Thoracic periaortic adipose tissue is increased in patients with subclinical hypothyroidism

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Abstract

Objective: To evaluate thoracic periaortic adipose tissue (TAT) volume in patients with subclinical hypothyroidism (SH) in comparison with controls and in relation to cardiovascular risk factors.

Methods: The study population consisted of 28 newly diagnosed SH patients (mean (s.d.) age: 37.3 (±11.4) years, 85.7% were females) and 37 healthy volunteers (mean (s.d.) age: 35.3 (±10.7) years, 81.5% were females). Comparisons between patient and control groups used demographic characteristics, anthropometrics, and laboratory findings. All participants underwent thoracic radiographic assessment in the supine position, using an eight-slice multidetector computed tomography scanner and TAT volume was measured.

Results: The TAT volume was determined to be 27.2 (±12.7) cm³ in the SH group and 16.3 (±8.1) cm³ in the control group, and the difference was statistically significant (P<0.001). In addition, TSH levels were significantly higher in the patient group compared with the control group (P<0.001). A significant correlation was also found between TSH levels and TAT volume (r=0.572; P<0.001). In SH patients, no significant difference was noted in TAT levels with respect to sex (P=0.383) or concomitant smoking status (P=0.426).

Conclusions: Our findings indicate that SH patients have significantly higher TAT values than controls and that increased TAT levels correlate with increased TSH levels.

Introduction

Subclinical hypothyroidism (SH) is defined biochemically as an elevated serum thyroid-stimulating hormone (TSH) concentration while the serum thyroid hormone concentration is in the normal range. This condition affects ~10% of the adult population, with a higher prevalence in older women (1). Although hypothyroidism is well known to be related to increased cardiovascular disease (CVD) risk and cardiovascular mortality, the question as to whether SH should be considered a cardiovascular risk factor is still a subject of ongoing debates (2). Razvi et al. (3) did not find any association between SH and coronary artery disease (CAD) after 20 years of follow-up in patients (4). However, one study provided data suggesting that SH may lead to the development of atherosclerosis (5) and another meta-analysis study confirmed an increased CAD risk in SH patients (6). Yet in another population-based study performed in Australia, SH was found to be an independent predictor for CAD (7).

There is growing evidence that excessive visceral adipose tissue (VAT) (including visceral abdominal, pericardial, and thoracic periaortic adipose tissue (TAT)) is linked to abnormal lipid profiles, enhanced systemic inflammation, diabetes mellitus (DM), and CVD (8, 9, 10, 11, 12, 13). Perivascular fat is considered to be highly metabolically active, secreting substances with known vascular actions (8, 9). TAT is a subtype of perivascular fat...
that can be quantified using multidetector computed tomography (MDCT) (11). TAT could be considered a novel risk marker for CVD (10, 11, 12). Studies have demonstrated that TAT is associated with certain metabolic risk factors, after adjustment for BMI, as well as abdominal, aortic, and coronary calcium levels, after adjustment for either BMI or VAT (8). Epicardial adipose tissue (EAT), which is a subtype of VAT, may play a key role in the pathogenesis and development of CAD. Unubol et al. (14) reported in their study increased EAT in patients with SH, but Santos et al. found similar EAT measurements in SH patients when compared with a control group. They therefore concluded that EAT measurements are not a good marker of cardiovascular risk in SH patients with serum TSH < 10.0 mIU/l (1).

Although several studies have demonstrated a relationship between TAT and CVD or CAD, there are no data in the literature about the effect of TAT in SH patients. Despite a comprehensive understanding of increased cardiovascular risk in SH patients, the role of TAT is still a subject of debate. The purpose of our study was to evaluate the effect of TAT on cardiovascular risk by measuring TAT volumes with MDCT and comparing TAT levels in SH patients with those in a control group.

**Subjects and methods**

**Patient selection**

This population-based cross-sectional study involved 28 newly diagnosed SH patients (mean (s.d.) age: 37.3 (± 11.4) years, 85.7% were females) and 37 healthy volunteers (mean (s.d.) age: 35.3 (± 10.7) years, 81.5% were females). The healthy volunteers had the same clinical variables as the patient group, who were referred to the Mevlana University Internal Medicine Department between March 2013 and June 2014. Diagnosis of SH was established using normal serum free thyroxine (FT4) and free triiodothyronine (FT3) levels and increased TSH levels in fasting blood samples (normal ranges: TSH: 0.27–4.20 mIU/ml; FT4: 0.93–1.7 ng/dl; FT3: 1.8–4.6 pg/ml). All SH patients had spontaneous elevation in serum TSH levels as a consequence of autoimmune thyroid disease, which was confirmed in a second measurement, which was taken at 8 weeks after the first one. SH patients with serum TSH >10 µIU/ml were excluded. The inclusion criteria for the control group were a demonstration of normal serum TSH and FT4 and negative antithyroidperoxidase antibodies (anti-TPO normal range 0–35 IU/ml). Patients and controls with a history of thyroid disease or treatment or who were prescribed drugs, such as amiodarone or corticosteroids, which could affect thyroid hormone levels, were excluded from the study. Patients were also excluded if they had CAD, hypertension, percutaneous or surgical revascularization, peripheral artery disease, atrial fibrillation, active chronic obstructive lung disease, heart failure, chronic kidney disease, DM, pulmonary or neurological disease, pericarditis, peripheral neuropathy, congenital heart disease, hepatic disease, alcohol abuse problems or BMIs indicating morbid obesity (BMI ≥ 40 kg/m²). The control group consisted of healthy subjects without chronic kidney disease, CAD, vasculitic lesions, DM, hypertension, hepatic parenchymal disease, or acute infection. This study was approved by the ethics board and written informed consent was obtained from all study participants.

Weight and height were measured in light clothing without shoes. BMI was calculated by dividing the weight by the height squared (kg/m²). Blood pressure measurements were obtained from each patient in the seated position, using a standard mercury sphygmomanometer on the right arm. Following a 12-h nighttime fast, venous blood samples were obtained from the antecubital vein to measure serum fasting blood glucose (FBG; mg/dl), TSH (mIU/ml), FT4 (ng/dl), FT3 (pg/ml), anti-TPO (UI/ml), total cholesterol (mg/dl), HDL-cholesterol (HDL-C; mg/dl), LDL-cholesterol (LDL-C; mg/dl), triglyceride (TG; mg/dl), aspartate aminotransferase (AST; mg/dl), alanine aminotransferase (mg/dl), blood urea nitrogen (mg/dl), and creatinine (mg/dl) in both patient and control groups. Levels of total cholesterol, HDL-C, and TG were determined by enzymatic colorimetric assays using a spectrophotometer. LDL-C was calculated using the Friedewald formula. Serum FT4, TSH, and anti-TPO concentrations were determined by an electrochemiluminescence immunoassay method.

Comparisons between patient and control groups used demographic characteristics, anthropometrics, and laboratory findings. The TAT volume was evaluated in relation to demographic and clinical characteristics of SH patients and compared with other clinical parameters.

**MDCT protocol and measurement of TAT volume**

All participants underwent thoracic radiographic assessment in the supine position using an eight-slice MDCT scanner (Somatom Sensation 64, Siemens, Forchheim, Germany). All image analyses were performed on a dedicated workstation (Volume Analysis Software, Siemens, Leonardo), while adipose tissue quantification was performed using a semi-automated method that
required manually defining region of interest borders. CT attenuation thresholds were used to identify fax pixels (window width $-200$ to $-450$ HU) to calculate adipose volumes (cm$^3$). TAT was defined as the area immediately surrounding the thoracic aorta anteriorly by a horizontal line through the esophagus, connected to the left costovertebral joint, posteriorly by the anterior edge of the vertebral body, and the right lateral border of the vertebral body (14). The TAT volume was evaluated using a CT protocol by an experienced radiologist, who was blinded from the baseline characteristics of patients (Fig. 1).

Cardiovascular risk factors

CVD and metabolic risk factors were measured using standardized definitions. BMI was calculated as weight in kilograms divided by the square of the height in meters. To measure blood lipids and glucose, fasting morning samples were collected. Smoking was defined as smoking at least one cigarette per day in the year before the physical exam. Hypertension was defined as using an anti-hypertensive medication or displaying a systolic blood pressure $\geq 140$ mmHg, or a diastolic blood pressure $\geq 90$ mmHg.

Statistical analysis

Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS; version 16.0, SPSS, Inc.). The Kolmogorov–Smirnov test was applied to check normality of variables. The $\chi^2$-test was used for the comparison of categorical data, and Student’s $t$-test was used for the comparison of parametric variables. Statistical correlation was assessed using Pearson’s test. Data are expressed as mean ($\pm$ S.D.) and percentage (%) accordingly. A value of $P<0.05$ was considered statistically significant.

Results

Demographic characteristics and clinical findings in the study groups

The SH patients and control subjects were homogenous in terms of age, sex, anthropometrics, and smoking status. TAT levels were significantly higher ($P<0.001$) in SH patients than in controls, similar to TSH serum levels ($P<0.001$) (Table 1).

TAT volume in patients with respect to demographic and clinical characteristics

In SH patients, no significant difference was noted in TAT levels with respect to sex ($P=0.383$) or smoking status ($P=0.426$) (Table 2).

Correlation of TAT volume with other clinical parameters

There was a strong correlation between TAT and TSH ($r=0.572; P<0.001$); however, there was no significant relationship found with other parameters (Table 3).

Discussion

The purpose of this study was to evaluate the relationship between TAT volume and cardiovascular risk in SH patients, and the results indicate that the TAT volume was significantly higher in SH patients than in the control group and that a positive correlation with TSH levels exists. No correlation was found for the TAT volume with respect to sex or smoking status in SH patients. The significance of our study is that the TAT volume was detected for the first time in patients with SH.

SH prevalence is $\sim 10\%$ in the world and is more common in females and aged subjects (1). The relationship between the manifestation of hypothyroidism with CVD in dyslipidemia and atherosclerosis is well known, but the effect of SH on cardiovascular endpoints and atherosclerosis is unclear (15). Several studies evaluating the relationship between SH and atherosclerosis have demonstrated...
that these patients have changes in lipid metabolism that result in a tendency toward atherosclerosis, which can be reversed with levothyroxine (L-T4) treatment (16, 17, 18). On the other hand, studies have also reported no differences between the lipid profiles of SH patients and that of euthyroid control groups (19, 20). Along with these studies, conflicting results have been published regarding changes in lipid profiles after L-T4 replacement therapy. Some studies have demonstrated that lipid profiles do not change in patients who become euthyroid after replacement treatment, but other studies have demonstrated favorable changes in lipid profiles after replacement therapy (21). In addition, some studies have demonstrated no relationship between SH and ischemic heart disease or related mortality after 20 years of follow-up (22). Yet another group of studies has demonstrated that thyroid hormone, regardless of its effect on lipid profiles, was related to the progression of atherosclerosis, with an effect on endothelial function (23).

Moreover, studies have demonstrated that SH is an independent risk factor for atherosclerosis and myocardial infarction (7). Conflicting results in studies that have searched for correlations between SH and CVD could be related to different patient populations and varying TSH levels. There is accumulating evidence to support the idea that SH increases CVD risk. SH may be related to resting left ventricular diastolic dysfunction, left ventricular systolic dysfunction during exercise, and increased risk of atherosclerosis and myocardial infarction (24). In addition, Luboshitzky et al. have demonstrated that systolic and diastolic blood pressures of SH patients were higher than that of control subjects (25, 26). In our study, the mean age of the patients was 37.3 (± 11.4) years, 85.7% were females, and no differences with regard to dyslipidemia between patient and control groups were found. Despite an increased SH prevalence in aged subjects, our young patient population can be explained based on our exclusion criteria. Patients with DM,
increased creatinine levels, and vascular disease were excluded from the study because these diseases would affect the results of the study and prevalence of these diseases increases with age. Consequently, older patients were excluded from the study because they had begun treatment at younger ages.

Visceral adiposity is associated with incident CVD and cancer, after adjustment for clinical risk factors and generalized adiposity (27). There is compelling evidence that adipose compartments differ in their endocrine activity and hence the accompanying metabolic risk and morbidity. Visceral abdominal fat is a more pathogenic fat depot compared with subcutaneous adipose tissue and is more closely connected to the risk of metabolic and CVD (28, 29). Perivascular fat is one such visceral fat depot that has been postulated to have a local pathogenic effect on blood vessels (30, 31). Higher periaortic fat is independently associated with a greater prevalence of peripheral artery disease (12). TAT is a subtype of perivascular fat (11) and because TAT can be directly wrapped around the aorta, this distinct anatomic location could explain the specific correlation between high TAT and high CVD among SH subjects. TAT may serve as a marker of perivascular fat throughout the body, including smaller blood vessels, and perivascular fat has been postulated to have adverse effects on the vasculature (31). Nonetheless, compared with other adiposity measures, TAT was shown to be more strongly associated with cardiometabolic risk profiles and subclinical atherosclerosis in an otherwise relatively healthy population (32). In past studies conducted with participants from the Framingham Heart Study, a high volume of TAT was reported to be associated with adverse cardiometabolic features among the subset of subjects with normal VAT, despite a similar prevalence of various fat depots (10). Additionally, besides TAT volumes being significantly higher in males (20.3 cm³) than in females (11.9 cm³), TAT was also shown to be significantly associated with both abdominal aortic and coronary artery calcification among subjects without known CVD (12).

In another study, the TAT volume was noted to be 13.2 cm³ and suggested to be associated with multiple vascular function measures (33). Relationships were noted between DM and TAT, BMI, hypertension, low HDL-C, serum TG, and FBG (10). In our study, the TAT volume was 16.3 (± 8.1) cm³ in the control group and 27.2 (± 12.7) cm³ in the SH group, and the difference was found to be statistically significant (P<0.001). We uncovered a strong positive correlation between TAT volume and TSH levels. This is related to an increased CVD risk in SH patients and shows that the risk is increasing with TSH levels. Another difference between our study and other studies is that TSH levels in our SH patient group were 7.2 (± 2.6) mIU/ml. Many studies in the literature that support the relationship between SH and increased CVD and the risk of atherosclerosis demonstrated that TSH levels were over 10 mIU/ml in their SH patient groups (34). Results of our study have indicated that even at lower TSH levels, the risk of CVD is increased in SH patients.

Studies have shown that TAT is associated with BMI, which is a definite metabolic risk factor (8, 10, 12, 13, 35). But in this study, there was no association between TAT and BMI. Hence, it may be concluded that TAT is an independent predictor of atherosclerosis and CVD.

Although the Framingham Heart Study revealed a higher prevalence of male smokers among subjects with high TAT levels (36) and correlations between perivascular fat and adverse cardiovascular risk profiles have been reported to be stronger in women than in men (10), our findings revealed no significant difference in TAT burden in smoker vs non-smokers and in males vs females in SH patients.

### Study limitations

The patients included in the study were a small group of subjects visiting the Internal Medicine Outpatient Clinic, which makes it difficult to extend the present findings to the general population. The study’s sample size and number of TAT volumes are adequate to provide sufficient statistical power. Our findings need to be confirmed and validated in much larger studies using appropriate reclassification statistics to provide value to existing risk scores.

### Table 3 Correlation of thoracic periaortic adipose tissue volume with other clinical parameters.

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.216</td>
<td>0.393</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.548</td>
<td>0.459</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>0.193</td>
<td>0.421</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (mIU/ml)</td>
<td>0.572</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free thyroxine (ng/dl)</td>
<td>0.311</td>
<td>0.694</td>
</tr>
<tr>
<td>Free triiodothyronine (pg/ml)</td>
<td>0.237</td>
<td>0.597</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0.373</td>
<td>0.178</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>0.189</td>
<td>0.345</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>0.271</td>
<td>0.132</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>0.149</td>
<td>0.146</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>−0.042</td>
<td>0.675</td>
</tr>
<tr>
<td>Aspartate aminotransferase (mg/dl)</td>
<td>−0.057</td>
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<tr>
<td>Alanine aminotransferase (mg/dl)</td>
<td>0.022</td>
<td>0.843</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>−0.026</td>
<td>0.814</td>
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Conclusions

Our findings indicate significantly higher values for TAT in SH patients than in controls, and that TAT values are positively correlated with TSH levels in SH patients, while not differing with respect to sex or smoking status.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 13 October 2014
Revised version received 15 January 2015
Accepted 2 February 2015