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Carotid Intima-Media Thickness and Lipid Profile In Children Patients With Hypothyroidism

Mecnun Çetin[1*], Aytül Eren[2], Eda Çelebi Bitkin[2], Eyyüp Yürektürk[2], Cemil Goya[3], Kamuran Karaman[2]

[1]*Department of Pediatric Cardiology, Van Yuzuncu Yil Universitiy, Van, Turkey*
[2]*Department of Pediatrics, Van Yuzuncu Yil Universitiy, Van, Turkey*
[3]*Department of Radiology, Van Yuzuncu Yil Universitiy, Van, Turkey*

ABSTRACT

Hypothyroidism is a condition where there is a decrease or absence of thyroid hormone production as a result of a disorder occurring anywhere in the hypothalamo-pituitary-thyroid axis. There are very few studies in the literature reporting on the effect of hypothyroidism on lipid metabolism and carotid intima-media thickness (CIMT) in children.
The present study was designed to determine whether hypothyroidism is associated with an increase in the CIMT and lipid levels in patients under thyroid hormone replacement therapy.
The study included 30 children (under thyroid hormone replacement therapy) diagnosed with hypothyroidi and a control group comprising 30 healthy, euthyroid children. All the patients were examined for clinical characteristics, and the serum lipid levels and the CIMT were measured.
Mean age was 8.47 ± 5.22 years in the patient group and 8.82 ± 4.91 years in the control group. Patient group TSH value was significantly higher than control group (9.95 ± 18.43, 1.93 ± 1.04, p = 0.021, respectively). The total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and TG values were similar in both group (p = 0.065, p = 0.429, p = 0.219, and 0.391, respectively). CIMT values of the patient and control groups did not differ significantly (0.40 ± 0.08 and 0.39 ± 0.07, p = 0.920, respectively)
In this study, contrary to the rare studies in the children's age group in the literature, no significant changes in lipid profile and CIMT were detected in patients with hypothyroidism. Further prospective studies are needed to substantiate these findings in children with hypothyroidism.

Keywords: Carotid intima-media thickness, childhood, dyslipidemia, hypothyroidism

Introduction

Hypothyroidism is a condition where there is a decrease or absence of thyroid hormone production as a result of a disorder occurring anywhere in the hypothalamo-pituitary-thyroid axis. The incidence is around 0.1-2 % on average (1). In primary hypothyroidism, plasma thyroid-stimulating hormone (TSH) is high and free thyroxine (fT4) is low. Free triiodothyronine (fT3), usually begins to decrease in the stage of advanced hypothyroidism. While fT3 and fT4 are normal, the state where the TSH value increases is also called subclinical hypothyroidism (SH) (2). In hypothyroidism, there is a slowdown in metabolic rate. Symptoms and signs vary depending on the duration of exposure to hypothyroidism and the degree of failure of thyroid hormones. Thyroid hormones have important effects on many tissues and organs in the body. One of the most obvious effects on the body is its effects on the cardiovascular system (3).

Hypothyroidism leads to greatly increased plasma levels of cholesterol, phospholipids and triglycerides and almost always excessive lipid storage in the liver. In long-term hypothyroidism, the risk of atherosclerosis increases significantly (4). The increased risk of atherosclerosis has been shown to be due to hypercholesterolemia, particularly an increase in low-density lipoprotein cholesterol (LDL-C). In some studies investigating the relationship of hypothyroidism with atherosclerosis, changes causing atherosclerosis have been reported to improve with levothyroxine (LT4) treatment (5, 6).

It is known that the increase in carotid intima media thickness (CIMT) is an early marker of atherosclerosis. There are studies showing that CIMT increases in patients with hypothyroidism as a result of hyperlipidemia and impaired endothelial function (7).

***Corresponding Author:** Mecnun Çetin, Department of Pediatric Cardiology, Van Yuzuncu Yil Universitiy, Van, Turkey
E-mail: drmecnun@hotmail.com, Tel: +90 (432) 217 76 00, Fax:+90 (432) 212 19 54
ORCID ID: Mecnun Çetin: 0000-0002-3267-8161, **Aytül Eren:** 0000-0002-4440-5427, **Eda Çelebi Bitkin:** 0000-0002-6586-7305, **Eyyüp Yürektürk:** 0000-0001-7867-0184, **Cemil Goya:** 0000-0003-4792-8722, **Kamuran Karaman:** 0000-0003-2991-3551
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In this study, we aimed to investigate the relationship between hypothyroidism and CIMT and lipid parameters in pediatric patients with hypothyroidism under thyroid hormone therapy.

Material and Methods

This study was carried out between September 2019 and January 2020 at *Yuzuncu Yıl University Faculty of Medicine*. A total of 30 patients who were diagnosed with hypothyroidism (receiving thyroid replacement therapy) in the Department of Pediatric Endocrinology, without systemic hypertension, any other acute or chronic disease or any known cardiac problems were included in the study. A total of 30 patients who applied to the pediatric cardiology outpatient clinic with a murmur complaint, who did not have an acute/chronic systemic disease or cardiac disease, were determined as the control group.

The height and weight of the groups, and after resting for 10 - 15 minutes, systolic blood pressure (sBP) and diastolic blood pressures (dBP) were measured. Venous blood samples were taken for TSH, fT4, fT3, LDL-C, total cholesterol (TC), Triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C). Samples were studied on the same day. TSH, sT4, sT3 LDL-C, TC, TG and HDL-C measurements were studied in the biochemistry laboratory, using commercial kits in the Architect Ci16200 autoanalizer. Ultrasonographic imaging of the groups was done on the day of studying biochemical parameters.

Ultrasonographic Evaluation: Carotid artery doppler ultrasonography (USG) examination was performed with Siemens ACUSON S2000™ (Siemens Healthcare, Erlangen, Germany) device using 14L5 linear probe. All USG examinations were performed by the same experienced radiologist in a quiet environment, after each individual had been resting for approximately 15 minutes. While the patients were in the supine position, CIMT was measured approximately one cm proximal to the both right and left carotid artery bifurcation.

Ethics committee approval was received by decision 04/06/18, numbered 04. Detailed consent was obtained from all patients and their parents included in the study.

Statistical Analysis: The studied variables were presented as mean, minimum and maximum values. Student t test was used to compare control and patient group means for the studied variables. SPSS (ver: 21) statistical program was used for all statistical computations. P value < 0.05 was considered statistically significant.

Results

While the mean age of the patient group was 8.47 ± 5.22 years, the mean age of the control group was 8.82 ± 4.91 years and there was no significant difference between the groups ($p > 0.05$). Twelve (40%) of both groups were boys and 18 (60%) were girls. There was no significant difference between groups in terms of height, body mass index (BMI), sBP and dBP ($p > 0.05$) (Table 1).

The TSH value of the study group was significantly higher than the control group (9.95 ± 18.43, 1.93 ± 1.04, $p = 0.021$, respectively). Although the mean fT3 value in the study group was significantly lower than the control group, the fT3 values in both groups were within the normal reference range. The fT4 value was similar in both groups (Table 2).

In the evaluation of lipid levels of the groups; although the TG level of the study group was higher than the control group, this difference was not statistically significant ($p = 0.391$). In addition, although the HDL-C level of the study group was lower than the control group, this difference was not significant ($p = 0.429$). There was no significant difference between the groups in terms of TC and LDL-C value (Table 2) In the evaluation of the groups in terms of CIMT; In the measurement made from the left carotid artery, the CIMT value of the study group was 0.40 ± 0.08 mm, while the control group was 0.39 ± 0.07 mm and there was no significant difference between the groups ($p = 0.920$). Similarly, there was no significant difference in the measurements made from the right carotic artery (Table 3).

Discussion

Thyroid hormones have important effects on many tissues and organs in the body. It shows its effects on the cardiovascular system directly and indirectly. It shows its direct effects by affecting myocytes at the receptor and nuclear levels, and indirect effects by changing the hemodynamic and sympathetic tone in the autonomic nervous system. Thyroid hormones directly and indirectly affect cardiac contractility and decrease systemic vascular resistance(SVR) by dilatation in arterioles. In the case of hypothyroidism, bradycardia, decrease in cardiac output and increase in systemic vascular resistanceoccur. In hypothyroidism, mild

Table 1. Demographic Characteristics of The Study and Control Groups

	Study (n=30)	Control (n=30)	P
Age (years)	8.47 ± 5.22	8.82 ± 4.91	0.792
Gender (female/mal)	18/12	18/12	1
Weight (kg)	28.58 ± 16.22	28.92 ± 19.33	0.943
Lenght (cm)	123.01 ± 29.12	119.10 ± 31.23	0.618
BMI (kg/m2)	19.20 ± 3.13	19.01 ± 4.20	0.842
sBP (mmHg)	106 ± 10	103 ± 10	0.279
dBP (mmHg)	65 ± 8	63 ± 9	0.407

BMI, Body Mass Index; dBP, diastolic blood pressure; sBP, systolic blood pressure

hypertension may occur, and as there is a greater increase in diastolic pressure, there may be a narrowing in the pulse pressure (3).

Considering the effects of thyroid hormones on many systems, early diagnosis and proper treatment of hypothyroid disease become important.

Atherosclerosis, which is common today, is the most common cause of mortality and morbidity. Cardiovascular diseases developing on the basis of atherosclerosis are still the leading causes of death (8). Atherosclerosis often affects elastic arteries such as aorta, carotid and iliac arteries, and large and medium-sized arteries such as coronary and popliteal arteries. Fatty streaks, the first sign of atherosclerosis, were also detected in the aorta in childhood. Atherosclerotic events that start from childhood affect the vascular structures in the body and clinical symptoms of this process appear in the future (9). Therefore, it is important to be able to diagnose atherosclerosis before organ involvement.

Thyroid hormones exert their most pronounced effects on the cardiovascular system (3). It is known that lipid metabolism is negatively affected in hypothyroidism. It is suggested that the major mechanism of the development of atherosclerosis in hypothyroidism is the defect in the lipid profile and endothelial dysfunction caused by the defect in this lipid profile. It is stated that the increased risk of atherosclerosis in hypothyroidism is due to hyperlipidemia, especially LDL-C increase (10). In some studies investigating the relationship between hypothyroidism and atherosclerosis, changes causing atherosclerosis have been reported to improve with LT4 treatment (5-7, 11). In summary, as a result of all these effects, when hypothyroidism is not treated properly, lipid metabolism deteriorates, and as a result, the incidence of cardiovascular disease increases. Unal et al. evaluated 38 pediatric patients with hypothyroidism, found high TC, LDL-C, HDL-C values in the patient group (12). In another study conducted by Dahl et al. in the child age group, 228 SH patients and 1215 control groups were compared. TC and non-HDL-C levels were found to be significantly higher in children with SH (13). In a study by Witte et al in 12756 healthy children age group, they found a significant relationship between TSH level and LDL-C, TC, TG level (14). Contrary to these studies, in the study of Catli et al., they did not find a significant difference between the group with SH and the control group in terms of LDL-C, TC and HDL-C value (15). Similar to the study of Catli et al., we did not find a significant difference between the patient group and the control group in terms of LDL-C, TC, TG, HDL-C values. However, in our study group, the TSH value was significantly higher than the control group (p = 0.021) (Table 2). We think that the lipid profile in our study was similar to the control group, it was due to early diagnosis and regular hormone replacement therapy.

CIMT, which is one of the parameters used in the evaluation of arterial stiffness, is increasingly used as a predictive marker for atherosclerosis in estimating the risk of cardiovascular disease (16, 17). The increase in CIMT causes an increase in arterial stiffness. The increase in arterial stiffnes implies an increased risk for the development of atherosclerosis (18, 19). Although there is no normal reference interval for CIMT in children by age, values above 0.75 mm or an annual increase of 0.03 mm in CIMT are considered abnormal (20).

It is known that the increase in CIMT in hypothyroidism is an early marker of atherosclerosis. In several studies, the increase of CIMT in patients with hypothyroidism has been linked to several mechanisms. It has been shown that endothelial functions are impaired as a result of adverse effects of lipid metabolism in patients with hypothyroidism, and as a result, CIMT has been shown to increase (7). There are studies that found that the damaged lipid profile improved and CIMT decreased as a result of levothyroxine

Table 2. Thyroid Hormone and Lipid Hormone Levels of The Groups

	Study (n=30)	Control (n=30)	P
TSH (mIU/L)	9.95 ± 18.43	1.93 ± 1.04	0.021
fT3 (pg/ml)	3.40 ± 0.68	3.90 ± 0.32	0.001
fT4 (ng/dl)	1.11 ± 0.21	1.05 ± 0.10	0.117
TG (mmol/L)	103 ± 47	92 ± 53	0.391
TC (mmol/L)	128 ± 29	131 ± 22	0.651
LDL-C (mmol/L)	59.7 ± 22.5	63.8 ± 16.6	0.429
HDL-C (mmol/L)	53.9 ± 16.1	58.9± 15.5	0.219

fT3, free triiodothyronine; fT4, free thyroxine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TSH: thyroid-stimulating hormone

Table 3. Carotid Artery Doppler Ultrasonographic Evaluations of The Groups

	Study (n=30)	Control (n=30)	P
CIMT (left) (mm)	0.40 ± 0.08	0.39 ± 0.07	0.920
CIMT (right) (mm)	0.41 ± 0.07	0.39 ± 0.06	0.731

CIMT, carotid intima-media thickness

treatment (21, 22). In the literature, there are many studies investigating the relationship between hypothyroidism and SH and cardiovascular disease in the adult age group. However, there are not enough studies done in the child age group. Studies in the pediatric age group are mostly related to SH and the number of studies investigating CIMT and lipid profile with hypothyroidism is very low. In the study carried out by Unal et al in a child patient with 38 SH, they found the CIMT value significantly higher in the patient group compared to the control group (12). In the study of Del Busto-Mesa et al. in 101 adults with hypothyroidism, they found LDL-C, TC and CIMT values significantly higher in the patient group. They found that these values of the patient group regressed after LT4 treatment (23). In another study with patients with 40 hypothyroidism and 36 SH, serum LDL-C, TC and CIMT were significantly higher than the control group. With thyroid hormone replacement therapy, it was determined that the CIMT and lipid parameters decreased in these patients, and the decrease in CIMT was thought to be related to the decrease in lipid parameters (22). In a meta-analysis study conducted by Gao et al., they found increased CIMT even in patients with hypothyroidism with a TSH value of < 10 mIU/L (24). Contrary to these studies, Almeida et al. did not detect a significant difference in both lipid parameters and CIMT parameters in their study with an adult patient with SH (25). In our study, similar to the study of Almeida et al., we did not find a significant difference between the groups in terms of CIMT values and lipid profile ($p > 0.05$). This can be because our patients are at an early age, receive regular LT4 therapy, and are in a euthyroid condition.

In hypothyroidism, arterial compliance decreases as a result of endothelial dysfunction and disruption of relaxation of vascular smooth muscle cells, which leads to increased SVR. In subclinical hypothyroidism, as a result of the decrease in the amount of nitric oxide, impairment in endothelium-dependent vasodilation was shown. These effects may narrow the pulse pressure by causing diastolic hypertension in approximately 30% of patients, and with thyroid hormone replacement therapy, endothelium-induced vasorelaxation occurs and blood pressure returns to normal in most patients (26). In a study by Itterman et al. in 17023 children, a positive correlation was found between serum TSH level and hypertension, and they emphasized that SH causes an increased risk of hypertension (27). In another study with 5872 adults, while a positive relationship was found between serum TSH level and dBP, no significant relationship was found between TSH and sBP (28). In a meta-analysis performed by Ye et al. in 50147 adult subjects, they found the sBP and the dBP of patients with SH similar to the control group ($p > 0.05$) (29). In our study, there was no significant difference between the groups in terms of sBP and dBP ($p > 0.05$). This may be because our patients received LT4 treatment and were in a euthyroid state. In addition, the mean age of our patients was 8.47 ±

5.22 years. In other words, the fact that our patients are at an earlier age may explain why BP is not affected. Therefore, this study does not exclude the possible relationship between hypothyroidism and blood pressure. More studies are needed to reach definitive opinion on this matter.

Study Limitations: There were some limitations of our study. Firstly, the number of cases is low, in the both group.

In our study, the lipid levels in both groups were between the normal values. This condition may be related to the young age groups or this may be due to patients being treated. Perhaps, if there was a third group of untreated hypothyroidism, this would be more clearly understood. The same can be said for CIMT. In addition, the average age of both groups is around 8 years old. We believe that these patients should be reevaluated in this respect at an older age, such as 16 - 18 years. The study would have been better if the carotid artery distensibility and carotid artery strain were observed with CIMT.

In conclusion, this study is one of the very rare studies evaluating lipid parameters and CIMT in pediatric patients with hypothyroidism under thyroid replacement therapy. We anticipated an increase in lipid parameters and CIMT, one of the early markers of atherosclerosis, in patients with hypothyroidism. However, in this prospective study, we did not find a significant difference between the patient group and the control group in terms of lipid profile and CIMT, in contrast to the rare studies in the pediatric age group in the literature. We think that the absence of any difference between the groups in terms of these parameters may be due to the low number of patients, early diagnosis of the patients, regular follow-up and treatment of the patients, and low average age of the sample group. This result we found does not exclude the relationship between hypothyroidism and lipid profile and CIMT. More and more long-term prospective studies are needed to understand whether there is a relationship between hypothyroidism and CIMT and lipid parameters in children with hypothyroidism under FT4 therapy. If there is a relationship, it is clear that this situation should be supported by new studies to clarify whether this relationship is temporary or permanent.

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