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Original article

HYPOTHYROIDISM AND ITS ASSOCIATION WITH CHANGES IN THE LIPID PROFILE

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Abstract

Introduction: Thyroid gland dysfunction is presented as overt or subclinical hypothyroidism and has repercussions on patient's lipid profile.

Aims: To present patients lipid status with hypothyroidism versus a control group and to determine an association of thyroid status elements with lipid parameters.

Material and methods: This case-controlled retrospective study included a sample of 82 patients, examined group (N=56), who were divided into two subgroups according to the established TSH level (TSH<4ulU/ml and TSH>4ulU/ml) and a control group (TSH<4ulU/ml) (N=26). We analyzed the parameters of the thyroid function (TSH, FT4, FT3, anti-TPO) and selected lipid status parameters (cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol).

Results: The comparative analysis between the examined and the control group of patients, as well as between the two subgroups, found no significant difference in the lipid parameter levels in relation to selected parameters of the lipid status. The performed correlation among the elements of the lipid status with the thyroid parameters determined a significant linear negative weak correlation between the fT4 and cholesterol, and between fT4 and triglycerides.

Conclusion: These three examined groups did not differ in lipid status, although dyslipidemia is an expected finding in untreated hypothyroidism. The statin therapy influenced on reduction of lipid fraction values in all groups. Therefore, in newly diagnosed patients with hypothyroidism and dyslipidemia, before starting statin therapy, levothyroxine is recommended to be initially administered. Even under conditions of concomitant use of statins, cholesterol and triglyceride levels showed a negative correlation with fT4 and anti-TPO.

***Keywords**:* hypothyroidism, TSH, cholesterol, triglyceride

Introduction

Thyroid dysfunction is presented as overt or subclinical hypothyroidism and has repercussions on the lipid profile of a patient. The connection between cholesterol levels and thyroid hormone levels was observed back in the 1930s, by Mason *et al.* [1]. Since then, a number of studies by different authors has referred to the analogy between the different fractions of lipids, their metabolism, and the incidence of occurrence of cardiovascular diseases with hypothyroidism.

In patients with hyperlipidemia who are treated on outpatient basis, the prevalence of hypothyroidism is 1.4 to 13%, which indicates that the thyroid failure is a common condition in this group of patients and it may pass undiscovered [2]. The close relationship between lipid metabolism and thyroid activity should be suggestive of hypothyroidism, even in cases where there are no other apparent clinical symptoms.

Objectives of the study

This study intended to compare the lipid status of the examined group of patients with hypothyroidism (EG) *versus* the control group that had normal thyroid functioning. At the same time, it intended to show possible differences in the lipid status between the subgroup of participants with euthyroid function (TSH<4ulU/ml)-E and the subgroup of patients in a hypothyroid state (TSH>4ulU/ml)-H, compared to the control group (C).

Additional objectives of this study were:

1. To make association of the individual elements of the thyroid status (TSH, FT4, FT3, anti-TPO) with the lipid parameters (cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol).
2. To perform an analysis of the demographic data of patients with hypothyroidism (sex, age, BMI, family anamnesis for thyroid disorders and pharmacological anamnesis of interest).

Material and methods

This study was designed as a case-controlled retrospective study conducted in a sample of 82 patients (N=82).

The examined group (N=56) was subdivided into two subgroups according to the TSH level:

1. Patients with hypothyroidism, receiving thyroid substitution therapy, that were in an euthyroid state at the moment of the examination (TSH<4ulU/ml), N=26 (E)
2. Patients that were in a hypothyroid state (TSH>4ulU/ml), N=30 (H).

Criteria for inclusion in the study:

- age over 18 years
- verified hypothyroidism and a regular substitution therapy or an established indication for initiating such therapy
- subjects that underwent specialist examination made at the Department of internal medicine and laboratory analysis in the Health Center of Skopje.

Exclusion criteria:

- oncological patients with a heavier clinical, on actual therapy
- pregnant women or lactating women.

The control group (N=26) consisted of adults with a regular thyroid function verified with laboratory analyses, with performed internal medical examination in the Health Center of Skopje by referral of a family physician or a specialist of different specialty. The data available in the national health database were consulted for a proper selection of patients (therapy, specialist appointments, procedures, surgical interventions and inpatient treatment). The laboratory analyses were performed in the laboratory of the Health Center of Skopje. The study complied with the code of ethics during its implementation, by using data without identification.

According to the Manual for Practicing Evidence-Based Medicine on Hypothyroidism ("Official Gazette of the Republic of Macedonia", no. 43/12), subclinical hypothyroidism treatment is indicated if a TSH>10 mU/ml or if the patient is pregnant. If TSH is slightly elevated, the following factors support the start of treatment: symptoms, even mild pointing to hypo-

thyroidism, young age, and increased concentration of TPO antibodies, goitre and hypercholesterolemia.

The data were statistically analyzed with the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA).

The analysis of the series with their attributing elements was performed by determining the coefficient of relations, proportions and rates that were displayed both as absolute and relative numbers. The numerical series were analyzed by implementing the measures of central tendency (average, median, minimum values, maximum values, interactive ranges) as well as the measures of dispersion (standard deviation). Shapiro-Wilk test was used for determining the rate distribution pattern. In order to test the significance of difference between numerical parameters with irregular rate distribution, Mann Whitney U test was utilized. Pearson Chi square test, Fisher exact test and Fisher Freeman Halton exact tests were used to determine the association between specific attributive features. Spearman coefficient of rank correlation was used to determine the relationship between the numerical variables with an irregular rate distribution.

The level of $p<0.05$ was used to determine the statistical significance.

Results

The study sample consisted of 82 participants, divided into examined group (EG), N=56, and control group (C), N=26.

The comparison between E/H in relation to TSH was consequently 1.91±1.01 *vs*. 8.28±5.66. In 50% of participants in group E or H the average level of TSH was lower than 1.8 for median IQR=1.8 (1.1-2.5) and/or lower than 6.6 for median IQR=6.6 (5.0 to 8.4). We found a significant difference of TSH level between E/H patients (p=0.00001), and between H/C (p=0.00001), with a significantly higher value of this parameter in H. There was no significant difference in TSH level between E/C (p=0.3137) (Table 1).

We made an additional comparison between E/H as well as between E/C and H/C in relation to fT4 and fT3 (Table 1). The average fT4 value in E/H was consequently 1.22±0.14 *vs*. 0.96±0.27. In 50% of patients in groups E and H, the average fT4 level was higher than 1.2 for median IQR=1.2 (1.1-1.3) and relevantly lower than 0.9 for median IQR=0.9 (0.9-1.2). We established a significant difference in fT4 level between patients in E/H (p=0.00001) and between E/C (p=0.00001), with a significantly higher value of this parameter in group E and no significant difference between H/C (p=0.1515) (Table 1).

In E/H the average values of fT3 amounted to 3.62±0.74 *vs*. 3.59±0.94 respectively, with 50% of patients having this value lower than 3.5 *vs*. 3.7, respectively. There was no significant difference in fT3 levels, neither between the two sub-groups E/H (p=0.9865) nor between groups E/C (p=0.5537) and H/C (p=0.2867) (Table 1).

According to the inclusion/exclusion criteria, the participants were divided into examined group (EG) of 56 (68.29%) participants with hypothyroidism and a control group (C) of 26 (31.71%) participants without this disease (Table 2). The women in the examined and the control group were 51 (91.07%) *vs*. 19 (73.08%), with a sex ratio (female/male) of 10.5:1 *vs*. 2.7:1. For $p<0.05$, there was a significant association of the female sex with patients from E group (p=0.0319). Female participants were 2,648 times more frequently present in E compared to C group [OR=3.76 (1.06–13.28) 95% CI].

In both groups (EG/C), the ratio in the range from 18-40 years of age was the largest and accounted for 27 (48.2%) *vs*. 13 (50%), without a significant association with the group to which they belonged (p=0.2571) (Table 2).

The average BMI in EG/C participants was consequently 30.65±6.46 *vs*. 29.11±5.32 where 50% of patients had BMI below 29.5, i.e. below 28.5 (Table 2). There was no significant difference between the two groups in terms of BMI (p=0.3910).

Table 1. Analysis of selected parameters in the three groups

Parameters	Number (N)	Mean± SD	Min/Max	Median (IQR)	p
TSH					
Euthyreosis (E)	24	1.91±1.01	0.5/4.0	1.8 (1.1-2.5)	E/H: Z=-5.589; p=0.00001*
Hypothyreosis (H)	28	8.28±5.66	0.5/23.3	6.6 (5.0-8.4)	E/C: Z=-1.001; p=0.3173
Control (C)	26	2.07±0.77	0.7/3.6	2.1 (1.7-2.7)	H/C: Z=5.583; p=0.00001*
fT4					
Euthyreosis (E)	24	1.22±0.14	0.9/1.6	1.2 (1.1-1.3)	E/H: Z=4.031; p=0.00001*
Hypothyreosis (H)	31	0.96±0.27	0.3/1.5	0.9 (0.9-1.2)	E/C: Z=3.981; p=0.00001*
Control (C)	26	1.07±0.11	0.9/1.3	1.1 (0.9-1.1)	H/C: Z=-1.454; p=0.1515
fT3					
Euthyreosis (E)	23	3.65±0.74	2.7/5.8	3.5 (3.0-3.9)	E/H: Z=-0.017; p=0.9865
Hypothyreosis (H)	30	3.59±0.94	1.0/5.4	3.7 (3.0-4.2)	E/C: Z=0.592; p=0.5537
Control (C)	24	3.39±0.55	2.2/4.3	3.5 (3.1-3.7)	H/C: Z=1.065; p=0.2867

Euthyreosis (E)=TSH<4ulU/ml, Hypothyreosis (H)=TSH≥4ulU/ml, Mann-Whitney U Test=Z,
*significant for p<0,05

Positive family anamnesis was observed in 16 (28.57%) participants in EG and 6 (23.08%) participants in C group (Table 2). The analysis did not point out to a significant association between a positive family anamnesis and the group to which the participants belonged (EG/C) (p=0.6013).

According to the analysis of TPO in EG, there were 42 registered patients (75%) with positive status, whereas no such patients were registered in C group. In EG subgroup with TSH<4ulU/ml (E), there were 17 (70.8%) registered patients with positive anti-TPO status, whereas in the subgroup with TSH≥4ulU/ml there were 25 (78.13%) such registered patients (Pearson Chi-square test: X^2=0.389; df=1; p=0.5329).

A total of 25 (44.64%) participants in EG and 17 (65.38%) participants in C group received statins. Atorvastatin or rosuvastatin was administered to 14 (25%) *vs.* 11 (19.64%) participants in EG, and 9 (34.62%) *vs.* 8 (30.77%) participants in C group. The analysis found no significant association between receiving statins, i.e. the type of statin therapy (atorvastatin/ rosuvastatin), and the group to which the participants belonged (EG/C) for p=0.0804 *vs*. p= 0.8451, respectively (Table 2). Fenofibrate treatment was administered to 5 (6.10%) patients of the total sample, i.e., 3 (5.36%) patients from EG and 2 (7.69%) participants from C group, with no significant association of this type of treatment to the group to which they belonged (p=0.6809) (Table 2).

A comparison of participants with euthyreosis (E), hypothyreosis (H), and control group (C) was made in terms of selected lipid status parameters (cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol) (Table 2). The average cholesterol value in E/H was 4.96±1.03 *vs*. 4.99±1.11 mmol/l, respectively. In 50% of subjects with euthyreosis the average cholesterol level was lower than 4.8 for median IQR=4.8 (4.3-5.3), whereas in the group with hypothyreosis it was lower than 5.0 for median IQR=5.0 (4.4-5.4) mmol/l. We found no significant difference in the cholesterol level between patients of both groups E/H (p=0.5238), i.e., between groups E/C (p=0.1835) and H/C (p=0,3021) (Table 3).

Table 2. Distribution according to groups, general characteristics and therapy

Parameters		Examined group (N=56)	Control group (N=26)	P
General characteristics				
Sex	Women	51 (72.86%	19 (73.08%)	X^2=4.603; df=1; p=0.0319
	Men	5 (8.93%)	7 (26.92%)	
Age groups (years)	18 - 40	27 (48.21%)	13 (50%)	[1]p=0.2571
	41 - 60	12 (21.43%)	2 (7.69%)	
	>61	17 (30.36%)	11 (42.31%)	
BMI	$\overline{X}$ ± SD	30.65±6.46	29.11±5.32	Z=0.858; p=0.3910
	Min/Max	19 / 48	20 / 43	
	Median IQR	29.5 (26-34)	28.5 (26-34)	
Family anamnesis	No	40 (71.43%)	20 (76.92%)	X^2=0.273; df=1; p=0.6013
	Yes	16 (28.57%)	6 (23.08%)	
Therapy				
Statins	No	31 (55.36%)	9 (34.62%)	X^2=3.057; df=1; p=0.0804
	Yes	25 (44.64%)	17 (65.38%)	
Types of statins	Atorvastatin	14 (25%)	9 (34.62%)	X^2=0.038; df=1; p=0.8451
	Rosuvastatin	11 (19.64%)	8 (30.77%)	
	None	31 (55.36%)	9 (34.62%)	-
Fenofibrate	No	53 (94.64%)	24 (92.31%)	[2]p=0.6809
	Yes	3 (5.36%)	2 (7.69%)	

[1]Fisher Freeman Halton test;[2]Fisher Freeman Halton test; Pearson Chi-square test=X^2; Mann-Whitney U Test = Z *significant for p<0,05

Table 3. Analysis of selected lipid status parameters in the three groups

Parameter	Number (N)	Mean± SD	Min/Max	Median (IQR)	p
Cholesterol (mmol/l)					
Euthyreosis (E)	24	4.93±1.03	3.2/7.7	4.8 (4.3-5.3)	E/H: Z=-0.637; p=0.5238
Hypothyreosis (H)	32	4.99±1.11	1.1/7.3	5,0 (4,4-5,4)	E/C: Z=-1.330; p=0.1835
Control (C)	26	5.46±1.35	3.2/8.4	5.3 (4.4-6.5)	H/C: Z=-1.031; p=0.3021
Triglycerides (mg/dL)					
Euthyreosis (E)	24	1.74±0.83	0.6/3.6	1.5 (1.2-2.4)	E/H: Z=-0.430; p=0.6668
Hypothyreosis (H)	32	2.01±1.62	0.6/9.8	1.6 (1.3-2.4)	E/C: Z=1.272; p=0.2034
Control (C)	26	1.58±1.01	0.5/4.7	1.3 (0.9-2.0)	H/C: Z=1.719; p=0.0854
HDL (mmol/L)					
Euthyreosis (E)	24	1.41±0.39	0.8/2.3	1.3 (1.1-1.7)	E/H: Z=-0.033; p=0.9736
Hypothyreosis (H)	32	1.45±0.52	0.6/3.2	1.3 (1.1-1.7)	E/C: Z=-0.786; p=0.4316
Control (C)	26	1.57±0.61	0.8/3.5	1.3 (1.2-1.9)	H/C: Z=-0.547; p=0.5842
LDL (mmol/L)					
Euthyreosis (E)	23	2.81±0.82	1.5/5.0	2.7 (2.4-3.3)	E/H: Z=-0.484; p=0.6280
Hypothyreosis (H)	30	2.90±0.73	1.5/4.6	2.9 (2.3-3.5)	E/C: Z=-1.159; p=0.2461
Control (C)	24	3.09±1.08	1.2/5.2	3.1 (2.3-3.9)	H/C: Z=-0.887; p=0.3756

Euthyreosis (E)= TSH<4ulU/ml; Hypothyreosis (H)= TSH≥4ulU/ml; Mann-Whitney U Test = Z, *significant for p<0,05

In E/H the average triglycerides level was 1.74±0.83 *vs.* 2.01±1.62 with 50% of patients that had values lower than 1.5 mg/d for median IQR=1.5 (1.2-2.4) for E and consequently lower than 1.6 mg/d for median IQR=1.6 (1.3-2.4) in H. There was no significant difference in triglyceride levels between patients of both groups E/H (p=0.6668) as well as between groups E/C (p=0.2034) and H/C (p=0.0854) (Table 3).

The analysis found no significant difference between the two subgroups of E/H in relation to HDL-cholesterol and LDL-cholesterol levels for p=0.9802 *vs.* p=0.6344, respectively. In terms of these two parameters of lipid status there was no significant difference neither between E/C (p=0.4316) and H/C (p=0.5842) for HDL nor between E/C (p=0.2464) and H/C groups (p=0.3756) for LDL (Table 3).

A non-parameter correlation was performed between each of the elements of the lipid status (total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol) with each of the following parameters, such as: TSH, fT4, fT3 and anti-TPO. A significant linear negative weak correlation was established between fT4 and cholesterol (Spearman Rank order correlations: R (81)=-0.231; p=0.038) - cholesterol level increased as fT4 level decreased, and fT4 and triglycerides (R (81)=-0.177; p=0.011). We observed no significant correlation in the other combinations (Table 4).

Table 4. Non-parameter correlation among selected parameters

Parameters	**Spearman Rank order correlations**			
	Total Cholesterol	**Triglycerides**	**HDL cholesterol**	**LDL cholesterol**
TSH	R (82)=-0.029; p=0.795	R (82)=0.144; p=0.196	R (82)=-0.034; p=0.756	R (77)=-0.028; p=0.804
fT4	R (81)=-0.231; p=0.038*	R (81)=-0.177; p=0.011*	R (81)=-0.025; p=0.823	R (81)=-0.063; p=0.590
fT3	R (81)=-0.122; p=0.277	R (81)=-0.164; p=0.142	R (81)=-0.047; p=0.674	R (81)=-0.047; p=0.516
Anti-TPO	R (82)=-0.213; p=0.055	R (82)=0.133; p=0.232	R (82)=-0.107; p=0.340	R (77)=-0.202; p=0.078

*significant for p<0,05

Discussion

Back in the 1930s Mason *et al.* noticed a connection between cholesterol level and thyroid hormones [1]. Since then, various authors have indicated that the dysfunction of the thyroid gland, i.e. its reduced activity (overt or subclinical hypothyroidism), carries its repercussions on the lipid profile of a patient and referred to the analogy between the different lipid fractions, their metabolism, and the incidence of occurrence of cardiovascular diseases and hypothyroidism.

The thyroid hormones are responsible for regulation of a wide range of metabolic processes, including the metabolism of lipoproteins, as one of the direct risk factors for cardiovascular events. Even within the normal range of TSH levels, an increase of TSH level initiates a linear increase in the total cholesterol, LDL-cholesterol and triglyceride levels on one hand, and a linear decrease in HDL cholesterol, on the other [3].

The effects of subclinical hypothyroidism upon the level of lipids and lipoproteins were variably evaluated in different studies. Some studies exhibited changes similar to those observed in patients with overt hypothyroidism, while other studies have not shown differences in patients with subclinical hypothyroidism compared to those in the control group of participants. These differences are probably related to the diversity of patients that were included in the study in terms of age, ethnicity, duration of the dysfunction of the thyroid gland and the presence of other metabolic abnormalities, such as insulin resistance [4].

In the study of Satpathy *et al*., pure hypercholesterolemia was most commonly present in patients with hypothyroidism, having significantly higher concentrations of LDL-cholesterol and apolipoprotein B (56%), followed by combined hypercholesterolemia and hypertriglyceridemia (34%) as well as isolated hypertriglyceridemia (1.5%), whereas lipid abnormalities were absent in only 8.5% of the respondents [5].

The mechanisms for the development of hypercholesterolemia in hypothyroidism include reduced fractioned clearance of LDL-cholesterol and a reduced number of LDL receptors in the liver in addition to the reduced activity of the receptors. In the case of a thyroid gland disease, dyslipidemia coexists with different metabolic abnormalities, causes insulin resistance predisposition and oxidative stress, leading all these instances towards a vicious circle. These associations, coupled with the thyroid hormone-induced hemodynamic changes, may explain the increased risk of coronary artery disease and the risk of cerebral ischemia in patients with either overt or subclinical form of hypothyroidism [5]. All these abnormalities in the metabolism of the lipids predispose development of an atherosclerotic coronary arterial disease [3, 6].

Thermogenic effects of the thyroid hormones, especially of T3, are also well known. Hypothyroid patients produce less heat and they are cold intolerant. The administration of thyroid hormone leads to an increased consumption of oxygen, acceleration of the metabolic processes, such as lipolysis, ATP utilization, thermogenesis, and increases the utilization of the energy reserves, such as the lipids from the adipose tissue [7].

Disruption of the lipid metabolism in hypothyroidism is one of the leading endocrine causes for the development of non-alcoholic fatty liver disease (NAFLD). It is well known that low levels of the thyroid hormones are most commonly associated with hypometabolism. This condition is defined by an increase in the body weight, reduced idle energy consumption and reduced gluconeogenesis and reduced lipolysis. Maybe hypothyroidism can directly or indirectly contribute to NAFLD through the three known mechanisms: accumulation of lipids in the liver, inflammatory status accompanied by oxidative stress and, consequently, impaired regeneration of the liver [8].

In daily clinical practice, it is to be noted that the dyslipidemia and hypothyroidism are in a close correlation and in case there are laboratory indicators for its affection, one needs to search for other signs and symptoms of alternation of the thyroid function. Secondary dyslipidemia, often present in the overt hypothyroidism, regresses during a thyroid substitution treatment. On the other hand, in the case where hypothyroidism simultaneously coexists with a primary dyslipidemia, we have a complete overview of a lipid alternation where the treatment does not fully repair the lipid profile. Subclinical hypothyroidism and lipid metabolism are still a subject of debates, but it is well known that treatment with levothyroxine normalizes the lipid levels in these patients [9].

According to Pearce [10], serum levels of total cholesterol and LDL-C increased in approximately 30% of patients with overt hypothyroidism, whereas more than 90% of patients with overt hypothyroidism had dyslipidemia. Also, Duntas and Brenta indicated that total cholesterol and LDL-cholesterol increased with the increase of TSH, which was not the case in our study [2]. The average cholesterol level in our E/H groups was consequently 4.96±1.03 *vs*. 4.99±1.11 mmol/l. We found no significant difference ($p>0.05$) of cholesterol levels between patients in the two groups E/H, as well as between groups E/C and H/C. The analysis found no significant difference between the two subgroups of E/H in relation to HDL-cholesterol and LDL-cholesterol levels, neither between E/C and H/C for HDL nor E/C and H/C for LDL-cholesterol. There was no significant difference in the triglycerides level between patients of both groups E/H as well as between groups E/C and H/C. In the study of Pearce, the level of triglycerides was in the normal range or increased in those with hypothyroidism [10]. An absence of the differences that were expected, especially those of

total cholesterol and LDL-cholesterol levels between the examined and the control group, might be attributed to the poor lipid control among our general population and the control group derived from it. At the same time, it is possible that the bad compliance of those patients who received statin therapy had a significant influence on the unsatisfactory lipid regulation. In the same context, the regular controls of the patients with hypothyroidism may have their own positive effects and improve the lipid profile in this group of subjects. It is especially important to point out the fact that the majority of the case studies following the lipid profile *vs*. thyroid status, exhibit no consequentiality about the use of statin therapy on the included participants or not. For example, the study of Risal *et al.*, [11] contains no data whether the patients were on statin therapy or not. In the multi-centric research study of T. Tagmi *et al.*, [14], patients on treatment with antilipemic and patients with and without treatment were simultaneously included, whereas the study of Teixeira *et al.*, [7] excluded patients that used lipid therapy.

Among our patients included in the study, a total of 44.64% of participants in EG and 65.38% of those in C group received statins. Atorvastatin or rosuvastatin was administered to 25% *vs*. 19.64% of participants in EG, and to 34.62% *vs*. 30.77% participants in C group. Atorvastatin probably has an advantage over rosuvastatin due to its long-term presence in the Republic of North Macedonia and its more affordable retail price. A therapy aimed at increased triglyceride levels - fenofibrate was received by only 6.10% of the participants of the total sample.

Our study determined a significant difference in the TSH levels between patients of E/H and H/C groups for a significantly higher value of this parameter in H group. There was no significant difference in the TSH levels between E/C. In addition, we determined a significant difference in fT4 levels between patients of E/H and between E/C, with a significantly higher value of this parameter in E group, whereas there was no significant difference between H/C. There was no significant difference in fT3 levels neither between the two subgroups E/H nor between groups E/C and H/C. These results are expected because in the treatment of patients with hypothyroidism, actually the correct TSH level is a guideline for modeling the thyroid substitution therapy, which, in clinical practice, we tend to target towards values between 1-2 mU/ml, whereas FT4 level needs to be in the upper third of the normal value. In elderly patients with ischemic heart disease, the dosage maintenance is often lower than usual and TSH is closer to the upper limit of the normal value.

A significant linear negative weak correlation was established between fT4 and cholesterol, i.e. cholesterol level increased as fT4 level decreased, and fT4 and triglycerides. We observed no significant correlation in the other combinations. The outcome that we obtained was in line with that of P. Risal *et al.*, [11], who found a significant negative correlation between the total cholesterol and fT4. At the same time, these authors obtained a significant positive correlation between triglycerides and TSH, an outcome that we did not determine in our research study. The study of Huang *et al*., [12] established that FT4 was in a positive correlation with HDL-cholesterol values. On the other hand, FT3 level was in a negative correlation with HDL-cholesterol levels, whereas TSH was in a negative correlation with HDL-cholesterol [12]. In our study, we found no correlation of HDL cholesterol, total cholesterol and any of the thyroid hormones. The efficiency of the substitutional therapy with L-T4 for normalizing the lipid status in patients with hypothyroidism was proven and more evident in patients with overt hypothyroidism. Although there is no consensus about the effect of lipid reduction as a result of the substitutional therapy with L-T4 in patients with subclinical hypothyroidism, some studies revealed clear benefits of the administering L-T4 for the reduction of triglycerides and LDL-cholesterol in patients with subclinical hypothyroidism with TSH < 10 mIU/L [2].

The analyses that we conducted revealed a positive family anamnesis for thyroid disease in 28.57% of participants in EG and 23.08% of those in C group. It is known that thyroid gland dysfunction is related to the changes of body weight. Subclinical and overt hypothyroidism are often related to an increase in body weight, reduced thermogenesis and metabolic rate. In a study of individuals over 40 years of age with a body mass index (BMI) of at least 30.0 kg/m2, subclinical and overt hypothyroidism were correlated with a higher BMI and a higher prevalence of obesity. These findings support the clinical proof that even a mild dysfunction of the thyroid gland is related to significant changes of the body weight and it is possibly a risk factor for overweight and obesity [13]. On the other hand, the multicentric study of Tagmi *et al*., did not find a statistically significant difference between BMI of patients with overt and subclinical hypothyroidism [14].

According to the anti-TPO analysis, 75% of the total number of patients with hypothyroidism in EG group had a positive status in terms of Hashimoto thyroiditis. In the United States of America, the annual incidence among the adult population is estimated at 3.5 per 1,000 in females and 0.8 per 1,000 in males [15]. Among European research studies, the Danish study of Hashimoto thyroiditis is of interest because it exhibited a consistency rate of 55% in monozygotic twins, compared to only 3% in dizygotic twins. This data suggest that 79% of the predisposition for the development of Hashimoto thyroiditis is attributed to genetic factors, whereas 21% to the environmental impact and sex hormones [16].

In our study, we established a significant association of the female sex with patients of EG group (91.07%), which is in correlation with the global trend, where hypothyroidism is more common among the female population. In general, the prevalence of thyroid gland diseases is 2-8 times higher in women. Among the population of more adult patients evaluated in the USA, the incidence of hypothyroidism is estimated at 0.5% in women, whereas a different study of Vanderpump that comprised women aged between 38 and 93 years, exhibited a prevalence up to 9.3% [17]. In Europe, the prevalence of hypothyroidism is also lower among men than among women; males, minimum 1.2% and maximum 8.5%; women, minimum 3.8% and maximum 17.5% [18].

Conclusion

The comparative analysis between the examined and the control group of patients, as well as between the two subgroups (according to TSH levels: TSH<4ulU/ml and TSH≥4ulU/ml), did not determine a significant difference in the lipid parameters levels in relation to selected parameters of the lipid status (total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol).

The performed non-parameter correlation between each of the elements of the lipid status (total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol) with each of the following parameters: TSH, fT4, fT3 and anti-TPO determined a significant linear negative weak correlation between levels of fT4 and cholesterol and between FT4 and triglycerides.

These three examined groups did not differ in lipid status, although dyslipidaemia is an expected finding in untreated hypothyroidism. In our study, a large percentage of hypothyroid patients were on statin therapy, which most likely influenced on reduction of lipid fraction values in all groups, especially in the hypothyroid group before therapy. Hence, the recommendation is that in newly diagnosed patients with hypothyroidism and dyslipidemia, before starting statin therapy, levothyroxine should be initially administered and an euthyroid state should be reached. The study showed that even under conditions of concomitant use of statins, cholesterol and triglyceride levels showed a negative correlation with fT4 and anti-TPO.

Conflict of interest statement. None declared.

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