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**Thyroid replacement therapy effects on cardiac function in patients with
hypothyroidism**

Ефекат тиреосупституционе терапије на функцију срца код пацијената са
ХИПОТИРЕОИДИЗМОМ

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Thyroid replacement therapy effects on cardiac function in patients with hypothyroidism

Ефекат тиреосупституционе терапије на функцију срца код пацијената са хипотиреозом

SUMMARY

Introduction/Objective Hypothyroidism is a hypometabolic syndrome with insufficient production or inadequate action of thyroid hormones. It is characterized by hypercholesterolemia, elevated LDL-C. The most common echocardiographic changes are in left ventricular (LV) diastolic function.

The aim of this study was to investigate the effects of achieving adequate thyroid hormone replacement therapy in hypothyroid patients on improving systolic and diastolic cardiac function and correcting serum lipid profile.

Methods Prospective study was conducted on 42 patients with newly diagnosed hypothyroidism, both sexes, aged 18–60 years, without comorbidity. The determined blood tests before, six, 12, and 24 weeks after starting the therapy with L-thyroxine were: FT4, TSH, total cholesterol, HDL-C, LDL-C and triglycerides. The effects of thyroid hormone replacement therapy on systolic and diastolic cardiac function were assessed by echocardiography.

Results 25 (59.5%) patients had subclinical and 17 (40.5%) overt hypothyroidism. The LV end-systolic diameter decreased statistically highly significant ($p < 0.01$) after 12 weeks and end-diastolic diameter of the right ventricle after six months of therapy. There was no significant decrease in LV end-diastolic diameter after six months of thyroid hormone replacement therapy. MAPSE, LVEF, and TAPSE values increased significantly ($p < 0.01$) after six weeks of therapy. Total cholesterol and LDL-C significantly decreased, HDL-C increased ($p < 0.01$) and there was no change in triglyceride concentrations after 24 weeks of therapy.

Conclusions Thyroid replacement therapy in hypothyroid subjects statistically significantly improves echocardiographic parameters of diastolic and systolic left and right ventricular function, reduces total serum cholesterol and LDL-C, and increases HDL-C.

Keywords: hypothyroidism, L-thyroxine, diastolic cardiac function, systolic cardiac function, lipid profile

САЖЕТАК

Увод/Циљ Хипотиреозам је синдром хипометаболизма са недовољном производњом или неадекватним дејством тиреоидних хормона. Карактерише се хиперхолестеролемијом, повишеним ЛДЛ-холестеролом, а најчешће ехокардиографске промене су поремећај параметара дијастолне функције леве срчане коморе.

Циљ истраживања је испитивање утицаја постизања адекватне супституције тироидним хормонима код хипотиреозних пацијената на побољшање систолне и дијастолне функције срца и кориговање липидног профила у серуму.

Метод Спроведена је проспективна студија на 42 пацијента са новооткривеном хипотиреозом, оба пола, узраста 18–60 година, без коморбидитета. Одређиване су вредности ФТ4, ТСХ, укупног холестерола, ХДЛ-Х, ЛДЛ-Х и триглицерида пре започињања, 6, 12 и 24 недеље након терапије Л-тироксином. Утицај супституције тироидним хормонима на систолну и дијастолну функцију срца процењиван је ехокардиографском прегледом.

Резултати 25 (59,5%) испитаника је имало субклиничку, а 17 (40,5%) манифестну форму хипотиреозидизма. Ендсистолни дијаметар леве коморе се значајно смањило ($p < 0,01$) после 12 недеља терапије, а енддијастолни дијаметар десне коморе након шест месеци терапије. Није било промена енддијастолног дијаметра леве коморе након шест месеци терапије тироидним хормонима. Вредности МАПСЕ, ЕФ леве коморе и вредности ТАПСЕ су статистички значајно повећане ($p < 0,01$) након 6 недеља терапије. Након 24 недеље од увођења тироидних хормона долази до статистички значајног смањења ($p < 0,01$) концентрација укупног холестерола и ЛДЛ-Х, пораста ХДЛ-Х, а без утицаја на серумске концентрације триглицерида ($p > 0,05$).

Закључак Супституционом терапијом тироидним хормонима код хипотиреозних испитаника значајно су побољшани ехокардиографски параметри дијастолне и систолне функције леве и десне коморе, смањен укупни холестерол и ЛДЛ-Х, а повећан ХДЛ-Х.

Кључне речи: хипотиреоза, Л-тироксин, дијастолна функција срца, систолна функција срца, липидни профил

INTRODUCTION

Thyroid hormone deficiency leads to changes in cardiovascular hemodynamics, phenotype and contractility, and accelerated atherosclerosis. Overt hypothyroidism exerts effects on systolic and diastolic cardiac function and cardiac anatomy [1, 2].

Hypothyroidism increases the risk of developing atherosclerotic cardiovascular disease by increasing circulating LDL cholesterol (LDL-C) levels, inducing the development of diastolic hypertension, increasing blood coagulability, as well as having direct effects on vascular smooth muscle. Overt hypothyroidism is characterized by hypercholesterolemia, significantly elevated LDL-C and apolipoprotein B [3].

In subclinical hypothyroidism, diastolic cardiac function is most commonly impaired, which is already manifested in patients with mild thyroid dysfunction with TSH between 5 and 10 mU/L [4]. Subclinical hypothyroidism is associated with a small increase in LDL cholesterol (LDL-C), a decrease in HDL cholesterol (HDL-C), increasing the risk of developing atherosclerosis and coronary artery disease [5].

The most common echocardiographic changes in hypothyroidism are characterized by changes in left ventricular (LV) diastolic function parameters resulting from impaired myocardial relaxation presented by prolonged isovolumic relaxation time (IVRT) and a significantly reduced early and late diastolic flow rate (E/A) of transmitral flow. Echocardiographically diastolic dysfunction is defined by the existence of at least one of the following parameters: $E/A < 1.0$, $IVRT > 100\text{ms}$, or decelerating time (DT) $> 220\text{ms}$ [6].

The interaction between the right and left ventricles is one of the most important causes of impaired right ventricular function that results from an increase in left ventricular filling pressure and the consequent increase in pulmonary flow and pressure in the right ventricle. It has been shown that impaired right ventricular mechanics are completely repaired after adequate thyroid hormone replacement therapy [7].

The aim of this study was to examine the effects of achieving adequate thyroid hormone replacement therapy in hypothyroid patients on: 1) improving systolic and diastolic cardiac function; 2) correction of serum lipid profile; 3) the effect of time needed to reach the euthyroid state on the repair of the examined parameters of cardiac function and lipid status.

METHODS

A prospective study was conducted on 42 patients over a 24-week follow-up period. The study was performed in the period September 2017 - March 2019 at the Special Hospital for Thyroid gland and Metabolic Diseases Zlatibor. The study was approved by the Ethics Committee and all study participants were informed of the study methodology and gave their consent to participate in the study.

The study included patients with newly diagnosed hypothyroidism whose TSH was greater than 10 mU/L, both sexes, aged 18–60 years, without comorbidity. Echocardiographic examinations were determined by transthoracic echocardiography on a Vivid 3 apparatus (GE Healthcare, Solingen, Germany). The systolic function was determined by the following echocardiographic parameters: left ventricular ejection fraction (LVEF), mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE). Diastolic function was determined by the following echocardiographic parameters: E wave (m/s), A wave (m/s), E/A ratio, the isovolumic relaxation time of the left ventricle - IVRT (ms). The left and right ventricular systolic function parameters were measured using the M-mode in the parasternal long-axis view and the apical 4-chamber view. The left ventricular ejection fraction (LVEF), expressed in %, was determined by a Teicholtz formula calculation. Transmitral flow rates were measured using a pulsed Doppler in the apical 4 chamber view. Using a continuous Doppler in the apical 5-chamber view, the isovolumic relaxation time (IVRT) was determined. Echocardiographic parameters were assessed before and after received L-thyroxine therapy at weeks six, 12, and 24.

The following laboratory parameters were determined from the blood: total cholesterol (TC), cholesterol fractions - HDL and LDL, and triglycerides (TG). Thyroid function was assessed by measuring free-thyroxine (FT4) and thyrotropin (TSH) levels. After determining basal FT4 and TSH levels, patients with TSH greater than 10 mU/L included in the study were administered L-thyroxine with a gradual increase in dose until euthyroid condition was achieved. Lipid status and thyroid function were assessed before and after received L-thyroxine therapy at weeks six, 12, and 24.

Descriptive and analytical statistical methods were used in this study. Descriptive methods used absolute and relative numbers, measures of central tendency (arithmetic means, median) and dispersion measures (standard deviation). Analytical statistical methods used

difference tests, parametric and non-parametric tests. The selected level of significance, that is, the probability of an error of the first type is 0.05. All data were processed in IBM SPSS Statistics, Version 20.0. (IBM Corp., Armonk, NY, USA) software package.

RESULTS

Of the 42 respondents included in the study, 9 (21.4%) were male and 33 (78.6%) were female. The mean age of studied patients was 40.1 ± 9.1 years. The youngest patient was 19 years old and the oldest was 59 years old. The mean BMI values were 24.67 ± 2.81 kg/m².

Of the 42 subjects enrolled, 25 (59.5%) had a subclinical form of hypothyroidism and 17 (40.5%) had an overt form of hypothyroidism.

FT4 before starting the therapy was 10.82 ± 3.19 pmol/L, in the repeated measurements after six, 12 and 12 weeks were in the reference range (10.2-24.5 pmol/L) for all subjects (table 1) and after 24 weeks were 16.23 ± 3.77 pmol/L indicating a statistically highly significant difference ($p < 0.01$). Out of the 42 enrolled subjects, 34 achieved TSH in reference range (0.3–4.2 mU/L) after 24 weeks of therapy while 8 did not. Of the 8 subjects with inadequate TSH values (greater than 4.2 mU/L) five patients had slightly elevated TSH values above the reference range (up to 6 mU/L) and only one subject had a TSH value greater than 10 mU/L. There was a statistically significant difference in the TSH value after 6 and 12 weeks ($p < 0.05$) and a highly statistically significant difference in the TSH value after 24 weeks of thyroid replacement therapy ($p < 0.01$) compared to the initial TSH values.

Results of the parameters of systolic cardiac function

The results of LV systolic function are presented in Table 2. There was no statistically significant decrease in left ventricular enddiastolic diameter (LVEDD) after 24 weeks of therapy ($p > 0.05$), whereas endsystolic left ventricular diameter (LVESD) decreased statistically highly significant ($p < 0.01$) from the 12th week of L-thyroxine therapy.

MAPSE and LVEF were statistically significant ($p < 0.01$) improved after six, 12 and 24 weeks of therapy - significant improvement in left ventricular function after beginning of thyroid hormone therapy (Table 2).

Results of the parameters of diastolic cardiac function

Hypothyroid subjects had a statistically highly significant ($p < 0.01$) increase in E wave velocity and increase in transmitral flow ratio (E/A), whereas the decrease in A wave velocity was a statistically highly significant ($p < 0.01$) after six, 12 and 24 weeks of therapy (Table 3). There was a trend of increasing the rate of E/A in successive measurements during L-thyroxine therapy.

The isovolumic left ventricular relaxation time (IVRT) was highly statistically significant ($p < 0.01$) decreased after six and 24 weeks of therapy, whereas the difference was not statistically significant ($p > 0.05$) in successive measurements of IVRT between six and 12 weeks, as well as between 12 and 24 week of therapy (Table 3). There was a constant decrease in IVRT during successive measurements after the beginning of L- thyroxine therapy.

Results of the parameters of right cardiac function

There was a highly statistically significant increase ($p < 0.01$) in TAPSE values six, 12 and 24 weeks after initiation of L-thyroxine therapy. No statistically significant difference was found in successive measurements of right ventricular (RV) enddiastolic diameter after six and 12 weeks of therapy, as well as successive measurements between the 12th and the 24th week ($p > 0.05$), and the difference was highly statistically significant ($p < 0.01$) at the end of the 24th week of therapy relative to baseline right ventricular diameter values - prior to initiation of therapy (Table 4).

Serum lipid profile test results

Triglyceride values were in the range of 0.50–5.94 mmol/L before therapy and in the range of 0.39–3.00 mmol/L after 24 weeks of therapy (Table 5). There was no statistically significant difference ($p > 0.05$) in serum triglyceride values after six, 12, and 24 weeks L-thyroxine therapy.

Total cholesterol values were in the range of 4.73–7.27 mmol/L, HDL-C in the range of 1.06–1.46 mmol/L and LDL-C in the range of 2.97–4.91 mmol/L before therapy and in the range of 4.36–6.10 mmol/L for total cholesterol, 1.14–1.66 mmol/L for HDL-C and 2.47–4.03 mmol/L for LDL-C after 24 weeks of therapy. Serum concentrations of total cholesterol (TC) and LDL-C were statistically highly significant decreased ($p < 0.01$), whereas serum values of HDL-C was a highly statistically significant ($p < 0.01$) increased after six and 24 weeks of therapy. There was no statistically significant difference ($p > 0.05$) in the measured serum concentrations of total cholesterol, HDL-C and LDL-C between sixth and 12th week and 12th and 24th week of therapy (Table 5).

The trend line of mean values of serum lipid concentrations (total cholesterol, HDL-C and LDL-C) in successive measurements (Figure 1) showed an increase in HDL-C which was observed after the beginning of thyroid replacement therapy. The trend lines for total cholesterol and LDL-C showed a decrease in serum concentrations after six weeks of therapy, with an unexpected increase in serum concentrations of total cholesterol and LDL-C after 12 weeks. After 24 weeks the serum levels of total cholesterol and LDL-C were lower in relation to values before the starting L-thyroxine therapy.

DISCUSSION

The prevalence of subclinical hypothyroidism (elevated serum thyrotropin-TSH and normal free thyroxine - FT4) is 8% in women (10% in women over 55 years) and 3% in men (UK Whickham cohort study) [8]. In our study, the distribution with a higher prevalence of a subclinical hypothyroidism (in 25 subjects - 59.5%) also corresponds to its higher prevalence in the general population compared to the overt form of hypothyroidism.

The panel of experts supports the use of L-thyroxine in patients with subclinical hypothyroidism when TSH is greater than 10 mIU/L. L-thyroxine administration might be considered in women planning a pregnancy or in pregnant women, as well as in symptomatic patients with subclinical hypothyroidism with TSH below 10 mIU/L [9].

The reported high values of TSH in our study after 24 weeks of therapy in 8 subjects can be explained by the various causes of intermittent or persistently elevated TSH levels in patients on thyroid replacement therapy, such as: 1) poor drug compliance and adherence; 2) interaction with other drugs; 3) using L-thyroxine with food; 4) drug malabsorption; 5) coexistent celiac disease or autoimmune gastritis; 6) interference with a laboratory test mediated by heterophilic antibodies; 7) the presence of resistance to thyroid hormones [10, 11].

Multiple meta-analyses involving patients with subclinical hypothyroidism under the age of 60 have shown that the prevalence of left ventricular diastolic dysfunction is significantly more common in subclinical hypothyroidism than in healthy subjects. In 10 randomized studies with selected patients with mild thyroid dysfunction, improvement in diastolic function was demonstrated as early as 3 months after L-thyroxine therapy [12, 13, 14].

There is a milder degree of left ventricular hypertrophy in the overt hypothyroidism with an increase in posterior wall thickness more than the interventricular septum, suggesting that concentric remodeling of the left ventricle is developed during thyroid dysfunction, which is reversible by L-thyroxine administration [15,16]. The LVEF is usually normal or slightly reduced in thyroid dysfunction, with a slight increase during therapy, mainly during exercise and less at rest [17].

Subclinical hypothyroidism is associated with systolic and diastolic dysfunction of the right ventricle, and L-thyroxine therapy leads to an improvement of right ventricular function. Some studies have shown an association between clinical hypothyroidism and right ventricular diastolic dysfunction, as well as an increase in right ventricular wall thickness. A number of studies have shown that damaged right ventricular mechanics are completely repaired after adequate thyroid hormone dose [18,19].

The thyroid replacement therapy in hypothyroid subjects significantly improves the echocardiographic parameters of left ventricular diastolic function, especially after 3 months

of L-thyroxine therapy with an average transmitral flow rate $E/A > 1.0$ (1.1 ± 0.17) and IVRT < 100 ms (87.59 ± 8.14 ms). The use of L-thyroxine significantly improves the echocardiographic parameters of left ventricular systolic function (LVEF, MAPSE). After 6 months of therapy there was no significant change in the diastolic diameter of the left ventricle. L-thyroxine therapy also improves the right ventricular systolic function. In our study, improvements of the parameters of left and right ventricular systolic and diastolic function after the administration of L-thyroxine were expected and consistent with the reported study results.

The increased prevalence of the atherosclerotic cardiovascular disease in subclinical hypothyroidism was demonstrated in a Rotterdam study, which showed that middle-aged women with subclinical hypothyroidism (with TSH greater than 4 mU/L) had a higher prevalence of coronary artery disease than the control sample with TSH less than 4 mU/L [20].

Increased serum concentrations of LDL cholesterol, triglycerides, apolipoprotein B and increased LDL oxidation might explain the association between subclinical hypothyroidism and cardiovascular disease. This pattern of serum atherogenic profile is more pronounced in patients with serum TSH levels greater than 10 mU/L and in smokers. A meta-analysis of 55,287 patients from 11 prospective cohort studies showed that subclinical hypothyroidism in patients with higher TSH levels were associated with higher mortality and prevalence of coronary diseases [21].

Studies have shown that increase in serum TSH levels by 1mU/L increased total serum cholesterol by 0.09 mmol/L in women and by 0.16 mmol/L in men [22]. A meta-analysis of studies that monitored the effects of levothyroxine therapy on lipid profile in subclinical hypothyroidism showed that serum total cholesterol decreased by about 0.2 mmol/L or serum LDL cholesterol by about 0.3 mmol/L after L-thyroxine therapy, while triglycerides and HDL-C remained unchanged [23]. McGowan et al. have shown a significant increase in HDL cholesterol by normalizing serum TSH concentrations by levothyroxine therapy [24].

In our study thyroid replacement therapy had been shown to reduce serum total cholesterol and LDL-C concentrations, increase HDL-C, and no significant effects on serum triglyceride concentrations. The effects of L-thyroxine therapy on the parameters of the lipid profile in the subjects described in our study indicate consistent and expected results, as

shown in the studies cited by other authors. The paradoxical and unexpected increase in total cholesterol and LDL-C after 12 weeks of therapy could be explained by the uncontrolled conditions of the trial, i.e. inability to control the dietary regime of the subjects in addition to the advice given at the controls, as well as fluctuations of thyroid hormones (FT4 and TSH), which is a characteristic at the beginning (in the first 3 months) of the use of levothyroxine therapy.

CONCLUSIONS

Thyroid replacement therapy in hypothyroid subjects significantly improves the echocardiographic parameters of left ventricular diastolic function, especially after the third month of initiation of therapy. Administration of L-thyroxine leads to a significant improvement in left and right ventricular systolic parameters. Levothyroxine therapy significantly reduced the risk factors for the development of atherosclerosis and coronary artery disease: reduction of total serum cholesterol and LDL-C, and increase of HDL-C.

Conflict of interest: None declared.

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Table 1. Thyroid hormone values in the function of time (n = 42)

Parameter	Before therapy	six weeks later	12 weeks later	24 weeks later
	(I)	(II)	(III)	(IV)
FT4 (pmol/L)	10.82 ± 3.19	15.34 ± 2.74	15.85 ± 3.81	16.23 ± 3.77
TSH (mU/L)	min-max	min-max	min-max	min-max
	10.2–100.00	0.62–39.40	0.05–53.70	0.29–18.50

FT4 – free- thyroxine; TSH – thyrotropin

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Table 2. Left ventricular size and systolic function parameters

Parameter	Before therapy (I)	Six weeks later (II)	12 weeks later (III)	24 weeks later (IV)
LVEDD (mm)	49.07 ± 3.70	49.02 ± 3.83	48.64 ± 3.45	48.48 ± 3.58
LVESD (mm)	31.02 ± 2.99	30.45 ± 3.39	29.21 ± 3.35	27.67 ± 2.82
MAPSE (mm)	14.52 ± 1.42	15.21 ± 1.37	16.24 ± 1.62	16.81 ± 1.67
LVEF (%)	65.19 ± 3.57	66.52 ± 3.74	69.09 ± 3.77	72.45 ± 3.55

LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; MAPSE – mitral annular plane systolic excursion; LVEF – left ventricular ejection fraction

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Table 3. Left ventricular diastolic function parameters

Parameter	Before therapy	Six weeks later	12 weeks later	24 weeks later
E (m/s)	0.71 ± 0.14	0.74 ± 0.12	0.77 ± 0.11	0.80 ± 0.11
A (m/s)	0.76 ± 0.12	0.72 ± 0.12	0.66 ± 0.10	0.61 ± 0.11
E/A	0.94 ± 0.13	1.04 ± 0.14	1.19 ± 0.17	1.32 ± 0.19
IVRT (ms)	102.59 ± 8.43	94.54 ± 8.76	87.59 ± 8.14	80.00 ± 7.29

E wave – early diastolic velocity of transmitral flow; A wave – late diastolic velocity of transmitral flow; E/A – a ratio of early and late diastolic velocity of transmitral flow; IVRT – isovolumic relaxation time of the left ventricle

Table 4. Parameters of right ventricular size and systolic function

Parameter	Before therapy (I)	Six weeks later (II)	12 weeks later (III)	24 weeks later (IV)
RV (mm)	24.79 ± 1.93	24.69 ± 2.02	24.36 ± 2.18	24.24 ± 2.13
TAPSE (mm)	19.88 ± 1.63	20.88 ± 1.74	21.78 ± 1.60	22.52 ± 1.61

RV – Right ventricular end-diastolic diameter; TAPSE – tricuspid annular plane systolic excursion

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Table 5. Blood lipid values as a function of measurement time

Parameter	Before therapy (I)	6 weeks later (II)	12 weeks later (III)	24 weeks later (IV)
TC (mmol/L)	6.00 ± 1.27	5.32 ± 0.84	5.49 ± 1.05	5.23 ± 0.87
HDL-C (mmol/L)	1.26 ± 0.20	1.36 ± 0.29	1.37 ± 0.29	1.40 ± 0.26
LDL-C (mmol/L)	3.94 ± 0.97	3.31 ± 0.74	3.45 ± 0.88	3.25 ± 0.78
TG (mmol/L)	min-max	min-max	min-max	min-max
	0.50–5.94	0.54–4.69	0.40–5.25	0.39–3.00

TC – plasma total cholesterol; HDL-C – high-density lipoprotein-associated cholesterol;

LDL-C – low-density lipoprotein-associated cholesterol; TG - triglycerides

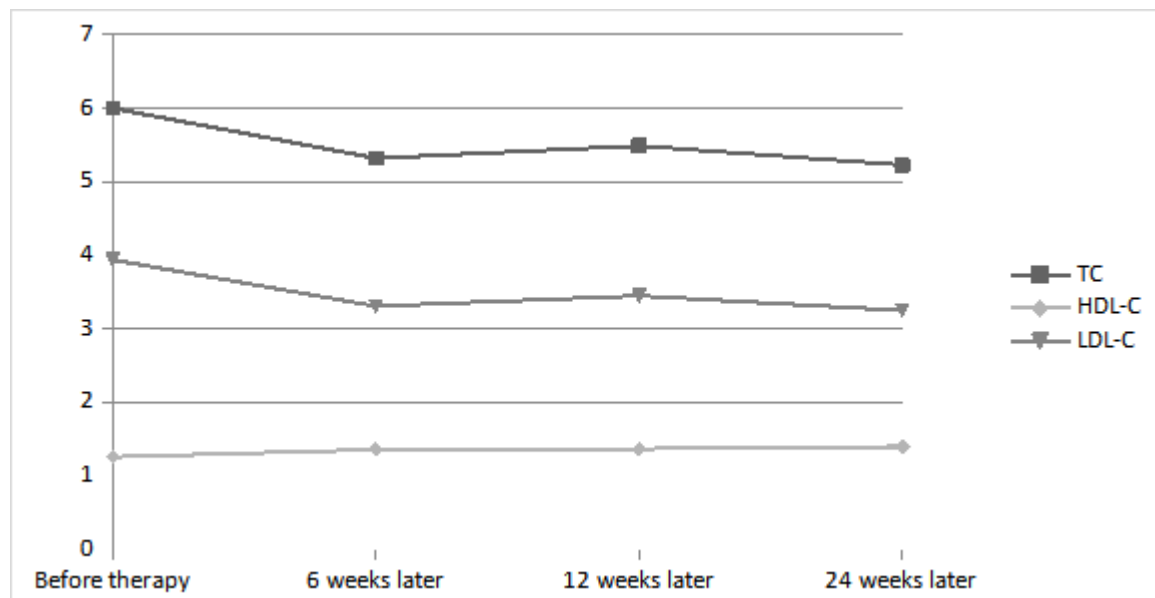


Figure 1. The trend line of mean lipid values in successive measurements: TC, HDL-C, LDL-C;

TC – plasma total cholesterol; HDL-C – high-density lipoprotein-associated cholesterol,

LDL-C – low-density lipoprotein-associated cholesterol, TG – triglycerides