

Original Research Article

## Assessment of Subclinical Hypothyroidism, Lipid Profile and CIMT Status in Prevention of Cerebrovascular Ischemic Events

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### ABSTRACT

**Introduction:** Cardiovascular system is rich in thyroid hormone receptors and is relatively sensitive to changes in the levels of thyroid hormones. Overt hypothyroidism is known to be a risk factor for atherosclerosis and cardiovascular disease but there is still controversy about its association with subclinical hypothyroidism (SCH). The present study was designed to determine the association between lipid profile, Carotid artery intima media thickness (CIMT) and subclinical hypothyroidism

**Material Method:** SCH is defined as high thyroid-stimulating hormone (TSH) levels in the presence of normal serum T4 and T3 levels. 50 patients with SCH and 43 controls were included in the study. Serum lipid profile, Carotid intima-media thickness were compared between patient and controls.

**Results:** Mean level of serum total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) was significantly higher in patients than controls whereas high density lipoprotein (HDL) were lower in patients. Mean CIMT values of patient (0.058±0.0105) was significantly higher than controls (0.054±0.004). TSH shows positive correlation lipid profile.

**Conclusion:** Subclinical hypothyroidism patients are at increased risk for atherosclerosis and cerebrovascular accident.

**Keywords:** Carotid intima media thickness (CIMT), Hypothyroidism, lipid profile, cerebrovascular accident.

### INTRODUCTION

In 21<sup>st</sup> century stroke has become a leading cause of death and the major cause of long-term disability worldwide. [1,2] About 80% of strokes are ischemic, as a consequence of embolic events or stenosis of cerebral arteries.

More specifically, Carotid atherosclerotic plaque and artery stenosis was found to be associated with 20%–30%

of cerebral infarctions. [3,4] Atherosclerosis is characterized by progressive thickening of the arterial wall, with the deposition of cholesterol, inflammatory cell infiltration, extracellular-matrix formation, and thrombosis. [5] A large portion of the general population exhibit nonsymptomatic atherosclerosis. Among the risk factors for atherosclerosis, nonmodifiable risk factors are increasing

age, family history, male gender and genetic abnormalities whereas modifiable risk factors include hyperlipidemia, hypertension, cigarette smoking, diabetes etc. Even in the absence of other factors, Hyperlipidemia-and more specifically hypercholesterolemia are sufficient to stimulate development of atherosclerosis. [6]

It is well documented that increasing levels of total plasma cholesterol (TC) and low density lipoprotein (LDL) cholesterol and decreasing level of high density lipoprotein (HDL) cholesterol, are strong risk factors for coronary heart disease. But the relationship between the levels of blood lipids and risk of stroke is much weaker. [7] However some recent studies clarified the relationship between lipids and stroke, as well as showing that the risk of stroke and amount of carotid atheroma can be reduced with cholesterol lowering drugs. [8,9]

Abnormal lipid metabolism is also seen in hypothyroidism, which may predispose to the development of atherosclerotic coronary artery disease (CAD). [10,11] Subclinical hypothyroidism (SCH), defined as the elevated serum thyrotropin (TSH) levels, with normal levels of thyroxine (T4) and triiodothyronine (T3), is a more common disorder than overt hypothyroidism. Prevalence of SCH is 1.4 –7.8% in older populations with greater percentiles among women. [12,13]

Association of atherosclerosis with overt hypothyroidism is well established but even after exclusive research there is still controversy about its association with SCH. [14] SCH may be related to endothelial dysfunction and atherogenesis in several ways. SCH is associated with increased cardiovascular risk factors which underlie atherosclerosis. [15] Increased levels of cholesterol and altered levels of coagulation parameters were shown in patients with SCH by several studies. [16,17]

B-mode sonography of the carotid intima-media thickness has also recently become a noted characteristic for assessment of cardiovascular risk. [18] Rundek et al have recently reported an association between the maximum carotid plaque thickness and the risk of cerebrovascular events. They suggested that maximum carotid plaque thickness is a simple marker of subclinical atherosclerosis. [19]

The carotid intima media thickness (CIMT) is a close marker of early atherosclerotic changes and is a widely accepted surrogate end-point for cardiovascular events. [20] The association of carotid intima media thickness with major cardiovascular risk factors has been well demonstrated. Nagasaki et al [21] demonstrated carotid artery intima media thickening in patients with overt hypothyroidism. But there are very few studies in our population, studying this relationship.

With this back ground, the objective of our present study was to find out if there is any relation between Lipid profile, CIMT and subclinical hypothyroidism.

## **MATERIALS AND METHODS**

The study was conducted in the Department of Biochemistry at Calcutta National Medical College and Hospital, Kolkata, West Bengal. Patients with diabetes mellitus, liver disease, thyroid disorder and malignant diseases, hypertension, patient with serum creatinine > 1.3 mg/dl, history of smoking, medications known to affect the lipid profile (e.g., statin), and in cases of females, current or previous pregnancy in the last 1 year and a postmenopausal state were excluded from this study. Among the newly diagnosed hypothyroid patients 50 cases were included in this study following the inclusion and exclusion criteria. Age and sex matched 43 healthy individuals were included as control subjects. The

study was preapproved by the institutional ethics committee and informed consent were obtained from the study individuals before collection of blood samples and examination of carotid artery intima media thickness measurement (CIMT) was done by ultrasonography .

**Blood Sampling and screening:** After 12hours of overnight fasting, 3ml of blood was drawn in plain vial from all the study participants by venipuncture .Blood was allowed to clot and after centrifugation serum was separated from cells, collected in separate aliquotes and stored in (-20°C). Biochemical parameters like serum total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) were analyzed on the day of sample collection. Total T3, totalT4 and TSH were tested within 48 hours by ELISA method, using standardized reagent kits in the department of Biochemistry.

**Examination of Carotid artery intima media thickness measurement (CIMT):** Examination of the carotid arteries was performed with a 10 MHz B-mode ultrasound system (Philips-HD7 Diagnostic Ultrasound System, USA) in the department of Radiology. The B-mode scanning protocol included the scanning of the right and left common carotid arteries 3 cm proximal to the carotid bifurcation. [22] CIMT measured on cross sectional images (i.e. on transverse section) and measurements were always performed in plaque-free arterial segments. [23] All examinations and measurements were performed by same examiner.

**Statistical analysis:** All the data obtained were presented as mean+/-SD and compared by Mann Whitney U test and p value of<0.05 was considered to be statistically significant, at a confidence interval of 95%. All the statistical analysis was done by SPSS 17 software of Microsoft windows.

## RESULTS

In this study, 50 patients were analyzed, among them 7 were male and 33 were female. Most of the patients with subclinical hypothyroidism were female.43 age and sex matched controls were analyzed. The clinical and biochemical parameters has been depicted in Table-1.In our study the mean level serum TSH was 15.677  $\mu$ IU/ml in patients and was significantly higher than controls. As per inclusion and exclusion criteria 50 patients with raised TSH were included in the study and they were having total T3 and T4 level within reference range. Although serum T3 was significantly lower than controls, T4 showed no significant difference. Mean value of CIMT of patient (0.058cm+/-0.0105) shows significant difference with controls ((0.054cm+/-0.004). Further on analysis of Lipid profile parameters in SCH we found serum TG, TC and VLDL were significantly higher than controls and HDL was significantly lower than patients.

Serum TSH showed significant (positive) correlation with serum TG, HDL, LDL and T3 (refer table-2).

**Table 1: Comparison of different biochemical parameters and Radiological findings of carotid artery intima media thickness (CIMT) by Mann Whitney test.**

Different parameters	Patients (mean+/-SD)	Control Subjects(mean+/-SD)	Z Value	P Value
T3 (ng/ml)	0.886+/-0.353	1.217+/-1.291	3.263	0.001
T4 ( $\mu$ g/ml)	5.602+/-1.917	5.703+/-1.129	0.833	0.405
TSH ( $\mu$ IU/ml)	15.677+/-3.389	2.260+/-1.210	8.285	0.000
CIMT in mm	0.058+/-0.0105	0.054+/-0.004	2.254	0.02
Total Cholesterol(mg/dl)	228.38+/-41.19	112.34+/-11.18	8.287	0.000
Triglyceride(mg/dl)	275.68+/-75.86	121.34+/-7.41	8.290	0.000
HDL(mg/dl)	37.64+/-2.455	39.32+/-2.34	3.049	0.002
LDL(mg/dl)	133.04+/-5.63	113.34+/-17.32	8.091	0.000

p<0.05 considered significant.

**Table 2: Correlation of TSH with other parameters**

	T3	T4	Cholesterol	Triglyceride	HDL	LDL	CIMT
R	0.203	0.028	0.890	0.800	0.414	0.593	0.173
p	0.051	0.789	<0.001	<0.001	<0.001	<0.001	0.094

R= Pearson correlation coefficient    statistical significant at p value <0.05

**Table 3: Correlation of CIMT with other parameters**

	T3	T4	TSH	Cholesterol	Triglyceride	HDL	LDL
R	0.085	0.048	0.175	0.351	0.385	0.133	0.107
p	0.419	0.650	0.094	0.001	<0.001	0.205	0.309

R= Pearson correlation coefficient    statistical significant at p value <0.05

CIMT showed significant (positive) correlation with serum Cholesterol and TG. Although positive correlation was present between TSH and CIMT, the correlation was not found to be statistically significant in our study (refer table-3).

## DISCUSSION

Coronary heart disease and Stroke are the important cause of mortality and morbidity worldwide. Increasing levels of total plasma cholesterol and low density lipoprotein cholesterol and decreasing level of high density lipoprotein cholesterol, are strong risk factors for coronary heart disease and Stroke. Deranged lipid metabolism due to various modifiable and non-modifiable risk factors leads to the pathogenesis of atherosclerosis. The increased risk of atherosclerosis in patients with SCH is usually due to dyslipidemia and hypertension, [24] but the results of this study, similar to other ones [25,26] showed that SCH is associated with carotid atherosclerosis independent of these factors.

In our study subjects having SCH had significant change in lipid parameters. Compare to controls serum TC, TG and LDL levels were higher among patients. Several studies have shown an association between SCH and hypercholesterolemia, [27] but some other studies have not found such association. [28] Besides TSH, triglycerides were also independent risk factors for mean CIMT. This study showed that patients with SCH have significantly higher concentrations of triglyceride.

In the present study serum TSH has shown significant correlation with TC, TG, HDL and LDL. In a population-based study from Australia, SCH was found to be an independent predictor for coronary artery disease. [29] Imaizumi and coworkers' study with 257 patients with SCH depicted that SCH is associated with ischemic heart disease. [30] A meta-analysis by Ochs *et al.* screening 14 449 participants suggested that SCH may be associated with a modest increased risk for coronary heart disease and mortality. [31]

In this study CIMT of SCH was significantly higher than controls and there was a positive correlation between CIMT and TC, TG and TSH. Cakal *et al* [32] have similarly demonstrated higher CIMT in primary hypothyroid patients. They also found positive correlation between lipids, CIMT, and TSH levels. They concluded that CIMT is an objective sign of accelerated atherosclerosis in patients with primary hypothyroidism. Monzani and co-workers [33] found early carotid wall alterations in sub-clinical hypothyroid patients that showed improvement after levothyroxine replacement. They also observed positive correlation between mean CIMT and serum TSH levels. Carotid IMT is increasingly used as a surrogate marker for atherosclerosis and has a high positive predictive value for CAD. [34] Monzani *et al.* were the first to show the association of CIMT and SCH. [33] In their study, CIMT was associated with age, TSH and LDL values, and CIMT improved by levothyroxine therapy. Although CIMT was similar between the control and the patient group when only patients younger than 35 were analyzed,

improvement with levothyroxine therapy was seen. Kim *et al.* also found increased CIMT in SCH which regressed by levothyroxine and this regression was associated with LDL- cholesterol levels. [35]

## CONCLUSION

In conclusion, our data revealed that SCH is indeed associated with increased CIMT and higher lipid parameters in our population and these SCH patients are at increased risk for atherosclerosis and Cerebrovascular accident (CVA). To more conclusively find out the relationship, future studies with higher number of study subjects is warranted.

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