Noninvasive indicators of atherosclerosis in subclinical hypothyroidism

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ABSTRACT

Introduction: Cardiovascular system is rich in thyroid hormone receptors and is one of the major sites of action for thyroid hormones. However, the effect of subclinical hypothyroidism (SCH) on atherosclerosis has not been cleared yet. Materials and Methods: SCH is defined as high thyroid-stimulating hormone (TSH) levels in the presence of normal serum T4 and T3 levels. A total of 32 patients with SCH and 29 controls were included in the study. Carotid intima-media thickness, flow-mediated dilatation, and aortic distensibility were compared between the groups. Results: FMD was lower in patients with SCH than in controls. GTN-induced vasodilatation was similar in the patients with SCH and controls. There was no statistically significant difference between the patients with SCH and controls with respect to CIMT and aortic distensibility. Conclusion: SCH is associated with endothelial dysfunction as established by FMD. Inconsistent results of CIMT and aortic stiffness can be explained by these parameters being measures of structural changes whereas FMD is a dynamic measure that reflects the impact of both acute and chronic influences on endothelial function.

Key words: Aortic distensibility, carotid intima-media thickness, flow-mediated dilatation, subclinical hypothyroidism

INTRODUCTION

Since cardiovascular system is rich in thyroid hormone receptors and is one of the major sites of action for thyroid hormones, it is relatively sensitive to changes in the levels of thyroid hormones.[1] Although the association of atherosclerosis with overt hypothyroidism has been well established, there is still controversy about its association with subclinical hypothyroidism (SCH) despite exclusive research.[2] However, considering relatively high prevalence of SCH even in asymptomatic population[3] together with the fact that atherosclerosis being the leading cause of mortality in the developed countries, the effect of SCH on atherosclerosis should be cleared.

In this context, this study aims to contribute to the area by investigating the effects of SCH on flow mediated dilatation, aortic distensibility, and carotid intima-media thickness (IMT) as surrogate markers of atherosclerosis.

MATERIALS AND METHODS

SCH is defined as high thyroid-stimulating hormone (TSH) levels in the presence of normal serum T4 and T3 levels. A total of 32 patients with SCH and 29 controls who were evaluated in our institution between April 2009 and December 2009 were included in the study. Exclusion criteria were as follows: Previous history of thyroid disease and its treatment, medications that could change thyroid hormone levels including amiodarone and corticosteroids, diabetes mellitus, hypertension, high serum creatinine, known atherosclerotic disease, any rhythm other than sinus, psychiatric conditions, and previous pregnancy in the last 2 years. The study was approved by our Local Ethics Committee, and written informed consent was obtained from each participant. The application of the methods was similar to that used in previous studies.[4]
Blood sampling
Levels of serum TSH, FT4 were measured by immunochemiluminescence (Cobalt 6000, E601). Reference ranges for TSH and FT4 were 0.27-4.2 μIU/mL and 0.93-1.7 ng/dL, respectively.

Echocardiographic measurements
All measurements were performed with the subjects in the left lateral decubitus position by echocardiography using a Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) with a 2.5-MHz probe. E and A waves were recorded by pulsed wave Doppler evaluations and placing the sample volume on the tips of mitral valve. Pulsed wave tissue Doppler imaging was performed at septal mitral annulus and lateral mitral annulus, and myocardial and annular peak systolic velocity (s), peak diastolic early (e) and late (a) velocities were recorded as indexes of regional and global myocardial function.

The aortic diameter was recorded by M-mode echocardiography at a level of 3 cm above the aortic valve. Internal aortic diameters were measured by means of a caliper in systole and diastole as the distance between the trailing edge of the anterior aortic wall and the leading edge of the posterior aortic wall. Aortic systolic (AoS) diameter was measured at the time of full opening of the aortic valve, and diastolic (AoD) diameter was measured at the peak of QRS. Ten consecutive beats were measured routinely and averaged. The percentage change of the aortic root was calculated as  \[
\text{Ao} (%) = 100 \times \frac{(\text{AoS} - \text{AoD})}{\text{AoD}}
\]
to obtain the aortic strain.\(^4\)

Blood pressure
All patients had blood pressure measured manually in the left arm while they were in the supine position by use of a mercury sphygmomanometer. Korotkoff phases I and V were used to determine the systolic and diastolic pressures, respectively, and the average of three readings was regarded as the clinical blood pressure. The aortic stiffness index (β) was calculated: \[
\beta = \ln \left( \frac{\text{SBP/DBP}}{(\text{AoS} - \text{AoD})/\text{AoD}} \right)
\]
where SBP is systolic arterial pressure and DBP is diastolic arterial pressure.\(^4\)

Flow-Mediated dilatation
For the assessment of flow-mediated dilatation, the related guideline was taken into consideration.\(^5\) On the vascular session day, subjects were instructed to report to the laboratory in the morning hours having fasted for at least 8 h, abstained from caffeine and tobacco products for 12 h, and abstained from exercise for 12 h. Women were studied during days 1-7 of their menstrual cycle to minimize the influence of cyclical changes in female hormones. All patients were allowed to rest for at least 10 min before the first scan. Measurements were made while patients were lying supine in a dark, climate-controlled quiet room. All examinations were performed by the same investigator using a high-resolution ultrasound device with a 12.0-MHz linear array transducer (Vivid 7 dimension, GE Vingmed Ultrasound). After a baseline rest image is acquired while a sphygmomanometric cuff is placed above the antecubital fossa, arterial occlusion is created by cuff inflation to at least 50 mm Hg above systolic pressure for 5 min. A second scan was obtained 45-60 s after cuff deflation. At least 10 min of rest was obtained before sublingual glyceryl trinitrate (400 μg - GTN) administration and 3-4 min later the last scan was obtained. Vessel diameters (VD) after reactive hyperemia and GTN administration were compared to the diameters at rest and expressed as a percentage to the average lumen diameter at rest which was considered 100%: FMD (%) = [(VD reactive hyperemia − VD at rest) × 100]/VD rest, and GTN (%) = [(VD after GTN − VD at rest) × 100]/VD rest.

Measurement of carotid intima-media thickness
IMT was measured by recording ultrasonographic images of both the left and right common carotid artery with a 12-MHz linear array transducer (Vivid 7 dimension, General Electric Medical Systems, Norway). Patients were examined in the supine position, with the head turned 45° from the side during the scanning procedure. The reference point for the measurement of IMT was the beginning of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. An R-wave-triggered optimal longitudinal image of the far wall was frozen. On this image, the sonographer traced the leading edges corresponding to the transition zones between lumen-intima and media-adventitia over a length of 1 cm proximal to the reference point at its thickest point, not including plaques. The mean IMT of the four measurements was calculated in each patient.

Statistics
All analyses were performed by the computerized SPSS 17.0 package program (Statistical Package for Social Sciences, SPSS). Results are given as means ± SD. Student’s t-test was used to compare continuous variables, and the Chi-square test was used to compare differences among groups. \(P < 0.05\) was considered statistically significant.

Results
There was no statistically significant difference between the patients with SCH and controls with respect to demographic characteristics except for the body mass index [Table 1]. TSH was higher in the SCH group by definition. Table 2 outlines the echocardiographic data of the study groups.
Similarly, some studies indicated a risk of atherosclerosis in subclinical hypothyroidism.[16–18] The role of these hormones in atherosclerosis was first shown by Lelakis et al.[19] Likewise, a population-based study from Australia, SCH was found to be an independent predictor for coronary artery disease.[20] Imaizumi and coworkers’ study with 257 patients with SCH indicated SCH is associated with ischemic heart disease.[21] A metaanalysis 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.[22] In contrast, in the 20 year follow-up of Whichham cohort, no evidence is found to support that evidence of autoimmune thyroid disease identified 20 years ago is associated with an increased risk of ischemic heart disease.[23] Likewise, a population-based prospective study conducted in Denmark failed to find any associations between SCH and cardiovascular disease.[24] These results show the uncertainty of the effects of SCH on atherosclerosis.

Echocardiographic parameters were also similar between the groups including IVRT, DT, E/A ratio, E′/E′ ratio which are indicators of diastolic dysfunction. Endothelial parameters of the patients with SCH and controls are shown in Table 3. FMD was lower in patients with SCH than in controls. GTN-induced vasodilatation was similar in the patients with SCH and controls. Analysis of the 31 patients and 29 controls revealed that aortic distensibility and carotid IMT were similar between the groups. When the analysis is specified for the patients over 35, mean IMTs were still similar [Table 3].

**Table 1: Comparison between patients with subclinical hypothyroidism and controls**

| Parameters | SCH | Controls | P  |
|------------|-----|----------|----|
| Gender     | Male 5 (%15) | 8 | NS |
|            | Female 27 (%85) | 21 |
| Age        | 41.5±12.0 | 38.1±11.4 | NS |
| SBP        | 118.0±16.8 | 116.9±15.5 | NS |
| DBP        | 79.0±10.8 | 74.6±9 | NS |
| BMI        | 28.6±5.9 | 24.9±6.5 | 0.02 |
| Smokers    | 6 (%19) | 5 (%17) | NS |
| Hyperlipidemia | 4 (%31) | 3 (%10) | NS |
| TSH        | 12.5±8.60 | 1.70±0.56 | NS |
| F T3       | 2.45±0.159 | 2.58±0.158 | 0.09 |
| F T4       | 1.04±0.41 | 1.09±0.20 | NS |

Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, TSH: Thyroid-stimulating hormone, FT3: Free T3 levels, FT4: Free T4 levels, NS: Nonsignificant, SCH: Subclinical hypothyroidism

**Table 2: Echocardiographic parameters in patients with subclinical hypothyroidism and controls**

| Parameters | SCH | Control | P  |
|------------|-----|---------|----|
| LA (mm)    | 34.0±3.3 | 31.5±3.5 | NS |
| LAV (ml)   | 27.7±7.0 | 24.1±6.3 | NS |
| IVS (mm)   | 8.1±1.5 | 8.3±0.9 | NS |
| PW (mm)    | 7.9±1.2 | 8.1±0.9 | NS |
| LVED (mm)  | 46.0±3.7 | 45.7±3.7 | NS |
| LVES (mm)  | 31.0±2.9 | 31.1±3.6 | NS |
| EF (%)     | 62.5±4.1 | 61.3±4.5 | NS |
| E (cm/sn)  | 0.8±0.2 | 0.8±0.1 | NS |
| A (cm/sn)  | 0.7±0.2 | 0.6±0.1 | NS |
| E/A        | 1.3±0.4 | 1.3±0.3 | NS |
| DT (ms)    | 211.9±33.6 | 197.3±32.2 | NS |
| IVRT (ms)  | 97.6±14.3 | 92.5±12.0 | NS |
| E' (m/sn)  | 0.15±0.05 | 0.14±0.04 | NS |
| A' (m/sn)  | 0.10±0.09 | 0.09±0.03 | NS |
| S′ (m/sn)  | 0.11±0.03 | 0.10±0.03 | NS |
| E/E′       | 5.94±1.72 | 5.80±1.95 | NS |

LA: Left atrium, LAV: Left atrial volume, IVS: Interventricular septum, PW: Posterior wall, LVED: Left ventricular diastolic diameter, LVES: Left ventricular systolic parameter, EF: Ejection fraction, E: Early diastolic peak flow velocity, A: Late diastolic peak flow velocity, DT: Deceleration time of E wave, E′: Early myocardial Doppler peak velocity, A′: Late myocardial Doppler peak velocity, S′: Peak velocity of myocardial systolic wave, IVRT: Ivosvolumetric relaxation time

Echocardiographic parameters were also similar between the groups including IVRT, DT, E/A ratio, E′/E′ ratio which are indicators of diastolic dysfunction. Endothelial parameters of the patients with SCH and controls are shown in Table 3. FMD was lower in patients with SCH than in controls. GTN-induced vasodilatation was similar in the patients with SCH and controls. Analysis of the 31 patients and 29 controls revealed that aortic distensibility and carotid IMT were similar between the groups. When the analysis is specified for the patients over 35, mean IMTs were still similar [Table 3].

**Discussion**

Due to its metabolic and hemodynamic effects such as hyperlipidemia and hypertension, overt hypothyroidism is associated with atherosclerosis.[1] However, the association of SCH with atherosclerosis is less clear. In the population-based Rotterdam Study, 1149 women were included in the study to investigate the association of SCH with atherosclerosis and myocardial infarction.[6] Atherosclerosis was diagnosed by chest X-rays and myocardial infarction was diagnosed by electrocardiogram. The authors concluded that SCH is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women. In another population-based study from Australia, SCH was found to be an independent predictor for coronary artery disease.[7] Imaizumi and coworkers’ study with 257 patients with SCH indicated SCH is associated with ischemic heart disease.[8] A metaanalysis 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.[9] In contrast, in the 20 year follow-up of Whichham cohort, no evidence is found to support that evidence of autoimmune thyroid disease identified 20 years ago is associated with an increased risk of ischemic heart disease.[10] Likewise, a population-based prospective study conducted in Denmark failed to find any associations between SCH and cardiovascular disease.[11] These results show the uncertainty of the effects of SCH on atherosclerosis.

SCH may be related to endothelial dysfunction and atherogenesis in several ways. First, SCH is associated with increased cardiovascular risk factors which underlie atherosclerosis.[12] Increased levels of cholesterol and altered levels of coagulation parameters were shown in patients with SCH.[13,14] Similarly, some studies indicated a risk for hypertension in SCH.[16,17] Second, thyroid hormones have substantial influence on the peripheral vasculature and thyroid hormone receptors have been identified in human vascular smooth muscle cells.[18] The role of these cells in atherosclerosis arises the hypothesis that thyroid hormone deficiency is associated with atherosclerosis. Also, low grade inflammation may cause endothelial dysfunction and impaired nitric oxide availability in patients with Hashimoto’s thyroiditis which is the leading cause of hypothyroidism.[19] Finally, slow-moving blood flow may contribute to the process.[20]

In the present study, we found impaired endothelial function in the patients with SCH. This negative association was first shown by Leakis et al.[22] Interestingly, they also showed impaired FMD even in patients with high normal TSH levels (TSH between 2.01 and 4) in their study. Our results are also consistent with the study of Çikım et al. in which they evaluated endothelial function in subclinical hyperthyroidism and SCH.[23] In a study of Taddei et al., the
forearm blood flow response to intrabrachial acetylcholine, an endothelium-dependent vasodilator, both at baseline and during infusion of a NO synthase inhibitor were evaluated with strain-gauge plethysmography to find endothelial dysfunction resulting from a reduction in NO availability and this is reversed by levothyroxine supplementation. Razvi and colleagues also showed beneficial effects of levothyroxine on FMD in SCH. However, Cabral et al. could not show endothelial dysfunction in their study.

Carotid IMT is increasingly used as a surrogate marker for atherosclerosis and has a high positive predictor value for CAD. Monzani et al. were the first to show the association of CIMT and SCH. In the 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. Tian et al. showed that SCH is associated with preclinical vascular alteration, characterized by increased CIMT, which had been shown to be related to the high sensitive CRP and TSH. However, not all studies showed an association between TSH and CIMT. In the study of Chiche et al. among a population of hyperlipidemic patients investigators found that neither prevalence nor severity of carotid plaques nor carotid IMT were significantly different between hypothyroid patients and controls. Likewise, in another study with 21 subclinical hypothyroid patient CIMT is found normal.

Alterations in the elasticity of arterial wall are also seen early in the course of atherosclerosis. Measurements such as carotid or aortic distensibility, pulse wave velocity, systemic arterial compliance, and augmentation index are used to define the mechanical characteristics of the arterial system. In a study in which Obuobie et al. investigated central arterial stiffness by the tonometric method, hypothyroid patients were shown to have higher augmentation indices together with a lower time of travel of the reflected wave. Dagre et al. found increased arterial stiffness even in mildly impaired thyroid function. This result is consistent with a study of Nagasaki et al.’s showing increased pulse wave velocity.

In our study, we found impaired FMD with normal CIMT and aortic distensibility in patients with SCH comparing with the control group. There are some possible explanations for these findings. First, CIMT and aortic distensibility are measures of structural changes whereas FMD is a dynamic measure that reflects the impact of both acute and chronic influences on endothelial function. Since it is not possible to detect the disease duration this may be directly related to the accumulated structural changes in the arterial wall, one can speculate that impaired FMD is preceding changes in CIMT and aortic distensibility in these patients with relatively short disease duration. In accordance with this, Yan et al. speculated that CIMT and FMD may be independent surrogates that measure different aspects and stages of early atherosclerosis for the reason that they could not find a significant correlation between these parameters in 1578 middle-aged healthy men. Second, patient selection may have affected the results. Since endothelial function is affected by a numerous number of factors which are also risk factors for atherosclerosis, excluding patients with these risk factors may have led to exclusion of many patients with atherosclerosis in any level. This exclusion also resulted in small sized groups which in turn might have prevented statistical difference. Finally, the inherent limitations of FMD should also be considered because of a variety of potential confounders, as well as an intraindividual variation to repeated measurements. In addition, manual assessment of FMD may have some drawbacks comparing with the automated and semiautomated systems.

### Table 3: Endothelial and intima-media thickness parameters

| Parameters                                      | SCH  | Controls | P     |
|------------------------------------------------|------|----------|-------|
| Baseline artery diameter (cm)                   | 0.36±0.05 | 0.34±0.05 | NS    |
| Brachial artery diameter after ischemia (cm)    | 0.39±0.05 | 0.39±0.05 | NS    |
| Flow mediated dilatation (%)                    | 11.5±4.9 | 14.9±4.2 | 0.006 |
| Brachial artery diameter after GTN (cm)         | 0.43±0.05 | 0.42±0.05 | NS    |
| GTN-induced dilatation (%)                      | 20.9±7.5 | 24.2±6.6 | NS    |
| CIMT (mm)                                       | 0.05±0.01 | 0.06±0.01 | NS    |
| CIMT in patients over 35 (mm)                   | 0.05±0.01 | 0.08±0.01 | NS    |
| AoS (mm)                                        | 28.84±3.15 | 28.88±3.68 | NS    |
| AoD (mm)                                        | 26.90±3.42 | 25.61±3.87 | NS    |
| Ao strain, %                                    | 7.48±3.72 | 7.94±3.59 | NS    |
| Ao distensibility                               | 4.14±2.45 | 4.05±2.24 | NS    |
| Aortic stiffness index                          | 7.25±4.55 | 7.49±4.85 | NS    |

GTN: Glyceryl trinitrate, AoS: Aortic systolic diameter, AoD: Aortic diastolic diameter, IMT: Intima-media thickness, SCH: Subclinical hypothyroidism

### Conclusion

SCH is associated with endothelial dysfunction as established by FMD. Considering the role of endothelium in vascular integrity and the association of endothelial dysfunction with atherosclerosis, one can speculate that there is link between SCH and atherosclerosis. Inconsistent results of CIMT and aortic stiffness can be explained in several ways including the inherent limitations of the techniques, small study population, and different stages of atherosclerosis being shown by these markers.
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