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Original Article

Does Subclinical Hypothyroidism Affect Lipid and Epicardial Fat Tissue Thickness in Children?

E *Unal*, A *Akin*, R *Yildirim*, M *Türe*, H *Balik*, FF *Taş*, AG *Pirinççioğlu*, YK *Haspolat*

Abstract

Objective: The aim of this study was to measure serum lipid levels and epicardial adipose tissue thickness in patients determined with subclinical hypothyroidism. ***Methods:*** The study included 61 paediatric patients with a diagnosis of subclinical hypothyroidism and a control group of 61 healthy children. The thyroid hormone levels, lipid parameters and epicardial adipose tissue thickness were examined in all the patients. ***Results:*** The mean epicardial adipose tissue thickness of the subclinical hypothyroidism patients was higher than that of the control group but not at a level of statistical significance (4.15±0.91 vs 4.06±0.99, p=0.598). The mean high-density lipoprotein cholesterol level of the subclinical hypothyroidism group was statistically lower than that of the control group (p=0.040). ***Conclusion:*** The results of this study showed a significant decrease in the high-density lipoprotein cholesterol levels of children with subclinical hypothyroidism. No significant increase was seen in the epicardial adipose tissue thickness of the children with subclinical hypothyroidism. This is the first study to have examined epicardial adipose tissue thickness in children with subclinical hypothyroidism.

Key words Children; Epicardial adipose tissue; Subclinical hypothyroidism

Department of Pediatric Endocrinology, Dicle University Faculty of Medicine, Diyarbakır, Turkey

E **Unal** *MD*
FF **Taş** *MD*
YK **Haspolat** *MD*

Department of Pediatric Cardiology, Dicle University Faculty of Medicine, Diyarbakır, Turkey

A **Akin** *MD*
M **Türe** *MD*
H **Balik** *MD*

Department of Pediatric Endocrinology, Diyarbakır Children's Hospital, Diyarbakır, Turkey

R **Yildirim** *MD*

Department of Pediatrics, Dicle University Faculty of Medicine, Diyarbakır, Turkey

AG **Pirinççioğlu** *MD*

Correspondence to: Dr E **Unal**
Email: edip76@yahoo.com

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Introduction

Subclinical hypothyroidism (SH) is defined biochemically as a state when the serum thyroid stimulating hormone (TSH) concentration is above the upper normal reference limit while serum free thyroxin (fT4) is within the normal range. The frequency of SH seen in adults has been reported as 4-20% with a clearly greater risk of progressing to hypothyroidism.[1] Although there is a limited number of epidemiological studies of children and adolescents, the SH prevalence in the paediatric population has been reported as <2%.[2]

Although SH is usually incidentally diagnosed, an association between SH and atherosclerotic heart disease has been demonstrated. Subclinical hypothyroidism features some of the risk factors that can accelerate the development of atherosclerosis. Such risk factors include an increased body mass index (BMI), greater visceral adipose tissue, insulin resistance, atherogenic dyslipidemia, hypercoagulability, and systolic and diastolic hypertension.[3-5] Moreover, higher TSH levels even in the

normal range are associated with an increased mass of visceral adipose tissue, which is an independent risk factor for the development of coronary heart disease.[6,7] Epicardial adipose tissue (EAT) is an important indicator of intra-abdominal visceral fat accumulation.[8] Therefore, it was aimed to investigate the thickness of EAT in patients with SH.

In recent years, non-invasive methods have started to be used in the determination of atherosclerosis, which constitutes a risk for cardiovascular disease. Epicardial adipose tissue is defined as the visceral adipose tissue between the pericardium and the myocardium and it is measured with transthoracic echocardiography (TE). There are few studies that have evaluated the relationship between EAT thickness and SH. Some of these studies have reported a relationship between EAT thickness and SH[9-12] and other studies have reported no relationship.[13,14] To the best of our knowledge, this is the first study to have evaluated the relationship between EAT thickness and SH in children.

Subjects and Methods

Study Population

The study included 61 children diagnosed with SH in the Paediatric Endocrinology Clinic and a control group of 61 healthy children with normal thyroid functions (serum TSH, fT4). The children with SH were referred to our paediatric endocrinology clinic from the community by their paediatricians because of the incidental finding of elevated TSH concentrations in their routine annual check-up. Subclinical hypothyroidism was diagnosed on the basis of elevated serum TSH levels (TSH, 4.2-20 µIU/L) and serum fT4 levels within the normal range in 2 separate fasting blood samples taken at an interval of 2-6 weeks. The aetiology of patients diagnosed with SH was investigated and only idiopathic patients were included in the study. Hashimoto's thyroiditis was diagnosed on the basis of the presence of either antithyroglobulin (anti-Tg) or antithyroid peroxidase (anti-TPOAb) antibodies (or both) in the serum. Hashimoto's thyroiditis patients were excluded from the study. None of the patient or control group subjects had hypertension, liver or kidney function disorders, cardiac pathology or chronic disease. Exclusion criteria for both groups included diabetes mellitus, obesity or a history of medication use. Height was measured using a Harpenden stadiometer with a sensitivity of 0.1 cm and weight was measured using a scale with a sensitivity of 0.1 kg (SECA, Hamburg, Germany). The weight of each subject was measured with all clothing removed except undergarments. Body mass index was calculated by dividing weight (kg) by height squared (m2).

The study protocol was approved by the Ethics Committee of Dicle University Faculty of Medicine, and written informed consent was obtained from all participants, prior to enrollment in the study (date: 16 December 2016, registration number: 21).

Serological Parameters

Serum TSH, free triiodothyronine (fT3) and fT4 levels were measured by electrochemilumines immunoassay (ECLIA) in a Cobos e601 analyser (Roche HITACHI Germany). In the laboratory where the study was conducted, the normal reference values were 0.27-4.2 µIU/mL for TSH, 3.69-9.85 pmol/L for fT3 and 12-22.8 pmol/L for fT4. Fasting blood samples were obtained by venipuncture in the morning at 8 a.m., after an overnight fast of at least 12 h. Serum concentrations of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured by enzyme assay (Abbott diagnostics C16000 chemistry analyser, IL, USA). The value of low-density lipoprotein (LDL) cholesterol was calculated using Friedwald's equation.

Echocardiographic Assessment of Epicardial Adipose Tissue

Before the procedure, all the patients were applied with 12-derivation surface electrocardiography (ECG) and 2-dimensional (2D), M-mode and colour Doppler echocardiography. The patients were then placed in the lateral decubitus position. Using 2D long and short heart axis views, EAT thickness was evaluated in the right ventricle free wall at the end of the systole (Vivid 3; GE Vingmed, Horten, Norvay). A total of 5 measurements were taken of EAT thickness during 5 cycles of 2D long and short heart axis views. For each patient an average of the values was calculated. Epicardial adipose tissue is seen as an echo-free space anterior to the right ventricular wall and the thickness is measured at the point between the epicardial surface of the right ventricle and the parietal pericardium.

Statistical Analysis

Data obtained in the study were analysed statistically using IBM SPSS 21.0 for Windows statistics software. Measured variables were stated as mean±standard deviation

(SD), and categorical variables as number (n) and percentage (%). Conformity to normal distribution of the data was evaluated. The Student's t-test was applied in the comparison of 2 selected groups with normal distribution, and in the comparison of 2 groups not showing normal distribution, the Mann Whitney U-test was used. Chi-square test analysis was applied for the comparison of qualitative variables between groups. To evaluate relationships between numerical variables, Pearson Correlation analysis was applied. The hypotheses were two-way and a value of $p<0.05$ was accepted as statistically significant.

Results

The 61 patients diagnosed with SH comprised 28 males and 33 females with a mean age of 8.0±3.3 years. The control group of 61 healthy euthyroid children comprised 28 males and 33 females with a mean age of 8.4±2.4 years. No significant difference was determined between the groups in respect of age, gender, weight and BMI. The demographic characteristics and the thyroid function test results of the patients are shown in Table 1.

In comparison with the control group, the TSH level in the SH group was statistically significantly high ($p<0.001$). Of the total 61 patients, TSH was <10 μIU/mL in 51 patients and ≥10 μIU/mL in 10 patients. No statistically significant difference was determined between the groups in respect of total cholesterol, LDL-C and triglyceride levels. The HDL-C level was statistically significantly lower in the SH patient group than in the control group ($p=0.040$).

No significant correlation was found in the two groups of children for mean EAT thickness ($p=0.598$). There was also no significant correlation between TSH and EAT thickness (r: 0.052; $p=0.689$). When the patients were separated into two groups as TSH <10 μIU/mL and ≥10 μIU/mL, no statistically significant difference was determined in respect of EAT thickness and lipid values. The EAT thickness values and biochemical parameters of the SH patient group and the control group are shown in Table 2.

Discussion

The effects of thyroid hormones on the cardiovascular system have long been known. Cross-sectional and cohort studies have concluded that hypothyroidism increases atherosclerosis. There is a clear relationship in particular of hypothyroidism with increased LDL-cholesterol, high diastolic blood pressure, a low degree of inflammation and hypercoagulability and this has been shown to contribute to the development of atherosclerotic plaque.[15,16] It is not clear whether or not SH increases the risk of cardiovascular disease. Just as there are studies that have shown no relationship between SH and cardiovascular risk, a relationship between coronary artery disease and atherosclerosis has been reported in a meta-analysis.[17-19]

In some placebo-controlled studies in adults, it has even been shown that L-thyroxin treatment had positive effects on atherosclerotic changes and cardiovascular risk in patients with SH.[20,21] However, all the above-mentioned studies have been conducted on adults and there have been very few studies that have evaluated the relationship

Table 1 Demographic characteristic of study groups

Variables	SH group (n=61)	Control group (n=61)	*p* value
Sex (Male/Female)	28/33	38/23	0.069
Age (year)*	8.0±3.37.3 (3.5-15)	8.4±2.48.1 (4.0-13.8)	0.501
Weight (kg)	24.3±10.4	25.1±7.3	0.645
Weight SDS	-1.01±1.03	-0.79±1.04	0.38
Height (cm)	120.7±18.2	126.0±13.3	0.072
Height SDS	-1.28±1.10	-0.56±1.07	0.01
BMI	16.0±2.1	15.6±1.9	0.283
BMI SDS	-0.40±0.95	-0.71±0.98	0.055

Data are given as mean ± SD

*Data are given as mean ± SD (range)

BMI, body mass index; SH, subclinical hypothyroidism SDS, standard deviation score

between SH and cardiac functions in children.[22,23] In a study by Çatli et al[22] it was shown that both systolic and diastolic impairments in the left ventricle led to an increase in the left ventricle mass index in children with SH. Sert et al[23] also showed that there was an increase in left ventricle mass index in SH children.

There are very few studies in literature that have evaluated the lipid profile of children with SH.[22,24-27] In a study which evaluated both paediatric and adult SH patients, it was reported that no lipid anomaly developed in paediatric SH patients with TSH <10 µlU/L and in those with TSH >10 µlU/L, there was only a decrease in the HDL level.[24] Çatli et al[22] reported no statistically significant difference between a paediatric SH patient group and a control group in respect of TC, TG, HDL and LDL levels. In a study of 49 children diagnosed with SH, Cerbone et al[25] determined a statistically significant lower HDL-C level compared to the control group. Paoli-Valeri et al[26] examined children aged 2-9 years diagnosed with SH and found that the HDL cholesterol level was significantly low in these children. Although Unal et al[27] found no difference between a paediatric SH patient group and a control group in respect of HDL-C and TG, the total cholesterol and LDL-C levels were seen to be significantly increased. In the current study, the HDL-C level of the SH patients was found to be significantly low compared to that of the control group and no significant change was observed in the other lipid parameters. As it was considered that the low HDL-C in the SH group could have been coincidental, power analysis was performed in this study. Using the HDL-C data in the power analysis, the power of the study was found to be 85%. This demonstrated that the low HDL-C values in the SH group were not coincidental.

In recent years, non-invasive methods have started to be used in the determination of atherosclerosis, which constitutes a risk for cardiovascular disease. Epicardial adipose tissue thickness is a new measurement tool in the early determination of atherosclerosis.[28] It is thought that an increase in EAT causes the development of coronary atherosclerosis through autocrine and vasocrine mechanisms.[29,30] In other studies, EAT thickness has been shown to have a relationship with coronary artery disease, independent of obesity[31] and a positive correlation has been shown between EAT thickness and the severity of coronary artery disease.[8] Epicardial adipose tissue is visceral fat tissue stored around the heart, especially on the right ventricle free wall and the left ventricle apex. It is also known to be stored around the atriums. Magnetic resonance imaging (MRI) is accepted as the gold standard test for the measurement of visceral body fat and it has been determined that MRI measurement of visceral fat tissue and EAT thickness measured with TE have shown a good correlation.[8,32]

There have been very few studies evaluating the relationship between EAT and SH. In some studies conducted on adults, EAT thickness has been shown to be greater in SH patients, compared to the control group.[10,11] In a study by Korkmaz et al[12] the EAT thickness was shown

Table 2 Biochemical characteristics and epicardial adipose tissue thickness of the study groups

Variables	SH group (n=61)	Control group (n=61)	*p* value
TSH (µIU/mL)*	7.44±2.31 6.5 (5-14.5)	2.52±0.79 2.5 (0.82-4.27)	0.000
fT4 (pmol/L)	16.77±1.85	17.12±2.03	0.061
fT3 (pmol/L)	6.86±0.68	6.87±0.66	0.926
Total cholesterol (mmol/L)	158.0±29.6	155.5±21.9	0.603
LDL-C (mmol/L)	87.2±26.8	82.4±16.0	0.234
HDL-C (mmol/L)	53.8±9.9	57.8±11.2	0.040
Triglycrides (mmol/L)	84.0±44.4	73.0±24.5	0.092
EATT (mm)	4.15±0.91	4.06±0.99	0.598

Data are given as mean ± SD

*Data are given as mean ± SD and median (range)

EATT, Epicardial adipose tissue thickness; fT4, free thyroxine; fT3, free triiodothyronine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone

to be greater in the SH patients compared to the control group, and the increase was more significant in patients with TSH ≥10 μIU/mL. In the same study, there was reported to be a significant correlation between TSH and EAT. In a cross-sectional study of adults, EAT thickness was found to be similar in the patient and control groups, but a positive correlation was determined between EAT and TSH in the SH group. However, an important drawback of that study is that all the patients had a TSH value <10 μIU/mL.[14] In another study of adults, no difference was found between the SH and control groups in respect of EAT thickness and there was not determined to be any relationship between EAT thickness and TSH. However, that study had the disadvantage of being cross-sectional, the patient numbers were low and there was no information about the duration of the disease.[13]

To the best of our knowledge, there has been no previous study in literature which has evaluated the relationship between SH and EAT thickness in children. In this study, EAT thickness in children with SH was greater than in the control group, but the difference was not statistically significant. In addition, no significant correlation was found in the current study between EAT thickness and TSH, total cholesterol, triglyceride, LDL-C and HDL-C. In a previous study of adult SH patients, EAT thickness was shown to be greater in those with TSH >10 μlU/mL.[14] However, in another study of patients with TSH <10 μIU/mL, no significant difference was determined between the patient and control groups in respect of EAT thickness and there was no positive correlation between EAT thickness and TSH.[7] In the current study patient group, only 10 patients had TSH ≥10 μIU/mL.

Study Limitations

This study had some limitations. First, it was a cross-sectional study and did not include any long-term follow-up, so the duration of exposure to subclinical hypothyroidism was not clear. The second point TSH >10 μIU/mL was found only 10 of 61 patients in subclinical hypothyroid group. In previous adult studies, the relationship between SH and EAT thickness has been determined especially in patients with TSH ≥10. Therefore, there is a need for further studies including many more patients with TSH ≥10 μIU/mL to be able to evaluate the relationship between TSH and EAT thickness.

In conclusion, the results of this study demonstrated that the HDL-C levels of children with SH were significantly low. Although there is known to be a relationship between low HDL and the risk of cardiovascular disease, there is a need for further long-term studies of greater numbers of patients to be able to better understand the clinical importance of low HDL in relation to subclinical hypothyroidism. In the current study, a significant increase in EAT thickness was not determined in the children with SH. As this study was cross-sectional, it did not include long-term follow-up, so until these patients are followed up in the long-term, it is not known how SH in paediatric patients affects EAT thickness. As this is the first study to evaluate EAT thickness in children with SH, there is a need for further studies to support these findings so that a more definitive conclusion can be reached.

Conflicts of Interest

The authors declare no conflict of interests.

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