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IMPACT OF SUBCLINICAL HYPOTHYROIDISM ON HEPATIC LYPOGENISIS

Alishba Tariq[*1], Muzamil Hussain[2], Ms. Rabia Butt[3], Dr. Atia Masood Ahmed Chaudhary[4], Syeda Iqra Batool Bukhari[5]

[*1]*BSc (hons) Medical lab Technology, Al-Razi Institute Lahore*
[2]*Senior Lecturer, Al-Razi Institute Lahore*
[3]*Head of MLT Department, Al-Razi Institute Lahore*
[4]*Assistant Professor of Biochemistry, Chandka Medical College (CMC), Pakistan*
[5]*Lecturer*

[2]khalifamuzamil12@gmail.com, [3]rabiabutt@alrazi.edu.pk, [5]iqrabukhari229@gmail.com

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Corresponding Author: *
Alishba Tariq

Abstract

Subclinical hypothyroidism (SCH), defined by elevated thyroid-stimulating hormone (TSH) with normal triiodothyronine (T3) and thyroxine (T4) levels, has been increasingly recognized as a metabolic condition associated with disturbances in hepatic lipid metabolism. The present cross-sectional analytical study aimed to evaluate the relationship between SCH and hepatic lipogenesis by comparing metabolic and liver function parameters between SCH patients and euthyroid controls. A total of 80 participants were included, equally divided into SCH patients (n = 40) and healthy controls (n = 40). Biochemical analyses included thyroid function tests, lipid profile, liver enzymes, and fasting glucose. Statistical analysis was performed using Mann–Whitney U test, Pearson correlation, and multiple regression analysis. Results demonstrated significantly higher levels of triglycerides, total cholesterol, LDL, ALT, AST, and fasting glucose in SCH patients compared to controls ($p < .001$), along with reduced HDL levels. TSH showed strong positive associations with triglycerides, LDL, total cholesterol, ALT, and AST, while HDL showed inverse relationships with metabolic and hepatic markers. Regression analysis revealed that TSH and fasting glucose were significant predictors of dyslipidemia and liver enzyme elevation, explaining up to 67% of variance in total cholesterol. No significant direct association was observed between Free T4 and lipid or liver parameters. In conclusion, SCH is significantly associated with dysregulation of lipid metabolism and hepatic enzyme elevation, suggesting a potential role in early hepatic lipogenesis and metabolic dysfunction. These findings highlight the clinical importance of early identification and monitoring of thyroid dysfunction to prevent progression toward metabolic and hepatic complications.

INTRODUCTION

Background

Subclinical hypothyroidism (SCH) is an early and often asymptomatic thyroid dysfunction characterized by elevated thyroid-stimulating hormone (TSH) with normal free thyroxine (FT4) levels. It affects approximately 3%–15% of adults worldwide and may reach higher prevalence in

older populations. SCH is clinically significant due to its progressive nature and its association with metabolic disturbances, particularly dyslipidemia and cardiovascular risk (Al-Hetar et al., 2025; Mawlood, 2026).

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is now recognized as the most prevalent chronic liver disorder globally. It is defined by hepatic fat accumulation exceeding 5% of hepatocytes in the absence of significant alcohol intake. MASLD is strongly associated with obesity, insulin resistance, and type 2 diabetes mellitus, and it may progress to steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma (Rinella & Sookoian, 2024; Zeng et al., 2025).

A central mechanism in MASLD pathogenesis is **hepatic lipogenesis**, driven by insulin resistance and activation of lipogenic transcription factors such as sterol regulatory element-binding protein-1c (SREBP-1c), carbohydrate-responsive element-binding protein (ChREBP), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC). These pathways increase de novo lipogenesis, resulting in triglyceride accumulation in hepatocytes and progressive liver injury (Bhatt et al., 2025; Paoli, 2025).

Rationale and Pathophysiological Link

Emerging evidence suggests a strong metabolic interaction between thyroid dysfunction and hepatic lipid metabolism. Thyroid hormones regulate basal metabolic rate, lipid oxidation, and hepatic cholesterol and triglyceride turnover. Even mild thyroid dysfunction, such as SCH, may disrupt hepatic lipid homeostasis through increased TSH-mediated activation of hepatic lipogenesis and insulin resistance pathways.

TSH receptors expressed in hepatocytes may directly influence SREBP-1c signaling, promoting lipogenesis independently of circulating thyroid hormone levels. Additionally, SCH is frequently associated with dyslipidemia, increased LDL cholesterol, and elevated triglycerides, all of which contribute to hepatic fat deposition and MASLD progression (Kuchay et al., 2024; Tamaki et al., 2026).

Despite increasing recognition of the thyroid–liver axis, the specific impact of SCH on hepatic lipogenic activity remains insufficiently defined, particularly at the molecular level.

Problem Statement

Although SCH is common and metabolically active, its direct role in regulating hepatic lipogenesis and lipid accumulation remains unclear. Existing studies primarily focus on overt hypothyroidism or clinical MASLD outcomes, with limited evidence on early molecular changes in lipogenic pathways under SCH conditions.

Objectives

The objective of this study was to evaluate the impact of subclinical hypothyroidism on hepatic lipogenesis by assessing changes in hepatic lipid metabolism markers (FAS and ACC), serum lipid profile (total cholesterol, triglycerides, LDL, and HDL), and key lipogenic transcription factors (SREBP-1c, PPAR-α, and ChREBP), and to determine their correlation with thyroid function parameters (TSH, FT3, and FT4).

Research Questions

1. How does SCH influence hepatic lipid metabolism markers (FAS and ACC)?
2. What changes occur in serum lipid profile in SCH compared to euthyroid individuals?
3. Does SCH alter hepatic expression of lipogenic transcription factors (SREBP-1c, PPAR-α, and ChREBP)?
4. What is the relationship between thyroid hormones and hepatic lipogenic activity in SCH?

Subclinical Hypothyroidism and Metabolic Risk

Subclinical hypothyroidism is increasingly recognized not merely as a benign biochemical abnormality but as a metabolic disorder associated with dyslipidemia, insulin resistance, and cardiovascular risk. Epidemiological studies indicate that SCH prevalence ranges from 0.76% to 16.7%, with higher rates in older populations and females (Hamid et al., 2024). SCH has been linked with metabolic syndrome components, including elevated triglycerides, increased waist

circumference, and impaired glucose metabolism (Al-Hetar et al., 2025).

MASLD represents a spectrum of metabolic liver disease characterized by excessive lipid accumulation in hepatocytes. Central to its pathogenesis is increased de novo lipogenesis (DNL), driven by insulin resistance and activation of lipogenic transcriptional regulators such as SREBP-1c and ACC. This process contributes to hepatic steatosis and progression toward inflammation and fibrosis (Paoli, 2025; Rinella & Sookoian, 2024).

Mitochondrial dysfunction, oxidative stress, and impaired fatty acid oxidation further exacerbate lipid accumulation in hepatocytes, reinforcing disease progression toward MASH and cirrhosis (Li et al., 2025).

Thyroid hormones play a crucial role in regulating hepatic lipid and glucose metabolism. They enhance fatty acid oxidation, modulate cholesterol synthesis, and influence bile acid metabolism. In the liver, thyroid hormones also regulate energy homeostasis through mitochondrial activity and thermogenesis (Hashimoto, 2022; Jeon et al., 2023).

The liver, in turn, is essential for thyroid hormone metabolism through deiodination and clearance pathways. Disruption of this axis in thyroid dysfunction contributes to metabolic imbalance and hepatic fat accumulation (Marino et al., 2025).

Multiple observational studies have demonstrated an association between SCH and MASLD. Elevated TSH levels, even within the mildly increased range, have been positively correlated with hepatic steatosis severity and fibrosis progression (Wang et al., 2024; Hu et al., 2026). Some studies suggest a dose-dependent relationship between TSH levels and liver fat accumulation.

However, findings remain inconsistent. While several cohort and meta-analytic studies support a positive association between SCH and MASLD, others report no significant relationship after adjusting for metabolic confounders (Kassem et al., 2025). These discrepancies may be due to heterogeneity in diagnostic criteria, population differences, and study design limitations.

Mechanistic Insights

Proposed mechanisms linking SCH to hepatic lipogenesis include:

- TSH-mediated activation of hepatic SREBP-1c signaling
- Increased insulin resistance and free fatty acid flux to the liver
- Dyslipidemia contributing to triglyceride accumulation
- Low-grade inflammation and adipokine imbalance
- Cross-talk between thyroid axis and gut–liver metabolic pathways

These mechanisms collectively promote de novo lipogenesis and hepatic fat deposition, contributing to MASLD development and progression (Kuchay et al., 2024; Bhatt et al., 2025).

Research Gap

Despite growing evidence linking thyroid dysfunction and MASLD, limited studies have specifically examined the **molecular effects of SCH on hepatic lipogenesis pathways**. In particular, the role of key transcription factors (SREBP-1c, ChREBP, PPAR-α) and enzymatic regulators (FAS, ACC) in SCH remains underexplored.

Materials and Methods

Study Design

This cross-sectional analytical study was conducted to investigate the impact of subclinical hypothyroidism (SCH) on hepatic lipogenesis by comparing biochemical and metabolic parameters between SCH patients and euthyroid controls.

Study Setting and Duration

The study was carried out in the clinical pathology laboratory of a tertiary care hospital over a period of 6–12 months, including participant recruitment, laboratory investigations, and data analysis.

Study Population

A total of 80 adult participants (aged 18–60 years) were enrolled and divided into two groups: (a) subclinical hypothyroid patients (n = 40) with

elevated thyroid-stimulating hormone (TSH) and normal free triiodothyronine (FT3) and free thyroxine (FT4), and (b) euthyroid healthy controls (n = 40). Groups were matched for age and sex.

Inclusion and Exclusion Criteria

Participants aged 18–60 years with SCH (elevated TSH with normal FT3 and FT4) or normal thyroid function were included after providing informed consent. Individuals with overt thyroid disease, chronic liver disease, diabetes mellitus, metabolic syndrome, alcohol consumption, pregnancy or lactation, or those receiving thyroid or lipid-altering medications were excluded.

Sampling Technique

A non-probability convenience sampling technique was used to recruit eligible participants from outpatient departments based on predefined criteria.

Data Collection and Sample Processing

Demographic and clinical data, including age, sex, body mass index (BMI), and medical history, were recorded using a structured proforma. After an overnight fast of 8–12 hours, 5 mL of venous blood was collected under aseptic conditions. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at 2–8°C for short-term analysis or −20°C for long-term storage. Hemolyzed samples were excluded.

Biochemical Analysis

Thyroid function tests (TSH, FT3, FT4) were measured using Chemiluminescent Microparticle Immunoassay (CMIA). Lipid profile parameters (total cholesterol, triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) and liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) were analyzed using standard enzymatic spectrophotometric methods. Hepatic lipogenesis markers, including fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), were assessed where available.

Analytical Methods

CMIA is based on antigen–antibody reactions with chemiluminescent signal detection measured in relative light units (RLU). Spectrophotometric assays determine analyte concentration based on light absorbance according to the Beer–Lambert law.

Quality Control

Internal quality control sera were analyzed daily, and instruments were calibrated according to manufacturer instructions. External quality assurance programs were followed to ensure analytical accuracy and reproducibility.

Statistical Analysis

Data were analyzed using SPSS software. Results were expressed as mean ± standard deviation (SD). Independent samples t-test was used to compare group differences, while Pearson's correlation was applied to assess relationships between thyroid and metabolic parameters. A p-value of $< .05$ was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Board. Written informed consent was obtained from all participants. Confidentiality and anonymity were strictly maintained throughout the study in accordance with ethical research guidelines.

Limitations

This study is limited by its cross-sectional design, relatively small sample size, and single-center setting. Potential confounders such as dietary habits, physical activity, and insulin resistance may also influence hepatic lipid metabolism.

RESULTS

Descriptive Characteristics of the Study Population

The present study included a total of 80 participants, comprising 40 subclinical hypothyroid patients and 40 euthyroid controls. The data were analyzed to compare demographic, biochemical, lipid, and hepatic parameters between the two groups and to examine the

relationship between thyroid function and markers of hepatic lipid metabolism. Statistical analyses included descriptive statistics, tests of normality, Mann–Whitney U test, Pearson correlation, and multiple linear regression. A p-value of $< .05$ was considered statistically significant for all analyses.

Table 1: ***Descriptive Statistics of Study Variables (N = 80)***

Variable	N	Min	Max	M	SD
Age (years)	80	20	59	38.99	11.36
TSH (mIU/L)	80	0.57	9.92	5.28	2.67
Free T4 (ng/dL)	80	0.81	1.79	1.27	0.29
Triglycerides (mg/dL)	80	93	278	169.73	49.91
Total Cholesterol (mg/dL)	80	155	280	212.35	35.65
HDL (mg/dL)	80	36	65	49.01	7.33
LDL (mg/dL)	80	81	190	129.91	31.63
ALT (U/L)	80	15	72	41.26	15.66
AST (U/L)	80	15	65	37.35	14.01
Fasting Glucose (mg/dL)	80	81	120	100.33	11.90

Note. *M = mean; SD = standard deviation.*

Table 1 presents descriptive statistics for all study variables, showing central tendency and variability across biochemical and clinical parameters. The results indicate elevated lipid and liver enzyme levels, suggesting metabolic dysregulation in the study population.

Table 2: ***Frequency Distribution of Study Participants by Group and Gender (N = 80)***

Variable	Category	f	%	Cumulative %
Group	Patients	40	50.0	50.0
	Controls	40	50.0	100.0
Gender	Female	63	78.8	78.8
	Male	17	21.3	100.0

Note. *f = frequency.*

Table 2 shows equal distribution of participants across study groups, ensuring balanced comparison. The sample was predominantly female, which may reflect higher healthcare utilization or disease prevalence in women.

Table 3: ***Test of Normality for Continuous Variables by Group***

Variable	Group	K-S Statistic	p (K-S)	S-W Statistic	p (S-W)
Free T4	Patients	.106	.200	.956	.118
Free T4	Controls	.109	.200	.932	.019
Age	Patients	.102	.200	.952	.087
Age	Controls	.113	.200	.944	.042
TSH	Patients	.094	.200	.957	.129
TSH	Controls	.121	.154	.942	.037

Note. K-S = Kolmogorov–Smirnov test; S-W = Shapiro–Wilk test.

Table 3 demonstrates partial violation of normality assumptions, as indicated by Shapiro–Wilk results in some variables. Therefore, non-parametric tests were applied for group comparisons.

Table 4: ***Mann–Whitney U Test Comparing Patients and Controls***

Variable	U	W	Z	p
Triglycerides	0.000	826.000	-7.698	< .001
Total Cholesterol	6.000	826.000	-7.640	< .001
LDL	0.000	820.000	-7.698	< .001
HDL	78.000	898.000	-6.947	< .001
ALT	24.000	844.000	-7.467	< .001
AST	16.000	836.000	-7.544	< .001
Fasting Glucose	8.000	828.000	-7.621	< .001

Note. *p < .05 indicates statistical significance.*

Table 4 shows significant differences between patients and controls across all metabolic and hepatic variables, indicating altered biochemical profiles in subclinical hypothyroidism.

Table 5: ***Pearson Correlation Matrix of Metabolic and Liver Parameters***

Variable	TG	TC	LDL	HDL	ALT	AST	Free T4
TG	1	.724**	.771**	-.650**	.604**	.722**	.126
TC	.724**	1	.710**	-.687**	.648**	.662**	-.002
LDL	.771**	.710**	1	-.653**	.689**	.703**	.095
HDL	-.650**	-.687**	-.653**	1	-.565**	-.639**	-.123
ALT	.604**	.648**	.689**	-.565**	1	.624**	.077
AST	.722**	.662**	.703**	-.639**	.624**	1	.112
Free T4	.126	-.002	.095	-.123	.077	.112	1

Note. ***p < .01 (two-tailed).*

Table 5 highlights strong positive associations among lipid and liver enzyme markers, while HDL shows consistent inverse relationships. Free T4 demonstrated weak, non-significant correlations with metabolic variables.

Table 6: ***Multiple Linear Regression Predicting Triglycerides***

Predictor	B	SE	β	t	p
Constant	7.450	42.035	—	0.177	.860
TSH	9.985	2.072	.534	4.820	< .001
Age	-0.482	0.317	-.110	-1.521	.133
Gender	7.119	8.801	.059	0.809	.421
Fasting Glucose	1.193	0.463	.285	2.577	.012

Note. R^2 = .614, Adjusted R^2 = .593.
TSH and fasting glucose emerged as significant predictors of triglyceride levels, explaining 61.4% of variance in the model.

Table 7
Multiple Linear Regression Predicting ALT

Predictor	B	SE	β	t	p
Constant	7.450	42.035	—	0.177	.860
TSH	9.985	2.072	.534	4.820	< .001
Age	-0.482	0.317	-.110	-1.521	.133
Gender	7.119	8.801	.059	0.809	.421
Fasting Glucose	1.193	0.463	.285	2.577	.012

Note. *R^2 = .631, Adjusted R^2 = .612.*

TSH and fasting glucose significantly predicted ALT levels, indicating thyroid-related hepatic involvement.

Table 8: *Multiple Linear Regression Predicting LDL*

Predictor	B	SE	β	t	p
Constant	-1.695	25.843	—	-0.066	.948
TSH	5.693	1.274	.480	4.470	< .001
Age	0.142	0.195	.051	0.727	.470
Gender	-1.754	5.411	-.023	-0.324	.747
Fasting Glucose	0.978	0.285	.368	3.436	.001

Note. *R^2 = .636, Adjusted R^2 = .617.*

TSH was the strongest predictor of LDL levels, indicating its role in lipid dysregulation.

Table 9: *Multiple Linear Regression Predicting Total Cholesterol*

Predictor	B	SE	β	t	p
Constant	43.499	27.766	—	1.567	.121
TSH	6.037	1.368	.452	4.412	< .001
Age	0.263	0.209	.084	1.257	.213
Gender	6.442	5.814	.074	1.108	.271
Fasting Glucose	1.185	0.306	.396	3.873	< .001

Note. *R^2 = .670, Adjusted R^2 = .652.*
This model explained the highest variance in lipid parameters, with TSH and fasting glucose as significant predictors.

Table 10
Comparison of Liver Enzymes Between Groups

Group	ALT (M ± SD)	AST (M ± SD)	N
Patients	53.94 ± 10.44	48.96 ± 9.93	40
Controls	28.59 ± 7.63	25.74 ± 4.74	40

Note. *M = mean; SD = standard deviation.*

Patients exhibited significantly higher ALT and AST levels compared to controls, indicating hepatic involvement in subclinical hypothyroidism.

DISCUSSION

This study demonstrated a significant association between subclinical hypothyroidism (SCH) and altered hepatic lipid metabolism, supporting its role as an early metabolic disorder rather than a purely asymptomatic endocrine condition. SCH patients exhibited significantly elevated triglycerides, total cholesterol, LDL, fasting glucose, and liver enzymes compared to euthyroid controls ($p < .001$), indicating early dysregulation of hepatic lipogenesis.

The strong association between TSH and lipid abnormalities suggests that even mild thyroid dysfunction contributes to metabolic imbalance. Regression analysis identified TSH as the most powerful predictor of triglycerides, LDL, total cholesterol, and ALT, explaining a substantial proportion of metabolic variance (R^2 up to 67%). These findings are consistent with evidence that thyroid hormones regulate hepatic lipid metabolism through control of de novo lipogenesis, fatty acid oxidation, and LDL receptor activity. In SCH, reduced thyroid hormone signaling and elevated TSH may enhance hepatic lipogenic pathways, particularly via SREBP-1c activation, leading to triglyceride accumulation and hepatic fat deposition.

The strong positive correlations between lipid parameters and liver enzymes further suggest hepatocellular stress associated with dyslipidemia. Elevated ALT and AST levels in SCH patients indicate early hepatic involvement, possibly reflecting subclinical progression toward

metabolic dysfunction-associated steatotic liver disease (MASLD).

Conversely, HDL levels showed significant inverse relationships with all metabolic markers, highlighting its protective metabolic role. The absence of significant association between FT4 and lipid parameters supports the hypothesis that TSH-mediated pathways may play a more direct role in metabolic regulation in SCH.

Overall, the findings reinforce the concept that SCH is metabolically active and may contribute to early hepatic lipogenesis through endocrine–metabolic interactions. Early identification of SCH may therefore be important for preventing progression toward dyslipidemia and MASLD.

Limitations

This study is limited by its cross-sectional design, modest sample size, and single-center setting, which restrict causal inference and generalizability. Dietary habits, physical activity, and insulin resistance were not fully controlled and may act as confounders.

Subclinical hypothyroidism is significantly associated with dyslipidemia and elevated hepatic enzymes, suggesting its role in promoting hepatic lipogenesis. TSH appears to be a key metabolic regulator influencing lipid accumulation and liver function. Early detection and management of SCH may help prevent progression to metabolic and hepatic disorders, including MASLD.