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ORIGINAL ARTICLE

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Evaluation of cardiovascular risk by growth-differentiation factor-15 and tissue Doppler imaging in children with subclinical hypothyroidism

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Abstract

Objective Subclinical hypothyroidism, defined as increased TSH serum levels and normal serum free T4 concentrations, has been associated with an increased risk of heart disease in adults. But, data in children and adolescents are scanty and treatment of subclinical hypothyroidism is controversial. Growth differentiation factor-15 (GDF-15) is a promising biomarker of cardiac remodeling. This study aimed to evaluate the cardiovascular risk factors in children with subclinical hypothyroidism, measured with tissue Doppler echocardiography (TDE), and conventional echocardiography and GDF-15 level.

Methods The study comprised a total of 41 pediatric patients with subclinical hypothyroidism (SH) (mean age 9.6 ± 4.7 years) and 31 healthy children (mean age 11.2 ± 3.4 years) as the control group. Subclinical hypothyroidism was defined as a thyroid-stimulating hormone level higher than 4 mIU/l and a normal free-thyroxine level (0.6–1.8 ng/dl). Tissue Doppler echocardiography was performed to all individuals in the control group and patient group at the beginning of the study. Global systolic function as assessed by left ventricular ejection fraction was compared between groups. The serum GDF-15 level was measured.

Results There were no significant differences in demographic parameters between the SH and control groups. The left ventricular internal diameter end systole, interventricular septal end diastole, left ventricular posterior wall end diastole, and tricuspid annular plane systolic excursion values were significantly different between the SH and control groups ($p = 0.038$, 0.028, 0.005, and 0.000, respectively). The mean mitral isovolumic relaxation time value of the SH group was 57.2 ± 9.3 ms, compared to 44.5 ± 5.6 ms for the control group ($p = 0.000$). The mean tricuspid isovolumic contraction time value of the SH group was 58.7 ± 9.4 ms, and that of the control group was 45.1 ± 5.3 ms ($p = 0.000$). The mean tricuspid isovolumic relaxation time value of the SH group was 58.03 ± 9.5 ms, and that of the control group was 45.1 ± 5.3 ms ($p = 0.000$). There were no significant differences in the other m-mode or pulse Doppler echocardiography values between two groups. The GDF-15 value of the SH group was 382.6 ± 268.2 pg/mL, and that of the control group was 473.6 ± 337.9 pg/mL; this difference was not significant.

Conclusion Patients with subclinical hypothyroidism versus healthy individuals had some changes in echocardiographic parameters that indicate involvement of diastolic function of the left ventricle. They were significantly different when compared SH group and the control group. This study demonstrated ventricle diastolic dysfunction in pediatric patients with hypothyroidism. The results of our study suggest that cardiac follow-up may be useful in patients with subclinical hypothyroidism and clinical trials are needed to explore therapeutic effects of T4 and T3 administration in this patients.

Keywords Subclinical hypothyroidism · Cardiovascular risk · GDF-15 · Child

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Introduction

Hypothyroidism manifests clinically as overt or subclinical. Subclinical hypothyroidism (SH) is defined as a thyroid-stimulating hormone (TSH) level above the upper limit of normal, with normal levels of the two thyroid hormones. SH is a common disorder in the general population [1]. The prevalence of SH among the adult population ranges from 4 to 20% [2] but is less common in children (prevalence, ~1.7%) [3].

In the literature, there is more information available about overt hypothyroidism than SH. The majority of patients with SH have no diagnostic symptoms, so the diagnosis is made based on laboratory findings. Patients with asymptomatic SH may subsequently develop a disease of the thyroid gland. Therefore, whether SH should be treated is an important question. Treatment with L-T4 benefits children with severe SH, but its value in those with mild disease is unclear. Changes in the levels of thyroid hormones can modulate the stability of vital organs and systems, including the cardiovascular (CV) system [3–5].

However, select patients with heart failure would benefit from thyroid hormone replacement if they are discovered to have SH. Some studies have shown that this therapeutic benefit is more so in patients with heart failure with preserved ejection fraction, a relatively less well-studied population [5].

Low circulating levels of thyroid hormones suppress sarco-/endoplasmic reticulum calcium-ATPase activity, which controls the contraction and relaxation cycle through an adenosine 5′-triphosphatase (ATPase) with an affinity for calcium, leading to myocardial stiffness and, eventually, left ventricular diastolic dysfunction. Alteration of the expression of certain genes leads to a cascade of events that modulate cardiac contractility, calcium cycling, and diastolic relaxation, in turn leading to development of heart failure [6].

Rodondi et al. reported that SH was associated with a higher rate of incident and recurrent congestive heart failure among participants with a TSH level of 7.0 mIU/L or greater compared with euthyroid participants. SH can cause abnormalities in lipid metabolism, oxidative stress, and endothelial function [7].

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor β family and is secreted at a low level by endothelial cells and macrophages in most tissues; its production is upregulated following tissue injury, inflammation, and mechanical or oxidative stress. In patients with CV disease, a high GDF-15 concentration is reportedly associated with adverse outcomes and disease progression [8].

Echocardiographic techniques, such as two-dimensional echocardiography (TTE), M-mode, and tissue Doppler echocardiography (TDE), are used to assess cardiac function. The wall motion at any point in the ventricular myocardium can be evaluated by TDE, as can ventricular function in patients with myocardial disease. Thus, subclinical myocardial dysfunction not evident on M-mode or two-dimensional Doppler echocardiography can be detected by TDE [9].

Few studies have focused on children with SH; therefore, the optimum screening and treatment protocols for SH in pediatric patients are controversial. The available data are insufficient to recommend replacement therapy for all children with mild or asymptomatic SH. Also, few data are available on the echocardiographic findings in SH patients, including children. Moreover, whether GDF-15 is a causative factor or a biomarker of CV disease in children is unknown. Therefore, we evaluated the cardiac function and structure of pediatric patients with SH by means of TTE, TDE, and analysis of the GDF-15 level.

Materials and methods

Study design

This study included 41 patients newly diagnosed with SH who were admitted to the Konya Education and Research Hospital Paediatric Endocrinology Clinic of the Health Sciences University from May to November 2017. The control group comprised 31 patients with chest pain or murmurs who were admitted to the Paediatric Cardiology Clinic during the same period. Patients were informed about the study and signed consent forms for participation. SH was defined as a TSH level higher than 4 mIU/l and a normal free-thyroxine level (0.6–1.8 ng/dl) [10, 11]. In this study, we have measured TSH and T4 to evaluate hypothyroidism. However, we measured thyroid antibodies (antiTG, antiTPO) in the SH group.

The exclusion criteria were: (1) additional diseases such as clinical hypothyroidism or hyperthyroidism, hypothalamic or pituitary disease or other endocrine diseases, liver failure, kidney dysfunction, hyperlipidaemia, or hypertension; (2) CV diseases such as congenital heart disease, cardiomyopathy, or valvular heart disease; (3) use of medications that affect thyroid or cardiac function; (4) smoking; and (5) age above 18 years or younger than 1 month. The study was approved by the Ethics Committee of Necmettin Erbakan University Meram Medical Faculty. Informed consent and data-release approval forms were obtained from the parents of all participants.

Echocardiography

Prior to the echocardiographic evaluation, the subjects were evaluated in the supine position using a Philips HD11XE

ultrasound machine with 3S and 7S transducers. Conventional M-mode, pulsed-wave (pw) Doppler examinations and TDE were performed. Echocardiographic examinations were performed using the imaging techniques recommended in the guidelines of the American Society of Echocardiography [9, 12, 13].

The interventricular and interatrial septa; the mitral, tricuspid, aortic (Ao), and pulmonary valves of both the atria and ventricles; the pulmonary artery; and the aorta and heart cavities were evaluated. The left atrial (LA) diameter, Ao diameter, left ventricular fractional shortening (LVFS), left ventricular ejection fraction (LVEF), left ventricular internal diameter end diastole (LVIDd), left ventricular internal diameter end systole (LVIDs), interventricular septal end diastole (IVSd), left ventricular posterior wall end diastole (LVPWd), main pulmonary artery diameter, Ao flow velocity, and pulmonary flow velocity were evaluated based on the M-mode measurements. The diastolic mitral and tricuspid inflow velocity was measured in the apical four-chamber view from the pw Doppler sample volume between the mitral and tricuspid leaflet tips, as well as the early (E) and the late (A) diastolic mitral and tricuspid inflow velocity peaks. Tricuspid annular plane systolic excursion (TAPSE) was measured in an ME four-chamber view by placing the 2D cursor at the tricuspid lateral annulus and measuring the extent of systolic annular RV excursion along a longitudinal line defining the end of systole as the end of the T wave in the electrocardiogram [14]. The following TDE variables were measured in each subject: peak early diastolic mitral annular velocity (Ea), peak late diastolic mitral annular velocity (Aa), and peak systolic mitral annular velocity (Sa). Similarly, the peak early diastolic, late diastolic, and systolic annular tricuspid and septal velocity were evaluated. In addition, the isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), and myocardial contraction time (CT) of all subjects were measured. All examinations and evaluations were performed by a single pediatric cardiologist.

Serum from routine blood draws was used for the study. The serum was separated by centrifugation at $1500 \times g$ for 10 min. Samples were stored at –80 °C until the day of the study. GDF-15 levels were analyzed with enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, catalogue no. E-EL-H0080, Wuhan, China) by using MRC UT-6100 Universal Microplate Reader.

Statistical analysis

Statistical analysis was performed using SPSS for Windows software (18.0; SPSS Inc.). Values are means ± standard deviation or medians (minimum–maximum). The Kolmogorov–Smirnov test was used to determine the normality of the data distribution. A value of $p < 0.05$ by *t*-test or Mann–Whitney *U* test was considered indicative of significance.

Results

The present study involved 72 subjects, comprising SH patients ($n = 41$) and healthy controls ($n = 31$); their demographic and clinical parameters are listed in Table 1. There were no significant differences in demographic parameters between the SH and control groups (Table 1). The LVIDs, IVSd, LVPWd, and TAPSE values were significantly different between the SH and control groups ($p =$ 0.038, 0.028, 0.005, and 0.000, respectively). There were no significant differences in the other m-mode or pulse Doppler echocardiography values between the two groups (Table 2). The GDF-15 value of the SH group was 382.6 ± 268.2 pg/mL, and that of the control group was 473.6 ± 337.9 pg/mL; this difference was not significant (Table 2).

Table 1 Demographic and clinical information of the case and control groups

Variables	Healthy subjects (control) ($n = 41$) (mean ± SD)	SH patients (case) ($n = 31$) (mean ± SD)	*p*-value
Gender (female/male)	23/18	18/13	NS
Age (year)	11.2 ± 3.4 (4.5–17)[a]	9.6 ± 4.7 (3–16.5)[a]	NS
Height (cm)	145.7 ± 17.6 (101–175)[a]	130.3 ± 27.8 (85–171)[a]	NS
Weight (kg)	38.8 ± 14.5 (16–73)[a]	33.4 ± 17.8 (11–71)[a]	NS
Systolic blood pressure (mmHg)	108 ± 11.1	111 ± 7.4	NS
Diastolic blood pressure (mmHg)	67 ± 5.2	63 ± 7.3	NS

SH subclinical hypothyroidism, *SD* standard deviation, *NS* not significant

[a](min-max)

Table 2 The comparison of growth differentiation factor-15 levels and echocardiographic parameters of patients and control groups

Conventional echocardiographic parameters	Healthy subjects (control) ($n = 41$) (mean ± SD)	SH patients (case) ($n = 31$) (mean ± SD)	p-value
LA (mm)	23.5 ± 2.8	22.9 ± 2.9	NS
Ao (mm)	20.4 ± 2.4	19.8 ± 2.8	NS
LVIDs (mm)	22.6 ± 3.1	21 ± 3.7	**0.038**
LVIDd (mm)	37.8 ± 5.1	36.2 ± 7.4	NS
LVEF (%)	70.6 ± 3.6	72.1 ± 3.1	NS
LVFS (%)	39.4 ± 2.9	40.5 ± 2.8	NS
IVSd (mm)	7.6 ± 0.9	7.1 ± 1	**0.028**
LVPWd (mm)	7.8 ± 0.9	7.1 ± 1	**0.005**
TAPSE (mm)	22.9 ± 2.2	19.4 ± 2.6	**0.000**
Doppler transmitral flow			
E (cm/s)	107.1 ± 8.3	103.1 ± 10.2	NS
A (cm/s)	65.5 ± 7	66.2 ± 12.6	NS
Doppler transtricuspid flow			
E (cm/s)	84.2 ± 7.4	86.4 ± 13.5	NS
A (cm/s)	53.09 ± 5.06	55.6 ± 12.4	NS
TSH (mIU/L)	2.09 ± 0.9	8.4 ± 3.2	**0.000**
Ft4 (ng/dl)	1.2 ± 0.1 (1.02–1.9)[a,b]	1.1 ± 0.1 (0.91–1.55)[c]	**0.009**
antiTG (ıu/ml)	–	827.3 ± 329.3	–
antiTPO (ıu/ml)[b]	–	261.6 ± 112.08	–
GDF-15 (pg/ml)	382.6 ± 268.2	473.6 ± 337.9	NS

SH subclinical hypothyroidism, *LA* left atrial diameter, *Ao* aortic diameter, *LVEF* left ventricular ejection fraction, *LVFS* left ventricular fractional shortening, *LVIDd* left ventricular internal diameter end diastole, *LVIDs* left ventricular internal diameter end systole, *IVSd* interventricular septal end diastole, *LVPWd* left ventricular posterior wall end diastole, *TAPSE* tricuspid annular plane systolic excursion, *E* peak early diastolic inflow velocity, *TSH* thyroid stimulating hormone, FT4 free thyroxine, *antiTG* anti-thyroglobulin antibody, *antiTPO* anti thyroid peroxidase, *GDF-15* growth differentiation factor-15

[a]The reference range of antiTG (ıu/ml):0–40

[b]The reference range of antiTPO (ıu/ml):0–35

[c](min–max)

The mean mitral IVCT value of the SH group was 57.7 ± 14.3 ms, and that of the control group was 44.3 ± 7.1 ms ($p = 0.000$). The mean mitral IVRT value of the SH group was 57.2 ± 9.3 ms, compared to 44.5 ± 5.6 ms for the control group ($p = 0.000$). The mean tricuspid IVCT value of the SH group was 58.7 ± 9.4 ms, and that of the control group was 45.1 ± 5.3 ms ($p = 0.000$). The mean tricuspid IVRT value of the SH group was 58.03 ± 9.5 ms, and that of the control group was 45.1 ± 5.3 ms ($p = 0.000$). The mean mitral peak early diastolic annular velocity (Ea) of the SH group was 13.7 ± 2.4 ms, and that of the control group was 15.6 ± 2.3 ms ($p = 0.001$). The mitral mean peak late diastolic annular velocity (Aa) of the SH group was 7.6 ± 1.2 ms, and that of the control group was 8.7 ± 2.06 ms ($p = 0.01$). The tricuspid mean peak early diastolic annular velocity (Ea) of the SH group was 13.9 ± 1.8 ms, and that of the control group was 15.5 ± 1.6 ms ($p = 0.001$). The tricuspid mean peak late diastolic annular velocity (Aa) of the SH group was 8.5 ± 1.8 ms, and that of the control group was 9.8 ± 2.1 ms ($p = 0.01$) (Table 3).

Discussion

SH is a common disorder in the general population (incidence of 4–20%) and can progress to overt hypothyroidism [15]. Hypothyroidism is associated with various diseases, such as coronary disease and heart failure), and replacement therapy with L-T4 is frequently recommended for adult patients with a serum TSH concentration of >10 or <10 m IU/L and symptoms suggestive of thyroid failure, which patients with TSH levels of 4.5–10 mIU/L will benefit is less certain [16, 17]. However, SH is asymptomatic and patients have normal levels of thyroid hormones; moreover, SH may be a precursor to disease of the thyroid gland, and thus may require treatment. Few data—particularly in

Table 3 Tissue Doppler echocardiographic parameters of patients and control groups

Tissue Doppler echocardiographic parameters	Healthy subjects (control) ($n = 41$) (mean ± SD)	SH patients (case) ($n = 31$) (mean ± SD)	p-value
Mitral annular velocity			
Ea (cm/s)	15.6 ± 2.3	13.7 ± 2.4	**0.001**
Aa (cm/s)	8.7 ± 2.06	7.6 ± 1.2	**0.01**
Sa (cm/s)	9.2 ± 1.5	8.6 ± 1.5	NS
Mitral			
IVCT (ms)	44.3 ± 7.1	57.7 ± 14.3	**0.000**
CT (ms)	217.6 ± 22.5	210.6 ± 39.2	NS
IVRT (ms)	44.5 ± 5.6	57.2 ± 9.3	**0.000**
Tricuspid annular velocity			
Ea (cm/s)	15.5 ± 1.6	13.9 ± 1.8	**0.001**
Aa (cm/s)	9.8 ± 2.1	8.5 ± 1.8	**0.01**
Sa (cm/s)	12.3 ± 1.2	12.2 ± 1.8	NS
Tricuspid			
IVCT (ms)	45.1 ± 5.3	58.7 ± 9.4	**0.000**
CT (ms)	222.3 ± 27.2	211.1 ± 20.3	NS
IVRT (ms)	45.1 ± 5.3	58.03 ± 9.5	**0.000**

SH subclinical hypothyroidism, *Ea* peak early diastolic annular velocity, *Aa* peak late diastolic annular velocity, *Sa* peak systolic annular velocity, *IVRT* isovolumic relaxation time, *IVCT* isovolumic contraction time, *CT* myocardial contraction time

pediatric patients—are available to resolve whether SH should in fact be treated. Here, we evaluated cardiac dysfunction in children with untreated SH. Individuals with other conditions that cause cardiac dysfunction; e.g. obesity, hypertension, and hyperlipidaemia, were excluded from this study.

Thyroid hormones play an important role in CV function and contribute to the maintenance of CV homeostasis [2]. TSH is implicated in the regulation of the lipid profile and blood pressure. SH has been associated with markers of CV risk and cardiac impairment, as even minor deviations from the serum TSH norm may accelerate the development of atherosclerosis and produce changes in CV performance [18]. In adults with SH was reported to be able to impair both flow-mediated dilation and intima-media thickness [15]. Unfortunately, few studies of pediatric patients with SH have been conducted. In our study; LVIDs, IVSd, LVPWd, and TAPSE values were significantly different between the SH and control groups. However, mitral IVCT, mitral IVRT, tricuspid IVCT, tricuspid IVRT values were significantly different between the SH and control groups. Also, tricuspid annular velocity Ea, Aa, mitral annular velocity Ea, Aa values were significantly different between the SH and control groups. Similar to our study, Irdem et al. reported that there were significant differences in hypothyroidism pediatric patients versus the control group in terms of E/A ratio, deceleration time (DT), IVRT, and the E/Em ratio. This study demonstrated ventricle diastolic dysfunction in pediatric patients with hypothyroidism [19]. There are many studies showing that systolic and diastolic function of the left ventricle is impaired in adults with SH. A study showed that DT and IVRT were significantly prolonged and E/A ratio was also significantly reduced in SH adult patients. The some of these studies suggest that L-T4 replacement therapy should be advised for these patients with the aim to correct preclinical cardiac dysfunction and prevent the development of clinically significant myocardial dysfunction [20–22].

Substitution therapy should be initiated in adult SH patients with a TSH value of >10 mU/L, because such patients are at increased risk of CV events, dyslipidaemia, neuromuscular disorders, psychiatric disorders, and general symptoms [11].

There is general agreement that patients with primary hypothyroidism with TSH levels above 10 mIU/L should be treated, which patients with TSH levels of 4.5–10 mIU/L will benefit is less certain. But, a substantial number of studies have been done on patients with TSH levels between 2.5 and 4.5, indicating beneficial response in atherosclerosis risk factors such as atherogenic lipids, impaired endothelial function, and intima media thickness [17]. However, there are virtually no clinical outcome data to support treating pediatric patients with SH with no clinical symptoms. Also, SH in children frequently resolves spontaneously, but may persist without progressing to overt hypothyroidism. The optimum management of mild SH in children is debated, the need for therapy is questionable, and the effect of mild hypothyroidism on health outcomes is unclear. However, there is concern over adverse CV outcomes in patients with untreated SH. According to the latest data, L-T4 therapy is recommended for children with severe SH, goitre, or symptoms suggestive of hypothyroidism. However, there is insufficient evidence to recommend treatment of children with mild or asymptomatic SH [23]. The very few studies of SH in pediatric patients have been conducted; therefore, the efficacy of substitution therapy in children with SH is unclear. The available data are insufficient to recommend replacement therapy for all children with mild or asymptomatic SH, and there is a need for assessment of subtle abnormalities that may be associated with even a modest increase in the serum TSH level [15]. Therefore, we recommend that patients with untreated SH undergo regular clinical examinations, thyroid function tests, and echocardiographic evaluation.

We evaluated the CV function of patients with SH by TTE, M-mode echocardiography, and TDE, as well as by analysing the GDF-15 level. Several of the measured parameters significantly differed between the patients with

SH and the controls. This study demonstrated ventricle diastolic dysfunction in pediatric patients with hypothyroidism.

However, this study was limited by the small number of patients, the lack of long-term follow-up and absence of reevaluation of the patients after medical therapy. Thus, further research is necessary prior to fully implementing the recommendations for management of children with mild SH.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of Necmettin Erbakan University Meram Medical Faculty. All procedures performed in studies involving human participants were in accordance with the ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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