Research Article

Biochemical studies in relation to the risk factors of metabolic syndrome and cardiovascular diseases in South Indian population with subclinical thyroid disease

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ABSTRACT

Background: Subclinical thyroid disease is more common in healthy middle-aged and older adults and it is being diagnosed with abnormal levels of thyroid-stimulating hormone (TSH), and thyroxine (T4) or triiodothyronine (T3). Metabolic syndrome has been linked to subclinical thyroid disease in adults due to pathophysiology of thyroid function on fat and glucose metabolism. Recent studies indicated that patients with subclinical hypothyroidism and metabolic syndrome with elevated high-sensitivity C-reactive protein (hs-CRP) are a known risk factor for cardiovascular diseases. **Objectives:** This study aimed at evaluating the levels of serum hs-CRP in South Indian population with subclinical thyroid disease. **Materials and Methods:** The study groups included 75 participants (25 patients with subclinical hypothyroidism, 25 patients with subclinical hyperthyroidism, and 25 healthy controls) aged between 30 and 60 years. Fasting serum glucose, lipid profile was analyzed by semi auto analyzer and the thyroid profile by chemiluminescent microparticle immunoassay. The hs-CRP levels were measured by latex immunoturbidimetry. **Results:** The serum hs-CRP levels (mg/L) significantly increased in subclinical hypothyroidism (1.3 ± 0.56), elevated but nonsignificant in subclinical hyperthyroidism (0.98 ± 0.47) on comparison with healthy controls (0.89 ± 0.27). Serum hs-CRP showed a positive correlation with TSH and body mass index. Negative correlation with high-density lipoprotein cholesterol, blood pressure, total cholesterol, triglycerides, and glucose. **Conclusion:** This study revealed a good relationship between subclinical thyroid disease and metabolic syndrome. hs-CRP is an independent risk factor for cardiovascular diseases. Addition of hs-CRP along with routine lipid profile in patients with thyroid dysfunction will improve global risk prediction for metabolic syndrome and cardiovascular diseases.

KEY WORDS: Subclinical Thyroid Disease; Metabolic Syndrome; Cardiovascular Diseases; High-sensitivity C-reactive Protein

INTRODUCTION

Subclinical thyroid disease is common among otherwise middle-aged and older adults with abnormal levels of thyroid-stimulating hormone (TSH), and thyroxine (T4) or triiodothyronine (T3).[1] Subclinical hypo- or hyperthyroidism is a more common than overt hypo- or hyperthyroidism and is being diagnosed more frequently in the recent times. Despite this clinical significance of this disorder is still debatable. Patients with subclinical hypothyroidism are asymptomatic, but they may have cardiac dysfunction, elevated low-density lipoprotein (LDL) and neuropsychiatric symptoms. Treatment may reduce progression to overt hypothyroidism and reduce the risk of adverse fetal effects in postpartum hypothyroidism. Patients with subclinical hyperthyroidism are also

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asymptomatic and treatment may reduce progression to overt hyperthyroidism.[2] Association between subclinical hypothyroidism and metabolic syndrome or cardiovascular risk factors has been well known for decades in postmenopausal women. Recent studies demonstrated that metabolic syndrome has been linked to subclinical thyroid disease in adults due to pathophysiology of thyroid function on fat and glucose metabolism. Thyroid hormones influence vascular smooth muscles and consequently reducing arterial resistance and causing a decline diastolic blood pressure (BP).[3,4] Abnormal TSH was associated with deleterious changes in serum lipids which may increase the cardiovascular mortality and morbidity in patients with subclinical hypothyroidism and metabolic syndrome.[5] It is generally believed that systemic inflammation measured by high-sensitivity C-reactive protein (hs-CRP) is known risk factor for cardiovascular disease.[6] hs-CRP is synthesized by the liver in response to factors released by macrophages and fat cells. It is a pentameric protein found in blood plasma, whose levels rise in response to inflammation. It is an acute phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead cells to activate the complement system.[7] To the best of our knowledge, no similar study has been reported so far with respect to hs-CRP levels in patients with subclinical thyroid disease in South Indian population.

MATERIALS AND METHODS

A total of 75 participants (25 patients with subclinical hypothyroidism, 25 patients with subclinical hyperthyroidism, and 25 ages matched healthy controls) from Tagore Medical College and Hospital Chennai, aged between 30 and 60 years were enrolled as study participants. Informed written consent form the patients with subclinical thyroid disease and healthy controls were obtained before the commencement of the study. This study was approved by the Institutional Ethics Committee. The patients with newly diagnosed subclinical hypothyroidism and subclinical hyperthyroidism were included in the study. Patients with a history of thyroid dysfunction or patients with any systemic disease taking any medication that may affect thyroid function were excluded from the study. Subclinical thyroid diseases are classified into three groups based on serum TSH levels.[2]

- Subclinical hypothyroidism: 5-10 μIU/ml.
- Subclinical hyperthyroidism: <0.5 μIU/ml.
- Euthyroid: 0.5-5 μIU/ml with normal concentration of T3 and T4.

The metabolic syndrome is classified according to the 2001 National Cholesterol Education Program (NCEP)/ adult treatment program (ATP) III presence of any 3 of the following 5 traits.

1. Abdominal obesity defined as a waist circumference (WC) in men >102 cm (40 inch) and in women >88 cm (35 inch).
2. Serum triglycerides (TG) ≥150 mg/dL or drug treatment for elevated TG.
3. Serum high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL-C.
4. BP ≥130/85 mmHg or drug treatment for elevated BP.
5. Fasting plasma glucose ≥100 mg/dL or drug treatment for elevated blood glucose.

The anthropometric measurements such as height, weight, body mass index (BMI), and the WC were recorded. BP levels were also recorded for all the subjects using mercury sphygmomanometer. 12 h fasting blood samples were collected from all the subjects and sera were separated, and the samples were stored at −20°C until the time of their analysis. The serum hs-CRP levels were measured by latex turbidimetry method. The thyroid profile which includes TSH, T3, and T4 were analyzed by chemiluminescent microparticle immunoassay. Total cholesterol (TC) levels were measured by CHOD- phenol + aminophenazone (PAP) method. TG was measured by glycerol-3-phosphate oxidase-PAP method. HDL-C levels were measured by phosphotungstic acid method, serum glucose by glucose oxidase-POD method.

Statistical Analysis

The statistical analysis of the data was performed using Statistical Package for the Social Sciences package, version 22.0. The results were expressed as mean ± standard deviation and a $P < 0.05$ was considered to be statistically significant. Mann-Whitney *U*-test was performed for the pair-wise *post-hoc* comparison between two groups.

RESULTS

The biochemical and anthropometric characteristics of study patients are described in Table 1. Out of 75 participants, 25 patients were subclinical hypothyroidism, 25 were subclinical hyperthyroidism, 25 were healthy control and the age ranged between 30 and 60 years. The anthropometric measurements were found to be nonsignificant in patients with subclinical hyperthyroidism, slightly elevated but nonsignificant in patients with subclinical hypothyroidism when compared to controls. Serum hs-CRP levels were significantly increased in subclinical hypothyroidism (1.3 ± 0.56 mg/L), elevated but nonsignificant in subclinical hyperthyroidism (0.98 ± 0.47 mg/L) on comparison with healthy controls (0.89 ± 0.27 mg/L).

The relationship between serum hs-CRP and biochemical and anthropometric parameters are shown in Table 2. Serum hs-CRP levels showed a positive correlation with TSH

Table 1: Comparison of different parameters between subclinical hypothyroidism, subclinical hyperthyroidism, and control group (n=25 in each group)

Parameter	Control	Subclinical hypothyroidism	Subclinical hyperthyroidism
Age	45.4±10.56	48.1±9.8^{NS}	47.08±10.8^{NS}
BMI	23.48±2.38	25.08±3.29^{NS}	23.28±3.4^{NS}
WC	88.24±9.47	91.12±9.81^{NS}	88.64±9.4^{NS}
Systolic BP	116.16±9.46	119.76±11.2^{NS}	118.16±9.89^{NS}
Diastolic BP	75.44±7.4	77.28±9.93^{NS}	75.6±9.16^{NS}
T3 (ng/ml)	82.76±15	87.4±24.6^{NS}	93.48±29.5*
T4 (µg/dl)	7.15±2.24	7.77±2.07^{NS}	6.71±2.31^{NS}
TSH (µIU/ml)	2.59±0.83	7.05±1.49*	0.3±0.17***
TC (mg/dl)	167.24±39.8	183.92±49.6*	160.84±37.7^{NS}
TG (mg/dl)	114.32±79.8	129.8±62.9^{NS}	135.48±72.7^{NS}
HDL-C (mg/dl)	42.4±9.82	41.64±10.4^{NS}	41.48±7.71^{NS}
LDL-C (mg/dl)	103.2±38.3	117.48±44.1^{NS}	92.2±35.8^{NS}
VLDL-C (mg/dl)	22.12±14	25.64±11.8^{NS}	26.96±14.5^{NS}
LDL/HDL-C	2.56±0.98	2.96±1.93^{NS}	2.27±0.97^{NS}
Glucose (mg/dl)	117.52±42.4	108.32±29^{NS}	101.7±30^{NS}
hs-CRP (mg/L)	0.89±0.27	1.3±0.56***	0.98±0.47^{NS}

Results are expressed in mean±SD. *P<0.05, **P<0.01, ***P<0.001, ^{NS}nonsignificant. hs-CRP: High sensitivity C-reactive protein, BMI: Body mass index, WC: Waist circumference, T3: Triiodothyronine, T4: Thyroxine, TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein, TSH: Thyroid stimulating hormone, VLDL: Very low density lipoprotein, SD: Standard deviation

Table 2: Karl Pearson's correlation analysis between serum hs-CRP and anthropometric and biochemical variables of the study subjects

Parameter	*r*	*P*
BMI	0.215	0.06
WC	0.068	0.561
Systolic BP	−0.112	0.337
Diastolic BP	0.026	0.828
TSH	0.354	0.002
TC	−0.061	0.603
TG	0.082	0.482
HDL-C	−0.124	0.290
LDL-C	−0.60	0.607
VLDL	0.053	0.65
Glucose	−0.037	0.752
LDL/HDL ratio	0.023	0.847

hs-CRP: High sensitivity C-reactive protein, BMI: Body mass index, WC: Waist circumference, TSH: Thyroid stimulating hormone, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, VLDL: Very low density lipoprotein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

and BMI. Negative correlation with HDL-C, and no association with WC, both systolic and diastolic BP, TC, TG, and glucose.

Among 25 controls, 8 were males and 17 were females. Out of 25 patients with subclinical hypothyroidism, 10 were males and 15 were females and 25 patients with subclinical hyperthyroidism, 5 were males and 20 were females. Patients with features of metabolic syndrome according to the NCEP/ATP III (2001) are described in Table 3.

The socioeconomic status and the physical activity of the patients who were enrolled in the study were found to be almost similar.

DISCUSSION

Thyroid diseases are common worldwide. According to a projection from various studies on thyroid disease it is well established that around 42 million people in India suffer from thyroid disease.[8] Many studies have reported that subclinical thyroid diseases particularly patients with subclinical hypothyroidism are increased the risk for metabolic syndrome and cardiovascular diseases and elevated hs-CRP are an independent risk predictor of coronary artery disease, myocardial infarction, and stroke.[7,9,10] However, no systematic data are available so far, to describe the role of hs-CRP in patients with subclinical thyroid disease of South Indian population. We, therefore, aimed to dissect the role of the serum hs-CRP levels and their correlation with the anthropometric, clinical and the biochemical parameters in South Indian population. We observed for the first time, to our knowledge, significantly elevated serum hs-CRP levels in patients with subclinical hypothyroidism. Whereas elevated but not significant in patients with subclinical hyperthyroidism. Our results were identical to the reports of earlier studies.[6,11,12] In contrast, another study observed no marginal difference in hs-CRP levels between patients with subclinical hypothyroidism and euthyroid patients.[13] Our findings indicate that subclinical hypothyroidism has a major role influence on low-grade inflammation. In this study, we identified 10 patients with subclinical hypothyroidism, 7 patients with subclinical hyperthyroidism, and 6 healthy controls with features of metabolic syndrome according to the NCEP/ATP III (2001). These findings indicated that adipocytes and preadipocytes express TSH receptors and that TSH induces preadipocytes to release adipokines which plays an important role in the onset of metabolic syndrome and cardiovascular diseases.[5,14-16] Metabolic syndrome patients with subclinical hypothyroidism may have systemic inflammation and conversely metabolic syndrome patients with elevated hs-CRP are at high risk for subclinical hypothyroidism.[17] We have observed slightly increased BMI, WC in patients with subclinical hypothyroidism but statistically not significant. This study confirmed the results of previous studies.[18] In this work, we found nonsignificant systolic and diastolic BP in patients with subclinical thyroid diseases as compared to those in the controls. Our results also at par with those of other investigators.[19,20]

Table 3: Subjects with features of metabolic syndrome

Sex	Control	Subclinical hypothyroidism	Subclinical hyperthyroidism
Males	2	1	3
Females	4	9	4

We have observed elevated T3 in subclinical hyperthyroidism, elevated TSH in subclinical hypothyroidism. This is natural as per the diagnostic criteria. In this study, we observed elevated TC, LDL-cholesterol (C), and TG and nonsignificant HDL-C levels in patients with subclinical hypothyroidism. Patients with subclinical hyperthyroidism showed elevated TG and nonsignificant TC, LDL-C, and HDL-C. It is generally believed that dyslipidemia is a common finding in patients with thyroid disease and thyroid hormones play a role in regulating the synthesis, metabolism, and mobilization of lipids. Our data agree with those which have been reported by others.[21,22] Similar to the previous study, we have also observed elevated LDL/HDL ratio in patients with subclinical hypothyroidism.[23]

The limitations of this study include the small sample size. However, further research should endeavor to build on the findings of this study. Larger sample size would elucidate the role of serum hs-CRP along with routine lipid profile in patients with thyroid dysfunction to draw a healthy conclusion for clinical management of the patients.

CONCLUSION

In conclusion, our findings indicated that subclinical thyroid diseases and metabolic syndrome are recognized risk factors for cardiovascular diseases. Hence, the addition of hs-CRP along with routine lipid profile in patients with thyroid dysfunction will improve global risk prediction of metabolic syndrome and cardiovascular diseases. Our study is an effort to identify the relation between these two entities and the risk factors involved in this association.

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