Evaluation of Carotid Intima-Media Thickness in Sub-clinical Hypothyroid Patients

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ABSTRACT

Objective: Endothelial dysfunction and atherosclerosis may be associated with subclinical hypothyroidism (SCH) in multiple ways. The intima-media thickness of the common carotid artery (CIMT) is an important parameter for early atherosclerotic change. Previously several studies addressed the association between SCH and CIMT. Some studies indicate that SCH might be related to increase CIMT, while other studies revealed no significant association. The aim of the study was to further examine the relationship between CIMT and SCH patients in our own laboratory setting in Bangladesh.

Patients and Methods: This cross sectional study was carried out at the Institute of Nuclear Medicine and Allied Sciences (INMAS), Dhaka Medical College Hospital Campus, Dhaka during the period of January 2016 to October 2016. The study included 56 consecutive patients. Out of 56 patients, 26 were in SCH group and 30 were in euthyroid control group. CIMT was measured in each subject via High resolution B-mode ultrasonography. Data were analyzed between these two groups in respect to age, sex, BMI, and mean CIMT.

Results: Out of 56 subjects, 26 were SCH group and 30 were euthyroid control group. Male to female ratio was 3:23 and 9:21 in SCH and control groups respectively. The mean age was 30±7.4 and 32±8.7 years in SCH and control groups respectively. The mean BMI was 25.6±4.7 kg/m2 in SCH and 25.1±4.1 kg/m2 in control group. The mean CIMT was significantly (p≤0.05) higher in SCH group (Right-0.80±0.05 mm, Left-0.80±0.07 mm) than control group (Right-0.60±0.05 mm, Left- 0.61±0.05 mm). SCH group was further subdivided into two groups with a cut off value of serum TSH at 10 mIU/L. The mean CIMT was significantly higher in SCH with TSH above 10 mIU/L than SCH group with TSH less than 10 mIU/L (p≤0.05). Pearson's rank correlation test showed significant positive correlation between both CIMT and TSH values.

Conclusion: Our study showed that CIMT was significantly higher in SCH group than euthyroid control group. The CIMT values were positively correlated with the TSH values. Therefore we may conclude that SCH is an independent risk factor for atherosclerosis in addition to other classical risk factors.

Key Words: Subclinical hypothyroidism, intima-media thickness, atherosclerosis.

INTRODUCTION

Subclinical hypothyroidism (SCH) is a disorder characterized by elevated serum thyroid- stimulating hormone (TSH) levels despite normal free thyroid hormone values (1). It is a common problem, with a prevalence of 3%- 8% in the population without known thyroid disease. The prevalence increases with age and is higher in women. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10% (2).

Cardiovascular diseases (CVD) are the main cause of death in the world. Carotid ultrasound provides quantitative measurements of carotid intima–media thickness (CIMT) that can be used to assess cardiovascular disease risk in individuals and monitor ongoing disease progression and regression on clinical trials. It is non-invasive, rapid, reproducible and carries no risk. The intima-media thickness of the common carotid artery is an established measure of early atherosclerotic changes and is used as a surrogate end point of vascular outcomes in clinical trials (3). This parameter is included in European guideline on prevention of cardio-vascular disorders. An increasing IMT over threshold value indicates progression of atherosclerosis. Similar to the classical

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risk factors such as diabetes, hyperlipidemia and obesity, this is an independent risk factor for coronary heart disease. Positive correlation has been reported between CIMT and degree of atherosclerotic changes (4).

Primary hypothyroid patients have greater risk for developing atherosclerosis. Several studies have investigated the association between SCH and carotid atherosclerosis. The results of some studies indicate that CIMT levels might be increased in SCH subjects. Recent meta- analysis suggested that SCH is associated with an increased CIMT, which may be due to elevated serum TSH, dyslipidemia and hypertension. Increased IMT can also be present in patients with serum TSH values less than 10 mIU/L (5). A few studies did not find any association between SCH and CIMT. As there are some controversies, the benefit from replacement therapy in SCH is still unclear. So the aim of the study was to examine the CIMT in SCH patients in our own laboratory setting in Bangladesh in order to find an association if any between the two.

MATERIALS AND METHODS

This cross sectional study was carried out at the Institute of Nuclear Medicine and Allied Sciences (INMAS) of Dhaka Medical College Hospital Campus, Dhaka during the period of January 2016 to October 2016. Total 56 subjects more than 17 years of age were included by non-random purposive sampling. Among 56 subjects, 26 newly diagnosed SCH were included and the criteria were: normal serum free thyroxin (FT4) and elevated TSH (> 5mIU/L). Thirty healthy euthyroid subjects (normal serum FT4 and TSH levels) were included as a control group. The exclusion criteria were: patients with known thyroid disease, current or past history of thyroid hormone or antithyroid drug intake, known cardiovascular disease, patients on medication for hypertension or lipid metabolism, any chronic debilitating illness and pregnancy. All relevant data collected during the investigations were recorded on a pre-designed data collection sheet for each patient.

A general physical examination was performed, including assessment of height (without shoes) and weight. Body mass index (BMI) was calculated as body weight (in Kg) divided by the square of the height (meter).

Carotid ultrasound scanning was performed in all participants by a skilled sonologist, who was blind to all clinical and laboratory data of patients, using DC-7 scanner, Mindray (China) with a 7.5-10 MHz linear transducer. Patients were examined in the supine position with the neck mildly extended and the head rotated to the contralateral side. The common carotid intima media thickness was calculated on both sides of two longitudinal images of each common carotid artery immediately 1.5 cm prior to the bifurcation on a segment free of plaque. IMT was the distance from the leading edge of the lumen intima-interface to the leading edge of the media-adventitia. Average of the two CIMT (proximal and distal) values from each side was used to calculate mean CIMT on each side.

Concentration of free thyroxin (FT4) was analyzed by radioimmunoassay and thyroid stimulating hormone (TSH) was analyzed by immunoradiometric assay. Normal reference laboratory values for FT4: 9.50-25.50 p mol/L and TSH: 0.3-5.0 m IU/L.

Statistical analysis:

Statistical analysis was performed using SPSS for windows, version 22.0. Categorical data was expressed in number. Parametric data was expressed in mean ± SD. Parametric data was evaluated by unpaired t test. Significance was defined by p value ≤ 0.05. Pearson's rank correlation analysis was used to assess the correlation between variables.

RESULTS

Out of 56 subjects, 26 were SCH group and 30 were euthyroid control group. Male to female ratio was 3:23 in SCH group and 9:21 in control group which indicate that SCH is more common in female than male. The mean age was found 30 ± 7.4 and 32 ± 8.7

years in SCH and control groups respectively. The mean BMI was found 25.6 ± 4.7 kg/m2 in SCH and 25.1 ± 4.1 kg/m2 in control group (Table 1).

Table 1: Personal characteristics of the SCH and control group.

Variables	SCH group (n = 26)	Control group (n= 30)
Sex (M:F)	3:23	9:21
Age (Yrs)	30±7.4	32±8.7
BMI (Kg/m2)	25.6±4.7	25.1±4.1

The mean right CIMT was 0.80±0.05 mm and 0.60 ± 0.05 mm in SCH and control groups respectively and the result was statistically significant. The mean left CIMT was 0.80 ± 0.07 mm in SCH and 0.61±0.05mm in control group and the result was statistically significant (Table 2). So patients with SCH had statistically significantly greater CIMT than euthyroid control group in both sides.

Table 2: Distribution of study population according to mean CIMT values in SCH and control group.

Variables	SCH group N=26	Control group N=30	P value
Right CIMT (mm)	0.80 ± 0.05	0.60 ± 0.05	≤0.0001
Left CIMT (mm)	0.80 ± 0.07	0.61 ± 0.05	≤0.0001

SCH group was further subdivided into two groups with a cut off value of serum TSH at 10 m IU/L. Among 26 SCH group, 12 were in SCH group with TSH less than 10 mIU/L and 14 were in SCH group with TSH above 10 m IU/L. The mean right and left CIMT were 0.75 ± 0.05 and 0.75 ± 0.05 mm in SCH group with TSH less than 10 m IU/L and 0.82 ± 0.04, 0.87 ± 0.06 mm in SCH group with TSH above 10 m IU/L respectively. The results were statistically significant (Table 3).

Table 3: Distribution of study population according to mean CIMT values in SCH groups with a cut off value of serum TSH at 10 mIU/L.

Variables	SCH group (TSH<10 mIU/L) N=12	SCH group (TSH>10 mIU/L) N=14	P value
Right CIMT (mm)	0.75±0.05	0.82±0.04	≤0.001
Left CIMT (mm)	0.75±0.05	0.87±0.06	≤0.00001

Figure 1 shows significant positive correlation between right CIMT and TSH values. Significant positive correlation was also found between left CIMT and TSH values (Figure 2). So, CIMT values were significantly increased with increased values of TSH.
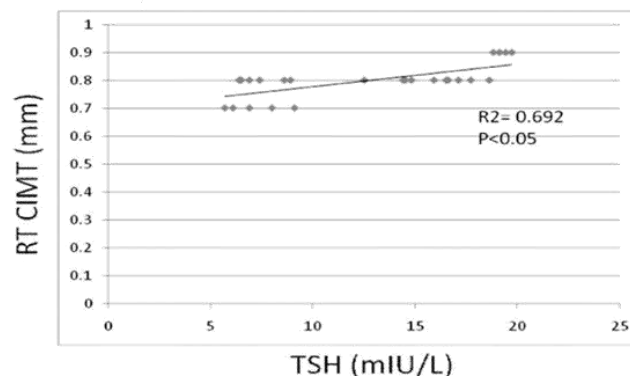

Figure 1: Scatter diagram showing correlation between right CIMT and TSH values.
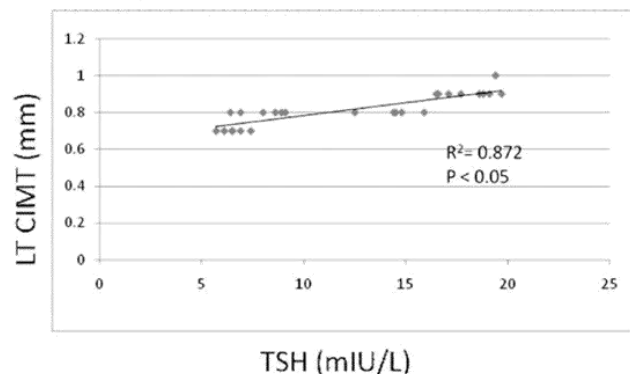

Figure 2: Scatter diagram showing correlation between left CIMT and TSH values.

DISCUSSION

The result of the present study showed significantly increased CIMT in SCH group than in euthyroid control group (0.80 ± 0.05 vs 0.6 ± 0.05 mm, p ≤ 0.05) that indicates SCH patients might have increased cardiovascular events. Previously many studies have examined the relationship between SCH and cardiovascular disease. However, contradictory results have been obtained. Some studies determined an increase in cardiovascular risk with SCH and some studies revealed no significant association. Valentina et al. reported that patient with SCH had significantly greater mean CIMT than in control group (0.61 ± 0.1 vs 0.56 ± 0.1 mm, p = 0.034). They concluded that

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SCH is associated with increased CIMT and presence of carotid plaques, independent of classical risk factors for atherosclerosis (6). Knapp et al. also showed a mean IMT in the SCH group was significantly higher than in the controls (0.7 mm vs 0.38 mm, p = 0.001). They included forty SCH subjects and fifteen healthy control subjects. They also suggested that the patients with SCH were at risk of the development of cardiovascular disease (4).

A recent meta-analysis by Gao et al. reported that SCH was associated with an increased carotid IMT, which may be due to elevated TSH, dyslipidemia and hypertension. Increased IMT can also be present in patients with serum TSH values less than 10 m IU/L (5) which was similar to our study.

Rawat et al. studied 25 consecutive patients into two groups: hypothyroid groups with TSH>10 mIU/L and SCH groups with TSH 6-10 mIU/L. They found significant difference (p ≤ 0.05) in CIMT between subclinical hypothyroidism (0.67 ± 0.10 mm) as compared to hypothyroidism (0.74 ± 0.14 mm). Their findings suggested that cardiovascular risk factors were increased in subclinical as well as in clinical hypothyroidism so efforts should be made to detect and treat hypothyroidism at an early stage (7). Akkoca et al. also reported that there was an increment of CA-IMT in clinical and subclinical hypothyroidism resulting from an adverse lipid profile and thyroid hormone replacement might reversed the adverse effects (8).

A recent cross sectional study by Franca et al. found that SCH with metabolic syndrome (MS) was higher CIMT than SCH without MS. They found that maximum (p = 0.012) and mean (p = 0.025) IMT were higher in SCH with MS group than SCH without MS group. Maximum IMT was higher in SCH with MS than euthyroid with MS group (p = 0.048). Their findings suggested that SCH may be one more cardiovascular risk factor in patients with the MS (9).

However an observational study by Cappola et al. demonstrated no significant relation between cardiovascular events, mortality and SCH (10).

In the current study, when SCH group was sub divided into two groups with a cut of value of serum TSH at 10 mIU/L, it was found that CIMT was significantly higher in SCH group with TSH above 10 mIU/L (Right- 0.82 ± 0.04 mm, Left-0.87 ± 0.06 mm) than SCH group with TSH less than 10 mIU/L (0.75±0.05 mm). The result was significant (p ≤ 0.05). Pearson's rank correlation test showed that both CIMT was positively correlated (r = 0.478 and r = 0.761) with TSH values and the result was significant (p ≤ 0.05). It indicates that CIMT values were significantly increased with increased values of TSH.

A recent cross sectional study found a significant positive correlation between TSH values and CIMT (r = 0.28, r = 0.29, p ≤ 0.05). In that study the mean TSH, FT4, CIMT and max CIMT were 7.9 ± 3.6 mIU/L, 14.5 ± 2.8 pmol/L, 0.61 ± 0.1 mm and 0.65 ± 0.1 mm respectively (11). However another study found no significant association (p ≥ 0.05) between two groups of TSH in terms of CIMT values. They divided SCH group into two as TSH level less than 7 µIU/L (n = 39) and TSH level higher than 7 µIU/L (n = 17) (12).

SCH may be associated with atherosclerosis in several ways. The increased risk of atherosclerosis in SCH patients may be due to dyslipidemia and hypertension. Increased levels of cholesterol and altered levels of coagulation parameters were found in patients with SCH (13, 14). Second, thyroid hormones have substantial influence on the peripheral vasculature and thyroid hormone receptors have been identified in human vascular smooth muscle cells (15). So thyroid hormone deficiency may affect these vascular smooth muscle cells and may develop atherosclerosis. Thyroid autoimmunity is one of the important mechanism. Hashimoto's thyroiditis is the most common condition causing SCH. Recently, it has been shown that Hashimoto's thyroiditis is responsible for chronic inflammation which causes endothelial dysfunction, a promoter of atherosclerosis. Abnormal immune response mediated by immune complex causes vascular

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damage (16). All these mechanism may favor the association of SCH and atherosclerosis.

There were some limitations in the present study. The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the population. Small sample size was also a limitation. Therefore, in future further study may be under taken with large sample size.

CONCLUSION

Our study suggests that subclinical hypothyroidism is associated with elevated cardiac risk as evidenced by CIMT. The result of CA-IMT was significantly higher in SCH group compared to the euthyroid control group and the values were also positively correlated with the TSH levels. Therefore we may conclude that SCH is an independent risk factor for atherosclerosis in addition to other classical risk factors. This finding justifies the use of effective hormone replacement therapy in SCH patients to at least slow down the atherosclerosis process and/or to prevent further cardiac adverse effects.

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