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REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN ORIGINAL ARTICLE

The effect of thyroid substitution therapy on serum lipids in patients with a mild form of subclinical hypothyroidism

Efecto de la terapia de sustitución tiroidea sobre el perfil lipídico de pacientes con hipotiroidismo subclínico leve

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ABSTRACT

Background: Overt hypothyroidism and severe subclinical hypothyroidism (ScH) are associated with dyslipidemia, and its condition is reversible after levothyroxine therapy (L-T4). **Objective:** We investigated the differences in lipids between patients with a mild form of ScH and healthy subjects, and the effect of L-T4 on lipid parameters in ScH group. **Materials and methods:** Fifty-seven patients with newly diagnosed ScH with thyroid-stimulating hormone (TSH) levels below 10 mIU/L and 30 healthy subjects were included in the study. Lipid parameters were evaluated at the first visit in both groups, and after 5 months euthyroid stage in patients with ScH. **Results:** Average value of TSH in patients with ScH was 8.1 ± 1.9 mIU/L. At the baseline, the ScH patients had a significantly higher total cholesterol, low-density lipoprotein (LDL-C), and non-high-density lipoprotein (non-HDL-C) levels, and lower HDL-C than the control group. Thyroid substitution therapy in the ScH group significantly decreased total cholesterol and LDL-C, and increased HDL-C. TSH positively correlated with total cholesterol ($r = 0.147$, $p < 0.05$). The effect of the L-T4 on lipid parameters was more pronounced in patients with positive thyroid antibodies. **Conclusion:** In a small sample, mild form of ScH is associated with hypercholesterolemia, which is reversible after L-T4 therapy. Large prospective studies should confirm these results.

Keywords: Subclinical hypothyroidism. Lipids (hyperlipidaemia). L-thyroxine therapy.

RESUMEN

Antecedentes: El hipotiroidismo manifiesto y el hipotiroidismo subclínico (ScH) severo se asocian con dislipidemia y su condición puede ser reversible luego de una terapia de sustitución de tiroides. **Objetivo:** Investigamos el efecto de la terapia de sustitución de tiroides con levotiroxina (L-T4) sobre el perfil lipídico en pacientes con hipotiroidismo subclínico leve. **Material y métodos:** Fueron incluidos 57 pacientes diagnosticados con ScH leve (concentración 10 mUI/l de TSH en suero; ScH) y 30 sanos (grupo control). Se tomaron muestras de sangre en la primera visita en ambos grupos y luego de los 5 meses en pacientes con ScH. **Resultados:** La concentración promedio de TSH en los pacientes con ScH fue de 8.1 ± 1.9 mUI/l. En la primera visita los pacientes con ScH tuvieron niveles significativamente más altos de colesterol total, c-LDL, no c-HDL y más bajos de c-HDL que el grupo de control. La terapia de sustitución tiroidea redujo significativamente el colesterol total, el c-LDL y aumentó el c-HDL en los pacientes con ScH. La concentración de TSH se correlacionó positivamente con el colesterol total ($r: 0.147$; $p < 0.05$). El efecto de la terapia de sustitución tiroidea con levotiroxina sobre el perfil lipídicos fue más pronunciado en pacientes con ScH y anticuerpos antitiroideos positivos. **Conclusión:** La forma leve de ScH se asocia con hipercolesterolemia, que es reversible luego del tratamiento con levotiroxina.

Palabras clave: Hipotiroidismo subclínico. Lípidos (hiperlipidemia). Terapia con l-tiroxina.

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INTRODUCTION

Overt hypothyroidism and severe subclinical hypothyroidism (ScH) are associated with dyslipidemia. Changes in the lipid profile in hypothyroidism were explained by the regulatory effect of the thyroid hormone on the activity of some key enzymes in lipoprotein metabolism[1]. Changes in the lipoprotein profile in hypothyroidism are considered a risk factor for a coronary heart disease.

Two meta-analyses evaluated the effect of treatment with L-thyroxine (L-T4) on the lipid profile in patients with ScH[2,3]. The first one favors treatment, but most of the selected studies were not randomized. The second meta-analysis which included only placebo-controlled studies has shown effect of L-T4 only in total cholesterol. Both meta-analyses[2,3] have shown benefits from treatment only in patients with thyroid-stimulating hormone (TSH) over 10,0 mIU/L. Only a few studies analyzed the effect of mild ScH (TSH bellow 10 mIU/L) on lipoprotein levels[4-7]. Existing studies[4-7] that worked on this issue showed contradictory results. They covered a small number of patients and often had restrictions in patients' ages. However, it is still unknown whether treatment of ScH is better than watchful waiting, when TSH is below 10.0 mIU/L[8]. One meta-analysis from 2010 proposed initiation with L-T4 therapy from TSH values above 7.0 mIU/L[9].

The presence of thyroid autoantibodies confirms the autoimmune etiology of ScH. However, thyroid autoimmunity may also play an important role in the elevation of lipid levels. The presence of thyroid autoimmunity has not been shown to influence the serum lipid parameters in patients with ScH[10]. One study found a beneficial effect of L-T4 on lipid parameters in subjects with high-normal TSH levels combined with anti-thyroid peroxidase (TPO) antibodies[11]. In this study, we compared the lipid parameters in patients with mild form of ScH and healthy controls and investigated the effect of levothyroxine therapy on lipid parameters in patients with a mild form of ScH. We also analyzed the effect of thyroid auto-antibodies on the lipid profile in ScH. As there are no universal guidelines for ScH treatment, confirmation of dyslipidemia in a mild form of ScH will move the boundaries of treatment in lower TSH values.

MATERIALS AND METHODS

Patients

The prospective study was conducted at the University Clinic of Endocrinology, Diabetes and Metabolic Disorders, Skopje, R. North Macedonia during the years 2014 and 2015. Fifty-seven consecutive patients with a newly diagnosed mild ScH and 30 euthyroid healthy subjects were included in the study. These patients were recruited during the first 10 months of 2014. Mild form of ScH was defined as normal FT4 (10.3-24.45 pmol/L), normal FT3 (4.2-8.1 pmol/L), and mildly elevated TSH ($4.2 < TSH < 10.0$ mIU/L) levels in two consecutive measurement 4 weeks apart. According to the recommendations of the British Thyroid Association, patients with ScH were placed on thyroid replacement therapy if one of the following criteria was present: at least three signs or symptoms of hypothyroidism, positive anti-TPO antibodies and positive anti-Tg antibodies, positive family history of thyroid disease, and thyroid enlargement or goiter on ultrasonography[12]. Only patients who fulfilled criteria for levothyroxine treatment were included in the ScH group. Euthyroid subjects as a control group were healthy people with reference values of FT4, FT3 and TSH (0.2-4.2 mIU/L). Those were recruited randomly and consequently as they came for routine check of their health. In all patients' measurements of weight, height, BMI (calculated as weight/height^2), previous medical history, whole blood analyses, including glycaemia, hepatic, and renal blood parameters were performed. The starting dose of L-T4 in the ScH group was 25 μg. TSH was measured every 8 weeks for dose adjustment. After 5 months of continuous euthyroid state, lipid parameters were repeated. The euthyroid state was achieved with a mean dose of 60.8 ± 19 μg in a mean duration of 7.5 ± 2.2 months.

The patients who had complications or conditions that affect lipid metabolism (hepatic disease, diabetes mellitus, renal disease, and pregnancy), using previous medical history and current laboratory investigation, were not included in the study. To exclude higher TSH value due to recovery, patients with a serious illness in the past 3 months were also not included in the study. None of the patients were previously diagnosed with hypercholesterolemia, nor received treatment for it.

Ethical aspects

All patients gave informed consent to participate in the study after careful explanation of the testing protocol. The study was made in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the Medical Faculty in Skopje, R. North Macedonia.

Laboratory evaluation

Venous blood samples were withdrawn from the brachial vein after 14 h overnight fast, between 08.00 and 09.00 a.m. TSH, FT4, and FT3 were determined by the super-sensitive chemiluminescent immuneassay (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The functional sensitivity for TSH was 0.004 μIU/mL, for FT4, 0.3 ng/dL and FT3 0.4 ng/dL. The blood samples for lipoproteins were analyzed using Cobas Integra 700, according to standard methods. Total cholesterol and triglycerides were determined by full enzymatic methods (TH-CHOD-POD-PAP and triglycerides-GPO; Cobas Integra 700, Hoffmann-La Roche, Basel, Switzerland). HDL-C was measured by the polyanion precipitation method, while LDL-C was calculated using the Friedewald formula. The non-HDL-C levels were calculated as total cholesterol minus HDL-C.

Statistical analysis

The data were analyzed using SPSS 14.0 version. The data are presented as mean ± SD and percentages. The normality of the data was tested by the Shapiro–Wilkinson test. An independent Student's t-test was used to compare the analyzed variables between the control and the ScH group. A paired t-test was used to compare the ScH group at baseline and after L-T4 therapy. For the comparison of categorical variables, the Chi-square test, Yates correction, was used. The correlation between the tested parameters was determined using Pearson correlation. $p < 0.05$ was taken as statistically significant.

RESULTS

In Table 1, the baseline and hormonal characteristics of the study population were presented. Patients and controls were not statistically significantly different in age, sex, BMI, and the number of women in menopause (Table 1).

The initial average value of TSH in patients with ScH was 8.1 ± 1.9 mIU/L. It was estimated as mean values of two consecutive measurements of each patient. The average value of TSH on the first visit after starting with the thyroid substitution therapy was 3.1 ± 2.5 mIU/L, and the final TSH levels after 5 months of continuous euthyroid state were 2.27 ± 0.9 mIU/L. The euthyroid state was achieved with a mean dose of 60.8 ± 19 μg in a mean duration of 7.5 ± 2.2 months.

TSH levels were significantly higher in the ScH group than in the control group. FT4 and FT3 levels, although in the reference range, were significantly lower in the ScH group at baseline than in the control group. After thyroid substitution therapy, FT4 and FT3 levels significantly increased in the ScH group (Table 1).

The statistically significant difference in lipids between the control group and the ScH group, and in the ScH group before and after L-T4 treatment, was presented in Table 2. The total cholesterol, LDL-C, and non-HDL-C levels were statistically significantly higher and HDL-C statistically significantly lower in the ScH group at baseline than in the control group. The average values of total lipids and triglycerides

Table 1. Baseline and hormonal characteristics of the study population

Variables	Control group (1)	ScH at baseline (2)	ScH after treatment (3)
	(n = 30)	(n = 57)	(n = 57)
Sex (m:f)	3:27 (10%)	3:63 (4.7%)	3:63 (4.7%)
Age (years)	39.3 ± 11.7	43.1 ± 13.2	43.1 ± 13.2
BMI (kg/m^2)	24.3 ± 3.0	26.2 ± 4.2	25.8 ± 3.6
Menopause	3 (10%)	10 (15.1%)	10 (15.1%)
TSH mIU/L	1.7 ± 1.05[a]	8.2 ± 1.9[a]	2.27 ± 0.9[a]
FT4 pmol/L	15.4 ± 2.2[b]	12.1 ± 1.6[b,c]	14.9 ± 1.7[c]
FT3 pmol/L	5.2 ± 2.1[d]	4.5 ± 1.0[d,e]	5.2 ± 0.8[e]

Displayed results are average ± standard deviation and percentages. Comparisons between the groups were performed by Student's t-test (independent and dependent) for continuous variables and χ^2–test for categorical variables.
[a,b,c]The mean values with the same superscript are statistical significantly difference at level $p < 0.001$.
[d,e]The mean values with the same superscript are statistical significantly difference at level $p < 0.05$.
BMI: body mass index.

Table 2. Lipid parameters in the study population

Lipid parameters	Control group (1)	ScH at baseline (2)	ScH after treatment (3)
	(n = 30)	(n = 57)	(n = 57)
Total lipids (mmol/L)	8.0 ± 1.5	8.60 ± 1.7	8.36 ± 1.7
Triglycerides (mmol/L)	1.43 ± 1.6	1.45 ± 0.7	1.38 ± 0.6
Total cholesterol (mmol/L)	4.8 ± 1.1[a]	5.57 ± 0.9[a,b]	5.28 ± 1.1[a,b]
HDL-C (mmol/L)	1.73 ± 0.9[c]	1.55 ± 0.5[c,d]	1.65 ± 0.5[d]
LDL-C (mmol/L)	2.9 ± 0.8[e]	3.45 ± 1.0[e,f]	3.20 ± 1.1[f]
non-HDL-C (mmol/L)	3.5 ± 0.9[g]	4.2 ± 1.1[g]	3.8 ± 1.2
Total cholesterol/HDL-C	3.3 ± 1.0[h]	3.94 ± 1.4[h,i]	3.49 ± 1.2[i]
LDL-C/HDL-C	2.2 ± 0.8[j]	2.47 ± 1.2[j,k]	2.15 ± 0.9[k]

Displayed results are average ± standard deviation and percentages. Comparisons between the groups were performed by Student's t-test (independent and dependent).
NS: not significant; HDL-C: high density cholesterol; LDL-C: low density cholesterol.
[a,b]The mean values with the same superscript are statistical significantly difference at level $p < 0.001$.
[e,f,i,k]The mean values with the same superscript are statistical significantly difference at level $p < 0.01$.
[c,d,g,h,j]The mean values with the same superscript are statistical significantly difference at level $p < 0.05$.

were higher and HDL-C lower in the ScH group at baseline compared to the control group, but the differences remained statistically insignificant. Atherogenic total cholesterol/HDL-C and LDL-C/HDL-C ratios were statistically significantly higher in the ScH group at baseline than in the control group (Table 2).

After 5 months of euthyroid state, total cholesterol and LDL-C statistically significantly decreased and HDL-C statistically significantly increased. Atherogenic total cholesterol/HDL-C and LDL-C/HDL-C ratios also statistically significantly decreased after treatment (Table 2 and Fig. 1).

Finally, the effect of the presence of anti-TPO antibodies on lipid parameters and on the outcome of treatment with L-T4 was examined. The lipid parameters did not respond to L-T4 treatment in patients with negative anti-TPO antibodies, while a decrease

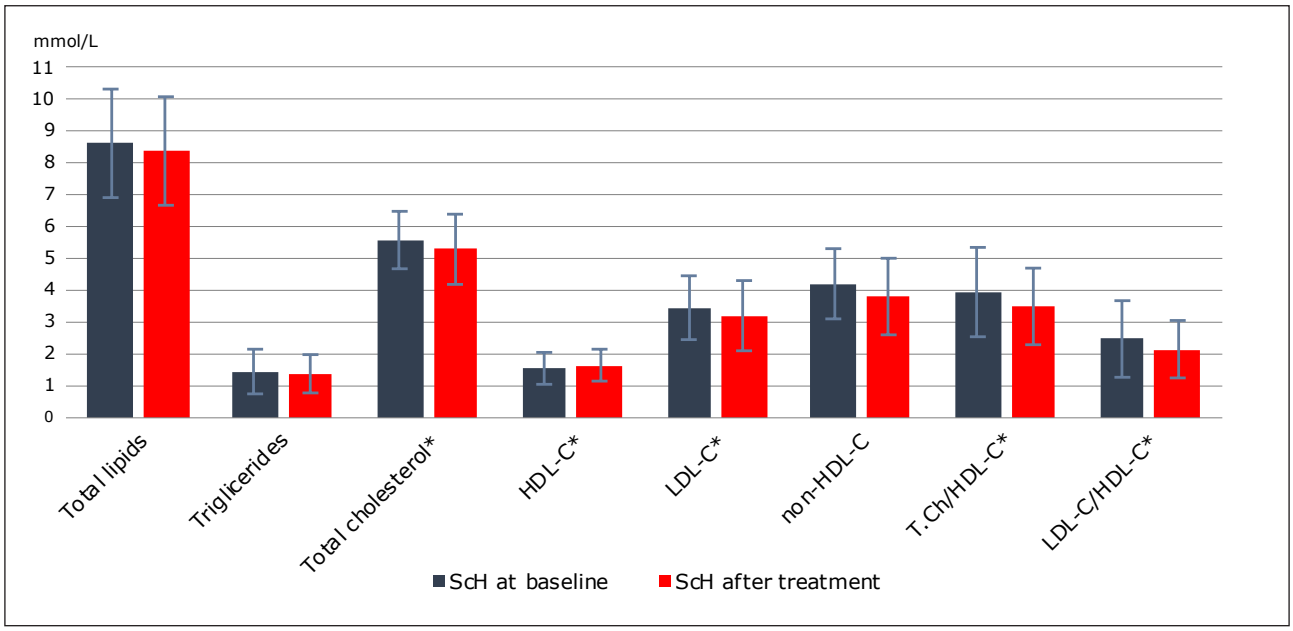

Figure 1. Average values of lipid parameters in ScH at baseline and after thyroid replacement therapy. Displayed results are average ± standard deviation. *Means statistically significant difference. ScH: subclinical hypothyroidism; HDL-C: high density cholesterol; LDL-C: low density cholesterol; T.Ch: total cholesterol.

Table 3. Comparison in lipid parameters before and after L-thyroxine treatment in the ScH group according to the presence of anti-TPO antibodies

Lipid parameters	Anti-TPO negative (n = 15)		anti-TPO positive (n = 42)	
	Before	After	Before	After
Total lipids (mmol/L)	8.6 ± 1.4	9.3 ± 1.7	8.9 ± 1.6	8.6 ± 0.6
Triglycerides (mmol/L)	1.6 ± 0.9	1.5 ± 0.8	1.5 ± 1.1	1.3 ± 0.4
Total cholesterol (mmol/L)	5.4 ± 1.1	5.2 ± 1.3	5.5 ± 1.1*	5.3 ± 00.9*
HDL-C (mmol/L)	1.4 ± 0.5	1.4 ± 0.4	1.6 ± 0.4	1.6 ± 0.4
LDL-C (mmol/L)	3.3 ± 1.0	3.4 ± 0.9	3.5 ± 1.0	3.3 ± 0.9
non-HDL-C (mmol/L)	4.4 ± 1.1	4.1 ± 1.1	4.3 ± 1.1	3.8 ± 1.1
Total cholesterol/HDL-C	4.1 ± 1.1	4.0 ± 1.1	3.9 ± 1.5*	3.5 ± 1.0*
LDL-C/HDL-C	2.5 ± 0.8	2.6 ± 0.8	2.5 ± 1.2*	2.2 ± 0.8*

Displayed results are average ± standard deviation and percentages. Comparisons between the groups were performed by student's t-test (independent and dependent).
*Statistically significant difference at level $p < 0.05$.
NS: not significant; HDL-C: high density cholesterol; LDL-C: low density cholesterol; TPO: thyroid peroxidase.

in total cholesterol, total cholesterol/HDL-C, and LDL-C/HDL-C was observed in patients with positive anti-TPO antibodies (Table 3).

TSH statistically significantly positively correlated with total cholesterol ($r = 0.147$, $p < 0.05$). FT4 statistically significantly positively correlated with HDL-C ($r = 0.197$, $p < 0.05$).

DISCUSSION

The results from this study showed that a mild form of ScH contributes to hypercholesterolemia, which is reversible with the thyroid substitution therapy. The thyroid substitution therapy was more

beneficial in lowering lipid levels in patients with ScH and positive thyroid antibodies.

Several previous studies showed the association of ScH with hypercholesterolemia[10,13,14].

Thus, Efstathiadou et al.[10] proved a statistically significant difference only in the values of total cholesterol and LDL-C. The average value of TSH in their study was above 10.0 mIU/L. The Fifth Tromso study showed an association between ScH and total cholesterol, but not LDL-C and triglycerides in women with a mild form of ScH[15]. A more recent prospective study found a significant increase in the values of total cholesterol in patients with ScH[16]. The mean age of the analyzed patients in the previous studies was higher than in this study. Considering the average age of the patients examined in this study, about 43 years, we can say that this study eliminated the influence of age. Considering lipids, age certainly had an additional effect on ScH, increasing its values. We found a positive correlation between TSH and total cholesterol. A large and cross-section study showed that with the increasing TSH value for 1 mIU/L, total cholesterol increased by 0.09 mIU/L[17]. Studies showed that this correlation was more pronounced in women. In this study, the presence of men in the ScH and control groups was appropriate; the ScH group included only three men. Hence, we do not expect the contribution of men with 3.5% to all study population to have a significant impact on results.

Two meta-analyses showed a benefit from L-T4 treatment on lipid profile in patients with ScH[2,18]. The second, comprising observational and randomized studies, concluded that the treatment with L-T4 in ScH led to a reduction of total cholesterol to 0.20 mmol/L, LDL-C to 0.26 mmol/L, with no change in the level of triglycerides[18]. Meier et al. showed a decrease of 0.24 mmol/L in total cholesterol and 0.33 mmol/L in LDL-C after 12 months of therapy with L-T4[7]. Similarly, Caraccio et al. showed an average reduction of 0.47 mmol/L and 0.41 mmol/L for total cholesterol and LDL-C, respectively, in patients with ScH with TSH value below 10 mIU/L[19]. In a randomized and double-blind study that included 100 patients with stable ScH, the treatment with L-T4 significantly reduced the serum total cholesterol and LDL-C[20]. This is consistent with the results of this study. Five months euthyroid stage in the ScH group led to a reduction of the total cholesterol of 0.29 mmol/L, LDL-C of 0.25 mmol/L, and an increase in HDL-C of 0.10 mmol/L, with no statistically significant change in the level of triglycerides. These differences may be due to different follow-ups of patients. May be long-term treatment with L-T4 or aggressive reduction of TSH leads to a significant reduction in lipid parameters.

The relationship between total cholesterol and LDL-C in a cardiovascular disease is well known. Large studies calculated that the risk of cardiovascular disease was reduced by 15-20% with 10% reduction in LDL-C[21]. The effects on additional cardiovascular markers such as non-HDL-C, total cholesterol /HDL-C, and LDL-C/HDL-C ratios were analyzed in this study. The serum non-HDL-C was used as a predictor of a cardiovascular disease. Non-HDL-C was higher in ScH at baseline compared to the control group, but there was not a statistically significant difference after L-T4 treatment. Elevated ratios of total cholesterol/HDL-C and LDL-C/HDL-C were used as an index to an increased risk of atherosclerosis. We showed a statistically significant reduction in atherogenic ratios. According to our results, ScH increases the risk of atherosclerosis and the same risk decreases after thyroid substitution therapy.

Reversibility in lipid parameters after L-T4 treatment warrants the use of L-T4 in patients with ScH at lower values of TSH (< 10.0 mIU/L). The inclusion of thyroid replacement therapy in lower values of TSH must not depend only on the TSH value, but on the presence of other parameters as well (clinical signs and symptoms, thyroid antibodies, and goiter), just as was done in this study. One study even showed decreased total cholesterol and LDL-C after L-T4 treatment in patients with TSH levels between 2 and 4 mIU/L[11].

The presence of thyroid antibodies did not influence the lipid parameters[10,11,22]. However, treatment with L-T4 was effective in lowering the total cholesterol, total cholesterol/HDL-C, and HDL-C/LDL-C in patients with ScH and positive anti-TPO antibodies. Hence, patients with mild ScH and positive anti-TPO

antibodies with high cholesterol levels may benefit from L-T4 treatment.

Srivastava et al.[23] found that dyslipidemia is significantly associated with anti-TPO positivity, especially in females. The number of included males in the study was very low. Kumar et al.[24] showed an increased incidence of dyslipidemia in ScH patients with positive anti-TPO antibodies. However, both studies[23,24] did not evaluate the effect of L-T4 treatment on lipids.

There are studies[23-28] demonstrating a relationship between thyroid autoimmunity and dyslipidemia, even in a euthyroid state[25]. In the anti-TPO-positive group, anti-TPO levels show a statistically significant correlation with total cholesterol and triglyceride levels[27]. Raut et al.[28] showed significant reduction in the total cholesterol, LDL, and VLDL after L-T4 therapy, analyzing 112 patients with ScH and positive anti-TPO antibodies. However, there are no studies evaluating the L-T4 effect of lipids according to anti-TPO positivity for comparison. Statistically significant lowering of lipids only in anti-TPO positive patients with ScH probably showed us that actually those patients were real patients with a ScH, and lipids were raised because of hypothyroidism. In long-term follow-up of TSH in patients with ScH and negative anti-TPO antibodies, TSH may drop down in the reference range, so these patients may have transitional ScH.

There were some limitations in this study. The design was not a blind or double-blind study that would include L-T4 and placebo. We did not directly observe cardiovascular morbidity and mortality, which requires a very long-term monitoring of patients. Some diseases, such as Hashimoto's thyroiditis, which is the main cause of ScH in our study, may affect cardiac function by autoimmune process, producing abnormalities such as fibrosis of the heart muscle. However, we did not analyze pathological changes in cardiac myocytes in patients with ScH. The diet and physical activity were not considered in both groups during the study. The advantage of the study compared to the previous similar studies is the inclusion of young people with no risk factors for cardiovascular disease. Lowering the lipids in mild form of ScH may reduce the future cardiovascular risk in this kind of patients. This is one of the few studies covering the analysis of patients with ScH at lower values of TSH < 10.0 mIU/L.

CONCLUSION

Mild form of ScH is associated with hypercholesterolemia, which is reversible after levothyroxine treatment. Carefully selected patients with a mild form of ScH, especially with positive anti-TPO antibodies can benefit from L-T4 therapy. Because of a small sample, large prospective studies should confirm these results.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest. This research has not received any specific funding from agencies in the public, commercial, or for-profit sectors.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained approval from the Ethics

Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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