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Original Scientific Paper

SUBCLINICAL HYPOTHYROIDISM AS A CONTRIBUTOR TO MACROVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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SUMMARY – This study aimed to evaluate changes of the lipid panel data in patients with comorbid type 2 diabetes mellitus (T2DM) and subclinical hypothyroidism (SCH) and to identify the probable prognostic values of the lipid profile for macrovascular complication (MVC) development. The study included 370 patients presented with only T2DM and 30 patients suffering from both T2DM and SCH. Receiver operating characteristic (ROC) analysis was used to identify prognostically significant values of the lipid profile with the optimal ratio of sensitivity and specificity for MVC development. All lipid profile values in the patients with T2DM combined with SCH were significantly higher compared to those with only T2DM. At the same time, SCH + T2DM increased the risk of exceeding target levels of triglycerides by 2.9 times and HDL-C by 4.1 times. Analysis of lipid profile values according to macrovascular involvement showed that total cholesterol, LDL-C and non-HDL-C in patients with T2DM and SCH were significantly higher compared to those with only T2DM. The levels of triglycerides >1.65 mmol/L, non-HDL-C >3.74 mmol/L and remnant cholesterol >0.74 mmol/L determined by the ROC analysis can be used for stratification of patients with T2DM combined with SCH into the category of increased risk of MVC development.

Key words: *Diabetes mellitus type 2; Subclinical hypothyroidism; Risk; Dyslipidemia; Macrovascular complications; ROC analysis*

Introduction

Diabetes mellitus (DM), especially type 2 (T2DM), has emerged as one of the major challenges to human health, reaching pandemic levels. In 2019, there were 463 million diabetic people worldwide, 91% of whom had T2DM; it projects the number of people with DM will reach 700 million by 2045[1-6]. The increase in the prevalence of T2DM is closely linked to obesity and associated with insulin resistance (IR)[7,8].

In Ukraine, around 3 million adults are diagnosed with T2DM; its prevalence is 8.4%, and annual cost is around 460 million US dollars[9]. Diabetes prevalence in the European countries is similarly heterogeneous with an age-standardized comparative prevalence ranging from 2.4% in Moldova to 14.9% in Turkey in 2013. Overall, the raw prevalence of diabetes in Europe in 2013 was estimated to 8.5%, which corresponds to 56 million cases (age 20-79 years)[10].

Diabetes mellitus affects multiple organs and systems of the body, resulting in rapid development of complications that cause disability and mortality[11,12]. T2DM reduces life expectancy by as much as 10 years, with cardiovascular disease (CVD) being the main reason of death in T2DM patients[13]. For instance, in the United States, CVD death rates are about 2.0

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times higher among adults with DM[14]. A prospective study of diabetic patients demonstrated a 2- to 4-fold increased probability of developing CVD, with T2DM being an independent risk factor for stroke and myocardial infarction (MI)[15]. People with T2DM had a 15% increased risk of premature all-cause mortality[16].

The linkage between T2DM and CVD is supported by chronic vascular inflammation, endothelial and platelet dysfunction, predisposing such patients to macrovascular complications (MVC) even before the T2DM diagnosis[17,18]. European Guidelines on CVD prevention list the following statistically significant factors for the development of fatal CVD: gender, age, cholesterol level, blood pressure, and smoking status[19]. At the same time, DM is associated not only with hypercholesterolemia, but also with other lipid metabolism disorders such as dyslipidemia[20,21], found in 72%-85% of patients with T2DM[22]. Dyslipidemia is defined as an abnormal lipid profile characterized by high total cholesterol (TC), high low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG). For diabetic patients, the target levels are as follows: LDL-C <100 mg/dL (2.6 mmol/L), HDL-C >40 mg/dL (1.02 mmol/L) and TG <150 mg/dL (1.7 mmol/L)[23].

In addition to these well-recognized cardiovascular risk factors, researches are looking into other causes such as chronic kidney disease, acute respiratory viral infections, periodontitis, obstructive sleep apnea syndrome, erectile dysfunction, cancer, and a number of autoimmune diseases including hypothyroidism[19]. Depending on diagnosis definition of subclinical or overt hypothyroidism, its prevalence in Europe is estimated to range from 0.1% to 12.5%[24,23]. In T2DM patients, a large proportion of thyroid disorders are due to subclinical hypothyroidism (SCH)[24-28]. There are a number of factors determining clinical progression of SCH in DM. These include potential progression to overt hypothyroidism, metabolic control of diabetes, and positive outcomes of thyroid hormone treatment achieved[29]. SCH hallmarks are pronounced changes in carbohydrate and lipid metabolism, such as decreased gastrointestinal glucose absorption, protracted peripheral glucose accumulation, increased gluconeogenesis, decreased hepatic glucose output, reduced hepatic disposal of glucose, and hyperlipidemia. Along with these changes, SCH affects insulin secretion and both micro- and macrovascular functions, elevating cardiovascular risks in DM patients[30-32]. However, some studies indicate that SCH can reduce non-cardiovascular mortality in T2DM patients[33].

This study aimed to evaluate changes of the lipid panel data in patients with comorbid T2DM and SCH, and to identify probable prognostic values of the lipid profile for MVC development.

Patients and Methods

Study design, subjects and data collection

This cross-sectional study involved 400 T2DM patients hospitalized at the Endocrinology Department, Ternopil University Hospital in 2019. Study subjects were divided into two groups, i.e. group 1 (370 patients presented with only T2DM) and group 2 (30 patients suffering from both T2DM and SCH). T2DM was diagnosed using the 2019 American Diabetes Association guidelines[34]. The diagnostic criteria for T2DM rely on the glycated hemoglobin (HbA1c) value of ≥6.5%, which was measured on a Cobas 6000 biochemical autoanalyzer (Roche Hitachi, Germany). SCH was diagnosed following the ETA Guidelines: Management of Subclinical Hypothyroidism, 2013, which include elevated (>4.0 mIU/L) level of thyroid stimulating hormone (TSH); normal (3.1-6.8 pmol/L and 12.0-22.0 pmol/L) levels of free triiodothyronine (fT3) and free thyroxine (fT4), respectively; and absence of clinical symptoms[35]. Thyroid hormone (TH) levels were determined by chemiluminescence assay on a Cobas E411 (Roche Hitachi, Germany).

Prospective participants were excluded from the study if they had a previous history of hypothyroidism or other thyroid diseases (except for hypothyroidism), kidney or liver disorders, psychiatric disorders, took medications affecting thyroid hormone levels, were pregnant or lactating, undergoing antidepressant and/or antipsychotic therapy, had HIV/AIDS or malignant tumors.

The patients were considered to be at a very high cardiovascular risk if they met the following criteria[36]:

- patients with DM and diagnosed with CVD; or
- other target organ damage (proteinuria, renal impairment, left ventricular hypertrophy, or retinopathy); or
- three or more major risk factors (age, hypertension, dyslipidemia, smoking, obesity).

Table 1. Clinical characteristics of study patients

Demographic and anthropologic data		Group				p
		T2DM		T2DM + SCH		
		n	% (95% CI)	n	% (95% CI)	
Age group (yrs)	<35	4	1.08 (0.30; 2.77)	1	3.33 (0.08; 18.57)	0.222
	35-44	39	10.54 (7.50; 14.41)	1	3.33 (0.08; 18.57)	
	45-54	112	30.27 (24.92; 36.42)	13	43.33 (23.07; 74.10)	
	55-64	160	43.24 (36.80; 50.49)	9	30.00 (13.72; 56.95)	
	>65	55	14.84 (11.20: 19.35)	6	20.00 (7.34; 43.53)	
Gender	Male	210	56.76 (49.34; 64.97)	2	6.67 (0.81; 24.08)	<0.001*
	Female	160	43.24 (36.80; 50.49)	28	90.00 (62.02; 100.00)	
Weight status	Underweight (BMI <18.5 kg/m^2)	4	1.08 (0.30; 2.77)	0	0	0.420
	Normal weight (BMI 18.5-24.9 kg/m^2)	65	17.57 (13.56; 22.39)	2	6.67 (0.81; 24.08)	
	Overweight (BMI 25-29.9 kg/m^2)	102	27.57 (22.48; 33.47)	10	33.33 (15.98; 61.30)	
	Obesity (BMI >30 kg/m^2)	199	53.78 (46.57; 61.80)	18	60.00 (35.56; 94.83)	

*statistically significant results; T2DM = type 2 diabetes mellitus; SCH = subclinical hypothyroidism; BMI = body mass index

Blood collection and biochemical analysis

Fasting venous blood (5 mL) was collected from each individual after an overnight fast of more than 10 hours. Serum lipid panel data were measured at the Clinical Laboratory, Ternopil University Hospital. TC, TG and HDL-C were determined with commercially available kits on a Cobas 6000 analyzer (Roche Hitachi, Germany).

Friedewald's formula was used to calculate LDL-C levels (if serum TG <4.5 mmol/L)[37]:

LDL-C (mmol/L)=TC-HDL-C-(0.45×TG).

Non-HDL-cholesterol was calculated using the formula (if serum TG >4.5 mmol/L)[37]:

non-HDL-C=TC-HDL-C.

Remnant cholesterol (RC) was calculated using the formula[36]:

RC (mmol/L)=TC-(HDL-C+LDL-C).

Lipid panel data were assessed according to the current guidelines that set target lipid levels for patients with different cardiovascular risks. LDL-C target level of <1.8 mmol/L is recommended for T2DM patients with high cardiovascular risk. LDL-C target of <1.4 mmol/L is recommended for T2DM patients with very high cardiovascular risk[36]. Non HDL-C secondary targets of 2.6 mmol/L and 3.3 mmol/L are recommended for very high and high risk groups, respectively. Target TG level is ≤1.7 mmol/L. Target HDL-C levels are ≥1.0 mmol/L in men and ≥1.2 mmol/L in women[35]. TC target level is <3.8 mmol/L[38].

Ethics

Ethical principles included in the Declaration of Human Rights adopted in Helsinki in 1975 and revised in 2008 were fully respected in our study. The enrolled subjects participated in this study voluntarily, completed and signed a written informed consent. Study protocol was approved by the Ethics Committee of the I Horbachevsky Ternopil National Medical University.

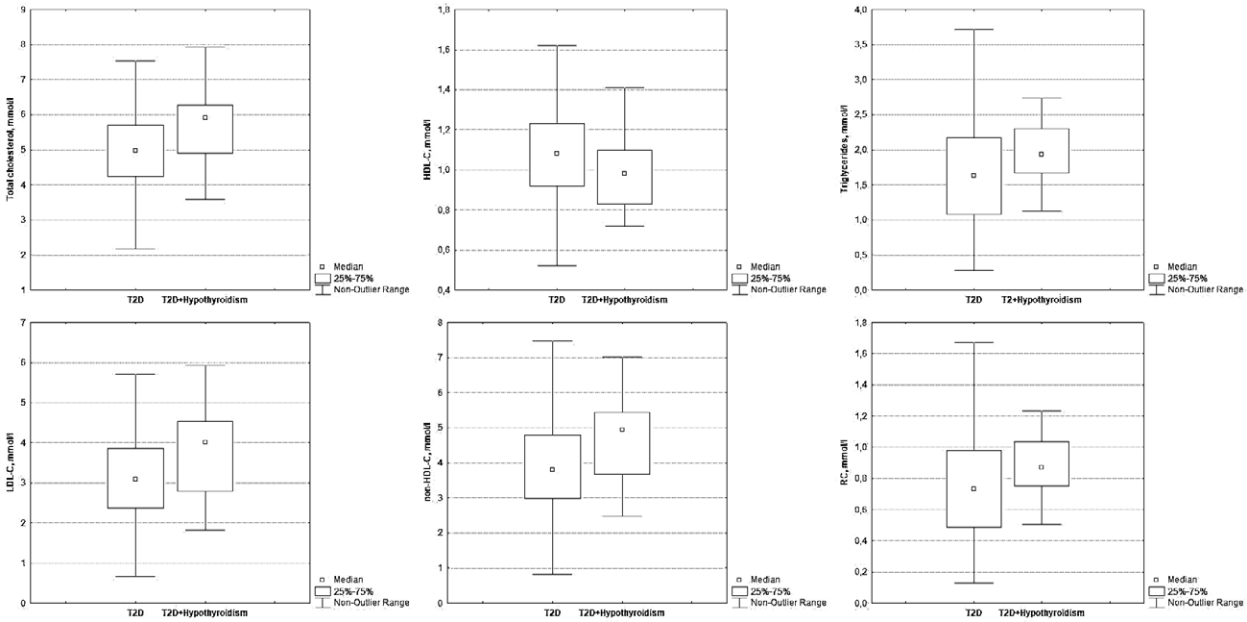

Fig. 1. Lipid profile characteristics of patients with T2DM (group 1) and patients with T2DM and SCH (group 2) (Me [Q25; Q75]).

T2DM = type 2 diabetes mellitus; SCH = subclinical hypothyroidism

Statistics

Study results were analyzed using STATISTICA 7.0 and MedCalc software. Kolmogorov-Smirnov test was used to compare probability distributions. Quantitative values, due to their non-parametric distribution, were expressed by median, lower and upper quartiles, and compared using Mann-Whitney test. For frequency values, the percentage ratio and its 95% confidence interval (95% CI) were calculated, and their comparative analysis was performed using Pearson's χ^2-test and Fisher bilateral test. To assess the effect of a factor on the development of an event, the odds ratio (OR) and its 95% CI were calculated. Receiver operating characteristic (ROC) analysis was used to identify prognostically significant values of the lipid profile with the optimal ratio of sensitivity and specificity for MVC development. Probability value $p<0.05$ was considered statistically significant.

Results

The prevalence of SCH in the study patients with DM was 7.0%. The incidence of T2DM and SCH comorbidity was independent of age and body weight. However, group 2 exhibited sex dissimilarity, with a significant predominance of females with T2DM and SCH comorbidity (Table 1).

Lipid profile analysis indicated a significant increase in the levels of TC ($p<0.001$), TG ($p=0.007$), LDL-C ($p=0.003$), non-HDL-C ($p<0.001$), and RC ($p=0.007$), which are associated with an increased risk of CVD in patients with T2DM and SCH comorbidity. The levels of HDL-C, associated with low risk of CVD, were significantly reduced (Fig. 1).

In the context of importance to attain target lipid levels, lipid profile distribution among the patients is worth noting. Most patients with a combined course of T2DM and SCH had low HDL-C levels and high TG levels, whereas in the group of those with only T2DM these indicators were at the target levels in most patients. The comorbid course of T2DM and SCH increased the risk of hypertriglyceridemia by 2.9 times and hypo-HDL cholesterolemia by 4.1 times (Table 2).

The majority (76.7%) of patients with T2DM and SCH comorbidity had a MVC diagnosis, in particular transient ischemic attack/stroke (23.3%), angina pectoris (16.7%), peripheral artery disease (10.0%), and others (Table 3).

Table 2. Lipid profile characteristics of patients meeting and failing to meet target lipid levels

Lipid level		Group				Fisher exact p, two-tailed	OR (95% CI)
		T2DM		T2DM + hypothyroidism			
		n	% (95% CI)	n	% (95% CI)		
Total cholesterol (mmol/L)	Target level	50	13.51 (10.03; 17.82)	1	3.33 (0.08; 18.57)	0.153	4.53 (0.60-34.01)
	High level	320	86.49 (77.27; 96.50)	29	96.67 (64.74; 100.00)		
HDL-C (mmol/L)	Target level	187	50.54 (43.56; 58.33)	6	20.00 (7.34; 43.53)	0.001*	4.09* (1.63-10.23)
	Low level	183	49.46 (42.55; 57.17)	24	80.00 (51.26; 100.00)		
Triglycerides (mmol/L)	Target level	204	55.14 (47.83; 63.240	9	30.00 (13.72; 56.95)	0.012*	2.87* (1.28-6.43)
	High level	166	44.84 (38.30; 52.23)	21	70.00 (43.33; 100.00)		
LDL-C (mmol/L)	Target level	14	3.78 (2.07; 6.35)	0	0	0.612	2.48 (0.14-42.61)
	High level	356	96.22 (86.48; 100.00)	30	100.00		
Non-HDL-C (mmol/L)	Target level	55	14.84 (11.20: 19.35)	2	6.67 (0.81; 24.08)	0.285	2.44 (0.57-10.56)
	High level	315	85.14 (75.99; 95.08)	28	93.33 (62.02; 100.00)		

*statistically significant results; T2DM = type 2 diabetes mellitus; OR = odds ratio; 95% CI = 95% confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; High/low lipid levels = outcome; Subclinical hypothyroidism = factor

Table 3. Presence of macrovascular complications

Macrovascular complications	Group				Fisher exact p, two-tailed
	T2DM		T2DM + SCH		
	n	% (95% CI)	n	% (95% CI)	
Present	203	54.86	23	76.67	0.022*
Absent	167	45.14	7	23.33	

*statistically significant result; T2DM = type 2 diabetes mellitus; SCH = subclinical hypothyroidism; 95% CI = 95% confidence interval

Close examination of lipid profiles in study groups while taking into account macroangiopathies revealed that the presence of MVC exacerbated the imbalance in lipid panel data associated with promoting atherosclerosis in both patient groups with T2DM alone and T2DM + SCH. Assessing the effect of SCH on lipid profile, we found that in the T2DM + SCH group, the absence of MVC was associated with significantly higher concentrations of TG and RC, while the presence of MVC was concomitant with significantly higher values of TC, LDL-C and non-HDL-C compared to the T2DM group (Table 4).

The MVC prediction models were produced using ROC analysis of lipid panel data. Using ROC analysis, the optimal cut-off points were calculated for the study parameters that determine the relative risk (odds) of MVC in patients with T2DM: TC >4.95 mmol/L (area under the ROC curve (AUC)=0.973; 95% CI 0.951-0.987; sensitivity 90% (95% CI 85.2-93.9) and specificity 98% (95% CI 94.8-99.6)); HDL-C ≤1.03

Table 4. Lipid profile characteristics and macrovascular involvement in patients with T2DM alone and those with T2DM and SCH (Me [Q25; Q75])

Variable	Group				p
	T2DM		T2DM + SCH		
	Present	Absent	Present	Absent	
Total cholesterol (mmol/L)	5.66 (5.20; 6.18)	4.21 (3.64; 4.56)	5.99 (5.78; 6.30)	4.41 (3.89; 4.80)	p_1=0.033* p_2=0.212
p	<0.001*		<0.001*		
HDL-C (mmol/L)	0.95 (0.78; 1.02)	1.22 (1.15; 1.31)	0.94 (0.78; 1.02)	1.21 (1.06; 1.33)	p_1=0.972 p_2=0.476
p	<0.001*		0.004*		
Triglycerides (mmol/L)	2.04 (1.72; 2.55)	1.12 (0.89; 1.43)	2.03 (1.74; 2.40)	1.48 (1.21; 1.65)	p_1=0.761 p_2=0.018*
p	<0.001*		<0.001*		
LDL-C (mmol/L)	3.77 (3,23; 4,36)	2.37 (1.84; 2.80)	4.18 (3.83; 4.56)	2.52 (1.99; 2.79)	p_1=0.044* p_2=0.419
p	<0.001*		<0.001*		
Non-HDL-C (mmol/L)	4.67 (4.20; 5.36)	2.98 (2.38; 3.34)	5.07 (4.82; 5.58)	3.25 (2.49; 3.67)	p_1=0.044* p_2=0.136
p	<0.001*		<0.001*		
RC (mmol/L)	0.92 (0.77; 1.15)	0.50 (0.40; 0.64)	0.91 (0.78; 1.08)	0.67 (0.54; 0.74)	p_1=0.762 p_2=0.018*
p	<0.001*		<0.001*		

*statistically significant results; MVC = macrovascular complications; p = difference between groups with and without MVC; p_1 = difference between subgroups with MVC; p_2 = difference between subgroups without MVC; T2DM = type 2 diabetes mellitus; SCH = subclinical hypothyroidism; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RC = remnant cholesterol

Table 5. Cut-off points for lipid panel data as predictors of macrovascular complications in patients with T2DM and SCH

Variable	Cut-off point	Sensitivity		Specificity	
		%	95% CI	%	95% CI
Total cholesterol (mmol/L)	>4.91	95.65	78.1-99.9	100.00	59.0-100.0
HDL-C (mmol/L)	≤1.04	86.96	66.4-97.2	85.71	42.1-99.6
Triglycerides (mmol/L)	>1.65	95.65	78.1-99.9	85.71	42.1-99.6
LDL-C (mmol/L)	>2.79	91.30	72.0-98.9	85.71	42.1-99.6
Non-HDL-C (mmol/L)	>3.74	91.30	72.0-98.9	100.00	59.0-100.0
RC (mmol/L)	>0.74	95.65	78.1-99.9	85.71	42.1-99.6

95% CI = 95% confidence interval; T2DM = type 2 diabetes mellitus; SCH = subclinical hypothyroidism; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RC = remnant cholesterol

mmol/L (AUC=0.891; 95% CI 0.855-0.921; sensitivity 80% (95% CI 73.6-85.1) and specificity 96% (95% CI 92.3-98.7)); TG >1.62 mmol/L (AUC=0.881; 95% CI 0.843-0.912; sensitivity 81% (95% CI 75.2-86.4) and specificity 88% (95% CI 82.1-92.5)); LDL-C >3.09 mmol/L (AUC=0.934; 95% CI 0.904-0.957; sensitivity 85% (95% CI 79.6-89.8) and specificity 91% (95% CI 85.6-94.9)); and RC >0.73 mmol/L (AUC=0.881; 95% CI 0.843-0.912; sensitivity 81% (95% CI 75.2-86.4) and specificity 88% (95% CI 82.8-93.0)) (p<0.001 all). Non-HDL-C showed 100% sensitivity (95% CI 98.2-100.0) and 1.2% specificity (95%

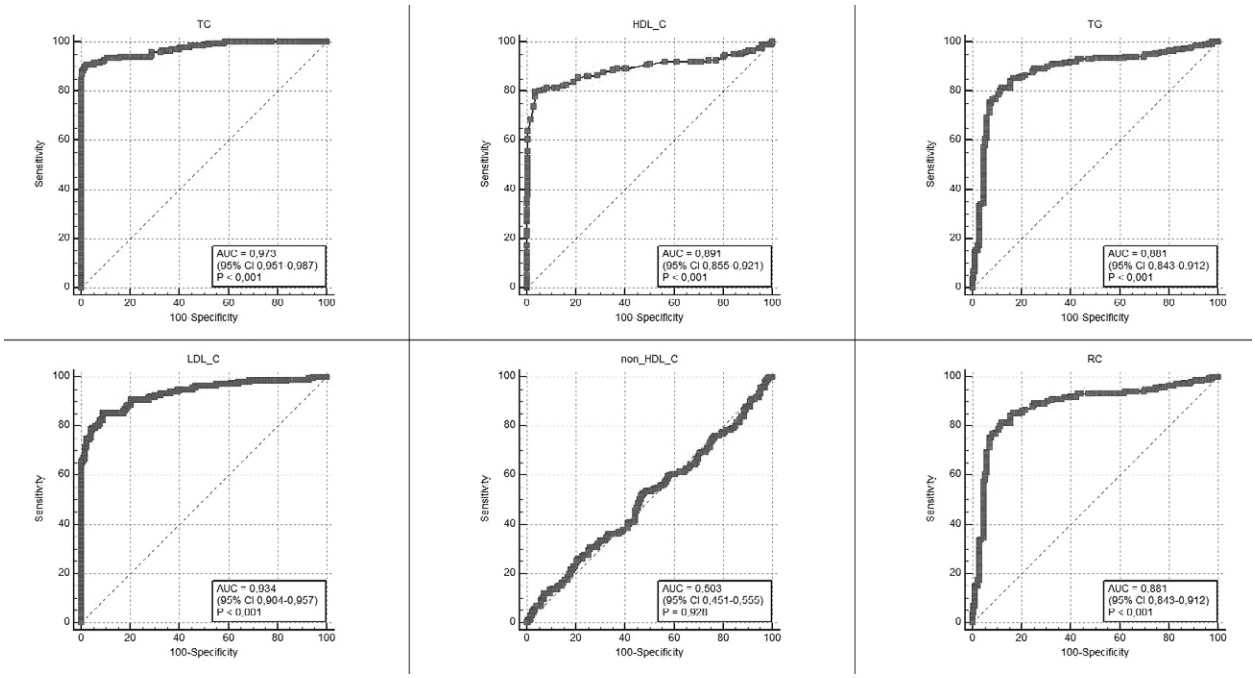

Fig. 2. Receiver operating characteristic curves of lipid panel data for prediction of MVC in patients with T2DM and SCH.

MVC = macrovascular complications; T2DM = type 2 diabetes mellitus; SCH = subclinical hypothyroidism

CI 0.1-4.3), with a cut-off value of >1.49 mmol/L; however, it cannot be used as a predictor of MVC because it had AUC >0.7 (AUC=0.503; 95% CI 0.451-0.555; p=0.628).

The optimal cut-off points for the study parameters of the lipid profile which determine the relative risk (odds) of MVC in patients with T2DM in combination with SCH are summarized in Table 5. All parameters can be used in predictive models of MVC in patients with T2DM and SCH because each of them had AUC >0.7 (Fig. 2).

Comparing these models to describe the relative risk (odds) of MVC in patients with T2DM or T2DM combined with SCH, the AUC under the ROC curve was significantly higher for TG, non-HDL-C and RC (p<0.001 all).

Discussion

The rapid increase in the prevalence of T2DM directly contributes to an increase in an array of micro- and macrovascular complications, and as a consequence, in substantial DM-associated mortality and morbidity[39,40]. In Ukraine, 38.0% of T2DM patients develop MVC[41]. Huang *et al.* estimated the worldwide CVD mortality to be the cause of death in 52.0% of T2DM patients[42]. For instance, a survey of 3,000 T2DM patients found the prevalence of coronary heart disease (CHD), stroke, and peripheral vascular disease to be 10.6%, 1.1%, and 4.7%, respectively[43]. The main additional risk factors for microvascular disease and diabetic foot were age, T2DM disease duration, and HbA1c levels, while age was the only risk factor for MVC. While a model estimating associations between the incremental risks of death and five specific CVD risk factors (elevated HbA1c levels, elevated LDL-C levels, albuminuria, smoking, and elevated blood pressure) in DM patients revealed no significant excess risk of death, MI, or stroke in T2DM subjects with these five risk factor variables within the target range when compared with control population, there was an increased risk of hospitalization for heart failure in T2DM subjects compared to control subjects[44]. Thus, even though studies show a correlation between T2DM and MVC, there are other risk factors present in DM patients, such as age, gender, smoking, hypertension, obesity and dyslipidemia[45].

On the other hand, the incidence of thyroid dysfunction in diabetic patients is higher than that in the general population, reaching up to 4%-17% in T2DM[46]. Clinically, excess as well as deficiency of both thyroid hormones (TH) can induce or exacerbate CVD. Several studies and meta-analyses found a connection between SCH and an increased risk of CHD, as well as connection between SCH and cardiovascular risk and mortality[47-49]. For instance, an Australian study found a significantly higher CHD prevalence in patients with SCH[50]. The risk of CHD events remained significantly larger even after adjusting for standard cardiovascular risk factors. The increase in the risk of CHD events and mortality is also dependent on TSH levels[51]. A meta-analysis confirmed SCH association with a significant risk of CHD at baseline[52]. Differences in the results of various studies can be attributed to variations in study design, SCH severity, gender and age of study cohorts[47].

There have been no previous studies of lipid panel data in regards to MVC in Ukrainian population of T2DM patients with SCH. We found that all lipid profile values in patients with T2DM combined with SCH were significantly higher compared to those with T2DM alone. Additionally, SCH combined with T2DM increased the risk of exceeding target levels of TG by 2.9 times and HDL-C by 4.1 times. Analysis of lipid profile values according to macrovascular involvement showed the levels of TC, LDL-C and non-HDL-C to be significantly higher in patients with T2DM and SCH compared to those with T2DM alone. This can be used to predict MVC risk in patients with T2DM and SCH. Furthermore, the ROC curve optimal cut-off points for lipid profile values indicating relative risk of MVC in patients with T2DM combined with SCH were as follows: TG >1.65 mmol/L, non-HDL-C >3.74 mmol/L and RC >0.74 mmol/L.

These results corroborate reports from previous studies. In diabetic patients, TG level is a risk factor for CVD independent of HDL-C level, and the risk persists even if the glycemic control measures are implemented[53,54]. Another marker of total atherogenic lipoprotein burden and relative risk of CVD is non-HDL-C, since this component encompasses all cholesterol present in atherogenic lipoprotein particles. In the presence of very high TG levels, non-HDL-C has been suggested to represent CVD risk better than LDL-C alone[55,56]. Another component of lipid panel abnormalities is RC, which is defined as cholesterol content of triglyceride-rich lipoproteins. In the fasting state, it comprises very low-density and intermediate-density lipoproteins, and in the non-fasting state these two lipoproteins plus chylomicron remnants[57]. Varbo *et al*. report on the increase in non-fasting RC to be associated with ischemic heart disease development[58]. The mechanism underlying the causal effect of elevated non-fasting RC on CVD risk could be explained by remnants (triglyceride-rich lipoproteins) entering the intima of the arterial wall and jamming it, similar to the instances of LDL trapped in the intima, resulting in atherosclerosis and ischemic heart disease[59,60].

Studies suggest that TH affect MVC risk factors directly by modulating lipid metabolism and inflammatory pathways[61,62]. TH control cholesterol synthesis by regulating the activity of the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) enzyme, as well as its degradation rate through the expression of sterol regulatory element-binding protein 2 gene[63]. Another enzyme shown to be affected by thyroid status is cholesterol 7α-hydroxylase, involved in the first stage of cholesterol degradation pathway, which in turn alters the rates of fecal cholesterol and bile acid excretion[64]. Subsequently, hypothyroidism is associated with higher LDL cholesterol and apolipoprotein B levels. TH deficiency also induces adverse changes in LDL particle size, number, and their oxidation[65]. Furthermore, hypothyroidism can inhibit the activity of lipoprotein lipase, sterol-regulatory-element-binding protein-2, and apolipoprotein A1, which results in increased concentrations of circulating TG[66]. Additionally, TH are involved in HDL metabolism, since they upregulate hepatic lipase and cholesteryl ester transfer protein[67]. Thyroid status was shown to affect reverse cholesterol transport in mice by increasing the levels of SR-B1, a hepatic HDL receptor[68]. Finally, a study of an independent CVD risk factor, serum atherogenic lipoprotein (a) [Lp(a)] levels, found them to be significantly elevated in newly diagnosed hypothyroidism patients compared to controls ($p<0.05$)[69].

The effect of SCH on hyperlipidemia and cardiovascular end points is less clear[62]. Villar *et al*. report that treatment of SCH had no effect on decreasing TC, but points to a trend towards falling LDL-C levels[70]. Additionally, levothyroxine replacement therapy for SCH did not result in improved survival or decreased cardiovascular morbidity. In a number of stud-

ies, patients with SCH had significantly elevated serum TC, LDL-C, and TG levels[71]; this was corroborated by a meta-analysis of TC, LDL-C, and TG levels in SCH subjects relative to euthyroid individuals[72]. Similarly, in a Korean study comparing SCH subjects with an intermediate-to-high risk of CVD to euthyroid subjects, the former were shown to have a higher incidence of plaque (expressed as coronary calcium score)[73], while asymptomatic carotid plaques of SCH patients exhibited higher inflammatory activity compared to euthyroid subjects[74].

The 5th Tromsø Study found a significant and positive correlation between serum TSH levels and serum TC and LDL-C levels[75]. Thus, SCH patients showed a significantly elevated TG and LDL-C levels and low HDL-C levels compared to control group. Notably, women with TSH levels higher than 10 mIU/L exhibited a significant increase in small dense LDL particles, which are associated with a higher atherogenic index of plasma[76]. In addition, the association between SCH and hyperlipidemia, low normal levels of free thyroxine (FT4) can also affect lipids, as they were significantly correlated with increased IR, indicating an increased cardiovascular risk in patients with SCH[77]. Another study found SCH to increase the secretion of VLDL-TG by the liver[78]. Moreover, in SCH, plasma VLDL-TG concentration was higher than in euthyroid controls as a result of increased release of large TG-rich VLDL particles from the liver.

Nevertheless, some studies show a statistically significant association between thyroid dysfunction and cardiovascular endpoints even after adjusting for CVD risk factors such as lipid levels and hypertension[47], suggesting that there are other, yet undetermined pathways involved in the increased risk of cardiovascular complications against the background of thyroid dysfunction. Elevated plasma homocysteine levels are one of such potential hallmarks, since they have been reported both in the cases of overt and, sometimes, subclinical hypothyroidism[79]. Other CVD risk factors that have been associated with SCH include a hypercoagulable state, elevated high-sensitivity C-reactive protein levels, decreased flow-mediated vasodilation, and reduced availability of nitric oxide[62]. Furthermore, researchers point out that SCH impairs relaxation of vascular smooth muscle cells, increasing arterial stiffness and systemic vascular resistance[80]. Other proposed mechanisms for the increased CV risk in SCH individuals include IR, respiratory burst[81], and endothelial dysfunction[82].

Our study had some limitations, i.e. sample size in the study was small, follow-up period was short, the study was observational, and it did not follow the effects of SCH treatment on MVC risk reduction. Further studies with larger samples assessing the predictive value of TG, non-HDL-C and RC on the development of MVC in patients with T2DM and SCH need to be considered.

Conclusion

We found that all lipid profile values in patients with T2DM combined with SCH were significantly higher compared to those with T2DM alone. At the same time, comorbid SCH in T2DM patients increased the risk of exceeding target levels of TG by 2.9 times and HDL-C by 4.1 times. The levels of TG >1.65 mmol/L, non-HDL-C >3.74 mmol/L and RC >0.74 mmol/L determined by ROC analysis can be used for stratification of patients with T2DM combined with SCH into the category of increased risk of MVC development.

Data Sharing Statement. The data set generated and/or analyzed during this study are included in this manuscript and are available from the corresponding author on reasonable request.

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Sažetak

SUBKLINIČKI HIPOTIREOIDIZAM DOPRINOSI MAKROVASKULARNIM KOMPLIKACIJAMA U BOLESNIKA S DIJABETES MELITUSOM TIP 2

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Cilj istraživanja bio je procijeniti promjene u lipidnom profilu kod bolesnika s dijabetes melitusom tip 2 (T2DM) i subkliničkim hipotireoidizmom (SCH) te utvrditi vjerojatne prognostičke vrijednosti lipidnog profila za razvoj makrovaskularnih komplikacija (MVK). U studiju je bilo uključeno 370 bolesnika koji su imali samo T2DM i 30 bolesnika koji su imali i T2DM i SCH. Prognostički značajne vrijednosti lipidnog profila s optimalnim omjerom osjetljivosti i specifičnosti za razvoj MVK utvrđene su analizom krivulje ROC. Sve vrijednosti lipidnog profila bile su značajno više u bolesnika s T2DM u kombinaciji sa SCH u usporedbi s bolesnicima koji su imali samo T2DM. Istodobna prisutnost SCH i T2DM povećala je rizik od prekoračenja ciljnih razina triglicerida 2,9 puta i HDL kolesterola 4,1 puta. Analiza vrijednosti lipidnog profila u odnosu na zahvaćenost makrovaskularnih struktura pokazala je da su ukupni kolesterol, LDL kolesterol i ne-HDL kolesterol značajno viši u bolesnika s T2DM i SCH u usporedbi s onima koji imaju samo T2DM. Razine triglicerida >1,65 mmol/L, ne-HDL kolesterola >3,74 mmol/L i ostatnog kolesterola >0,74 mmol/L utvrđene analizom ROC mogu poslužiti za prepoznavanje bolesnika s T2DM i SCH kao skupine s povišenim rizikom za razvoj MVK.

Ključne riječi: *Dijabetes melitus tip 2; Subklinički hipotireoidizam; Rizik; Dislipidemija; Makrovaskularne komplikacije; Analiza ROC*