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The role of echocardiography in monitoring the therapeutic effect of levothyroxine replacement therapy in subclinical hypothyroidism

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Abstract: Current controversies related to the treatment of subclinical hypothyroidism (SCH) with thyrotropin (TSH) < than 10 mU/L are based on the lack of evidence that levothyroxine therapy has beneficial effects. The aim of our study is to estimate the effect of levothyroxine treatment on cardiac morphology and function in subclinical hypothyroidism. Body mass index, waist circumference, blood pressure, electrocardiographic and standard echocardiographic parameters were measured before levothyroxine therapy and 3 months after TSH normalization. Significant reduction in systolic and diastolic blood pressure, PR, QT and QT corrected intervals, as well as increase in heart rate were recorded in the group on levothyroxine therapy. The following parameters of the left and right ventricle were significantly decreased in the treatment group: left ventricular mass index and volume, systolic and diastolic time intervals, and mitral annular plane systolic excursion (MAPSE). The increase was recorded as fractional shortening and pressure rise in early systole (dP/dt), right atrial wall thickness and diameters. Our study did not confirm differences in basic echocardiographic parameters between the treated and control groups, apart from an echocardiographic improvement of cardiac structure and function in treated individuals. The findings suggest electrocardiographic and echocardiographic screening in monitoring the therapeutic effect.

Keywords: subclinical hypothyroidism; electrocardiography; echocardiography

Abbreviations: subclinical hypothyroidism (SCH); thyroid-stimulating hormone (TSH); levothyroxine (LT4); free thyroxine (FT4); free triiodothyronine (FT3); thyroid antibodies (tAbs); ejection fraction (EF); fractional shortening (FS); early/late transmittal peak velocity ratio (E/A ratio); myocardial performance index (TEI index); mitral annular plane systolic excursion (MAPSE); pressure rise in early systole (dP/dt); amplitude of systolic motion of the lateral tricuspid annulus segment (TAPSE); systolic pressure in the right ventricle (SPRV)

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined biochemically as a persistent increase in serum thyroid-stimulating hormone (TSH) and normal serum thyroxine (FT4) and triiodothyronine (FT3) levels [1]. A clinical picture of SCH is generally absent or could be mild. Whickam survey data registered SCH in 7.5% of women and 2.8% of men, with the highest incidence in women aged over 60 years [2-3]. Although there are controversies about the treatment of SCH, current guidelines clearly suggest a thyroxine replacement trial in individuals aged less than 70 if mild symptoms of hypothyroidism are present, when TSH is between 4.12 and 10 mIU/L [4-6].

Having in mind the pivotal role of thyroid hormones in cardiovascular system function, the adverse effects of SCH on the heart could be expected. According to the literature, diastolic hypertension, coronary heart disease based on accelerated arterial

wall thickening and stiffening, endothelial dysfunction and heart failure are clearly linked with SCH, but the beneficial effects of LT4 treatment have not been confirmed [3-12]. Clarification of the influence of LT4 treatment on cardiovascular risk in SCH would contribute to planning the strategy in cardiovascular prevention for these patients.

Some studies showed that morphological alterations of the heart, global, as well as systolic and diastolic cardiac dysfunctions and pulmonary hypertension found in SCH were improved after substitutive thyroxine therapy [13-16]. More recent data underlined measurable differences in some echo parameters when the SCH group was compared to the control group at baseline, and in the SCH group tested before and after thyroxine treatment [6,17]. These findings point to the need for monitoring cardiac morphology and function in individuals with SCH on substitutive therapy in order to provide better objectivity in the assessment of LT4 effects and the rationale for its early introduction.

The aim of our study was to specify the type and the extent of changes in cardiac morphology and function and the effect of LT4 on its reversion in individuals with SCH who had persistently increased serum TSH levels between 4.5-10 mIU/L, positive thyroid antibodies and symptoms of mild hypothyroidism as reason for treatment. The finding could be of interest for supporting early introduction of an LT4 trial treatment and better validation of its effects, not only on symptoms but also on cardiac structure and function.

MATERIALS AND METHODS

Ethics statement, patient samples and clinical information

This is a pilot study within a prospective open-label study [5-6]. Informed consent was obtained from all participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethical Commission of Belgrade University of Medical Sciences and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The criteria for inclusion were the presence of untreated SCH defined as TSH levels between an upper normal level and 10 mIU/L for more than 3 months, normal FT4, positive thyroid antibodies (tAbs) and/or an ultrasound scan characteristic for chronic autoimmune thyroiditis. The exclusion criteria were missing vital data (TSH), previous history of thyroid disease and treatment, conditions that affect thyroid status and lipid metabolism [18], the taking of any medicine that affects the thyroid or lipid metabolism in the past 6 months [10], past or current serious medical diseases including diabetes mellitus and coronary heart disease, use of any medication, including aspirin or diuretics, that might affect the study parameters, presence of symptoms and signs of clinical bleeding, smoking. The appropriate control group had 40 healthy respondents.

Study protocol and measurements

Weight, height, body mass index (BMI), waist circumference (WC) and blood pressure as well as electrocardiographic (ECG) variables (heart rate, PR interval, QT interval, and corrected QT interval) were measured before intervention with thyroxine and 3 months after the euthyroid state was achieved.

The protocol included the analysis of morphology and function of the left and right heart. An IE33xMATRIX ultrasound machine (Philips Healthcare) with a X5-1 transducer was used for measurement cardiac morphology and function parameters.

The following cardiac morphology parameters of left ventricle were evaluated: the anteroposterior dimension of the left atrium (LA), the thickness of inter-ventricular septum (IVS), left ventricular posterior wall thickness, relative thickness of the posterior wall (calculated as: 2x left ventricular posterior wall thickness/end-diastolic diameter (EDD)), index of LV hypertrophy. LV mass was calculated by using cube- function formula (LV mass = 0.8 (1.04 (EDD+posterior wall thickness) ^{3} -EDD^3) + 0.6g). LV mass index was calculated as LV mass/height.

In assessment of right heart morphology, end-systolic (ESD) and end-diastolic (EDD) diameter of right atrium (RA), as well as the size of RA in short and long axes, right ventricular (RV) posterior wall thickness, end-systolic and end-diastolic diameter of RV, end-systolic (ESA) and end-diastolic (EDA) area of the right ventricle were also measured.

Beside morphology, the cardiac function parameters were also checked. The study protocol included left ventricle global, systolic, and diastolic function parameters as well as right ventricle systolic and diastolic function parameters.

LV global function was expressed through the index of myocardial performance (Tei index). Tei index was calculated as isovolumetric contraction time (IVCT)+isovolumetric relaxation time (IVRT))/ejection time (ET)). The IVCT, IVCT/ET, pre-ejection period (PEP) were also estimated.

Left ventricle systolic function was assessed by ejection fraction (EF) calculated by Simpson method. Ejection fraction was classified as normal, borderline, or abnormal (55%, 55-45%, and less than 45% respectively). Except EF, for left ventricle systolic function assessment mitral annular plane systolic excursion (MAPSE), fractional shortening (FS) (calculated by Teicholz's formula: FS=(EDD-ESD)/EDD) in %), systolic mitral annular velocity (s), and dP/dt were measured. Doppler-derived dP/dt determined from the continuous-wave Doppler spectrum of the mitral regurgitation jet [19-20]. Cardiac output was also calculated as heart rate x stroke volume (EDV-ESV).

LV diastolic function was expressed by the following parameters: early diastolic peak filling velocity (E), late diastolic peak filling velocity (A), E/A, early diastolic mitral annular velocity (e), late diastolic mitral annular velocity(a), E/e, and some diastolic intervals (deceleration time of E velocity (DT), IVRT, PEP /ET).

RV global function was assessed by Tei index and pre-ejection period (PEP). RV systolic function was measured by FS, the amplitude of systolic motion of the lateral tricuspid annulus segment (TAPSE), and systolic tricuspid annular velocity (s). S is the average value, calculated by measuring s to the septal and lateral tricuspid ring segment.

Right ventricular diastolic function was assessed by the the following measurements, done on the tricuspid orifice: E, A, E/A (all measured in the lateral tricuspid ring segment at the end of expirium), e, a, (obtained by measuring e and a to the septal and lateral tricuspid ring segment and calculating averages values), e/a, E/e, and PEP/ET.

Recommended variables for identifying diastolic dysfunction and their abnormal cutoff values are annular e velocity: septal e<7 cm/sec, lateral e<10 cm/sec, average E/e ratio>14, LA volume index>34 mL/m^2, and peak TR velocity>2.8 m/s (LV diastolic dysfunction is present if more than half of the available parameters meet these cutoff values) [21].

Two-dimensional echocardiography, pulsed and tissue Doppler echocardiography were used. The ventricular dimensions and systolic function were assessed with the help of M-mode. MAPSE is defined as the mitral annular plane systolic excursion (normal value from 0.8 to 1.4 cm). TAPSE (normal value from 2.1 to 2.9 cm) is defined as the amplitude of systolic motion of the lateral tricuspid annulus segment. The pulsed Doppler measured transvalvular velocities (E, A), and deceleration time of E velocity (DT) in the apical four-chamber view. Doppler filling velocities were measured and their ratios, which were consistent with impaired relaxation (E/A<0.7) and restrictive filling (E/A>1.5). The tissue Doppler echocardiography analyzed systolic intervals (IVCT, IVRT and ET) in the apical four-chamber views. It was also used for measuring e, a, s of the mitral and tricuspid orifice.

After the initial investigation, LT4 treatment was initiated in all patients. Doses sufficient to normalize TSH ranged from 25 mcg to 75 mcg daily with a mean dose of 50 mcg. Three months after TSH normalization all tests were repeated. The control group consisted of healthy subjects with normal serum TSH levels, matched by age, sex, weight and height, investigated at baseline.

Statistical analysis

Data were analyzed using methods of descriptive and analytical statistics. Normality of distribution for numerical data was tested with mathematical and graphical methods and according to the distribution data they are presented as mean±SD or median (25^{th}-75^{th} percentile). Categorical data are presented as N (%) and the difference between patients with subclinical hypothyroidism and the control group was tested with the Chi square test. The difference between echocardiographic parameters among patients with subclinical hypothyroidism and the control group was tested with the t-test for independent samples. A paired t-test

or Wilcoxon's signed rank tests were used (according to data distribution) to test the change before and after LT4 substitution for numerical variables. The Pearson or Spearman correlation coefficient (according to data distribution) was used to analyze the relationship between study variables. The Bonferroni correction was applied according to 0.05/131, and p<0.0004 was considered statistically significant. All statistical analyses were performed in SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline findings did not differ between the treated and control groups

Our study included 35 patients with SCH (mean age 51.6±15.4 years, 29 females – 82.9%, 6 males – 17.1%) and 40 healthy controls matched for age (47.3±13.1 years) and sex (32 females – 80% females, 8 males – 20%). Mean WC and BMI in SCH group were 87.1±16.0 cm and 25.5± 4.0 kg/m^2 respectively, and in the control group they were 86.2±15.0 cm and 24.5±3.5 kg/m^2, respectively. The baseline findings did not differ statistically and significantly between the SCH and control groups (Table 1). A significant reduction in systolic and diastolic blood pressure were recorded (p=0.024, p=0.019) in the SCH group on LT4 therapy.

Electrocardiographic (ECG) parameters in treated patients improved

The ECG parameters in patients with subclinical hypothyroidism before and after therapy are shown in Table 2. There was a statistically significant increase in heart rate (p=0.001) and a significant decrease in PR (before: 0.16±0.02, after: 0.15±0.02; p<0.001), QT (before: 389.58±10.12, after: 383.54±8.62; p<0.001) and QT corrected (before: 428.77 ±20.11, after: 411.77±14.73; p<0.001) intervals.

Echocardiographic indices exhibited a favorable trend in individuals on LT4

The following parameters of the left ventricle were decreased after the treatment in the SCH group: LV mass index (before: 76.81±13.52, after: 70.62±16.45;

Table 1. Comparison of baseline data between individuals with subclinical hypothyroidism (SCH) and control group (MV±SD)

Baseline findings	Patients with SCH ($\bar{x}$±sd)	Control group ($\bar{x}$±sd)	p value
TSH (mmol/l)	6.9±2.1	2.8±0.6	<0.001*
Blood pressure systolic (mmHg)	126.9± 10.2	125.0± 10.5	0.477
Blood pressure diastolic(mmHg)	75.3± 6.8	75.5± 5.5	0.472
Heart rate (beats per minute)	64.8±3.7	65.6±5.7	0.479
QT corrected (ms)	428.8±20.1	422.8±16.6	0.195
Left atrium (cm)	3.4±0.3	3.5±0.4	0.474
Septum (cm)	0.9±0.2	0.9±0.1	0.425
Posterior wall (cm)	0.9±0.1	0.9±0.1	0.318
ESD (cm)	3.0±0.4	3.2±0.4	0.029
EDD (cm)	5.1±0.4	5.1±0.4	0.668
FS (Teicholz) (%)	41.4±7.5	41.2±5.3	0.870
ESV(Simpson)(cm)	39.8±9.5	36.9±6.0	0.114
EDV(Simpson)(cm)	111.7±26.5	119.2±13.3	0.117
EF (Simpson) (%)	65.9±3.2	66.3±3.2	0.630
IVRT (ms)	78.7±11.4	77.5±7.7	0.587
IVCT (ms)	53.2±11.1	56.3±8.8	0.195
Etav (ms)	289.3±14.1	286.5±14.1	0.397
dp/dt(mmHg/ms)	2163.3±454.5	2221.1±395.6	0.557
TAPSE (cm)	2.5±0.3	2.6±0.2	0.165
TEI DK	0.4±0.1	0.4±0.1	0.520
SPRV (mmHg)	27.6±4.9	27.6±4.4	0.963

Thyroid-stimulating hormone (TSH), end-systolic diameter (ESD), end-diastolic diameter (EDD), fractional shortening (FS), end-systolic volume (ESV), end-diastolic volume (EDV), ejection fraction (EF), isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT), ejection time (ET), pressure rise in early systole (dP/dt), amplitude of systolic motion of the lateral tricuspid annulus segment (TAPSE), myocardial performance index (TEI index), systolic pressure in right ventricle (SPRV); p-value from t-test for independent samples; $\bar{x}$ arithmetic mean; SD – standard deviation; * – statistically significant difference (Bonferroni correction was applied alpha=0.0004)

Table 2. ECG parameters of patients with subclinical hypothyroidism before therapy and after (MV±SD).

ECG parameters	before $\bar{x}$±sd	after $\bar{x}$±sd	p
Heart rate (beats per minute)	64.77±3.69	67.23±4.09	0.001
PR interval (ms)	0.16±0.02	0.15±0.02	<0.001*
QT interval (ms)	389.58±10.12	383.54±8.62	<0.001*
QT corrected interval (ms)	428.77±20.11	411.77±14.73	<0.001*

p-value from paired t-test, $\bar{x}$ arithmetic mean; SD – standard deviation; * – statistically significant difference (Bonferroni correction was applied alpha=0.0004)

Table 3. Echocardiographic (ECHO) parameters of left atrium and ventricle morphology and function (MV±SD).

Echo parameters	before $\bar{x}$±sd	after $\bar{x}$±sd	p
Left atrium (cm)	3.41±0.32	3.38±0.33	0.365
Septum in diastole (cm)	0.89±0.16	0.85±0.16	0.012
Posterior wall in diastole (cm)	0.89±0.14	0.9±0.16	0.586
RWT (cm)	0.4±0.08	0.4±0.08	0.624
Index of LV hypertrophy	0.4±0.08	0.4±0.08	1.000
LV mass (Cube)(g)	138.97±28.56	133.43±29.4	0.003
LV mass index (g/m)	76.81±13.52	70.62±16.45	<0.001*
ESD (cm)	2.96±0.38	2.91±0.47	0.412
EDD (cm)	5.06±0.42	4.98±0.46	0.197
EF (Simpson) (%)	65.91±3.21	67.29±3.58	0.001
FS (Teicholz) (%) $^{\varepsilon}$	39.40 (35.40-46.80)	42.40 (38.80- 47.20)	<0.001*
ESV(M-mode) (mL)	38.86±9.6	36.95±9.25	<0.001*
EDV (M-mode) (mL)	114.83±20.6	108.43±18	<0.001*
EDV (M-mode) (mL/m^2)	62.6±11.03	60.72±10.42	0.028
ESV (Simpson) (mL)	39.75±9.49	39.13±12	0.630
EDV (Simpson) (mL)	111.69±26.47	108.71±24.84	0.001
EDV(Simpson) (mL/m^2)	57.61±16.72	55.48±15.92	0.001
MAPSE 2D (mm)$^{\varepsilon}$	1.67(1.55-1.89)	1.53 (1.34-1.65)	<0.001*
Stroke volume (mL)	75.97±11.0	71.05±8.75	<0.001*
Cardiac output(mL/min)	2527.3±673.3	2486.8±641.4	0.244

Relative thickness of the posterior wall in diastole (RWT), left ventricle (LV), end-systolic diameter (ESD), end-diastolic diameter (EDD), ejection fraction (EF), fractional shortening (FS), end-systolic volume (ESV), end-diastolic volume (EDV), mitral annular plane systolic excursion (MAPSE); *p*-value from paired t-test; $^{\varepsilon}$ data are presented as median (25th-75th percentile) Wilcoxon test was performed, $\bar{x}$ arithmetic mean; SD – standard deviation; * statistically significant difference (Bonferroni correction was applied alpha=0.0004)

Table 4. ECHO parameters of the mitral orifice (MV±SD).

Echo parameters	before $\bar{x}$±sd	after $\bar{x}$±sd	p
Mitral valve area(mm^2)	400.34±28.23	395.11±27.88	0.013
E (cm /s)	71.09±19.43	79.26±20.89	0.179
A (cm /s)	59.47±11.04	62.52±10.60	0.272
E/A	1.20±0.31	1.29±0.35	0.004
e (mm/s)	13.56±4.66	12.11±4	0.001
a(mm/s)	10.49±3.18	11.05±2.87	0.065
e/a	1.41±0.61	1.15±0.48	0.001
E/e	5.74±1.92	7.65±4.32	0.017
s (cm/s)	10.05±2.21	9.93±2.52	0.459
DT (ms)	191.11±25.62	187.26±25.55	0.201
IVCT (ms)	53.23±11.07	46.54±11.13	<0.001*
IVRT (ms)	78.71±11.35	72.69±10.1	<0.001*
TEI	0.4±0.06	0.4±0.05	0.542
ET (ms)	289.31±14.14	298.06±19.32	0.009
IVCT/ET	0.18±0.04	0.16±0.04	<0.001*
PEP (ms)	83.74±9.75	89.06±13.55	0.001
PEP /ET$^{\varepsilon}$	0.31 (0.27-0.34)	0.29 (0.27-0.32)	0.001
dp/dt (mmHg/ms)	2163.29±454.48	2385.17±542.83	<0.001*

E (early diastolic peak filling velocity), A (late diastolic peak filling velocity), e (early diastolic mitral annular velocity), a (late diastolic mitral annular velocity), s (systolic mitral annular velocity), DT (deceleration time of E velocity), isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), myocardial performance index (TEI index), ejection time (ET), pre-ejection period (PEP), pressure rise in early systole (dP/dt); *p*-value from paired t-test, $^{\varepsilon}$ data are presented as median (25 th-75th percentile) Wilcoxon test was performed; $\bar{x}$ arithmetic mean; SD – standard deviation; * – statistically significant difference (Bonferroni correction was applied alpha=0.0004)

p<0.001 respectively), ESV (before: 38.86±9.6, after: 36.95±9.25; p<0.001), EDV (before: 114.83±20.6, after: 108.43±18; p<0.001), MAPSE 2D ((before: 1.67 (1.55-1.89), after: 1.53 (1.34-1.65); p<0.001)). Fractional shortening increased significantly after LT4 treatment ((before: 39.40 (35.40-46.80), after: 42.40 (38.80-47.20), p<0.001)), (Table 3).

After therapy, the following parameters of mitral orifice decreased as follows: IVCT (before: 53.23±11.07, after: 46.54±11.13; p<0.001), IVRT (before: 78.71±11.35, after: 72.69±10.1; p<0.001), IVCT/ET (before: 0.18±0.04, after: 0.16±0.04; p<0.001). Dp/dt increased after LT4 therapy (before: 2163.29±454.48, after: 2385.17±542.83; p<0.001) (Table 4).

There was no significant change in the frequency of diastolic dysfunction after therapy compared to the initial finding (Table 5).

Table 5. The frequency of diastolic dysfunction baseline and after the therapy.

Criteria for diastolic dysfunction	before n (%)	after n (%)	p-value
e septal<7 cm/s	10(28.6)	8(22.9)	0.625
e lateral<10 cm/s	5 (14.3)	3(8.58)	0.615
average E/e>14	0(0)	(0)	NA
Left atrium volume index>34ml/m^2	2(5.7)	0(0)	0.500
Peak TR velocity>2.8 m/s	5(14.3)	4(11.4)	1.000
Diastolic dysfunction	13(37.1)	11(31.4)	0.625

e (early diastolic mitral annular velocity), E (early diastolic peak filling velocity), tricuspid regurgitation (TR); *p*-value from McNemar test; NA – not applicable

Table 6. Echocardiographic (ECHO) parameters of right atrium and ventricle morphology and function (MV±SD).

Echo parameters	before $\bar{x}$±sd	after $\bar{x}$±sd	p
RA long axis (cm)$^{\varepsilon}$	4.59 (4.18-5.11)	4.81 (4.31-5.70)	<0.001*
RA short axis (cm)$^{\varepsilon}$	3.67 (3.16-3.87)	3.88 (3.38-4.14)	<0.001*
Wall thickness of RV (cm)$^{\varepsilon}$	0.43 (0.40-0.46)	0.44 (0.40-0.48)	<0.001*
EDD (cm)	1.77±0.55	1.86±0.55	0.054
ESA (cm^2)	5.56±1.15	5.14±1.23	<0.001*
EDA (cm^2)	11.41±3.3	9.8±3.49	<0.001*
FS (%)$^{\varepsilon}$	57.99 (54.60-60.14)	59.01 (57.02-64.40)	0.002
ET (ms)	292.6±18.74	301.94±27.99	0.044
Tricuspid valve area (mm^2)	413.83±24.36	403.11±40.42	0.013
TAPSE (cm)	2.53±0.26	2.4±0.28	0.007
TEI	0.4±0.06	0.36±0.06	<0.001*
PEP (ms)	74.34±13.02	77.09±10.02	0.092
PEP/ET	0.25±0.05	0.26±0.04	0.284
PEP LV-PEP RV (ms)$^{\varepsilon}$	6.0 (0-24.0)	18.0 (-2.0-23.0)	0.246

Right atrium (RA), right ventricle (RV), left ventricle (LV), end-diastolic diameter (EDD), end-systolic area (ESA), end-diastolic area (EDA), fractional shortening (FS), ejection time (ET), amplitude of systolic motion of the lateral tricuspid annulus segment (TAPSE), myocardial performance index (TEI index), pre-ejection period (PEP); *p*-value from paired t-test, $^{\varepsilon}$ data are presented as median (25th-75th percentile) Wilcoxon test was performed; $\bar{x}$ arithmetic mean; SD – standard deviation; * – statistically significant difference (Bonferroni correction was applied alpha=0.0004)

Table 7. ECHO parameters of the tricuspid et pulmonary orifice (MV±SD).

Echo parameters	before $\bar{x}$±sd	after $\bar{x}$±sd	p
Et (cm/s)	48.82±9.66	51.75±9.82	<0.001*
A (cm/s)	36.5±10.35	38.18±9.84	0.096
E/A	1.4±0.31	1.4±0.23	0.967
e (mm/s)	8.54±2.44	10.36±2.66	<0.001*
a (mm/s)	10.12±5.45	9.48±4.75	0.035
e/a$^{\varepsilon}$	1.0 (0.9-1.4)	1.(0.7-2.0)	0.108
E/e	6.04±1.6	5.3±1.47	0.001
E pulmonary (cm/s)	10.65±3.35	11.83±3.79	<0.001*
A pulmonary (cm/s)	27.6±4.88	25.49±4.84	<0.001*

E (early diastolic peak filling velocity), A (late diastolic peak filling velocity), e (early diastolic tricuspid annular velocity), a (late diastolic tricuspid annular velocity); *p*-value from paired t-test, $^{\varepsilon}$ data are presented as median (25 th-75th percentile) Wilcoxon test was performed; $\bar{x}$ arithmetic mean; SD – standard deviation; * – statistically significant difference (Bonferroni correction was applied alpha=0.0004)

After LT4 substitution therapy, there was a reduction of the following parameters: ESA (before: 5.56±1.15, after: 5.14±1.23; p<0.001), EDA (before: 11.41±3.3, after: 9.8±3.49; p<0.001), TEI (before: 0.4±0.06, after: 0.36±0.06; p<0.001). A statistically significant increase was recorded in the RA long axis ((before: 4.59 (4.18-5.11), after: 4.81 (4.31-5.70); p<0.001)) and short axis ((before: 3.67 (3.16-3.87), after: 3.88 (3.38-4.14); p<0.001)), wall thickness ((before: 0.43 (0.40-0.46), after: 0.44 (0.40-0.48); p<0.001)) (Table 6).

After LT4 therapy there was an increment in the following parameters of the tricuspid and pulmonary orifice: E (before: 48.82 ± 9.66, after: 51.75 ± 9.82; p<0.001), e (before: 8.54 ± 2.44, after: 10.36 ± 2.66; p<0.001), Ep (before: 10.65 ± 3.35, after: 11.83 ± 3.79; p<0.001) and decrease of Ap (before: 27.6 ± 4.88, after: 25.49 ± 4.84; p<0.001) (Table 7).

There was no correlation between changes in thyroid and echocardiographic parameters (Table 8).

DISCUSSION

Some studies have shown that subclinical thyroid dysfunction results in changes in heart rate, blood pressure, cardiac output and contractility, as well as vascular resistance [18,22]. These alterations in cardiac morphology and function may be objectified by

Table 8. The correlation of the changes in parameters of cardiac function with changes in TSH, FT4, FT3, tAbs and the average dose of LT4.

	TSH		fT4		fT3		tAbs		average dose of levothyroxine	
	r	p	r	p	r		r	p	r	p
EF(Simpson)	-0.114	0.513	0.096	0.596	0.107	0.575	-0.055¥	0.761	-0.027	0.879
EDV(M-mode)	0.074	0.671	0.055	0.761	-0.255	0.173	0.202¥	0.260	0.003	0.987
EDV(Simpson)	0.302	0.078	-0.015	0.936	-0.287	0.125	0.173¥	0.334	0.355	0.036
IVCT	-0.016	0.926	0.202	0.259	-0.007	0.971	0.343¥	0.051	0.175	0.314
IVCT/ET	0.109	0.533	0.093	0.607	-0.031	0.871	0.363¥	0.038	0.234	0.175
IVRT	-0.097	0.581	0.035	0.848	0.082	0.665	0.079¥	0.664	0.183	0.293
TEI LV	-0.140	0.424	-0.050	0.782	-0.001	0.995	0.186¥	0.300	-0.067	0.704
TEI RV	0.289	0.092	-0.042	0.816	0.114	0.549	0.175¥	0.330	0.517	0.001

Ejection fraction (EF), end-diastolic volume (EDV), isovolumetric contraction time (IVCT), ejection time (ET), isovolumetric relaxation time (IVRT), myocardial performance index (TEI index), left ventricle (LV), right ventricle (RV); Pearson's rank correlation coefficient; ¥Spearman's rank correlation coefficient

observing changes in several echocardiographic parameters: increased LV mass index, increments of the index of myocardial performance (IVCT, IVCT/ET), mild systolic dysfunction, impaired diastolic function (prolonged IVRT, higher PEP/ET, reduced E/A) [13-15,23-29]. Most of these shifts are responsive to LT4 treatment, so the restoration of normal thyroid function principally leads to the normalization of cardiovascular hemodynamics [13,28].

Hypothyroidism is accompanied by a rise in diastolic blood pressure and consequently low cardiac output and narrowed pulse pressure [30]. Normalization of thyroid hormone levels in our study group was associated with blood pressure reduction, heart rate increment and stroke volume extenuation, all resulting in unchanged cardiac output. Bradycardia is also a common feature of SCH, and stimulation of β-adrenergic receptors by T3 was found to improve it [22]. Prolongation of QT interval, which is a risk factor for malignant ventricular irritability and sudden cardiac death, is also found to be linked with a rise in TSH and is shown to be completely reversible with LT4 treatment [31-33]. We have also demonstrated the potential of thyroxine therapy to significantly reduce PR and QT intervals.

Beside ventricular irritability, it was suggested that substitutive therapy improves decreased LV global contractility evaluated by dP/dt ratio [34-35]. Our results have confirmed previously listed study data. Isovolumic phase measurement was previously used as an index of LV function estimated by noninvasive methods; recently dP/dt measurement has been proposed as being less load-dependent and more accurate. Some studies evaluated LV global contractility by the dP/dt ratio as we did, and also demonstrated that decreased LV function in SCH was improved by LT4 treatment [34-35].

Recent findings have reported higher values of mean left ventricular wall thickness (IVS and left ventricular posterior wall (LVPW), and a greater increase of LV mass and mass index in SCH individuals in comparison to controls [15,36-37]. It was also highlighted that LT4 therapy can reduce LV wall thickness and LV mass [15,36]. We also demonstrated a favorable reduction in left ventricular mass index after LT4 substitutive therapy.

Myocardial performance index (Tei index) reduction was also noted after LT4 replacement in accordance with previous data [27-28]. The Tei index combines both systolic (IVCT and ET) and diastolic (IVRT) time intervals as indices of the peripheral hypothyroidism and echocardiographic markers of SCH [27-28]. Impaired development of myocardial force was the most likely explanation for the increases in IVCT and the IVCT/ET ratio, which is also observed in our patients with SCH and which was improved after thyroxine replacement. This points to the possible role of tissue hypothyroidism or the autoimmune process *per se* in events leading to the upgrading of systolic time intervals. It also appears to be important that improvements of both RV and LV Tei indices did not correlate with the dose of LT4, and higher initial doses may not lead to faster improvement of RV and LV pump functioning.

We also separately estimated the systolic and diastolic left ventricular functions that are often impaired in SCH. The left ventricular systolic function is influenced by changes in preload, afterload and myocardial inotropic function. Without invoking simultaneous impairment in myocardial inotropic function, the changes in preload and afterload were not sufficient to explain the decrease in systolic pump performance observed in our SCH patients [32,34]. Substitutive therapy in patients with SCH contributed to higher EF, but within a referent range. After comparison of baseline findings of the SCH group with the control group, we could not demonstrate any significant difference. The more precise findings of magnetic resonance imaging study are in accordance with our results [38].

In order to provide objective interpretation of the data obtained before and after treatment and to make the relation of the findings to subclinical hypothyroidism more certain, we used the Bonferroni correction for confirmation of statistical significance. In addition, all measured ultrasound parameters were in the normal range. This is why we believe that the significance of the measured improvements in our study is actually compatible with the known effects of serum and tissue LT4 on cardiac performance.

After the normalization of TSH by LT4 treatment, participants in our study showed a reduction in EDV (decreased preload as a result of LT4-induced systemic vasodilatation), higher heart rate and higher FS. Despite EDV reduction, central and peripheral thyroid hormone effects synergistically improved systolic LV performance measured by the FS of individuals in the follow-up group.

The slowing of LV relaxation is associated with aging [39]. The greatest changes are observed in seniors, overlapping with the hallmarks seen in mild diastolic dysfunction in younger patients (40-60 years of age). Our study was designed to minimize age as a confounding factor by choosing a population of early middle age.

The alterations of left ventricular diastolic function in SCH were represented by the prolongation of the isovolumetric relaxation time and deceleration time, an increased pre-ejection/ejection time ratio and reduced early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio [14-15,17,28,36,40]. Although the diastolic time intervals and the mitral flow velocity ratio have been proven to be significantly impaired only in overt primary hypothyroidism, the improvement of these parameters by thyroxine was found in both overt and subclinical primary hypothyroidism [41].

Despite the positive trend that has been observed in other trials, in our study the treatment with LT4 did not influence the frequency of diastolic dysfunction, although IVRT was improved [14-15,22,28-29,35-36].

CONCLUSIONS

Current controversies about the treatment of subclinical hypothyroidism are related to insufficient evidence that therapy with LT4 has beneficial effects. According to the guidelines, a thyroxine replacement trial is clearly suggested only in symptomatic SCH patients, aged less than 70 years. Comparing the findings obtained by basic heart ultrasound examination, our study did not confirm significant difference between SCH patients and the control group. Our study demonstrated improvements in cardiac output, heart rate, rhythm, contractility, blood volume and systemic vascular resistance, as well as in cardiac morphology, global, systolic, diastolic and pulmonary function in patients with SCH three months after normalization of TSH by thyroxine replacement therapy. These changes did not correlate with the dose of thyroxine used for TSH correction. The improvement of cardiac structure and function, measured by electrocardiographic and echocardiographic indicators, should be a useful factor in monitoring the therapeutic effect. This may also be a better approach when deciding whether a patient should be permanently treated with LT4, and more objective than loss or reduction of symptoms.

The present work is a pilot study, with 35 patients that were followed for 3 months after achieving an euthyroid state. The insufficient amount of evidence to support the benefit of early LT4 substitution is the main limiting factor, since its restoring effect on the cardiovascular system is still under investigation. The small differences in findings between groups led to the question of their clinical relevance. The findings obtained from our study reflect only initial and probably mild changes on the heart, and at most, they can

be interpreted as a tendency to become risk factors. Future studies with larger numbers of participants are needed to ascertain the clinical and hemodynamic significance of these findings.

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