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Original Article

Internal Medicine Section

Assessment of Clinical and Biochemical Cardiac Risk Factors in Patients with Subclinical Hypothyroidism: A Cross-sectional Study

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ABSTRACT

Introduction: Cardiovascular Diseases (CVD) are among the leading causes of morbidity and mortality in the current era, and the focus is gradually shifting towards identifying the risk factors and pathways leading to CVD. While hypothyroidism has been extensively studied and linked to CVD risk, the association between subclinical hypothyroidism and CVD risk factors is not well established.

Aim: To investigate the association between subclinical hypothyroidism and cardiac risk factors such as obesity indicators {Body Mass Index (BMI) and Waist-hip Ratio (WHR)}, blood pressure, and lipid parameters.

Materials and Methods: This cross-sectional study was conducted at the Department of Medicine, ESI PGIMSR, Basaidarapur, New Delhi, India, from December 2020 to April 2022. The study included 200 patients, with 100 patients recruited in the subclinical hypothyroidism group (Thyroid Stimulating Hormone (TSH) >4.8 µIU/mL with normal fT4) and 100 patients with euthyroid status (TSH 0.5-4.8 µIU/mL and normal fT4) included in the comparison group. Both groups were assessed for CVD risk factors including obesity indicators (BMI and WHR), blood pressure, and lipid parameters. The two groups were analysed for statistical significance using Student's t-test.

Results: Both groups had similar age distributions. However, there was a greater percentage of female patients in the subclinical hypothyroidism group (61%) compared to the euthyroid group (52%). As expected, TSH levels in the subclinical hypothyroidism group were significantly higher than in the euthyroid group. The subclinical hypothyroidism group recorded significantly higher mean values of BMI, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), total cholesterol, and triglycerides, which were higher by 18%, 17%, 17%, 41%, and 16% compared to the euthyroid group, respectively. Other parameters like WHR and Low-Density Lipoprotein-Cholesterol (LDL-C) were found to be raised in subclinical hypothyroidism compared to the euthyroid group, while High-Density Lipoprotein-Cholesterol (HDL-C) levels were significantly lower by 16% in subclinical hypothyroidism.

Conclusion: Subclinical hypothyroidism is significantly associated with cardiac risk factors like obesity indicators (BMI and WHR), blood pressure, and lipid parameters.

Keywords: Blood pressure, Cardiovascular disease, Lipid profile, Obesity, Thyroid disorders

INTRODUCTION

Thyroid disorders are among the most commonly occurring endocrine diseases worldwide, and it has been estimated that about 42 million people in India are currently suffering from thyroid diseases [1]. Subclinical hypothyroidism is defined as an elevated serum TSH concentration above the upper limit of normal in the presence of normal serum free thyroxine (fT4) levels, with minimal or no hypothyroid symptoms [2]. Subclinical hypothyroidism has a high prevalence rate (4-20%) and is gaining prominence due to the risk of progression to overt hypothyroidism and its association with cardiac, lipid, and other biochemical abnormalities, which are increasingly recognised [3].

With the advent of the 21st century, the world has witnessed an alarming surge in the incidence and prevalence of Cardiovascular Disease (CVD) worldwide, and India is not immune to this phenomenon. In fact, recent studies estimate that CVDs account for over a quarter of total mortality in India [4,5]. Against this backdrop, researchers, stakeholders, and policymakers have renewed their focus on identifying and controlling the risk factors associated with CVDs to curtail the rising disease burden. To date, multiple clinical and biochemical CVD risk factors have been identified. Among them, obesity is known to contribute to the development of CVD and CVD-related mortality independently of other cardiovascular risk factors [6].

Obesity indicators like BMI and WHR have been found to be associated with an increased prevalence of CVD. A recent population-based study demonstrated that higher BMI leads to an increased lifetime risk for CVD in middle-aged adults [7]. WHR, which has a significant association with abdominal fat, is also found to be associated with CVD risk even when BMI is normal [8]. Similarly, elevated blood pressure has been associated with an increased risk of CVD, and the risk has been shown to increase steadily with progressively higher levels of blood pressure beyond the baseline of 115/75 mmHg [9]. Among the biochemical parameters, lipid fractions like raised total cholesterol, LDL-C, and triglycerides, as well as low HDL-C levels, are considered to be associated with an increased risk of CVD [10,11].

The cardiovascular abnormalities in hypothyroidism are postulated to be partly because of its association with altered lipid profiles. Thyroid hormones play a key role in lipid metabolism as they regulate lipid synthesis, degradation, and mediate the activity of enzymes in the lipid metabolism pathways. While the relationship between overt hypothyroidism and CVD risk factors like obesity, hypertension, and dyslipidaemia has been well established [12-14], whether subclinical hypothyroidism also predisposes to CVD in a similar fashion is poorly understood, and the actual relationship between subclinical hypothyroidism and CVD risk is still a topic of debate [15].

There have been studies that assessed the association of subclinical hypothyroidism with CVD risk factors. However, most of these studies were performed on a small sample size or a specific subgroup of the population, like the geriatric age group [16-19]. Additionally, the majority of these studies were performed on Western populations [16,17,19], and Indian context is lacking in most of them. The present study differs in this regard as it was undertaken on a larger sample size consisting of patients in a tertiary care hospital in North India.

The objective of the present study was to explore the association between subclinical hypothyroidism and clinical and biochemical cardiac risk factors, like BMI, WHR, blood pressure, and lipid parameters.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Medicine, ESI PGIMSR, Basaidarapur, New Delhi, India, in which 200 subjects were recruited from December 2020 to April 2022. Ethical clearance was taken from the Institutional Ethics Committee (vide IEC approval no. ESIPGIMSR-IEC/202000017).

Inclusion criteria: The study included patients aged 18 years or older. Subclinical hypothyroidism patients were included in the study group, defined as patients with raised TSH value (>4.8 µIU/mL) with normal Thyroxine (fT4) levels (0.8-2.0 ng/dL). The comparison group consisted of patients with a euthyroid profile (normal TSH 0.5-4.8 µIU/mL with normal fT4 0.8-2.0 ng/dL) [2].

Exclusion criteria: Patients over the age of 65 years, those with co-morbid conditions like established CVD, diabetes, heart failure, chronic liver disease, chronic kidney disease, chronic inflammatory disorders, and autoimmune diseases, patients already on treatment for thyroid disorders, patients with infectious states, and patients receiving immunosuppressive agents were excluded from the study.

Sample size: Considering the study duration and patient flow, it was decided to sequentially recruit all available subjects sequentially till the sample size was reached.

Study Procedure

All cases of subclinical hypothyroidism and euthyroid profiles that met the inclusion and exclusion criteria, after taking a detailed history, were included in the study upon obtaining written informed consent.

Thereafter, subjects were clinically examined, and parameters like BMI, WHR, and blood pressure were recorded for all participants. This was followed by the assessment of biochemical parameters like total cholesterol, serum HDL-C, and triglyceride levels for all participants. Overnight fasting blood samples (5 mL) were collected from all participants under aseptic precautions to measure these biochemical parameters. The samples were then centrifuged at 10,000 rpm for 10 minutes to separate the serum. The sera were stored at 20°C until assayed. Free T4 in the thyroid profile was tested using the Electrochemiluminescence Immunoassay (ECLIA) method, and TSH assay was performed using Enzyme-linked Immunoassay (ELISA). The lipid profile was estimated using the Cholesterol Oxidase: P-aminophenazone (CHOD-PAP) method. LDL-C was calculated using the Friedewald formula: LDL=Total cholesterol-HDL-TGs/5 [20]. The normal reference range of the testing laboratory was 0.8-2.0 ng/dL for fT4, 0.5-4.8 µIU/mL for TSH, 130-200 mg/dL for total cholesterol, 45-170 mg/dL for triglycerides, and 27-67 mg/dL for HDL-C. Mean values of BMI, WHR, SBP, DBP, total cholesterol, HDL, LDL, and triglyceride levels were calculated for both groups, and a comparison between the two groups was performed. Data analysis was conducted using appropriate statistical methods, and conclusions were drawn accordingly.

STATISTICAL ANALYSIS

The data was compiled and entered into an Microsoft excel spreadsheet, and analysis was performed using standard statistical methods. Relevant conclusions were drawn using the computer-based software Statistical Package for Social Sciences (SPSS) version 24.0. Continuous data was expressed as mean±Standard Deviation (SD) and compared using Student's t-test for normally distributed variables. The correlation between two continuous variables was calculated using Pearson's correlation coefficient. A p-value of <0.05 was considered statistically significant.

RESULTS

In the present study, both groups were similar in terms of demographic composition, including age and gender distribution. However, as expected, mean TSH levels in the subclinical hypothyroidism group were significantly higher compared to the euthyroid group, and the condition was found to have a predominantly female predilection [Table/Fig-1].

Parameters	Subclinical hypothyroidism group (n=100)	Euthyroid group (n=100)	p-value (Unpaired t-test)
Mean age (in years)	43.8±7.3	41.7±8.8	0.205
No. of males	39	48	0.20*
No. of females	61	52	
Mean TSH (µIU/mL)	7.9±1.24	2.2±0.92	<0.001
Mean fT4 (ng/dL)	0.94±0.05	1.14±0.16	<0.001

[Table/Fig-1]: Baseline characteristics of subjects.
*=Chi-square Test p-value

The mean BMI of subjects in the subclinical hypothyroidism group was significantly higher (26.98±1.79 kg/m^2) compared to the euthyroid group (22.87±2.30 kg/m^2). The mean WHR of subjects in the subclinical hypothyroidism group was significantly higher than in the euthyroid group (p<0.001). Similarly, the mean SBP and DBP of subjects in the subclinical hypothyroidism group were higher compared to euthyroid subjects, and the difference was statistically significant (p<0.001) [Table/Fig-2].

S. No.	Parameters	Subclinical hypothyroidism group (n=100)	Euthyroid group (n=100)	p-value
1.	Body Mass Index (BMI) (Kg/m^2)	26.98±1.79	22.87±2.30	<0.001
2.	Waist Hip Ratio (WHR)	0.88±0.03	0.81±0.06	<0.001
3.	Systolic Blood Pressure (SBP) (mmHg)	131.00±9.79	112.44±11.87	<0.001
4.	Diastolic Blood Pressure (DBP) (mmHg)	84.40±5.80	72.12±6.58	<0.001

[Table/Fig-2]: Clinical parameters in subclinical hypothyroidism and euthyroid groups.

The mean total cholesterol level of subjects in the subclinical hypothyroidism group was higher compared to the euthyroid group, and the difference was statistically significant (p<0.001). The mean HDL levels of subjects in the subclinical hypothyroidism group were significantly lower compared to the euthyroid group. It can also be inferred from the table that the mean triglyceride levels of subjects in the subclinical hypothyroidism group were significantly higher compared to the euthyroid group [Table/Fig-3].

S. No.	Parameters	Subclinical hypothyroidism group (n=100)	Euthyroid group (n=100)	p-value
1.	Total cholesterol (mg/dL)	227.54±67.89	161.16±16.17	<0.001
2.	LDL-C (mg/dL)	123.04±27.71	114.28±18.13	0.064
3.	HDL-C (mg/dL)	42.60±2.81	49.40±6.66	<0.001
4.	Triglyceride (mg/dL)	141.70±40.91	121.96±30.42	0.007

[Table/Fig-3]: Lipid parameters in subclinical hypothyroidism and euthyroid groups.

Regarding the LDL fraction, although the mean LDL levels in the subclinical hypothyroidism group (123.04±27.71) were higher compared to the control group (114.28±18.13), the difference was not statistically significant (p-value=0.064). Therefore, to further explore any relation between LDL levels and TSH, the coefficient of correlation was calculated between the two parameters. Interestingly, LDL levels showed a moderately positive correlation (r=0.523) with TSH, and this correlation was found to be statistically significant (p<0.001) [Table/Fig-4].

Variables		TSH	Interpretation
LDL	Pearson's correlation coefficient	0.523	Moderate positive correlation
	Sig. (2-tailed)	<0.001	Significant

[Table/Fig-4]: Correlation of LDL with TSH in subclinical hypothyroidism.

DISCUSSION

Subclinical hypothyroidism has generated significant interest among clinicians and researchers in recent years due to its possible association with CVD risk factors. While overt hypothyroidism has been clearly demonstrated to have an increased risk for CVD, there is limited, variable, and conflicting data regarding the association of subclinical hypothyroidism with CVD risk factors like obesity, blood pressure, and dyslipidaemias, especially in the Indian context as depicted in [Table/Fig-5].

S. No.	Authors	Place of the study/year	Number of subjects	Age and gender distribution of subclinical hypothyroidism patients	Clinical findings	Biochemical findings
1	Pesic MM et al., [16]	Serbia, 2015	60 cases of subclinical hypothyroidism and 60 euthyroid subjects	Mean age: 52 years, 42 (70%) females	• Significantly higher levels of BMI, Diastolic blood pressure in subclinical hypothyroidism • No significant difference in the waist circumference and SBP	• Significantly higher levels of all lipid parameters except for HDL-C in subclinical hypothyroidism • No significant difference in the HDL levels
2	Dey A et al., [18]	India, 2019	25 cases of subclinical hypothyroidism	Mean age: 35 years, 20 (80%) females	• 20% of the patients had both high BMI and high Waist Hip Ratio (WHR) • 16% had stage 1 hypertension and 4% had stage 2 hypertension	• 92% had dyslipidaemia
3	Aljohani NJ et al., [21]	Saudi Arabia, 2013	42 cases of subclinical hypothyroidism and 52 controls	Mean age: 35.5 years, 39 (93%) females	• Higher BMI in subclinical hypothyroidism	• Higher serum triglycerides in subclinical hypothyroidism • Total cholesterol, LDL- and HDL-cholesterol not significantly altered
4	Ejaz M et al., [30]	Pakistan, 2021	Total 900 participants of which 179 subjects had subclinical hypothyroidism	Mean age: 53.2 years, 112 (62.5%) females	• Significantly higher percentage of patients with BMI greater than 25 kg/m^2 in subclinical hypothyroidism • No significant difference in percentage of patients with hypertension	• Total cholesterol and LDL cholesterol significantly higher in subclinical hypothyroidism
5	Hussain A et al., [31]	Libya, 2019	36 cases of subclinical hypothyroidism	Mean age: 42.8 years, 23 (64%) females	--	• Significantly higher total cholesterol, serum triglycerides, and LDL-C levels • Significantly lower HDL-C in subclinical hypothyroidism
6	Present study	India, 2023	100 cases of subclinical hypothyroidism and 100 euthyroid subjects	Mean age: 43.8 years, 61 (61%) females	• Significantly higher levels of BMI, WHR and blood pressure in subclinical hypothyroidism	• Significantly higher levels of total cholesterol and serum triglyceride levels • Significantly lower levels of HDL-C and a non significant increase in LDL-C levels in subclinical hypothyroidism

[Table/Fig-5]: Comparative features of studies on CVD risk factors in subclinical hypothyroidism [16,18,21,30,31].

The link between obesity indicators and subclinical hypothyroidism has been explored in previous studies, and both conditions were found to be closely intertwined in most studies, with subclinical hypothyroidism patients exhibiting significantly higher BMI and WHR compared to controls [21,22]. The results of the present study are consistent with such studies, and the mean BMI and WHR of subclinical hypothyroidism patients were higher by 18% and 9%, respectively, compared to the euthyroid group. However, whether these findings hold true for the elderly age group is conjectural. A Rotterdam study conducted on elderly women with a mean age of 69 years did not report any increase in BMI among subclinical hypothyroidism subjects compared to the euthyroid group [19]. The probable explanation could be age-related factors like physiological anorexia and the loss of muscle and bone mass in such patients, which could have countered the tendency for weight gain.

Obesity has been proposed to lead to a hypothyroid state through multiple mechanisms, such as direct lipotoxicity to the thyroid gland [23], increased proinflammatory mediators in obesity influencing iodide uptake and deiodinase activity in the thyroid gland, leptin-induced suppression of TSH action on the thyroid, palmitic acid-mediated suppression of thyroid hormone synthesis [24], and immune-mediated thyroid dysfunction [12]. On the other hand, hypothyroidism-induced weight gain can be attributed to decreased basal metabolic rate and energy expenditure and expansion of the extracellular water compartment in the body [25].

Hypothyroid states are also believed to have a significant effect on blood pressure. Some studies have underscored the significant association of subclinical hypothyroidism with both high SBP and DBP [26], while a few have reported an association only with SBP [27]. The results of the present study are in consonance with such studies, and the mean SBP and DBP of subclinical hypothyroidism patients were higher by 17% compared to the euthyroid group. The mechanisms leading to a rise in blood pressure in hypothyroid states are thought to be multifactorial in nature, with an increase in systemic vascular resistance and slowed ventricular diastolic relaxation and filling, and decreased renin release with consequent renal sodium reabsorption leading to an expansion of blood volume by 5.5% being prominent factors [28].

Regarding the lipid profile, there is an abundance of medical literature that shows that overt hypothyroidism has an adverse effect on the lipid profile. Many studies have reported that in patients with overt hypothyroidism, there is an increase in serum total cholesterol, LDL cholesterol, apolipoprotein B, lipoprotein(a) levels, and triglyceride levels [29]. However, in stark contrast, studies regarding subclinical hypothyroidism and its effect on the lipid profile are few in number. Moreover, these limited studies have reported variable and conflicting results regarding the lipid profile in subclinical hypothyroidism. Most of these studies have shown elevated levels of total cholesterol, LDL-C, and triglycerides, and

lower HDL-C in subclinical hypothyroidism [30-32], which is in agreement with the results of the present study where levels of total cholesterol, LDL-C, and triglycerides were found to be higher by 41%, 8%, and 16%, respectively, and HDL-C was lower by 16% in subclinical hypothyroidism compared to the euthyroid group.

On the contrary, there have been occasional reports where no significant association between subclinical hypothyroidism and lipid parameters was found [33,34]. In one such study, the mean total cholesterol was found to be lower at 259 mg/dL in subclinical hypothyroidism compared to 271 mg/dL in the euthyroid group [19]. It may be argued that conclusions were drawn based on a predominantly elderly female population, while younger and male populations were not included in the study, limiting its significance.

A previous study attempted to explore the mechanisms involved in subclinical hypothyroidism leading to an altered lipid profile. It has been reported that TSH, which is raised in subclinical hypothyroidism, binds to TSH Receptors (TSHRs) on the surface of hepatocytes and adipocytes [35], thereby regulating cholesterol metabolism. TSH action results in an increase in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), HMG-CoA Reductase (HMGCR), and Hormone-Sensitive Lipase (HSL) levels, and a decrease in CYP7A1, all of which are vital components of cholesterol metabolism [14]. It has been postulated that TSH-mediated upregulation of HMGCR (the rate-limiting enzyme in cholesterol synthesis) by action on TSHR in the hepatocyte membranes [36] results in increased cholesterol synthesis in the liver, leading to elevated cholesterol levels.

It has also been observed in some studies that the relationship between thyroid dysfunction and cardiovascular endpoints remained statistically significant even after eliminating the impact of traditional CVD risk factors like dyslipidaemia and hypertension [37]. This emphasises the fact that there may be other hitherto unknown and hidden risk factor pathways through which thyroid dysfunction leads to cardiovascular complications.

Limitation(s)

One major limitation of the present study is that the causal relationship between subclinical hypothyroidism and CVD risk factors could not be assessed. Additionally, the authors were unable to assess the impact of thyroid hormone supplementation in patients with subclinical hypothyroidism on CVD risk factors, which could have enhanced the authors understanding.

CONCLUSION(S)

In the present study, the levels of CVD risk factors like obesity indicators BMI and WHR, and blood pressure are higher in subclinical hypothyroidism. Among the lipid parameters, serum cholesterol and triglyceride levels are significantly higher, while HDL levels are significantly lower in this condition. There is also a strong positive correlation between TSH levels and LDL levels. Therefore, subclinical hypothyroidism might represent a potentially modifiable risk factor for preventing CVD-related morbidity and mortality. However, further large-scale longitudinal studies are required to establish the causal relationship and elucidate the mechanisms involved in this association between subclinical hypothyroidism and cardiac risk factors. Furthermore, until the current treatment recommendations for subclinical hypothyroidism are further refined and updated, the decision on whether to treat or not to treat subclinical hypothyroidism should be based on a combination of clinical judgement and current practice guidelines.

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