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Research Article

Assessment of Cardiovascular Disease Risk in Females with Subclinical Hypothyroidism

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Background. Subclinical hypothyroidism (SCH) is a common endocrine disorder prevalent in the Nepalese female population. Dyslipidemia, a prerequisite to the development of cardiovascular disease, links the thyroid profile and cardiovascular disease risk. This study is aimed at assessing the cardiovascular disease risk in females with SCH. *Methods*. This laboratory-based cross-sectional study was carried out at Manmohan Memorial Teaching Hospital, Kathmandu, Nepal, where 100 females with SCH and 100 euthyroid controls were included. Estimates of thyroid and lipid profiles were made, and lipid variables were used to calculate lipid indices. *Results*. In comparison to controls, females with SCH had significantly higher lipid profiles, thyroid profiles, and lipid indices but significantly lower HDL-C. The TSH ($p < 0.001$), TG ($p = 0.039$), VLDL ($p = 0.039$), and AIP ($p = 0.031$) were significantly associated with mild and severe SCH. AIP was significantly correlated with TSH ($r = 0.256$, $p = 0.010$) among SCH females. *Conclusion*. Our findings suggest that women with SCH are more likely to get CVD. Hence, timely monitoring of cardiovascular status among females with SCH is crucial, and it can be performed using simple lipid indices like AIP, AI, and LCI.

1. Introduction

Thyroid hormones are produced under the control of thyroid-stimulating hormone (TSH), an anterior pituitary hormone regulated by hypothalamic thyrotropin-releasing hormone (TRH) [1]. Tetraiodothyronine or thyroxine (T_4) and tri-iodothyronine (T_3) are the major hormones of the thyroid gland, which utilize iodine as a sole source of trace elements and regulate the metabolic pathways that are needed for proper growth and development of the body [2].

Alterations of the thyroid gland, ranging from asymptomatic problems to symptomatic thyroid disease, are known as thyroid dysfunction. [3]. Based on the laboratory findings, thyroid dysfunction is either overt or subclinical [4, 5]. Overt hypothyroidism is signified by elevated TSH and subnormal free thyroxine, whereas subclinical hypothyroidism (SCH) refers to elevated TSH and normal free thyroxine [6, 7].

SCH is asymptomatic; however, it can share the symptoms of hypothyroidism [8]. SCH patients have elevated lipid peroxidation, altered lipid profiles, and diminished arylesterase (ARE) activity compared to the control group [9]. Elevated lipid levels, increased arterial stiffness, disrupted coagulability, elevated homocysteine, carbohydrate reactive protein (CRP) levels, insulin resistance, and diastolic hypertension are possible risk factors for developing cardiovascular disease (CVD) in SCH [10, 11]. In addition, CVDs like atrial fibrillation, heart failure, pericardial effusion, atrial

tachyarrhythmia, and mitral valve dysfunction are associated with thyroid dysfunction [12].

Around 2 to 6% of SCH progresses to overt hypothyroidism every year, with a higher risk in women having TSH of greater than 10 mIU/ml and positive thyroid peroxidase (TPO) antibody [13, 14]. Therefore, screening for subclinical hypothyroidism is necessary in order to initiate levothyroxine therapy, and factors that need to be considered include a TSH level > 10 mIU/L, positive anti-TPO, having hypothyroid symptoms, and the presence of cardiovascular disease risk factors [7].

Various studies have investigated the association between dyslipidemia and SCH [15–20]; however, markers better than conventional lipid profile variables—aitherogenic index plasma (AIP), atherogenic index (AI), and lipoprotein combined index (LCI)—were not assessed for the prediction of cardiovascular disease.

The clinical significance of mild thyroid under activity is uncertain, prompting disagreement over hyperdiagnostic tests and potential therapy choices. Moreover, the cardiovascular system, bone, and other organs and systems are linked to SCH. This study is aimed at evaluating cardiovascular disease risk through lipid indices in females with subclinical hypothyroidism. Additionally, this study is also aimed at assessing the CVD risk in females with SCH.

2. Methods

This laboratory-based cross-sectional study was performed at the Manmohan Memorial Medical College and Teaching Hospital (MMTH), Kathmandu, Nepal, from November 2020 to January 2020. Based on the values of TSH, subclinical hypothyroidism was classified into 2 categories, i.e., mild SCH having TSH values ≤ 10.0 mU/L and severe SCH with > 10.0 mU/L [21].

2.1. Inclusion and Exclusion Criteria. Females with subclinical hypothyroidism who visited the hospital throughout the study period were included in the study based on their thyroid profiles. The study involved 200 participants who attended MMTH, of whom 100 were subclinically hypothyroid females diagnosed on the basis of their thyroid profile, and 100 were euthyroid controls (normal thyroid function with normal fT3, fT4, and TSH).

The study excluded women with hepatic disease, diabetes mellitus, and any thyroid disorders other than subclinical hypothyroidism, and females who were on thyroid medication were also excluded from the study. Females under medication for thyroid disorders were also disallowed from participating in the trial.

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

2.2. Experimental Protocol. The data was collected using a pretested self-administered questionnaire. A 5 ml fasting (8-12 hours) blood sample was collected by venipuncture in a serum separator tube (BD Vacutainer® SST™ Tubes). The biochemical parameters such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were analyzed using a fully automated chemistry analyzer (VITROS® 350 Chemistry System, USA). In addition, thyroid profiles—fT_3, fT_4, and TSH—were performed using a fully automated MAGLUMI® 800, Chemiluminescence Immunoassay (CLIA) System (Snibe China). All the biochemical parameters were expressed in mg/dl; fT_3 and fT_4 were expressed in pg/ml and TSH in μIU/dl.

Based on the thyroid profile, subclinical hypothyroid females and normal euthyroid controls were differentiated for the study. Thyroid dysfunction was characterized by changes in TSH together with normal or abnormal levels of fT_3 and/or fT_4 hormones.

Lipid indices such as AIP [22], AI [23], and LCI [24] were calculated using the formula:

$$\begin{aligned} \text{AIP} &= \log\left(\frac{\text{TG}}{\text{HDL}-\text{C}}\right), \\ \text{AI} &= \frac{\text{LDL}-\text{C}}{\text{HDL}-\text{C}}, \\ \text{LCI} &= \frac{(\text{TC}\times\text{TG}\times\text{LDL}-\text{C})}{\text{HDL}-\text{C}}. \end{aligned} \tag{1}$$

2.3. Statistical Analysis. A database was constructed using Microsoft Excel 2013 and analyzed by SPSS version 18 (IBM Corporation, Armonk, NY, USA). Mann–Whitney U test, independent t-test, Chi-square test, Spearman's correlation, and linear regression were applied in SPSS. For normally distributed data, the mean and standard deviation were taken, and for data without normal distribution, the median and interquartile range (IQR) were taken. For non-normally distributed data, the Mann–Whitney U test and Spearman's correlation were applied; for normally distributed data, an independent t-test was used for mean comparison. Linear regression analysis predicted the association between TSH and AIP. Statistical significance was set at a p value less than 0.05.

3. Results

A total of 200 female populations were included in this study: 100 were euthyroid controls and 100 were subclinically hypothyroid females. Among the 100 euthyroid populations, the maximum population was under the age group 41-50 years, whereas among the 100 subclinical hypothyroidism females, the equal majority were distributed under 41-50 years and 51-60 years. Age was not significantly different between cases and controls (p =0.679) (Table 1).

There was a significant increase in all variables of thyroid profile and lipid profile among SCH females except HDL, which was significantly decreased in SCH cases (Figures 1 and 2). In addition, all lipid indices were significantly higher in SCH females than in euthyroid controls (Table 2).

The females with severe SCH showed a significantly higher level of TSH ($p < 0.001$), TG ($p = 0.039$), VLDL ($p = 0.039$), and AIP ($p = 0.031$) in comparison with females having mild SCH. The mean AIP was 0.85 in the severe

Table 1: Distribution of euthyroid and SCH cases in different age groups.

Age (years)	Euthyroid	SCH	p value
20-30	16 (16%)	10 (10%)	
31-40	23 (23%)	23 (23%)	
41-50	27 (27%)	25 (25%)	0.679
51-60	20 (20%)	25 (25%)	
>60	14 (14%)	17 (17%)	

∗: Chi-square test, χ^2: 2.307; SCH- Subclinical hypothyroidism.

group, which indicated a higher risk for CVD than in the mild group (Table 3).

The correlation between TSH and lipid indices was assessed, where only TSH and AIP were significantly correlated ($r = 0.256$) with a p value of 0.010 (Table 4).

Linear regression analysis between TSH and AIP demonstrated that a 7.2% portion of the variance in AIP can be predicted from TSH. The predictor variable TSH explains 6.3% of the variance in our outcome with a p value of 0.007, considered significant. Therefore, a 1 unit increase in TSH is associated with an elevation of 1.4% risk for CVD through AIP (Table 5).

4. Discussion

The decrease in fT3 and fT4 is characterized by primary hypothyroidism with increased serum TSH due to a feedback mechanism by the hypothalamus-pituitary-thyroid axis [25]. The diagnosis of subclinical hypothyroidism is based on laboratory variables as the patient does not show symptoms, unlike with primary hypothyroidism. The progression of subclinical hypothyroidism to overt hypothyroidism is 2%-5% each year [26]. Although dyslipidemia plays a crucial role in developing atherosclerosis, insulin resistance, inflammation, hypertension, oxidative stress, and coagulation abnormality also show the multifactorial basis of atherosclerosis [27, 28].

Our study demonstrated a mean age of 46.75 years in subclinical hypothyroidism which is parallel to the study conducted in Southern India [20], Greece [29], and Chennai, India [17], whereas higher in the studies conducted in Italy [30] and Turkey [31]. This mean difference might be due to different study populations. The fT_3 and fT_4 were significantly different in subclinical hypothyroidism than in euthyroid, which is in contradiction with Karthick et al.'s study [17] but similar to James et al.'s study [20], and this contradiction might be due to larger population size, ethnicity, age, and iodine intake [20]. TSH was significantly higher in the SCH group than in the euthyroid group which was consistent with several studies [17, 20].

A significant alteration of lipid profiles in subclinical hypothyroid females makes them more prone to CVD risk. Our study outlined a significant increase in LDL-C and TC, which was supported by Lioudaki et al. [16], Canaris et al. [32], and Hussain et al. [33]. The study illustrated decreased LDL-C in subclinical hypothyroid females than in euthyroid populations [20]. The most frequent lipid alterations in SCH are hypercholesterolemia as LDL-C concentration was found to be elevated, LDL-C receptor activity diminishes the catabolism of LDL, and intermediate-density lipoprotein gets affected, which ultimately increases TC and LDL-C in the circulations [20]. Furthermore, thyroid dysfunction accelerates LDL-C oxidation besides increasing their concentrations, so when macrophages engulf the oxidized LDL-C, they convert to foam cells which are more atherogenic and promote cardiovascular disease [17]. Our study enumerates a significant increase in TG in SCH than in euthyroid females, which supports similar studies [17]. The elevated TG in subclinical hypothyroidism is due to decreased lipoprotein lipase (LPL) activity which accounts for the diminished clearance of triglyceride-rich lipoproteins and the significant increase in VLDL. Another possible mechanism is enhanced esterification of fatty acids at the hepatic level [17]. The HDL-C was significantly higher in the euthyroid group than in the subclinical hypothyroidism group, which is in agreement with Karthick et al. [17], James et al. [20], Caron et al. [34], and Erdem et al. [35] but contradicts Regmi et al., who found increased HDL-C in the subclinical hypothyroid population compared to normal euthyroid females [36]. However, some studies did not show any significant difference in HDL-C between euthyroid and subclinical hypothyroid females [20]. Some studies found a reduced plasma clearance rate of HDL-C as thyroid hormones affect the expression of HDL binding sites in liver cells, an important site for HDL metabolism, so HDL-C might be lower in subclinical hypothyroid females compared to normal euthyroid subjects. In our study, AIP was significantly higher in the subclinical hypothyroidism group compared to euthyroid females, which is similar to other studies [20]. The elevated AIP among subclinical hypothyroidism is due to increased TG and decreased HDL-C compared to normal euthyroid control. The mean AIP of subclinical hypothyroid females revealed that SCH females were at higher risk for cardiovascular disease than euthyroid females [25].

In contrast to euthyroid females, our study revealed a considerable rise in AI in subclinical hypothyroid females. Increased AI is due to elevated LDL-C and decreased HDL-C. This statement coincides with the study by Althaus and Staub, et al. [37, 38]. According to another study, the risk of myocardial infarction increases by 75% for every 1 unit higher AI. [39]. Moreover, our study elucidates a significant increase in LCI in subclinical hypothyroid females compared to normal euthyroid females, which is similar to the study by Cai et al. [24], which outlined increased LCI in coronary artery disease (CAD) than normal controls. The increased LCI is due to elevated TG, TC, and LDL-C values, whereas HDL-C is decreased.

Our study does not explicate any significant difference in fT_3 and fT_4 between mild and severe subclinical hypothyroidism, whereas TSH values were significantly elevated in severe SCH compared to mild SCH. The TSH and fT3 levels dramatically increased, according to research by Kumar et al., while fT4 levels showed no significant change between moderate and severe SCH [40].

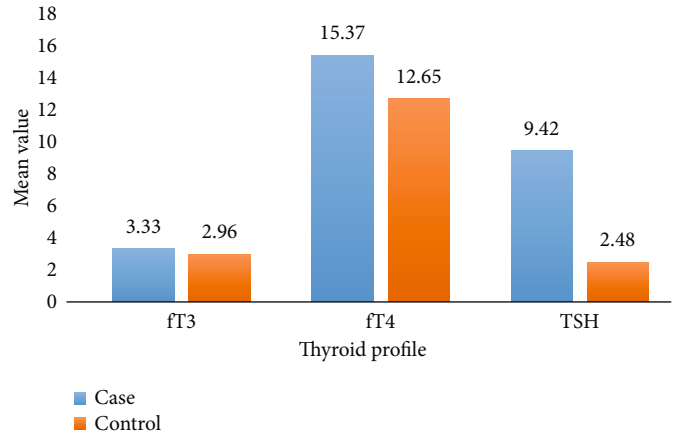

Figure 1: Bar diagram representing mean values of thyroid profile in SCH females and euthyroid control.

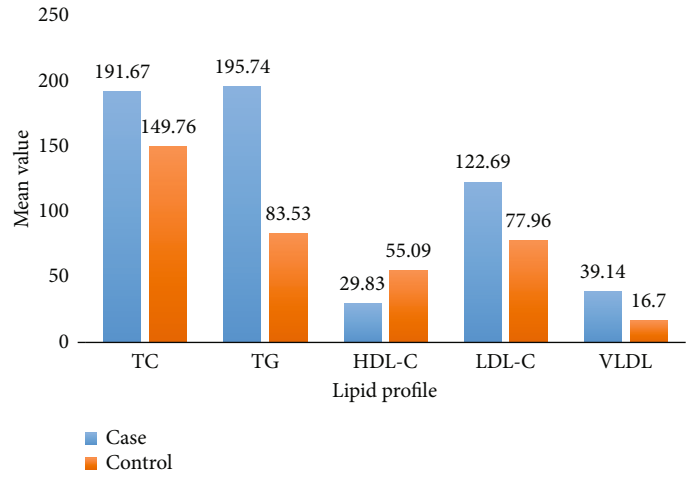

Figure 2: Bar diagram representing mean values of lipid profile in SCH female and euthyroid control.

Table 2: Association of biochemical parameters and lipid indices between euthyroid and SCH cases.

Variables	Euthyroid Median (IQR)	SCH Median (IQR)	*p* value
Age (years)	44 (34-55)	47 (37.25-55)	0.282
FT3 (pg/ml)	2.99 (2.62-3.28)	3.25 (3.01-3.55)	**<0.001**
FT4 (pg/ml)	12.5 (11.32-13.57)	15.44 (12.45-17.74)	**<0.001**
TSH (μIU/dl)	2.20 (1.33-3.43)	8.46 (6.77-10.53)	**<0.001**
TC (mg/dl)	145 (133-170.75)	189 (166-214.75)	**<0.001**
TG (mg/dl)	87 (76.0-98.0)	190 (136-246.25)	**<0.001**
HDL-C (mg/dl)	56 (50-60)	31 (28-34)	**<0.001**
LDL-C (mg/dl)	75.40 (59.45-99.45)	120.80 (102.20-148.35)	**<0.001**
VLDL (mg/dl)	17.40 (15.20-19.60)	38.0 (27.20-49.25)	**<0.001**
AIP	0.19 (0.10-0.26)	0.79 (0.66-0.94)	**<0.001**
AI	1.45 (0.99-1.92)	4.02 (3.24-5.06)	**<0.001**
LCI	17766.11 (10167.62-26525.27)	146581.64 (88810.31-231392.87)	**<0.001**

Abbreviations: TSH: thyroid stimulating hormone; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL: very low-density lipoprotein cholesterol; AIP: atherogenic index plasma; AI: atherogenic index; LCI: lipoprotein combined index; SCH: subclinical hypothyroidism. *p* value calculated using Mann- Whitney U test.

Table 3: Association of different variables in mild and severe subclinical hypothyroidism (SCH).

Variable	Mild SCH Median (IQR)/mean ± SD	Severe SCH Median (IQR)/mean ± SD	p value
Age (years)	46.95 ± 12.73	46.35 ± 11.86	0.819[a]
FT3 (pg/ml)	3.25 (3.0-3.53)	3.25 (2.99-3.64)	0.942[b]
FT4 (pg/ml)	15.75 (12.58-18.35)	14.78 (16.76-11.62)	0.348[b]
TSH (μIU/dl)	7.03 (6.39-8.51)	12.54 (10.42-14.79)	**0.001**[b]
TC (mg/dl)	192.67 ± 37.88	189.74 ± 41.73	0.724[a]
TG (mg/dl)	176 (128.50-226.75)	231.50 (156.75-259.25)	**0.039**[b]
HDLC (mg/dl)	31.0 (28-34)	30.0 (25.75-34.0)	0.349[b]
LDLC (mg/dl)	124.91 ± 33.03	118.38 ± 37.68	0.374[a]
VLDL (mg/dl)	35.20 (25.70-45.35)	46.30 (31.35-51.85)	**0.039**[b]
AIP	0.76 ± 0.19	0.85 ± 0.20	**0.031**[a]
AI	4.24 (3.38-4.97)	3.72 (3.02-6.03)	0.711[b]
LCI	132112.76 (89013.14-220748.92)	154666.23 (87824.10-314646.42)	0.428[b]

Abbreviations: TSH: thyroid stimulating hormone; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL: very low-density lipoprotein cholesterol; AIP: atherogenic index plasma; AI: atherogenic index; LCI: lipoprotein combined index; SCH: subclinical hypothyroidism. [a]Student's t-test and expressed as mean ± SD. [b]Mann–Whitney U-test and expressed as median ($Q_1 - Q_3$).

Table 4: Correlation between TSH and Lipid indices among subclinical hypothyroid females.

Variable		AIP	AI	LCI
TSH	r value	**0.256**	-0.048	0.140
	p value	**0.010**	0.638	0.164
	N	100	100	100

Abbreviations: TSH: thyroid stimulating hormone; AIP: atherogenic index plasma; AI: atherogenic index; LCI: lipoprotein combined index; N: total number of participants. r value denotes correlation coefficient. Correlation is significant at the 0.05 level.

Table 5: Linear regression of TSH on AIP.

Number	B value	R	R square	Adjusted R^2	p value
1	0.014	0.269	0.072	0.063	0.007

Dependent variable: AIP. Predictors: (constant), TSH.

According to Kumar et al., TG and VLDL levels were considerably higher in severe SCH than moderate SCH [40]. AIP is markedly higher in severe SCH than in moderate SCH. The mean AIP of severe SCH is higher, showing that severe SCH populations are at higher risk of cardiovascular disease than mild SCH females. Although LCI was higher among the severe SCH group than the mild SCH group, it was statistically insignificant. AI was higher among moderate SCH than severe SCH. Our study depicted the correlation between TSH and lipid indices, where TSH showed a significant positive correlation with AIP only ($r = 0.256$ and $p = 0.010$). Madhura et al. [25] pictorialized a significant positive correlation between TSH and AIP in SCH females. It revealed that the increased level of TSH elevated the risk of cardiovascular diseases. TSH is directly linked to lipid metabolism, so elevated TSH causes dyslipidemia due to the alteration of lipid metabolism. AIP is also elevated in the case of dyslipidemia, so dyslipidemia is bridging the gap between TSH and AIP. However, our findings contradict the findings by James et al., which failed to correlate TSH with AIP [20]. AI and LCI were not correlated with TSH; hence, AIP can be used as a better index to monitor the dyslipidemic patterns in subclinical hypothyroid females. Furthermore, to find the relations of dependent and independent variables, i.e., TSH as an independent variable and AIP as the dependent variable, we performed a linear regression between TSH and AIP, which concluded that a 1 unit increase in TSH is associated with an increment of 1.4% in AIP.

Our study had a limited number of subjects; a large-scale population study is needed to establish a strong relationship between SCH and CVD. In addition, our study explored only lipid indices, and as dyslipidemia is not only the sole factor; other sensitive markers such as hs-CRP, adiponectin, IL-6, TNF–alpha, and leptin are also risk factors for developing CVD; further study to evaluate these additional variables is required.

5. Conclusion

Significant alterations were found in lipid profiles of females with subclinical hypothyroidism compared to normal euthyroid females. Subclinical hypothyroid females were more

prone to develop cardiovascular disease than normal euthyroid females. A dyslipidemic state was encountered in females with SCH, which is a requisite for cardiovascular disease. Among lipid indices, AIP was significantly correlated with TSH. Thus, AIP was considered a better marker to assess CVD risk, followed by AI and LCI.

Data Availability

All the data generated during this study are presented in this paper. The primary raw data will be made available to interested researchers by the corresponding author, if requested.

Ethical Approval

This research work was approved by the Institutional Review Committee of the Manmohan Memorial Institute of Health Sciences (MMIHS-IRC 486), Kathmandu, Nepal.

Consent

Informed written consent was taken from the patients before participating in the study. Data regarding personal information were coded and kept confidential.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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