UNMASKING CARDIOVASCULAR RISK IN SUBCLINICAL HYPOTHYROIDISM: THE INTERPLAY OF DYSLIPIDEMIA AND OXIDATIVE STRESS

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ABSTRACT:

Background: Subclinical hypothyroidism (SCH) is an endocrine disorder characterized by elevated thyroid-stimulating hormone (TSH) levels and normal concentration of circulating thyroid hormone. Emerging evidence suggests that SCH may contribute to dyslipidemia, impaired glucose metabolism, oxidative stress, and increased cardiovascular risk. The present study aimed to evaluate alterations in the extended lipid profile, sugar profile, and total antioxidant capacity (TAC) in patients with SCH and to investigate their association with serum TSH levels.

Methodology: In this study, we have considered a total of 410 subjects, consisting of 205 controls and 205 cases of subclinical hypothyroidism. This cross-sectional study included adults aged 18–60 years diagnosed with SCH and age- and sex-matched euthyroid healthy controls. Fasting blood samples were collected for estimation of thyroid profile, extended lipid profile [total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, VLDL-C, non-HDL-C, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), ApoB/ApoA1 ratio, and atherogenic indices], sugar profile [fasting blood sugar (FBS), postprandial blood sugar (PPBS), and HbA1c], and total antioxidant capacity. Statistical analysis was performed to compare biochemical parameters between groups and to assess correlations between TSH levels and study variables by using the Statistical Package for the Social Sciences (SPSS) software version 29.

Results: Patients with SCH demonstrated significantly higher levels of TC, TG, LDL-C, non-HDL-C, ApoB, ApoB/ApoA1 ratio, and atherogenic indices compared with controls, while HDL-C and ApoA1 levels were significantly lower. The SCH group also exhibited significantly elevated FBS, PPBS, and HbA1c levels, indicating impaired glucose metabolism. The total antioxidant capacity was significantly reduced among SCH subjects, indicating increased oxidative stress. Serum TSH levels showed significant positive correlations with atherogenic lipid parameters and glycemic indices and a significant negative correlation with TAC.

Conclusion: Subclinical hypothyroidism is associated with adverse alterations in lipid metabolism, impaired glycemic status, and reduced antioxidant defense, all of which may contribute to increased cardiovascular risk. Assessment of extended lipid parameters, sugar profile, and total antioxidant capacity may provide valuable insights for early identification and management of cardiovascular risk in patients with SCH.

Keywords: Subclinical hypothyroidism; thyroid-stimulating hormone; Total antioxidant capacity

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Introduction:

In addition to being the primary cause of death globally, cardiovascular diseases (CVDs) are also the primary cause of morbidity and have a significant financial impact on healthcare systems. To lessen the burden of CVD, treatment and preventative measures must be improved. Over 10% of adults in general suffer from thyroid abnormalities, which are the most common endocrine illnesses. Since they control growth, development, and energy metabolism

beginning during intrauterine life, thyroid hormones (THs), namely free triiodothyronine (fT3) and free thyroxine (fT4), are crucial to human homeostasis. Because TH receptors (TRs) are widely distributed, the heart and vascular endothelial tissues also have them. [1-4]

Deficient thyroid hormone production is the hallmark of hypothyroidism, a common endocrine illness that can range from overt disease to the more common subclinical form (SCH). A notable female preponderance (female-to-male ratio up to 4-5:1) and a discernible rise in occurrence with increasing age, especially beyond 60 years, are repeatedly shown by epidemiological research. The incidence of hypothyroidism in adults in China is around 9.3% overall, with the prevalence of SCH being significantly higher at 8.7% as opposed to 1.1% for the overt type. Additionally, there are geographical differences; northwest China has been shown to have greater incidence rates.[5-9]

Subclinical hypothyroidism has been conclusively shown to be an independent risk factor for the onset of cardiovascular disease (CVD) and related death. The danger goes beyond SCH since a greater thyroid-stimulating hormone (TSH) level is linked to a negative cardiovascular risk profile even within the traditional euthyroid reference range. Although the exact pathophysiological processes behind this link are still unclear, this shows a continuum of risk associated with TSH concentrations.[10-14]

These pathways are thought to entail systemic metabolic changes and direct impacts on vascular endothelial function. Patients with SCH frequently have dyslipidaemia, which is characterized by high levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C). Moreover, these people often have increased homocysteine (Hcy), a hallmark of endothelial dysfunction and thrombotic risk. Notably, Hcy and oxidized low-density lipoprotein (ox-LDL) both exacerbate atherosclerosis by promoting inflammatory processes and endothelial dysfunction. While Hcy causes oxidative stress and reduces nitric oxide bioavailability, ox-LDL promotes foam cell production and plaque instability.[15-18] As a result, there is increasing interest in the function of other newly discovered biomarkers that are essential to atherogenesis, such as ox-LDL, which is a major cause of plaque formation; apolipoproteins (ApoA1 and ApoB), which offer a detailed evaluation of cardiovascular risk; and lipoprotein(a) [Lp(a)], a significant independent genetic risk factor. In clinical practice, ox-LDL and Hcy are not regularly examined despite their proven involvement in atherosclerosis. This emphasizes how important it is for research like ours to assess their usefulness in risk categorization.

It's crucial to remember that SCH seldom happens alone. It is often linked to elements of the cardio-metabolic renal (CMR) syndrome, such as insulin resistance, dyslipidaemia, and hypertension, indicating common underlying pathways of endothelial dysfunction and chronic inflammation.[19] Comprehensive research is essential because to the high occurrence of SCH, its metabolic aftereffects, and the possible cardiovascular effects of high-normal TSH levels.

Thus, the present study was undertaken to systematically evaluate the relationship between TSH levels, spanning from high to normal euthyroid status to overt hypothyroidism, and a range of potential cardiovascular and metabolic risk markers. These include an extended lipid profile (lipid profile with Apo A and Apo B), glycaemic parameters such as FBS, PPBS, and HbA1c, as well as Total antioxidant capacity (TAC), a marker for oxidative stress status. By examining these parameters collectively, the study aims to provide a comprehensive assessment of the metabolic alterations associated with thyroid disfunction.

Furthermore, the findings are compared with those reported in similar studies across diverse populations and geographical regions and are interpreted within the broader framework of oxidative stress, insulin resistance, dyslipidemia, and cardiovascular risk associated with subclinical hypothyroidism.

Material & methods:

In this study, we included a total of 410 subjects, consisting of 205 controls and 205 cases of subclinical hypothyroidism based on serum TSH and FT4 levels to assess the extended lipid profile (including TC, TG, HDL, LDLC, VLDLC and Apo A and Apo B), oxidative stress marker like total antioxidant capacity (TAC) and, sugar profile (FBS, PPBS, HbA1c) in patients with subclinical hypothyroidism and correlate these findings with cardiovascular risk. All questionnaires and investigations which are mentioned were done at OPD, Department of Biochemistry and Department of General Medicine of Santosh Medical College & Hospital, SDTU Ghaziabad, Uttar Pradesh, India and Saraswathi Medical college, Pilkhuwa, Hapur, Uttar Pradesh, India. The study protocol was approved by the institutional review and ethics board **(**letter no- **F. No. SU/R/2024/1548 [1])**. Written informed consent was obtained from all the patients.

Inclusion &exclusion criteria:

Adult participants aged 18–60 years of either sex who were diagnosed with subclinical hypothyroidism based on clinical and biochemical criteria were included in the study. Eligible participants were recruited after obtaining informed consent and underwent detailed clinical and laboratory evaluation.

Individuals with a known history of overt thyroid disorders, including hypothyroidism or hyperthyroidism, thyroid malignancy, or those receiving treatment for any thyroid condition were excluded to avoid potential confounding effects on thyroid function and metabolic parameters. Participants with a history of cardiovascular disease, renal failure, or HIV infection were also excluded because these conditions may independently influence lipid metabolism and oxidative stress status. In addition, individuals receiving medications known to interfere with thyroid hormone synthesis, metabolism, or serum thyroid hormone concentrations, such as amiodarone, were excluded from the study. These criteria were applied to ensure a relatively homogeneous study population and to minimize the influence of factors that could affect the biochemical variables under investigation.

Estimation of biochemical parameters:

Each participant underwent a thorough review of their medical history followed by a comprehensive questionnaire and physical examination. After this initial assessment, fasting blood samples were collected, allowed to clot and serum or plasma were separated and stored at 4^0C for further analysis. Thyroid hormone levels—including free T4, free T3, and TSH—were analyzed using the MINI VIDAS immunoassay system. Lipid parameters such as total cholesterol (TC), HDL-C, triglycerides (TG), Apo A and Apo B, Sugar profile (FBS, PPBS, HbA1c) were directly measured with the help of the Erba XL 640 Clinical Chemistry Analyzer using standard kits as per the manufacturer's protocol. Total antioxidant capacity was measured by using a commercially available kit from Amplicon Biotech (Abokine) on a microplate reader, the ferric reducing antioxidant power (FRAP) technique was used to estimate total antioxidant capacity. Meanwhile, the values for LDL-C and VLDL-C were calculated using Fried Ewald's formula.

Statistical analysis:

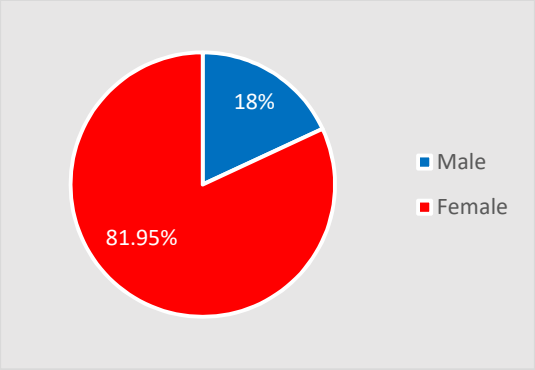
A statistical analysis was conducted to evaluate the relationship between thyroid function tests and extended lipid profile parameters, sugar profile and total antioxidant capacity in individuals with subclinical hypothyroidism, as well as their potential impact on cardiovascular risk. Continuous data were expressed as means with standard deviations, while categorical data were presented as frequencies and percentages. Pearson's correlation coefficient was used to assess linear relationships between continuous variables. Data visualization included bar charts for categorical data comparisons and scatter plots to illustrate correlations. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software version 29.

Results:

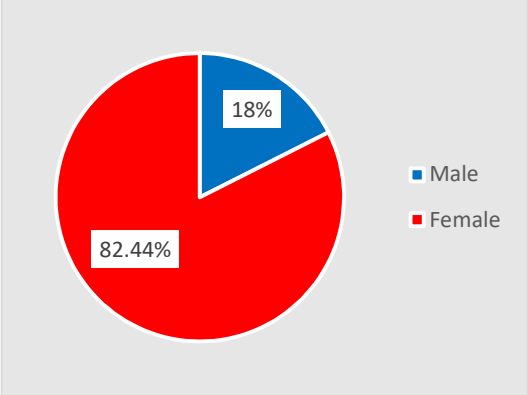
Gender and age distribution by the proportion and frequency between healthy controls and individuals with subclinical hypothyroidism (SCH) are presented in Table 1 and illustrated in graph 1 and 2. Initial demographic and clinical features and comparative analysis of control subjects and SCH patients are shown in Table 2, and depicted in Graph 3, which comprises the SCH. Comparative analysis of the extended lipid profile, glycemic parameters [fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycated hemoglobin (HbA1c)], and total antioxidant capacity (TAC) between the two groups is summarized in Table 3 and depicted in graphs 4, 5, and 6. Furthermore, the associations between serum thyroid-stimulating hormone (TSH) levels and extended lipid parameters, glycemic indices, and TAC were evaluated using correlation analysis. The results of these analyses are presented in Tables 4 and 5. Calculated values of atherogenic indices of SCH cases for assessment of cardiovascular risk are shown in Table 6,

Table1: Gender and age distribution by the proportion and frequency between control and case participants.

Demographical data	Categories	Groups	
		Controls N= 205	Case N= 205
Gender	Female	168	169
	Percentage	81.95%	82.44 %
	Male	37	36
	Percentage	18.05%	17.56 %
Age	Mean ± SD	35.81 ± 12.04	36.58 ± 12.47



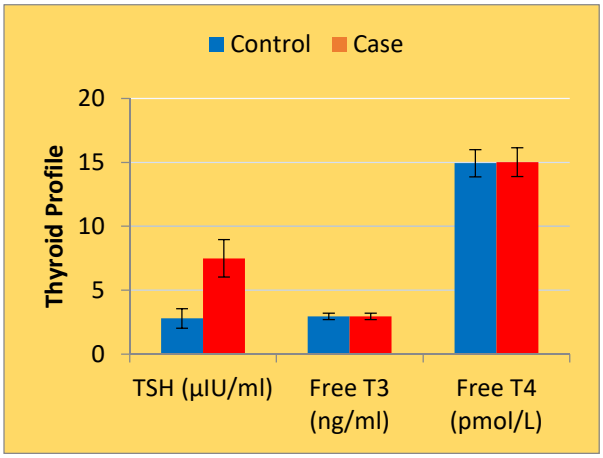
Graph 1: Percentage distribution of gender in control group.



Graph 2: Percentage distribution of gender in case group.

Table 2: Initial demographic and clinical features of Control subjects and SCH patients.

	Healthy Control (N=205) Mean ± SD	**SCH Cases (N=205) Mean ± SD**	**t-value**	**p-value**
Age	35.81 ± 12.04	36.58 ± 12.47	0.636	0.525
Sex (F/M)	168/37	169/36		0.89
BMI (kg/m^2)	24.21±3.13	23.81±2.33		0.33
TSH (µIU/ml)	2.79 ± .77	7.49 ± 1.46	40.48	0.001
Free T3 (ng/ml)	2.95 ± .25	2.95 ± .24	0.00	1.000
FreeT4 (pmol/L)	14.93 ± 1.06	15.02 ± 1.12	0.889	0.375



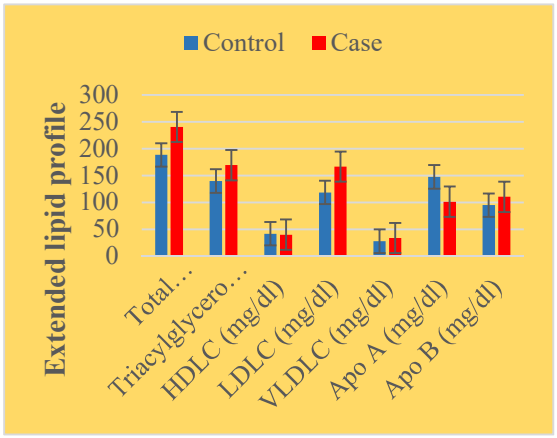
Graph 3: A bar graph that compares the thyroid profile features of SCH patients and healthy controls.

Table 3: Comparative study of Extended lipid profile, Sugar profile and Total antioxidant capacity between Control and SCH patients.

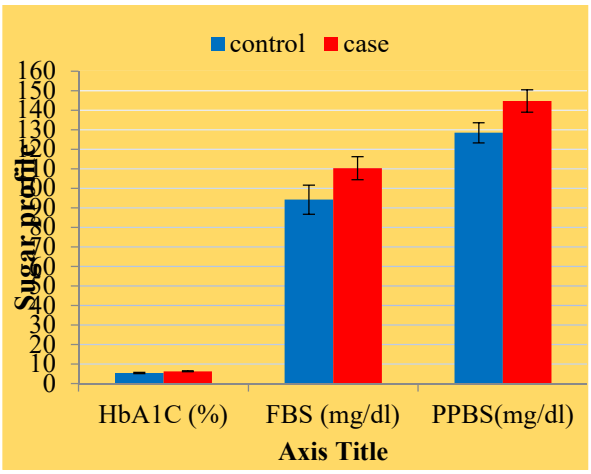
"Independent t test applied for comparison between control and case."

Parameters	Healthy Controls (N=205)	SCH Cases (N =205)	t-value	p-value
TC (mg/dl)	188.36 ± 13.17	240.28 ± 40.12	17.60	0.001
TG (mg/dl)	139.84 ± 15.92	169.32 ± 47.70	08.39	0.001
HDLC (mg/dl)	41.79 ± 3.08	39.93 ± 1.73	-07.53	0.001
LDLC (mg/dl)	118.60 ± 13.75	166.53 ± 38.29	16.86	0.001
VLDLC (mg/dl)	27.96 ± 3.18	33.77 ± 9.50	08.29	0.001
Apo A (mg/dl)	147.65 ± 9.58	101.22 ± 13.00	-41.13	0.001
Apo B (mg/dl)	94.92 ± 4.47	110.39 ± 12.11	17.15	0.001
HbA1C (%)	5.42 ± 0.40	6.29 ± 0.28	25.26	0.001
FBS (mg/dl)	94.15 ± 7.41	110.26 ± 5.87	24.38	0.001
PPBS (mg/dl)	128.41 ± 5.15	144.69 ± 5.71	30.27	0.001
TAC (µmol/L)	1273.53 ± 43.50	1095.53 ± 117.62	-20.32	0.001

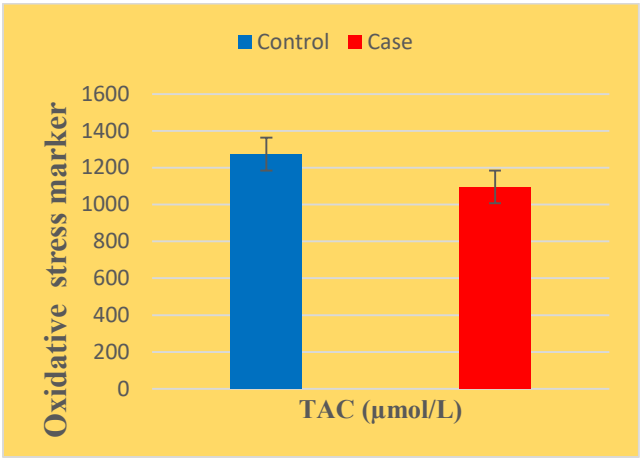
Correlation	Correlation coefficient (r value)	p – value
Total Cholesterol (mg/dl)	-0.040	0.570
Triacylglycerol (mg/dl)	- 0.092	0.192
HDL- C (mg/dl)	- 0.011	0.874
LDL– C (mg/dl)	- 0.015	0.836
VLDL (mg/dl)	- 0.092	0.192
Apo- A (mg/dl)	- 0.049	0.481
Apo- B (mg/dl)	0.075	0.283
HbA1C (%)	0.028	0.689
FBS (mg/dl)	-0.120	0.086
PPBS (mg/dl)	-0.137	0.051
TAC (µmol/L)	-0.033	0.642



Graph 4: Bar graph showing comparative distribution of extended lipid profile and apolipoprotein parameters in healthy controls and SCH subjects.



Graph 5: Bar diagram showing the glycemic indices HbA1c, fasting blood sugar (FBS) and postprandial blood sugar (PPBS) in healthy controls and subclinical hypothyroidism (SCH) participants.



Graph 6: This bar diagram represents a comparison of total antioxidant capacity (TAC) between healthy controls and SCH subjects.

Table 4: Correlation of TSH with Extended lipid profile, sugar profile and Total antioxidant capacity in Control.

Atherogenic Indices	Calculated values	Normal range	Interpretation
Atherogenic index of plasma	0.268	Low risk < 0.11 Intermediate 0.11 – 0.21 High risk > 0.21	High risk
Castelli risk index I	6.02	Ideal < 4 Border line: 4- 5 High risk: > 5	High risk
Castelli risk index II	4.17	Ideal: < 3	High risk
Atherogenic coefficient	5.02	< 3	High risk
Non-HDLC	200.35	Optimal: < 130mg/dl Border line: 130 – 159mg/dl High: ≥160mg/dl	High risk

Table 5: Correlation of TSH with Extended lipid profile, sugar profile and Total antioxidant capacity in SCH Case.

Correlation	Correlation coefficient (r value)	p – value
Total Cholesterol (mg/dl)	0.494	0.001
Triacylglycerol (mg/dl)	0.079	0.259
HDL- C (mg/dl)	-0.186	0.008
LDL– C (mg/dl)	0.499	0.001
VLDL (mg/dl)	0.092	0.190
Apo- A (mg/dl)	-0.247	0.001
Apo- B (mg/dl)	0.111	0.113
HbA1C (%)	0.481	0.001
FBS (mg/dl)	0.159	0.023
PPBS (mg/dl)	0.009	0.897
TAC (µmol/L)	-0.772	0.001

Table 6: Calculated values of atherogenic indices of SCH cases for assessment of cardiovascular risk.

Discussion:

The present cross-sectional study evaluated alterations in the extended lipid profile, glycaemic parameters, total antioxidant capacity (TAC), and cardiovascular risk indices in patients with subclinical hypothyroidism (SCH). The study included SCH patients (N =205) and age- and sex-matched healthy controls (N= 205). A higher prevalence of SCH was observed among females, consistent with previous reported studies indicating increased susceptibility of women to thyroid dysfunction and its associated metabolic disturbances.

The biochemical profile of SCH patients were characterized by significantly elevated serum TSH levels with normal FT3 and FT4 concentrations, confirming the diagnosis of SCH. Despite preserved circulating thyroid hormone levels, SCH patients demonstrated significant metabolic abnormalities, suggesting that even mild thyroid dysfunction may adversely affect cardiovascular health.[20,21]

SCH patients exhibited a markedly atherogenic lipid profile, including increased total cholesterol, triglycerides, LDL-C, VLDL-C, Apo B, and non-HDL-C, along with reduced HDL-C and Apo A levels. These findings support the hypothesis as role of thyroid hormones in regulating lipid metabolism and indicate impaired clearance of atherogenic lipoproteins in SCH. The elevated Apo B and reduced Apo A levels further suggest an increased burden of atherogenic particles and early atherosclerotic changes.[22,23]

In addition, SCH patients showed significantly higher fasting blood glucose, postprandial blood glucose, and HbA1c levels, indicating impaired glycaemic control and possible insulin resistance. These metabolic

alterations may contribute synergistically to cardiovascular risk. A significant reduction in TAC was also observed, reflecting compromised antioxidant defense and increased oxidative stress. Oxidative stress promotes LDL oxidation, endothelial dysfunction, and vascular inflammation, thereby accelerating atherosclerotic processes.[24]

Correlation analysis revealed significant positive associations of TSH with total cholesterol, LDL-C, fasting glucose, and HbA1c, while significant negative correlations were observed with HDL-C, Apo A, and TAC. Among these, the strong inverse relationship between TSH and TAC suggests that oxidative stress may represent an important mechanism linking SCH to cardiovascular disease. These findings support the concept that elevated TSH may exert direct metabolic effects independent of circulating thyroid hormone concentrations.[25,26]

Furthermore, all calculated atherogenic indices, including AIP, Castelli Risk Indices I and II, Atherogenic Coefficient, and non-HDL-C, were significantly elevated in SCH patients, indicating a high cardiovascular risk profile. These indices provide a more comprehensive assessment of cardiovascular risk than conventional lipid parameters alone.[27]

Overall, the findings suggest that SCH is associated with significant dyslipidaemia, impaired glucose metabolism, reduced antioxidant capacity, and increased atherogenic risk despite normal FT3 and FT4 levels. Therefore, SCH should not be regarded as a benign condition. Early identification and comprehensive evaluation of lipid abnormalities, glycaemic status, oxidative stress, and atherogenic indices may help in identifying individuals at increased cardiovascular risk and facilitate timely intervention.

Conclusion:

In SCH, elevated TSH levels correlate with an atherogenic lipid profile, impaired glucose regulation, and reduced total antioxidant capacity, indicating increased oxidative stress and cardiovascular risk. The significantly higher atherogenic indices further support the presence of early cardiometabolic dysfunction in SCH. These findings suggest that SCH should not be considered a benign condition, and early screening with comprehensive metabolic and oxidative stress assessment may help identify individuals at increased risk of future cardiovascular disease.

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