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Serum Lipid Transfer Proteins in Hypothyreotic Patients Are Inversely Correlated with Thyroid-Stimulating Hormone (TSH) Levels

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Background: Plasma cholesteryl ester transfer protein (CETP) activity is often decreased in patients with hypothyroidism, whereas less is known about the phospholipid transfer protein (PLTP). We aimed to evaluate simultaneously serum CETP and PLTP activity in patients diagnosed with hypothyroidism.

Material/Methods: The selection criteria for control group members (without thyroid dysfunction) in this case to case study were levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides similar to those in study group patients (101 patients diagnosed with hypothyroidism). Serum CETP and PLTP activities were measured by homogenous fluorometric assays using synthetic donor particle substrates.

Results: Serum CETP and PLTP activities in hypothyreotic patients were lower ($p<0.001$) compared with those in healthy subjects. This lowering was associated with significant changes in HDL-C subclasses: decrease in HDL_2- and increase in HDL_3 cholesterol levels. Multiple linear regression analyses adjusted for age, sex, body mass index, smoking habits, and alcohol drinking showed a strong association between hypothyroidism and activity of lipid transfer proteins. A linear inverse relationship between thyroid-stimulating hormone (TSH) and CETP ($r=-0.21$; $p<0.01$) and between TSH and PLTP ($r=-0.24$; $p<0.001$) was shown. There also was a positive correlation ($p<0.001$) between CETP and HDL_2 cholesterol ($r=0.27$) and between PLTP and HDL_2 cholesterol ($r=0.37$). A negative correlation between CETP and HDL_3 cholesterol ($r=-0.22$: $p<0.01$) and between PLTP and HDL_3 cholesterol ($r=-0.24$; $p<0.001$) has been demonstrated as well.

Conclusions: The decreased HDL_2 and increased HDL_3 cholesterol levels in subjects with hypothyroidism are consequences of decreased activity of lipid transfer proteins. These changes are early symptoms of lipid disturbances in hypothyroidism.

MeSH Keywords: Cholesterol Ester Transfer Proteins • Phospholipid Transfer Proteins • Thyrotropin

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Background

Hypothyroidism is known to be associated with premature atherosclerosis and increased frequency of cardiovascular events [1–3]. The increased cardiovascular risk in hypothyroid patients is mainly associated with hypercholesterolemia and an increased low-density lipoprotein cholesterol (LDL-C) level, caused by a decrease in the number of LDL-C receptors in the liver [4–6]. However, in hypothyroid patients increased high-density lipoprotein cholesterol (HDL-C) also has been observed, as well as changes in size and composition of plasma HDL-C [7–9]. Lately, it has been suggested that subclinical hyperthyroidism may be not associated with cardiovascular mortality or disorders, except for development of atrial fibrillation [10,11]. Regardless of possible impact on atherosclerosis progression, hypothyroidism is associated with changes in lipoprotein metabolism, including not only lipid disturbances, but also abnormal plasma protein levels. An increase in apolipoprotein B and apolipoprotein A [12] and changes in lipid transfer protein activity [4,5] in hypothyreotic patients were observed. Lipid transfer proteins such as cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) are responsible for the formation of mature forms of HDL-C and regulate the concentration, size, and composition of the circulating HDL particles [13,14]. Moreover, in some studies CETP activity was positively correlated with total cholesterol (TC), LDL-C, and non-HDL-C levels, whereas PLTP activity was related to body mass index (BMI) and serum glucose concentration [7,8]. All these metabolic dependences have been influenced by dysfunction of thyroid gland. Increased CETP or PLTP mass/activity is considered to be a pro-atherosclerotic factor, mainly related to the decrease in HDL-C level, but also to increased pro-oxidant and pro-inflammatory potential [16–18]. A decrease in CETP or PLTP activity is intended to have anti-atherosclerotic properties, mainly by causing an increase in circulating, small, dense HDL_3 particles with increased antioxidative activity and increased reverse cholesterol transport efficiency [19,20].

In some observations CETP activity was decreased in patients with hypothyroidism [21,22]. Less is known about the PLTP activity in patients with dysfunction of the thyroid gland. The aim of this study was to evaluate simultaneously serum CETP and PLTP activity in patients diagnosed with hypothyroidism (studied group). The selection criteria for control group members (without thyroid dysfunction) in this case to case study were levels of TC, LDL-C, HDL-C, and triglycerides (TGs) similar to those in study group patients. The next criteria were the following: the same gender, similar BMIs, smoking habits, and alcohol consumption. The differences in lipid transfer proteins between the studied and control groups were related to the level of thyroid-stimulating hormone (TSH).

Material and Methods

Subjects

The study was performed in the group of 202 residents of Lower Silesian region in Poland: 166 women aged 59.6±10.4 years and 36 men aged 57.9±10.1 years. There were 101 patients (83 women and 18 men) diagnosed with hypothyroidism (HT group) and 101 healthy volunteers (83 women and 18 men) constituting the control group (euthyreotic [ET] group).

In all subjects, anthropometric data (body weight, height) were collected using calibrated equipment and standardized methodology. BMI was estimated as the ratio of weight to height squared (kg/m^2). In the overall population, the median BMI value was typical for overweight. About 23% of women and 33% of men were tobacco smokers, and about 58% of women and 77% men reported moderate alcohol consumption (women: 1 alcohol unit per day; men: 1–4 alcohol units per day).

Because the selection criteria for control group members matched to study patients included the same sex and similar age, BMI, TC, LDL-C, HDL-C, and TGs, these parameters did not differ significantly between HT and ET groups. Also, the percentages of smokers or alcohol drinkers among females and males were similar in the studied and control groups. The TSH level was higher in the study group in comparison with controls (Table 1). Only 10 hypothyreotic women were taking L-thyroxine substitution therapy; the remaining patients began treatment after this study.

The study was approved by the Polish Ethics Committee (No. KB-443/2006).

Biochemical measurements

Venous blood was taken from subjects after 12 hours of fasting and centrifuged at 1000 g for 20 minutes at 4°C. Serum samples were stored at a temperature of –80°C. The thyrotropin in serum was determined using the ROCHE test by electrochemiluminescence method (normal value: 0.5–4.0 µIU/mL). Serum TC, TGs, and HDL-C were measured using the SPINREACT (SantEsteve De Bas, Girona, Spain) enzymatic assay. LDL-C was estimated among patients with a TG concentration lower than 4.52 mmol/L (400 mg/dL) by means of the Friedewald formula. The QUANTOLIP® HDL (Technoclone GmbH, Vienna, Austria) precipitation test was used to measure HDL_2 and HDL_3 cholesterol (HDL_2-C and HDL_3-C). The non-HDL-C was calculated as a difference between TC and HDL-C concentrations. Serum CETP and PLTP activities were determined using the CETP Activity Assay Kit and the PLTP Activity Assay Kit (BioVision Research Products, 2455-D Old Middlefield Way, Mountain View, California, USA) with the fluorescence spectrophotometer HITACHI F-2500. The

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Table 1. The characteristic of studied groups. Hypothyreotic patients group to healthy subjects group comparison.

		Hypothyreotic patients	Healthy subjects
Whole group (n)		**101**	**101**
Age (yr)	Mean ±SD	59.6±10.4	57.9±10.1
BMI (kg/m^2)	Median (IQR)	27.1 (23.3; 31.4)	27.7 (24.8; 31.6)
Smokers	n (%)	29 (28.7)	22 (21.7)
Moderate drinkers	n (%)	60 (59.4)	65 (64.3)
Type 2 diabetes mellitus	n (%)	8 (8)	0 (0)
Coronary heart disease	n (%)	7 (7)	0 (0)
Total C (mmol/L	Mean ±SD	5.62±1.16	5.66±1.16
LDL-C (mmol/L)	Mean ±SD	3.33±1.33	3.40±1.02
HDL-C (mmol/L)	Mean ±SD	1.49±0.36	1.58±0.39
Non-HDL-C (mmol/L)	Mean ±SD	4.13±1.11	4.08±1.18
TG (mmol/L)	Mean ±SD	1.40±0.56	1.50±0.81
TSH (µIU/ml)	Mean ±SD	6.89±8.46***	2.57±5.14
	Median (IQR)	5.08 (4.32; 6.73)	1.62 (1.01; 2.17)
Female group (n)		**83**	**83**
Age (yr)	Mean ±SD	59.1±10.9	57.6±10.6
BMI (kg/m^2)	Median (IQR)	26.4 (22.7; 30.6)	27.2 (24.0; 31.2)
Smokers	n (%)	22 (21.7)	17 (16.8)
Moderate drinkers	n (%)	48 (47.5)	49 (48.5)
Total C (mmol/L)	Mean ±SD	5.71±1.16	5.57±1.08
LDL-C (mmol/L)	Mean ±SD	3.37±1.35	3.30±0.93
HDL-C (mmol/L)	Mean ±SD	1.53±0.37	1.61±0.35
Non-HDL-C (mmol/L)	Mean ±SD	4.18±1.12	3.96±1.10
TG (mmol/L)	Mean ±SD	1.38± 0.57	1.45±0.79
TSH (µIU/ml)	Mean ±SD	7.21± 9.30***	2.75± 5.66
	Median (IQR)	5.10 (4.27; 6.74)	1.62 (0.96; 2.44)
Male group (n)		**18**	**18**
Age (yr)	Mean ±SD	62.0±7.7	59.1±7.8
BMI (kg/m^2)	Median (IQR)	28.5 (23.6; 31.5)	29.3 (27.7; 33.0)
Smokers	n (%)	7 (6.9)	5 (4.9)
Moderate drinkers	n (%)	12 (33.3)	16 (44.4)
Total C (mmol/L)	Mean ±SD	5.21± 1.12	5.94±1.38
LDL-C (mmol/L)	Mean ±SD	3.10±1.27	3.84±1.27
HDL-C (mmol/L)	Mean ±SD	1.29± 0.25	1.45±0.53
Non-HDL-C (mmol/L)	Mean ±SD	3.91±1.10	4.61±1.41
TG (mmol/L)	Mean ±SD	1.47±0.55	1.72±0.88
TSH (µIU/ml)	Mean ±SD	5.41±1.19	1.76±0.61
	Median (IQR)	4.91 (4.61; 5.96)	1.68 (1.36; 2.03)

*** Differences statistically significant in comparison to healthy people; p<0.001. C – cholesterol; LDL – low density lipoprotein; HDL – high density lipoprotein; TG – triglycerides; TSH – thyrotropin; SD – standard deviation; IQR – interquartile range; n – number of people.

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Table 2. Serum lipid transfer protein activity in hypothyreotic and healthy subjects.

		Hypothyreotic patients	Healthy subjects
Total group (n)		**101**	**101**
CETP (nmol/ml/h)	Mean ±SD	35.35±12.00***	59.70±13.59
PLTP (nmol/ml/h)	Mean ±SD	37.25±11.10***	77.24±18.85
HDL_2-C (mmol/L)	Mean ±SD	0.35±0.19***	0.65±0.33
HDL_3-C (mmol/L)	Mean ±SD	1.06±0.28***	0.92±0.18
HDL_2-C/HDL_3-C	Mean ±SD	0.41±0.15***	0.73±0.38
Female group (n)		**83**	**83**
CETP (nmol/ml/h)	Mean ±SD	35.94±12.19***	60.00±13.36
PLTP (nmol/ml/h)	Mean ±SD	37.20±11.08***	78.45± 18.83
HDL_2-C (mmol/L)	Mean ±SD	0.44±0.15***	0.67±0.30
HDL_3-C (mmol/L)	Mean ±SD	1.08±0.29***	0.93±0.18
HDL_2-C/HDL_3-C	Mean ±SD	0.43±0.13***	0.75±0.37
Male group (n)		**18**	**18**
CETP (nmol/ml/h)	Mean ±SD	32.65±10.95***	58.31±15.12
PLTP (nmol/ml/h)	Mean ±SD	37.44± 11.47***	71.67± 18.43
HDL_2-C (mmol/L)	Mean ±SD	0.32±0.09**	0.56±0.43
HDL_3-C (mmol/L)	Mean ±SD	0.97±0.20	0.89±0.19
HDL_2-C/HDL_3-C	Mean ±SD	0.34±0.04**	0.63±0.40

, * statistically significant differences between groups of hypothyreotic and healthy subjects; ** p<0.01, *** p<0.001.
CETP – cholesteryl ester transfer protein; PLTP – phospholipid transfer protein; HDL_2-C – subfraction of high density lipoprotein 2 cholesterol; HDL_3-C – subfraction of high density lipoprotein 3 cholesterol; SD – standard deviation; n – number of people.

CETP assay uses a synthetic fluorescent CE donor particle and apo-B-containing lipoprotein acceptor particles. CETP-mediated transfer was determined by an increase in fluorescent intensity in the acceptor. The serum PLTP assay uses a fluorescent phospholipid donor and a synthetic acceptor, and again, PLTP-mediated transfer was measured by an increase in fluorescent intensity. For both assays, the intra-assay and inter-assay coefficients of variation ranged from 11% to 15%, similar to fluorometric assay procedures that are described by others [23].

Statistical analysis

Results were presented as mean ± standard deviation or median and interquartile range. In the case of normal distribution, t-tests were applied, and a statistical significance between means was calculated using analysis of variance and post hoc Tukey's (checked by least significant difference) tests. In case of qualitative variables, nonparametric tests were used. The association between presence of hypothyroidism and lipid metabolism was analyzed in the multivariable linear regression model. The independent variable was defined as diagnosis of hypothyroidism, and was individually analyzed in relation to lipid transfer protein and lipid parameters. The following variables were included as potential confounders: age, BMI (BMI ≤25 kg/m^2 was treated as normal, BMI >25 kg/m^2 as overweight, BMI >30 kg/m^2 as obesity), tobacco use (smokers or nonsmokers), alcohol consumption (moderate drinkers or nondrinkers), and coexistence of coronary heart disease or diabetes mellitus (present or absent). Three-way analysis of variance (using presence of hypothyroidism, smoking habits, and alcohol consumption as independent factors) was also applied with one-dimensional or multidimensional significance tests. Correlations between variables were checked using Spearman coefficient. P values less than 0.05 were accepted as statistically significant. All analyses were conducted using the STAT statistical package, version 12.0 (STATISTICA 12 PL. StatSoft).

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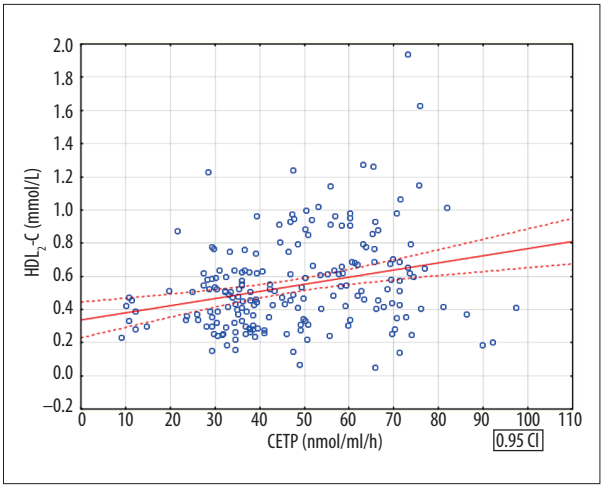

Figure 1. Relationship between cholesteryl ester transfer protein (CETP) activities and high-density lipoprotein 2 (HDL_2) cholesterol subfraction levels (r=0.2732; p<0.001). CI – indicates confidence interval; r – correlation coefficient.

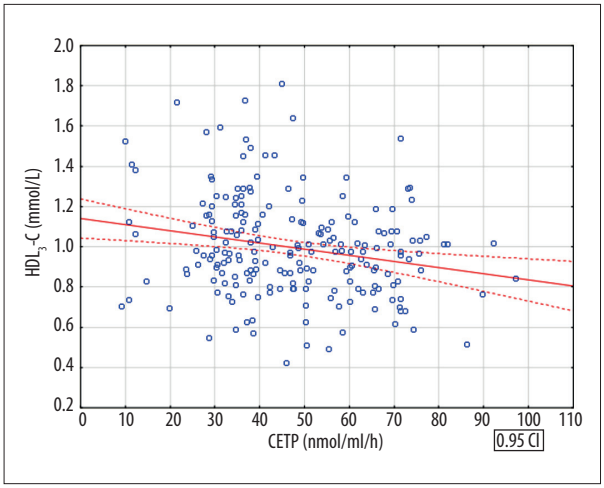

Figure 3. Relationship between cholesteryl ester transfer protein (CETP) activities and high-density lipoprotein 3 (HDL_3) cholesterol subfraction levels (r=–0.2172; p<0.01). CI – indicates confidence interval; r – correlation coefficient.

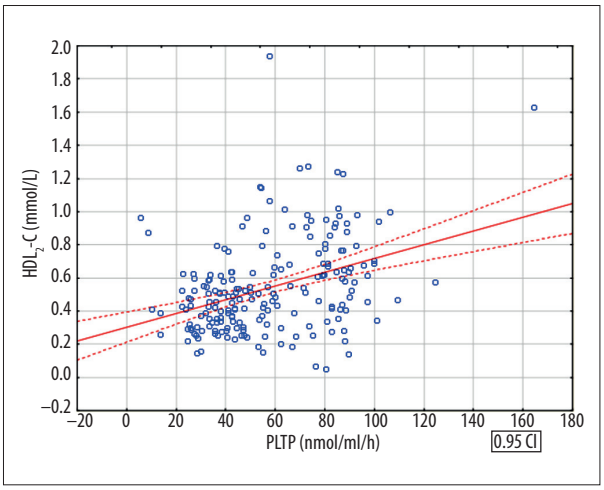

Figure 2. Relationship between phospholipid transfer protein (PLTP) activities and high-density lipoprotein 2 (HDL_2) cholesterol subfraction levels (r=0.3737; p<0.001). CI – indicates confidence interval; r – correlation coefficient.

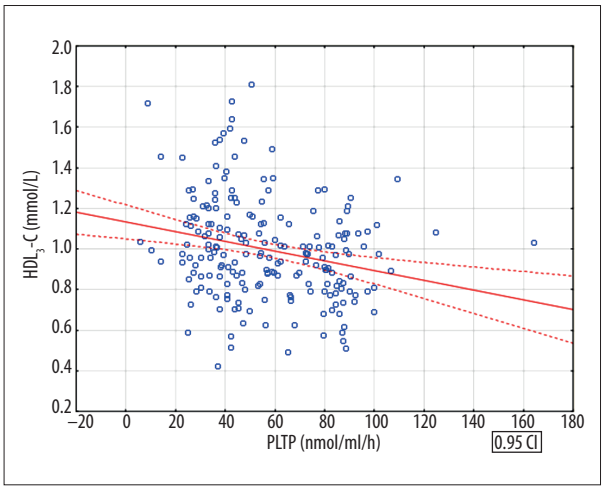

Figure 4. Relationship between phospholipid transfer protein (PLTP) activities and high-density lipoprotein 3 (HDL_3) cholesterol subfraction levels (r=–0.2438; p<0.001). CI – indicates confidence interval; r – correlation coefficient.

Results

In the total population of 202 people, the linear, positive correlations between TSH and TC (r=0.21; p<0.01), LDL-C (r=0.16; p<0.05), non-HDL-C (r=0.21; p<0.01), and TGs (r=0.18; p<0.05) were shown. There were no linear correlations between TSH and HDL-C (p=0.9796), HDL_2-C (p=0.4574), or HDL_3-C (p =0.3391). On the other hand, at similar concentrations of serum lipids (TG, TC, LDL-C, non-HDL-C, and HDL-C), the differences between hypothyreotic and control groups (among females and males) occurred in HDL subclasses (Table 1). In hypothyreotic patients, the HDL_2-C concentrations were lower and the HDL_3-C concentrations were higher compared with those observed in healthy subjects (Table 2).

Serum CETP and PLTP activities in hypothyreotic patients were lower (p<0.001) in comparison with those in healthy subjects. This lowering in the proteins' activities was associated with a significant decrease in the HDL_2-C level and an increase in the HDL_3-C level; however, in men the increase in HDL_3-C was not statistically significant (Table 2).

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Table 3. Association between presence of hypothyroidism and serum activity of CETP and PLTP or lipids in studied population.

Effect		β-coeficient (95% CI)
Hypothyroidism		CETP β-coefficient (95% CI)
	p=0.0003	0.62 (0.28 to 0.95)
		PLTP β-coefficient (95% CI)
	p=0.0000001	0.81(0.52 to 1.10)
		Total C β-coefficient (95% CI)
	p=0.07	0.42 (–0.03 to 0.89)
		LDL-C β-coefficient (95% CI)
	p=0.06	0.42 (–0.02 to 0.87)
		HDL-C β-coefficient (95% CI)
	p=0.13	0.34 (–0.11 to 0.80)
		HDL2-C β-coefficient (95% CI)
	p=0.06	0.40 (–0.02 to 0.83)
		HDL3-C β-coefficient (95% CI)
	p=0.65	0.10 (–0.33 to 0.53)
		Non-HDL-C β-coefficient (95% CI)
	p=0.18	0.31 (–0.14 to 0.78)
		TG β-coefficient (95% CI)
	p=0.71	–0.08 (–0.54 to 0.37)

Multiple linear regression analysis adjusted for age, sex, BMI, smoking habits and alcohol drinking. CETP – cholesteryl ester transfer protein; PLTP – phospholipid transfer protein; C – cholesterol; LDL – low density lipoprotein; HDL – high density lipoprotein; HDL_2-C – HDL_2 cholesterol subfraction; HDL_3-C – HDL_3 cholesterol subfraction; TG – triglycerides; SD – standard deviation; CI – confidence interval, p-value in bold letter indicates statistical significance.

In linear regression analysis a positive correlation between CETP and HDL_2-C (r=0.27; p<0.001) and between PLTP and HDL_2-C (r=0.37; p<0.001) as well as a negative correlation between CETP and HDL_3-C (r=–0.22; p<0.01) and between PLTP and HDL_3-C (r=–0.24; p<0.001) has been demonstrated (Figures 1–4).

Multiple linear regression analyses adjusted for age, sex, BMI, smoking habits, and alcohol drinking showed an association between hypothyroidism and activity of lipid transfer proteins. The significant beta coefficients (95% confidence intervals) for CETP (p<0.0003) and PLTP (p<0.0000001) were estimated. Simultaneously, no statistically significant association between thyroid function and lipid classes was observed (Table 3). At the same time the linear inverse relationship between TSH and CETP (r =–0.21; p<0.01) and between TSH and PLTP (r=–0.24; p<0.001) was shown (Figures 5, 6).

The high values of beta coefficients (until 0.82) estimated for impact of smoking on lipids and the statistically significant impact of alcohol consumption on TGs and HDL_3-C (beta coefficient=0.17; p<0.05) were the reason for exclusion of smoking and alcohol drinking as confounders and treating them, together with a thyroid dysfunction, as independent variables.

Three-way analysis of variance showed that activities of CETP and PLTP, being dependent on thyroid function, were not influenced by single confounders such as smoking or alcohol drinking. However, CETP activity was influenced by the interaction between smoking and moderate alcohol drinking (Table 4).

Discussion

Hypothyroidism is considered to be a condition associated with an increased cardiovascular risk because of changes in lipid metabolism [10], plasma viscosity [3], and pro-oxidative and inflammatory potential [1]. Because hypothyroidism has pro-oxidative and inflammatory potential, it may trigger carcinogenesis [24,25]. The linear positive correlations observed in this study between TSH and TC, LDL-C, non-HDL-C, and TGs are consistent with the proatherogenic potential of hypothyroidism. In fact, even within the normal range of TSH values, a linear increase in TC, LDL-C, and TGs has been observed with increasing TSH [26]. In this study, the TSH concentration in the studied group was moderately elevated, reaching a maximal value of 7 μIU/mL. Because of absence of clinical symptoms, subhypothyroidism rather than hypothyroidism could

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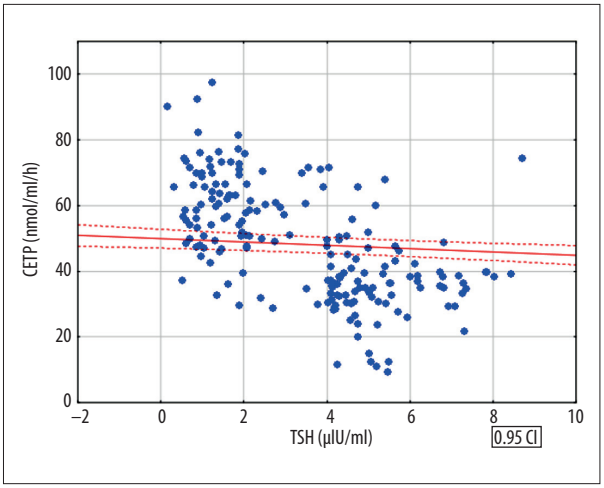

Figure 5. Relationship between thyroid-stimulating hormone (TSH) levels and cholesteryl ester transfer protein (CETP) activities (r=–0.2072; p<0.01). CI – indicates confidence interval; r – correlation coefficient.

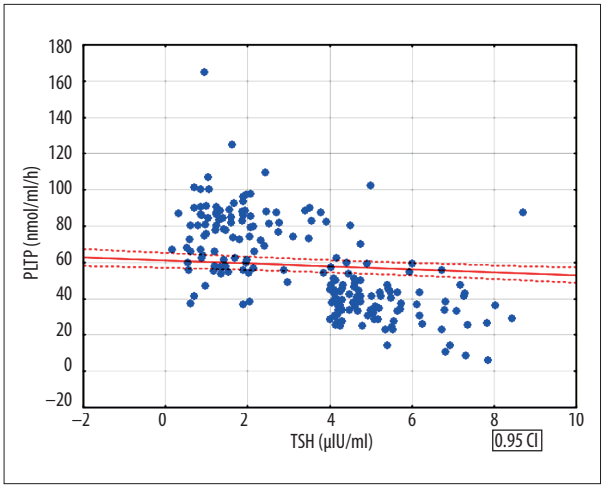

Figure 6. Relationship between thyroid-stimulating hormone (TSH) levels and phospholipid transfer protein (PLTP) activities (r=–0.2357; p<0.001). CI – indicates confidence interval; r – correlation coefficient.

Table 4. The effect of smoking, alcohol drinking and hypothyroidism and interaction between these factors on their effect on CETP and PLTP activity.

Effect	F	p
Tests of significance for CETP		
Smoking	0.005	0.946
Drinking	0.710	0.399
Hypothyroidism	10.879	**0.001**
Smoking* drinking	6.853	**0.009**
Smoking* hypothyroidism	0.002	0.965
Drinking* hypothyroidism	1.927	0.165
Smoking* drinking* hypothyroidism	0.213	0.644
Tests of significance for PLTP		
Smoking	0.657	0.418
Drinking	0.041	0.839
Hypothyroidism	30.740	**0.000**
Smoking* drinking	0.127	0.721
Smoking* hypothyroidism	0.893	0.345
Drinking* hypothyroidism	0.003	0.955
Smoking* drinking* hypothyroidism	0.390	0.532

A spreadsheet is a three-way analysis of variance. F – F-test value for the respective effects; p – the probability level of p; CETP – cholesteryl ester transfer protein; PLTP – phospholipid transfer protein.

be diagnosed. The main novelty of this study is an observation that moderate hypothyroidism is associated with simultaneous decrease in CETP and PLTP activities. This association does not depend on lipid pattern, because the HT patients displayed lower lipid transfer proteins compared with healthy subjects, whereas TC, LDL-C, HDL-C, and TGs were similar in both groups. It can be hypothesized that the reduction of PLTP and CETP activities is related directly to the thyroid function. It was confirmed in our study by linear negative correlations between TSH and CETP, and also between TSH and PLTP, but first of all, by a multiple linear regression analysis adjusted for age, sex, BMI, smoking habits, and alcohol drinking. The

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association between increased TSH and lipid transfer proteins was strong for CETP (beta coefficient was significant at the level of 0.0003) and very strong for PLTP (p=0.0000001; 95% CI).

Decreased CETP activity in clinically manifesting hypothyroidism in adults was observed in some studies [6–8,21]. On the contrary, hypothyroidism in children was associated with unchanged activity of CETP [27]. Also in transgenic mice hypothyroidism did not change CETP activity [12]. However, there are no published data about concomitant changes in PLTP mass or activity in patients with hypothyroidism, neither in clinical nor in experimental studies. In the present study, more important than the demonstration of a reduction in CETP activity alone was the demonstration of simultaneous reduction in PLTP and CETP activities in patients with subclinical hypothyroidism. The extent of the reduction of PLTP activity in patients with hypothyroidism was found to be similar to the reduction of CETP activity. The role of PLTP in lipid metabolism is still under investigation, and most observations have been made on PLTP changes in patients diagnosed with diabetes or metabolic syndrome [17,18]. It seems that reduced PLTP activity, as well as reduced CETP activity, has a protective effect on the cardiovascular system. The main common mechanism for these effects could be the increase of total HDL-C fraction.

In other studies in HT patients, reduced CETP activity was associated with a decrease in hepatic lipase activity. Both proteins take part in HDL-C metabolism, increasing this fraction through reduction of cholesteryl ester transport from HDL-C to VLDL-C and LDL-C [6]. However, the increase in HDL-C levels does not necessarily indicate an increased antiatherogenic potential, because hypothyroidism can induce dysfunctional HDL-C with increased pro-oxidative and pro-inflammatory properties [28]. Thyroid hormones can influence HDL-C metabolism by increasing the activity of CETP, which transfers cholesteryl esters from HDL_2-C to VLDL particles, and TGs from VLDL particles to HDL_2-C [29]. Thyroid hormones also stimulate the lipoprotein lipase, which catabolizes the TG-rich lipoproteins, and the hepatic lipase, which hydrolyzes HDL_2-C to HDL_3-C and contributes to the conversion of intermediate-density lipoproteins to LDL-C, and the next LDL-C to small, dense LDL particles [29]. In our study, the total HDL-C concentration was similar in subjects with hypothyroidism and euthyreosis. However, significant changes in HDL-C subfractions in patients with hypothyroidism was observed. HDL_2-C levels were lower and HDL_3-C concentrations were higher in the group with hypothyroidism compared with the group with euthyreosis, both in women and, to a lesser extent, in men.

In some other studies, clinically manifesting or clinically silent hypothyroidism was connected with an increase in HDL_2-C subfractions [7,22], which was explained by a reduction in CETP activity and in consequence, attenuated transfer of cholesteryl esters from HDL_2-C to HDL_3-C. In our study, the HDL_2-C subfraction decreased, whereas the HDL_3-C subfraction increased (the ratio of HDL_2/HDL_3 significantly decreased). It is possible that the cause of this discrepancy in relation to observations from other authors is another degree of thyroid gland dysfunction in studied patients, i.e., subclinical hypothyroidism in our study versus clinical hypothyroidism in other studies. If so, changes in CETP, PLTP, and HDL-C subfractions constitute very sensitive indicators of thyroid function disorders. Moreover, changes in HDL-C subfractions in patients with subclinical hypothyroidism were directly caused by reduction in CETP and PLTP activity, which was demonstrated in a linear regression analysis by a positive correlation between CETP (PLTP) and HDL_2-C, as well as a negative correlation between CETP (PLTP) and HDL_3-C. Simultaneously, there was no effect of subclinical hypothyroidism on HDL-C subfractions (Table 3), as was observed in other studies [28].

There were no significant differences between smokers and nonsmokers or between alcohol drinkers and nondrinkers in CETP or PLTP activity. On the other hand, the impact of the interaction between smoking and drinking on CETP activity was observed. In the study, neither coexistence of chronic diseases (such as diabetes type 2 or coronary heart disease) nor chronic treatment with pharmacological drugs had any significant effect on lipid transfer proteins. This may be attributed to a relatively small number of patients diagnosed with these diseases (fewer than 10%) and a small number of patients treated with pharmacological drugs (only 10 women were treated with L-thyroxine).

Changes observed in our study are beneficial with regard to the cardiovascular risk. Reduction in CETP activity with the aim of reducing cardiovascular risk is the subject of continued research using CETP inhibitors [30–32]. The increase in HDL-C levels reduces the risk of complications of atherosclerosis through various mechanisms, among which the most important one is the increased reverse cholesterol transport [33]. Increased concentration of HDL_3-C increases the antioxidant and anti-inflammatory potential [34]. All these mechanisms are included in the inhibition of atherosclerosis progression. Therefore, patients with a moderate increase in TSH reveal simultaneously pro-atherosclerotic changes (increase in LDL-C, TGs, apolipoprotein B) as well as anti-atherosclerotic changes (reduced CETP and PLTP activities, increased TC and HDL_3-C levels) in lipid metabolism.

Conclusions

Hypothyroidism is associated with decreased activity of CETP and PLTP, as well as changes in serum HDL-C subclasses. Decreased HDL_2-C and increased HDL_3-C levels in subjects with hypothyroidism are consequences of decreased activity of lipid transfer proteins. These changes are early symptoms of lipid disturbances in hypothyroidism because they appear in hypothyreotic patients with normal levels of TC, LDL-C, HDL-C, and TGs.

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