ORIGINAL ARTICLE

METABOLIC SYNDROME AND AGGRAVATED CARDIOMETABOLIC PARAMETERS AMONG NEPALESE ADULTS WITH SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Introduction: Subclinical hypothyroidism (SCH) and metabolic syndrome (MetS) both prevalent disorders associated with an elevated risk of cardiovascular disease (CVD). Thyroid hormones are crucial regulators of lipid and glucose metabolism, suggesting a significant pathophysiological link between SCH and the components of MetS. This study aimed to determine the burden of MetS among individuals with SCH in a Nepalese cohort.

Method: Cross-sectional study of 111 adults (≥18 years) undergoing thyroid function tests at Manmohan Memorial Teaching Hospital, Kathmandu (October 2021–March 2022). Participants were classified as euthyroid (n=35), SCH (n=57), or hyperthyroid (n=19). Blood pressure, BMI, and WC were measured, and biochemical parameters FBS, lipid profile, and Thyroid profile were estimated by a fully automated biochemistry analyzer and chemiluminescence immunoassay. MetS was defined according to the NCEP ATP III criteria. Analysis used done in SPSS v23 using ANOVA, post-hoc tests, t-tests, and Pearson's correlation ($p<0.05$).

Result: Subclinical hypothyroidism exhibited dyslipidemia (elevated TC, TG, LDL-C; reduced HDL-C) and higher BMI versus euthyroid and hyperthyroid groups ($p<0.01$). Among thyroid disorders, the majority (71.05%) of the cases were with subclinical hypothyroidism (SCH). The overall incidence of MetS was 27.9% where the incidence was higher (90.8%) among females and major (41.94%) affected age group was 36-55 years. The incidence of MetS was higher (35.18%) among SCH (35.18%) as compared to other thyroid disorders. SCH with MetS showed significantly elevated blood pressure, waist circumference, and adverse lipids ($p<0.05$) as compared to SCH without MetS. TSH was positively correlated with waist circumference ($r = 0.325$, $p = 0.017$), implicating TSH in promoting central obesity.

Conclusion: Subclinical hypothyroidism is strongly associated with an adverse cardiometabolic profile and a high burden of metabolic syndrome. The coexistence of SCH and MetS identifies individuals with the worst parameters, highlighting a critical subgroup for targeted intervention to reduce diabetes and CVD risk

Key words: Subclinical hypothyroidism; Metabolic Syndrome; dyslipidemia; cardiovascular risk

INTRODUCTION

Thyroid hormones (T3 and T4) are critical regulators of metabolism, produced under a precise hypothalamic-pituitary-thyroid axis[1,2]. Any disturbance on this axis leads to thyroid dysfunction, among which subclinical hypothyroidism (SCH) is the most prevalent one, and the majority of females are affected. SCH is characterized by elevated TSH with normal free T3 and T4 levels[3].

Simultaneously, Metabolic Syndrome (MetS) is a major global health challenge defined as a cluster of interconnected risk factors, including central obesity, dyslipidemia, hypertension, and impaired fasting glucose[4] MetS significantly elevates the risk for type 2 diabetes and cardiovascular disease (CVD)[5]. Pathogenic mechanisms like insulin resistance and chronic inflammation accelerate atherosclerosis, increasing cardiovascular morbidity and mortality[6].

A substantial pathophysiological link exists between these two prevalent conditions. Thyroid hormones critically influence lipid metabolism, glucose homeostasis, and body weight, which are core components of MetS[7]. As both hypothyroidism and MetS are independent CVD risk factors, their co-existence likely has a compounding effect, substantially escalating individual cardiovascular risk[8].

This problem is highly relevant in Nepal, where hypothyroidism has a reported prevalence of up to 17% [9–12]and MetS affects 20.7% of adults[13,14]. Given international studies indicating a 2 to 5-fold increased risk for MetS in hypothyroid subjects, the convergence of these two common conditions poses a significant public health threat.

This study aims to determine the association of cardiometabolic parameters with thyroid disorders and cardiometabolic parameters between subclinical hypothyroidism with and without MetS. This investigation is crucial for early identification and risk stratification to inform timely interventions and mitigate long-term diabetic and cardiovascular risks.

METHODS

This cross-sectional study was conducted at Manmohan Memorial Teaching Hospital (MMTH), Swoyambhu, Kathmandu, from October 2021 to March 2022.

Inclusion and Exclusion Criteria: Adult participants (aged ≥18 years) who attended the hospital and were advised to undergo a Thyroid Function Test (TFT) during the study period were included. A total of 111 participants were enrolled in the study.

The study excluded subjects with a history of diabetes, cardiovascular disease, on a lipid-lowering agent, malignancies, or pregnancy.

Informed Consent: Informed written consent was obtained from all the participants included in the study.

Ethical Approval: Ethical approval was taken from the Institutional Research Committee (IRC) of Manmohan Memorial Institute of Health Sciences with Reg No: MMIHS-IRC 636 on Dec 19, 2021.

Experimental protocol: The data were collected using a pretested self-administered questionnaire. Anthropometric measurements (Height, weight, BMI, and Waist circumference) and Blood pressure were measured. A 5 ml

fasting (8-12 hrs) blood sample was collected by venipuncture in a serum separator tube (BD vacutainer®SST™ Tubes). Serum thyroid Profiles (FT3, FT4, TSH) were estimated by an automated chemiluminescence Immunoassay (CLIA) system (MAGLUMI® 800, Snibe, China). Fasting Blood glucose (FBS) and lipid profiles (TG, TC, HDL, and LDL) were estimated by a fully automated analyzer (VITROS® 350 Chemistry System, USA).

Statistical analysis: All data were collected and entered into Microsoft Excel 2019, and SPSS version 23 (IBM Corporation, Armonk, NY, USA) was used for analysis. Normality of the data was assessed using the Kolmogorov–Smirnov test before analysis. One-way ANOVA was used to compare means across multiple groups, with post-hoc analyses conducted to identify specific group differences underlying significant ANOVA results. An additional student T-test was used to compare means across two groups, and Pearson's correlation to assess linear relationships. Descriptive statistics are reported as mean ± standard deviation. statistical significance was defined as $p < 0.05$.

RESULTS

A total of 111 participants were included in this study, with a majority being female (80.18%, n=89) and 19.82% (n=22) male. Based on thyroid function tests (TFTs), participants were initially categorized into three groups: euthyroid (31.53%, n=35), Hypothyroid (51.35%, n=57), and hyperthyroid (17.12%, n=19).

A one-way ANOVA revealed significant differences in several key parameters across the thyroid disorder groups. Specifically, we found statistically significant variations in Body Mass Index (BMI, p<0.01), triglycerides (TG, p<0.01), total cholesterol (TC, p<0.001), high-density lipoprotein cholesterol (HDL-C, p<0.001), and low-density lipoprotein cholesterol (LDL-C, p<0.001). No significant differences were observed in systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference (WC), or fasting blood Sugar (FBS), as shown in Table 1.

Table 1: Anthropometric and biochemical parameters of the study population

Parameters	Euthyroid	Hypothyroidism	Hyperthyroidism	p-value
BMI(Kg/m2)	25.19±3.06	28.73±5.49	25.8±3.99	0.006
SBP (mmHg)	123.43±8.73	126.48±14.29	122.50±12.82	0.740
DBP (mmHg)	84.57±9.5	85.19±9.66	81.25±9.91	0.223
WC (cm)	93.17±9.94	93.89±10.5	89.25±9.27	0.303
FBS (mg/dl)	103.71±47.36	97.30±14.44	84.50±7.76	0.348
TG (mg/dl)	225.94±134.56	184.83±100.27	130.5±134.75	0.008
HDL (mg/dl)	36.49±9.77	41,24±8.91	49.25±8.58	<0.001
TC (mg/dl)	166.14±32.38	170.22±36.46	126.38±31.03	<0.001
LDL (mg/dl)	94.55±27.94	89.31±35.62	38.25±16.62	<0.001

One-way ANOVA

Post-hoc analyses were conducted to identify the specific group differences driving these significant ANOVA results. Post-hoc analyses show the significant differences in lipid parameters among the thyroid function groups ($p < 0.05$). TC, TG, and LDL-C levels were significantly higher in euthyroid and hypothyroid subjects compared to hyperthyroid individuals. In contrast, HDL-C levels were significantly lower in the hyperthyroid group. These findings indicate a clear alteration in lipid metabolism associated with thyroid dysfunction, particularly in hypothyroid states, as shown in Table 2.

Table 2: comparisons of lipid profile parameters among euthyroid, hyperthyroid, and subclinical hypothyroid groups

Parameter	Subject group	95% CI	P-value
TC	Euthyroid vs hyperthyroidism	15.44-82.30	0.001
	Euthyroid vs Hypothyroidism	1.86-77.67	0.033
	Hyperthyroidism vs Hypothyroidism	20.95-84.95	<0.001
TG	Euthyroid vs Hyperthyroidism	22.07-30.73	0.007
HDL-C	Euthyroid vs Hyperthyroidism	-22.73- -2.80	0.004
	Hypothyroidism vs Hyperthyroidism	-17.80- -99.00	0.018
LDL-C	Euthyroid vs Hyperthyroidism	16.55-79.82	<0.001
	Hypothyroidism vs hyperthyroidism	12.99-72.91	0.001

Post hoc analysis

Furthermore, thyroid disorder cases (n=76) were subdivided into primary hypothyroidism, subclinical hypothyroidism, primary hyperthyroidism, and subclinical hyperthyroidism. The hypothyroid group included primary (3.95%) and subclinical (71.05%) hypothyroidism, while the hyperthyroid group included primary (14.47%) and subclinical (10.53%) hyperthyroidism. However, due to low sample sizes, primary hypothyroid, primary hyperthyroid, and subclinical hyperthyroid subgroups were excluded from the final analysis. The study thus focused on subclinical hypothyroidism (n=54) cases as shown in Table 3:

Table 3: Distribution of Thyroid Disorders among Study Participants

Thyroid Disorder	Number of participants	(%)
Primary Hypothyroidism	3	3.95
Subclinical Hypothyroidism	54	71.05
Primary Hyperthyroidism	11	14.47
Subclinical Hyperthyroidism	8	10.53
Total	76	100.0

Using the NCEP ATP III criteria, metabolic syndrome (MetS) was identified in 27.9% (n=31) of the study population. MetS was more prevalent in females (90.8%, n=29) than males (9.2%, n=2) and was most common in the 36-55 years age group (41.94%, n=13). Crucially, the incidence of MetS was overwhelmingly highest among patients with subclinical hypothyroidism, who accounted for 90.32% (n=28) of all MetS cases, as shown in Table 4

Table 4: Incidence of metabolic syndrome in different groups

Thyroid Disorder	Groups	n (%)
Age (Years)	18-35	7(22.58%)
	36-55	13(41.94%)
	56-75	8(25.80%)
	≥76	3(9.68%)
Gender	Male	2(9.2%)
	Female	29(90.8%))
Thyroid Disorder	Subclinical Hypothyroid	19(35.18%)

A comparison of subclinical hypothyroid patients with (n=19) and without (n=35) MetS revealed that those with MetS had a significantly worse cardiometabolic profile. The MetS group exhibited significantly higher systolic and diastolic blood pressure, waist circumference, triglycerides, total cholesterol, LDL-C, and VLDL-C, alongside considerably lower levels of protective HDL-C, as shown in Table 5.

Table 5: Comparison of metabolic parameters in subclinical hypothyroidism cases with and without MetS

Parameters	Subclinical Hypothyroidism Cases		p-value
	With MetS (Mean ± SD)	Without MetS (Mean ± SD)	
BMI (Kg/m2)	30.08±4.95	27.28±5.78	0.061
SBP (mmHg)	130.36±13.19	122.31±14.51	0.037
DBP (mmHg)	88.21±10.20	81.92±8.01	0.015
WC (cm)	98.54±8.45	88.88±10.32	<0.001
FBS (mg/dl)	98.79±15.61	95.69±17.44	0.495
TG (mg/dl)	224.71±118.41	141.88±49.73	0.003
TC (mg/dl)	181.04±38.03	158.58±31.38	0.022
HDL-C (mg/dl)	38.29±7.43	44.42±9.34	0.010
LDL-C (mg/dl)	100.08±33.59	78.96±35.03	0.033
VLDL-C (mg/dl)	38.52±15.76	29.12±11.63	0.021

Student t-test

In the subclinical hypothyroidism cohort (N=54), Pearson's correlation analysis assessed the relationship between TSH levels and metabolic parameters. A significant negative correlation was found only between TSH and waist circumference (r = -0.325, p = 0.017), indicating that higher TSH levels were associated with a larger waist circumference. No other significant correlations were observed, as shown in Table 5.

Table 6: Correlation of TSH with different components of metabolic syndrome

Parameters	TSH(μIU/ml)	
	r-value	p-value
BMI (Kg/m2)	-0.218	0.114
SBP (mmHg)	-0.106	0.445
DBP (mmHg)	0.034	0.805
WC (Cm)	+0.325	0.017
FBS (mg/dl)	0.115	0.409
TG (mg/dl)	0.095	0.494
TC (mg/dl)	0.104	0.452
HDL-C (mg/dl)	-0.145	0.295
LDL-C (mg/dl)	0.016	0.911
VLDL-C (mg/dl)	0.196	0.177

Pearson Correlation

DISCUSSION

This study elucidates that the patients with thyroid disorders exhibit different metabolic patterns as compared to the euthyroid state. This finding has revealed a significant association between thyroid disorders and cardiometabolic parameters, especially in subclinical hypothyroidism. Furthermore, SCH cases with MetS have shown significantly worse cardiometabolic parameters as compared to SCH without MetS.

SCH is a common thyroid disorder with global prevalence ranging up to 15%.[15] In this study, majority of the cases were SCH among all type of thyroid disorders affecting mainly the females of general adult population. As compared to the hyperthyroidism cases, cardiometabolic parameters among hypothyroidism cases were found significantly worse where, BMI, TG, TC, and LDL-C were higher, and HDL-C was lower, which is in accordance with substantial publications. [12,16–18] Hypothyroidism fundamentally disrupts the basal metabolic rate, leading to increased fat accumulation and a higher BMI. Simultaneously, the downregulation of hepatic LDL receptors impairs LDL clearance, leading to elevated LDL and total cholesterol levels. It also suppresses lipoprotein lipase activity, leading to accumulation and increased blood level of TG. Furthermore, hypothyroidism impairs the LCAT (Lecithin: cholesterol acyltransferase) and CETP (Cholesteryl ester transfer protein) enzymes, resulting in low HDL levels.[19]

The extant literature substantiates the association between SCH and MetS. The prevalence of MetS in SCH patients ranges from 24%-50% globally, according to Lai et al.20 and up to 57% in the Nepalese population according to Sharma et al., Yadav et al., K.C. et al.12,18,20,21. In this study, the overall incidence of MetS was found to be 27.9% and the incidence of MetS was higher among SCH (35.18%) affecting the major (41.94%) age group of 36-55 years. Our findings in this study revealed the worst cardiometabolic parameters among SCH with MetS cases, where SBP, DBP, WC, TG, TC, and LDL were significantly higher; however, HDL were significantly lower as compared to SCH without MetS cases, which is in accordance with the numerous studies.[12,17,18,21] Furthermore, this study shows a significant positive correlation with WC, which demonstrates that hypothyroidism-induced obesity may be the main offender behind the worse cardiometabolic profile among SCH, which is similar in findings with Mamtani et al.[22]

Hypothyroidism induces obesity by significantly reducing the BMR and lipolysis. Concurrently, it induces a worse cardiometabolic profile by disrupting lipid metabolism, leading to elevated LDL cholesterol and triglycerides, and by fostering insulin resistance and hypertension, resulting in systemic inflammation.[23,24] Furthermore, obesity impairs leptin levels, which can dysregulate the hypothalamic-pituitary-thyroid axis, potentially increasing TSH levels and creating a vicious cycle.[25] This bidirectional relationship means each condition amplifies the others, significantly increasing the risk of metabolic syndrome, followed by diabetes and cardiovascular disease.[26–28]

CONCLUSION

In conclusion, this study confirms that individuals with subclinical hypothyroidism exhibit significantly worse cardiometabolic parameters. The risk is profoundly amplified when SCH coexist with metabolic syndrome, resulting in the most adverse cardiometabolic profile. The SCH-MetS cohort carries a substantially higher burden of diabetes and an elevated risk for cardiovascular disease. The pathophysiological interplay between elevated TSH, obesity, and dyslipidemia appears to drive this deterioration. Therefore, proactive management of SCH, particularly in the context of MetS, through appropriate clinical interventions could be a pivotal strategy to mitigate the escalating burden of diabetes and CVD risk in this vulnerable population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to this study. Dipika Gautam, Anit Lamichhane, Govardhan Joshi, and Mahendra P. Bhatt conceived and designed the study. Sudip Khanal, Sujan Gautam and Aashish Acharya performed the data analysis and interpretation. Anil Khadka, Pabitra Bista, Sahara Bistha, Dipika Gautam and Rajesh Kumar Thakur drafted and wrote the manuscript, including literature review, data organization, and administrative assistance. All authors reviewed and approved the final manuscript.

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