 ± 0.23	< 0.001
CRI-I (ratio)	7.03 [5.56 – 10.51]	4.28 [3.17 – 5.26]	< 0.001
CRI-II (ratio)	4.63 [3.30 – 7.53]	2.73 [1.76 – 3.48]	< 0.001
AC (ratio)	6.03 [4.56 – 9.51]	3.28 [2.17 – 4.26]	< 0.001

Data are presented as Mean ± Standard Deviation (SD) or Median [Interquartile Range, IQR] based on data distribution (Shapiro-Wilk test). Categorical data is presented as n (%). p-values calculated using Independent t-test (for normal data), Mann-Whitney U test (for skewed data), or Chi-square (χ^2) test (for categorical data). Abbreviations: BMI, Body Mass Index; TSH, Thyroid-Stimulating Hormone; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol; AIP, Atherogenic Index of Plasma; CRI-I, Castelli's Risk Index I; CRI-II, Castelli's Risk Index II; AC, Atherogenic Coefficient.

TSH levels were markedly elevated in the patient group (median: 46.0 µIU/mL) compared to the euthyroid controls (median: 1.80 µIU/mL, $p < 0.001$).This hormonal difference was accompanied by a highly significant worse atherogenic profile in the hypothyroid patients. The primary finding, Non-HDL-C was significantly higher in the patient cohort (median: 170.0 mg/dL) than in controls (median: 111.0 mg/dL, $p < 0.001$ Figure 1A). Furthermore, hypothyroid group demonstrated significantly worse (higher risk) values for the Atherogenic Index of Plasma (AIP)(as revealed by figure 1B), Castelli's Risk Index I (CRI-I), Castelli's Risk Index II (CRI-II), and the Atherogenic Coefficient (AC). All these atherogenic ratios were highly statistically different between the groups ($p < 0.001$ for all).

Figure 1: Atherogenic lipids and ratios are significantly elevated in hyptiohorid patients.

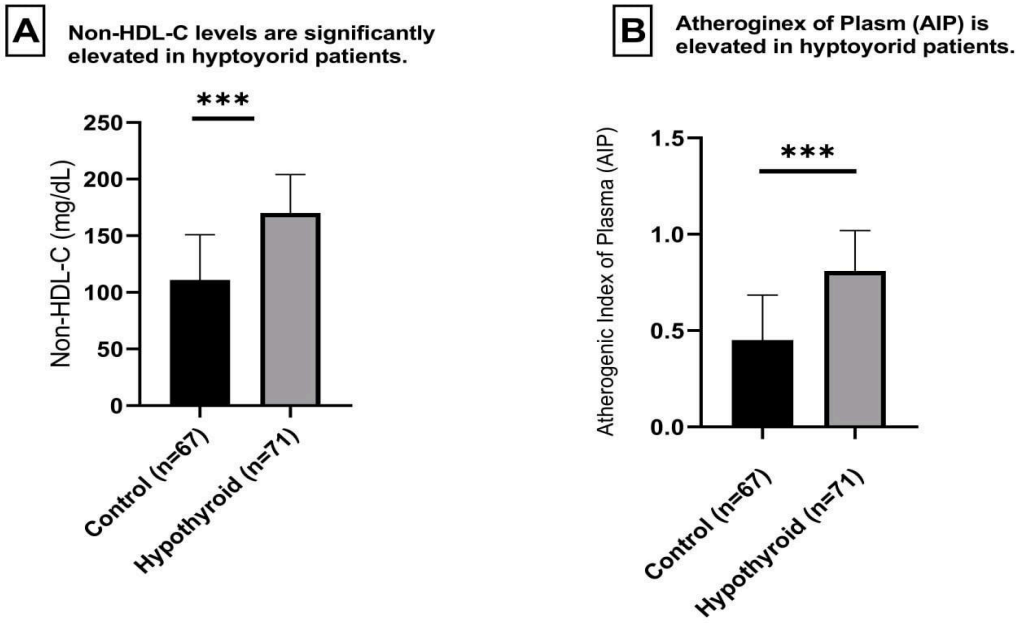

Figure 1: Atherogenic lipids and ratios are significantly elevated in hyptiohorid patients A: Compares Non-HDL-C (Non-High-Density Lipoprotein Cholesterol) levels between control and hypothyroid. B: Compares the Atheroginex of Plasm (AIP) between control and hypothyroid. *** = $p < 0.001$ (Highly Significant).

A bivariate correlation analysis was generated for hypothyroid patients (Table 2). This analysis revealed a statistically significant positive correlation between TSH and Non-HDL-C ($\rho = 0.368$, $p < 0.05$: Figure 2). This finding indicates that in this unadjusted analysis, higher serum TSH levels are associated with higher, more atherogenic Non-HDL-C levels. Interestingly, TSH showed no significant correlation with the primary confounders of Age ($\rho = -0.198$, $p > 0.05$) or BMI ($\rho = -0.160$, $p > 0.05$). Similarly, Non-HDL-C also showed non-significant unadjusted association with Age ($\rho = -0.063$, $p > 0.05$) or BMI ($\rho = -0.016$, $p > 0.05$).A significant positive correlation was observed between the covariates Age and BMI ($\rho = 0.449$, $p < 0.01$). The presence of a significant primary association between TSH and Non-HDL-C, in the absence of strong confounding from Age or BMI, supports the further exploration of this link in a multivariate regression model.

Table 2: Spearman Correlation Matrix for Key Variables in the Hypothyroid Regression Cohort.

Variable	TSH	Non-HDL-C	Age	BMI
TSH	—	0.368*	-0.198	-0.160
Non-HDL-C	0.368*	—	-0.063	-0.016
Age	-0.198	-0.063	—	0.449**
BMI	-0.160	-0.016	0.449**	—

*Data represents Spearman's rank-order correlation coefficients (ρ) for the hypothyroid patients. * $p < 0.05$, ** $p < 0.01$*

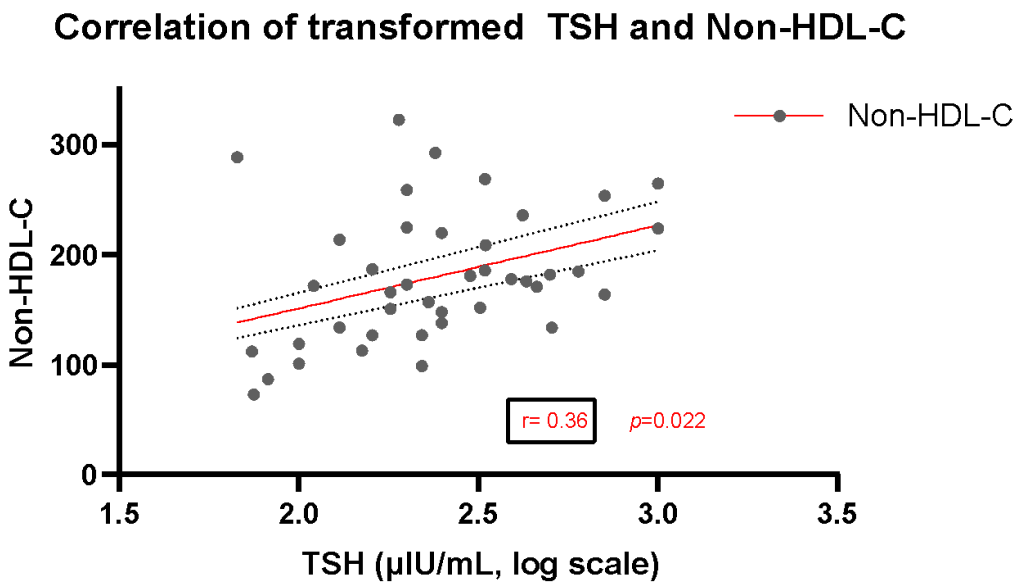

Figure 2: Correlation between serum TSH and Non-HDL-C (n=71).

To determine the independent effect of TSH on Non-HDL-C in hypothyroid patients, a hierarchical multiple linear regression was performed. The results, presented in Table 3, which shown progressively adjustment for key confounders(age, sex and BMI).

In the initial, unadjusted Model (crude or Model 1), TSH as the sole predictor showed a positive association with Non-HDL-C that was borderline and did not reach statistical significance (β = 0.713, p = 0.055). This model explained 7.0% of the variance in Non-HDL-C (Adj. R^2 = 0.070).

After the model was adjusted for age and sex (Model 2), the relationship between TSH and Non-HDL-C strengthened and became statistically significant (β = 0.938, p = 0.022). The explanatory power of this model increased to 11.4% (Adj. R^2 = 0.114).

In the final, fully adjusted model (Model 3), which controlled for age, sex, and BMI, TSH remained a significant and independent predictor of Non-HDL-C levels (β = 0.869, 95% CI [0.057, 1.681], p = 0.037), for every 1 µIU/mL increase in serum TSH, Non-HDL-C is expected to increase by 0.869 mg/dL. In this fully adjusted model, none of the other covariates—Age (p = 0.493), Sex (p = 0.096), or BMI (p = 0.323) were found to be significant independent predictors of Non-HDL-C. The final model passed all assumption checks, with variance inflation factors (VIF) below 1.5, confirming no issues with multicollinearity.

Table 3: Hierarchical Multiple Linear Regression Predicting Non-HDL-C in Hypothyroid Patients.

Model and Predictors	Coefficient (β*)	95% Confidence Interval	*p*-value

Model 1 (Crude)			
Adj. $R^2 = 0.070$			
TSH	0.713	[-0.016, 1.442]	0.055
Model 2 (Age + Sex Adjusted)			
Adj. $R^2 = 0.114$			
TSH	0.938	[0.145, 1.730]	0.022*
Age	-1.137	[-2.433, 0.158]	0.081
Sex (Male)	33.00	[-8.514, 74.51]	0.116
Model 3 (Fully Adjusted)			
Adj. $R^2 = 0.106$			
TSH	0.869	[0.057, 1.681]	0.037*
Age	-0.472	[-1.871, 0.926]	0.493
Sex (Male)	36.31	[-6.712, 79.34]	0.096
BMI	-1.418	[-4.275, 1.439]	0.323

**β = unstandardized regression coefficient. * $p < 0.05$. Model 1: TSH only. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, and BMI. All models passed assumption checks; VIF for all predictors in Model 3 was < 1.5, indicating no multicollinearity.*

To evaluate the specificity of the primary finding that, TSH as independent predictor of Non HDL, we conducted a sensitivity analysis. The fully adjusted regression (Model 3) was repeated but substituted the primary outcome (Non-HDL-C) with four other commonly used atherogenic indices: the Atherogenic Index of Plasma (AIP), Castelli's Risk Index I (CRI-I), Castelli's Risk Index II (CRI-II), and the Atherogenic Coefficient (AC). The results are presented in Table 4. Demonstrate a distinect contrast to the significant association observed with Non-HDL-C, TSH was not a significant independent determinant for any of these alternative indices.

After adjusting for age, sex, and BMI, TSH showed no statistical association with AIP ($\beta = -0.0002$, $p = 0.888$), CRI-I ($\beta = 0.012$, $p = 0.678$), CRI-II ($\beta = 0.013$, $p = 0.628$), or AC ($\beta = 0.012$, $p = 0.678$). This lack of association suggests that the independent metabolic effect of TSH is specifically related to the Non-HDL-C metric and does not extend to these other composite lipid ratios.

Table 4: Association of TSH with Alternative Atherogenic Indices (Fully Adjusted Model).

Dependent Variable (Atherogenic Index)	**TSH Coefficient (β)**	**95% Confidence Interval**	***p*-value**
AIP (log ratio)	-0.0002	[-0.004, 0.003]	0.888
CRI-I (ratio)	0.012	[-0.046, 0.070]	0.678
CRI-II (ratio)	0.013	[-0.040, 0.066]	0.628
AC (ratio)	0.012	[-0.046, 0.070]	0.678

Values represent the coefficient (β) and p-value for TSH from separate multiple linear regression models for each index. All models are fully adjusted for age, sex, and BMI.

Discussion

All atherogenic ratios were elevated in the hypothyroid patient group ($p < 0.001$ for all) which consistent with our previous study.[12] The principal finding of this study is that serum thyroid-stimulating hormone (TSH) is a statistically significant and independent determinant of non-high-density lipoprotein cholesterol (Non-HDL-C) levels in patients with hypothyroidism (Table 3). This association, initially observed in the unadjusted analyses, persisted after adjustment for age, sex, and BMI. Furthermore, this independent effect of TSH appears highly specific, as no significant association was found with other atherogenic indices, including the atherogenic index of plasma (AIP), Castelli's Risk Index I (CRI-I), or CRI-II (Table 4). Our finding that the TSH–Non-HDL-C association is independent of BMI contrasts with studies such as Ruhla et al., which demonstrated that the association between high-normal TSH and dyslipidemic components of metabolic syndrome was present only in individuals with obesity (BMI ≥ 30 kg/m²) and absent in lean individuals (BMI <25 kg/m²).[13] It aligns, however, with emerging evidence that TSH may have metabolic effects dissociated from adiposity.[14]

This challenges other models, such as that proposed by Chubb et al,[15] which assume that the TSH-dyslipidemia relationship is dependent on insulin sensitivity. Additional evidence suggests a complex interplay, with one study indicating that the TSH-obesity link can exist independently of its effect on dyslipidemia and that TSH was not an independent risk factor for nonalcoholic fatty liver disease.[16] A compelling biological basis for our results is provided by the documented presence of functional TSH receptors (TSHR) in extra-thyroidal tissues,[17] including hepatocytes,[18] and adipocytes,[19] suggesting direct pathways through which TSH may influence metabolic homeostasis.

By direct action on TSH receptors on preadipocytes, TSH, influence differentiation of adipocytes and contributes to regulation of lipolysis in adipocytes,[20] and thermogenesis through induction of uncoupling protein-1,[21] providing a pathway for TSH to correlate with body fat percentage and BMI without BMI being a confounder in the statistical model so TSH could influence adiposity independently of its classic endocrine axis by direct mechanism. Biologically, this association may be explained by the presence of functional TSH receptors (TSHR) in hepatocytes. Activation of hepatic TSHRs has been shown to upregulate HMG-CoA reductase via the cAMP/PKA/CREB pathway, directly increasing cholesterol synthesis,[22] and by suppressing the enzyme AMPK,[23] which normally inactivates HMGCR via phosphorylation. TSH contributes to the expression of PCSK9, a serum protease that degrades the LDL receptor (LDL-R) in the liver. With fewer LDL-Rs, the liver cannot effectively clear LDL-C from the bloodstream, leading to its accumulation.[24] This effect is mediated through the transcription factors SREBP-1C/2.

TSH upregulates the cholesterol efflux transporter ABCA1, which can paradoxically increase plasma cholesterol levels by promoting the release of cellular cholesterol into the bloodstream.[25] It also alters the activity of key proteins such as cholesteryl ester transfer protein (CETP)and lecithin–cholesterol acyltransferase (LCAT), which are critical for HDL maturation and function, further contributing to an atherogenic profile.[26] These findings, integrated within the conceptual framework of an "adipose-liver axis," provide a coherent physiological basis for our statistical model, explaining how TSH can function as an independent predictor of Non-HDL-C.

The specificity of this association is a pivotal finding of our study. While TSH demonstrated a significant, independent relationship with Non-HDL-C (p=0.037), it showed no such association with other atherogenic indices (all $p > 0.6$). We hypothesize that this specificity arises because Non-HDL-C serves as the most robust simple surrogate for the total burden of apolipoprotein B (ApoB)-containing lipoproteins. The mechanistic pathways described namely, decreased ApoB particle clearance via PCSK9 upregulation and increased hepatic very-low-density lipoprotein (VLDL) production driven by adipocyte lipolysis directly modulate the concentration of atherogenic particles in the bloodstream. Non-HDL-C quantifies the cholesterol content within this entire spectrum of atherogenic particles, including VLDL, intermediate-density lipoprotein (IDL), LDL, and lipoprotein(a),[27] thereby capturing the cumulative pro-atherogenic risk conferred by elevated TSH levels. In contrast, composite ratios like AIP or CRI can appear normal even when the absolute burden of atherogenic particles is high, making them less sensitive to this specific TSH-driven effect. Clinically, These findings reinforce contemporary clinical guidelines that advocate for Non-HDL-C as a primary or secondary lipid target, especially in patients with metabolic risk factors. Our results align with recent findings by Al Fahdi et al,[28] who reported significantly higher atherogenic lipid fractions in hypothyroid patients compared to euthyroid controls in a distinct regional cohort. For clinicians managing hypothyroidism, monitoring Non-HDL-C may provide a more comprehensive assessment of atherogenic risk than LDL-C alone.[29] After emerging therapies such as PCSK9 inhibitors, bempedoic acid, and inclisiran which have benefits in lowering both non-HDL-C and Apo B and in reducing cardiovascular events, further validating their clinical relevance.[30,31] However, we emphasize caution in extrapolating these results to subclinical hypothyroidism (SCH), as our cohort had overt disease. Dedicated studies in SCH are required to determine if a similar independent relationship exists at lower TSH levels and whether it influences treatment thresholds.

This study has several key strengths, most notably its investigated of TSH as an independent predictor of atherogenic risk, the application of the comprehensive lipid metric Non-HDL-C, and a robust analytical approach that carefully controlled for confounders like BMI. The interpretation of our results, however, should be tempered by certain limitations. First, the study design precludes definitive causal

inferences; we observe associations, not direct causation. Second, while we adjusted for BMI, we lacked data on Free T4 (fT4) and direct markers of insulin resistance (e.g., HOMA-IR). Consequently, we cannot fully rule out that the observed effects are partially mediated by subtle differences in thyroid hormone levels or insulin sensitivity. Finally, as a single-center study in Iraq, the generalizability of these findings to other ethnic populations requires validation

Conclusion

This work demonstrated that serum TSH is an independent determinant of Non-HDL-C in hypothyroidism, an association not mediated by adiposity. This finding lends credence to the concept of an extra-thyroidal, direct metabolic role for TSH in promoting an atherogenic lipid profile.

Disclosure

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