Acta Clin Croat 2024; 63: 89-100
doi: 10.20471/acc. 2024.63.01.11

Original Scientific Paper

PROGNOSTIC VALUES OF LIPID PANEL DATA FOR MACROVASCULAR COMPLICATION DEVELOPMENT IN TYPE 2 DIABETIC PATIENTS WITH COMORBID THYROID DYSFUNCTION

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SUMMARY – This study aimed to evaluate prognostic values of the serum lipid panel data for development of macrovascular complications (MVC) in patients with type 2 diabetes mellitus (T2DM) alone and those with comorbid hypothyroidism (HT), diffuse non-toxic goiter (DNTG), or a combination of these disorders. The study included 596 inpatients. Receiver operating characteristic (ROC) analysis was used to identify prognostically significant values of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-cholesterol (non-HDL-C) and remnant cholesterol (RC). The following cut-off points that determine the relative risk of MVC development were established: TC >5.11 mmol/L, TG ≥2.03 mmol/L, LDL-C ≥2.97 mmol/L and non-HDL-C ≥4.29 mmol/L in T2DM patients with comorbid HT; TC ≥4.97 mmol/L, TG ≥2.54 mmol/L, LDL-C ≥3.21 mmol/L and non-HDL-C ≥4.20 mmol/L in T2DM patients with comorbid DNTG; and TC ≥4.89 mmol/L, TG ≥1.56 mmol/L, LDL-C ≥2.93 mmol/L, non-HDL-C ≥4.04 mmol/L and RC ≥1.14 mmol/L in those with comorbid HT and DNTG. Thus, serum levels of TC, TG, LDL-C, non-HDL-C and RC can be used for stratification of T2DM patients with comorbid thyroid dysfunction into the category of increased risk of MVC development.

Key words: *Diabetes mellitus type 2; Hypothyroidism; Diffuse non-toxic goiter; Dyslipidemia; Macrovascular complications*

Introduction

Diabetes mellitus (DM) is among the most serious public health challenges due to its increasing incidence, significant health complications if not diagnosed or treated, and the high cost of patient care[1]. It is estimated that in 2019, the number of adults with DM reached 451 million globally, resulting in an estimated 5 million deaths among people aged 20-99 years worldwide[2]. The costs associated with DM across the globe have been estimated to 827 billion US dollars (USD) annually[3]. It is projected that by 2030, the worldwide number of DM patients will increase to 552 million (or 1 diabetic patient *per* 10 healthy adults), and by 2035 to 592 million.

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Received September 22, 2022, accepted December 19, 2022

In Ukraine, currently more than 1.3 million DM patients are enrolled in an official registry, however, the total number of diabetics in the country may reach 3.5 million people. Additionally, Ukraine has a very high rate of hospitalization for patients with diabetes; a 2016 International Diabetes Management Practice study[4] shows that 77% of patients with type 2 DM (T2DM) reported that they were hospitalized at least once in the last 12 months. In 2019 in Ukraine, the total economic loss (economic burden) related to the costs spent on the treatment of diabetes and its complications calculated using the PROSIT pharmacoeconomic model[5] amounted to 36-104 billion Ukrainian hryvnia (UAH), with the mid-2019 exchange rate of 1 USD=25.80 UAH. Direct medical expenses accounted for 65% of all economic losses, and 35% were the costs of premature disability and premature mortality[6].

In diabetic patients, a negative prognosis regarding the course of the disease, duration and quality of life is usually linked to the development of microvascular and macrovascular complications. Moreover, micro- and macrovascular complications may be related to COVID-19 outcome in T2DM patients. A French multicenter observational study included 1317 diabetic subjects (with a predominance of T2DM (88.5%)) hospitalized for COVID-19[7]. Microvascular and macrovascular complications were found in 46.8% and 40.8% of cases, respectively. The primary outcome was recorded in 29.0% of participants, while 10.6% died and 18.0% were discharged on day 7. On admission, dyspnea, as well as lymphocyte count, C-reactive protein and aspartate aminotransferase levels were independent predictors of the primary outcome. Finally, age, treated obstructive sleep apnea, and microvascular and macrovascular complications were independently associated with the risk of death on day 7.

In Ukraine, 38% of T2DM patients have macrovascular complications (MVC)[4]. At the same time, cardiovascular disease (CVD) is the primary cause of death in diabetic patients. Einarson *et al.* showed that over 30% of T2DM patients suffered from cardiovascular complications, and in nearly half of T2DM-related deaths CVD was the main cause[8]. Despite direct connection between T2DM and CVD, other risk factors are also almost always present in diabetic patients, including hypertension, obesity, and dyslipidemia[9,10]. Moreover, thyroid dysfunction, either overt or subclinical, is closely associated with cardiovascular deterioration[11].

Dyslipidemia, an abnormal aggregation of lipids in the blood, is common in patients with diabetes and CVD[12]. Thyroid hormones (THs) are involved in lipid metabolism regulation as they exert coordinated and specific effects on the liver and adipocytes[13-15]. In particular, THs stimulate breakdown of lipids stored in white adipose tissue and those from dietary sources, resulting in production of circulating free fatty acids (FFAs). High levels of FFAs in turn stimulate triglyceride (TG) synthesis, which promotes formation of apolipoprotein B (ApoB) and very low density lipoprotein (VLDL) cholesterol. Low levels of high-density lipoprotein cholesterol (HDL-C) is a hallmark of hyperinsulinemia, in addition to high ApoB and VLDL-C[16]. THs also induce *de novo* lipogenesis *via* transcriptional activation of several key genes, including transcription factors, such as sterol regulatory element-binding protein 1C, liver X receptors and carbohydrate-responsive element-binding protein. Finally, THs also regulate serum total cholesterol (TC) through a number of mechanisms, including activation of cholesterol biosynthesis, its export from the liver in the form of VLDL, LDL, and reverse transport from peripheral tissues, reuptake in the liver mediated by LDL receptors and conversion into bile acids[17]. Therefore, THs could contribute to the pathogenesis of vascular complications in T2DM. Recent clinical studies demonstrated the link between THs and diabetic microvascular complications[18-21]. However, in contrast to the clearly established association between diabetes and microvascular complications, the evidence for linking THs and diabetic MVC is more limited and inconsistent[22]. In obese individuals in particular, high TSH levels were correlated with a higher incidence or risk of CVD[23]. In a cross-sectional study, total THs were not found to be independent risk factors for cardiovascular events in patients with T2DM[24]. Our previous study found more pronounced proatherogenic changes of lipid metabolism in T2DM patients with comorbid subclinical HT compared to those with T2DM only[25]. In a study by Hu *et al.* on 311 euthyroid patients with T2DM, the authors looked for the association of THs with MVC[26]. After adjusting for the potential confounders including age, sex, T2DM duration, body mass index (BMI), systolic blood pressure, diastolic

blood pressure, glycated hemoglobin (HbA1c), TG, TC, HDL-C, LDL-C, and VLDL-C, the results indicated that low-normal free triiodothyronine (fT3) and free thyroxine (fT4) levels were related to an increased risk of MVC. Significant associations were found between free THs and diabetic MVC among overweight or obese patients (as defined by BMI). However, no association was found between THs and diabetic MVC in normal weight patients.

To date, no nationwide survey has been published in Ukraine on the prevalence of thyroid dysfunction in T2DM population. Published studies of lipid panel levels among T2DM patients, as well as other predictors of MVC, are also lacking. This study aimed to evaluate prognostic values of the serum lipid panel data for development of MVC in patients with T2DM and comorbid hypothyroidism (HT), diffuse non-toxic goiter (DNTG), or with a combination of these disorders.

Patients and Methods

Study design, subjects and data collection

This cross-sectional study involved 596 patients with T2DM, who were hospitalized at the Endocrinology Department, Ternopil University Hospital, Ternopil, Ukraine, in 2019-2020. The patients were divided into 4 groups, as follows: group 1 (501 patients with T2DM alone), group 2 (37 diabetic patients with comorbid HT), group 3 (40 diabetic patients with comorbid DNTG), and group 4 (37 diabetic patients with comorbid HT and DNTG).

Type 2 diabetes mellitus was diagnosed following the 2019 American Diabetes Association guidelines[27]. The diagnostic criteria for T2DM include HbA1c value of ≥6.5%, which was measured using a Cobas 6000 automated biochemical analyzer (Roche Hitachi, Germany). Thyroid function was assessed by quantifying serum TSH and fT4 levels using chemiluminescent analysis on a Cobas E411 automated analyzer (Roche Hitachi, Germany). HT was diagnosed following the criteria of the European Thyroid Association, i.e., elevated levels of TSH in combination with reduced fT4[28]. If fT4 values were within the normal limits, subclinical HT was diagnosed. The diagnosis of DNTG was confirmed using the World Health Organization (WHO) guidelines[29]. Goiter was diagnosed if an enlarged thyroid was visible (grade 1) or palpable but not visible (grade 2) when the neck is in the normal position; additional criteria include an increase in the total volume of the thyroid gland on ultrasonography and normal serum TSH levels.

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

Patients were considered to be at a very high cardiovascular risk if they met the following criteria: 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)[30].

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 in the Clinical Laboratory, Ternopil University Hospital. TC, TG and HDL-C were determined using commercially available kits on a Cobas 6000 analyzer (Roche Hitachi, Germany).

Friedewald formula was used to calculate LDL-C levels (if serum TG <4.5 mmol/L)[31]:

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):

non-HDL-C = TC – HDL-C[31].

Remnant cholesterol (RC) was calculated using the formula[30]:

RC (mmol/L) = TC – (HDL-C+LDL-C).

Serum lipid panel data were assessed according to the current guidelines, which 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 a high cardiovascular risk. LDL-C target of <1.4 mmol/L is recommended for T2DM patients with a very high cardiovascular risk[29]. 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[32]. Target TC level is <3.8 mmol/L[33].

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; they completed and signed a written informed consent form. Study protocol was approved by the Ethics Committee of the I Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.

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 compared 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 serum lipid panel data with the optimal ratio of sensitivity and specificity for macrovascular complication development. Probability value $p<0.05$ was considered statistically significant.

Results

In the study of serum lipid panel data in the context of achieving target levels of indicators, the OR above target values for TC and non-HDL-C and below target values for HDL-C in patients with comorbid T2DM + HT and T2DM + DNTG was significantly different compared to patients with T2DM alone. In addition, in the significant majority of patients with T2DM + HT, the level of LDL-C was higher than the target values. In the group of T2DM + HT + DNTG, all patients had a level of TC higher than the target one. Significantly more patients were also diagnosed with higher than target TG levels and below target HDL-C levels, which was significantly different from the T2DM only group. At the same time, patients with comorbidity of T2DM, HT and DNTG had OR significantly above the target TG (7.1 times) and below the target HDL-C levels (8.4 times) (Table 1). Macrovascular complications were found in the vast majority of patients with T2DM and HT comorbidity (76.7%) (Table 2). In those with T2DM alone, about half of the patients had MVC (57.5%), which was significantly different from the group of patients with T2DM + HT (p=0.037). When comparing patients with T2DM alone and those with comorbid T2DM and DNTG, there were no significant between-group differences for MVC. In patients with comorbid T2DM, HT and DNTG, most patients also had MVC (77.8%). In the presence of diagnosed macroangiopathy, the patients in two groups, T2DM alone and T2DM + HT, had more severe dyslipidemia, including a significant increase in the levels of TC, LDL-C and non-HDL-C, and a significant decrease in the level of HDL-C. At the same time, in the presence of MVC, TG levels were significantly higher only in the T2DM alone group. When comparing lipid data of the patients diagnosed with MVC, we found significantly higher levels of TC (by 14.8%), LDL-C (by 17.9%), non-HDL-C (by 33.8%), RC (by 38.2%), as well as a lower level of HDL-C (by 19.3%) in the T2DM + HT group relative to the data on the T2DM alone group. Notably, in patients without MVC, the lipid profile in the group with T2DM and HT comorbidity was not significantly different from that in the group with T2DM alone. TheT2DM and DNTG comorbidity with macroangiopathy also affected the serum lipid profile. In particular, we found significantly higher levels of TC (14.9%) and non-HDL-C (15.4%) in patients with macroangiopathy in the T2DM + DNTG group compared to the patients without MVC (p=0.036 and p=0.029, respectively). In addition, we noted significantly higher rates of TC (by 10.9%), LDL-C (by 27.8%), non-HDL-C (by 26.7%), RC (by 30.3%), and a lower level of LDL-C (by 13.8%) in patients with MVC and T2DM + DNTG compared to patients with MVC in T2DM alone group.

In the T2DM + HT + DNTG group patients, the presence of macroangiopathy also correlated with dyslipidemia; in particular, the levels of TC (p=0.026), LDL-C (p=0.008) and non-HDL-C (p=0.008) were significantly higher in subjects with MVC. In addition, the patients with comorbid T2DM, HT, DNTG and MVC had significantly higher levels of TC (8.9%), TG (30.4%), non-HDL-C (24.8%), RC (by 64.5%), and a lower level of HDL-C (22.9%) compared to T2DM alone patients with MVC (Table 2).

The ROC analysis was used to calculate optimal cut-off points of the investigated serum lipid panel data, which determine the relative risk of MVC in

patients with T2DM in combination with HT. These points were: TC ≥5.11 mmol/L (area under the ROC curve (AUC)=0.73; 95% CI 0.52-0.94; sensitivity 0.79 and specificity 0.67); TG ≥2.03 mmol/L (AUC=0.77; 95% CI 0.52-0.94; sensitivity 0.79 and specificity 0.78); LDL-C ≥2.97 mmol/L (AUC=0.74; 95% CI 0.51-0.97; sensitivity 0.86 and specificity 0.67); and non-HDL-C ≥4.29 mmol/L (AUC=0.77; 95% CI 0.56-0.98; sensitivity 0.75 and specificity 0.78) (Table 3). The relative risk (odds) of MVC in patients with T2DM and DNTG based on the serum lipid panel data was: TC ≥4.97 mmol/L, AUC=0.71; 95% CI 0.53-0.89; sensitivity 0.82 and specificity 0.54; TG ≥2.54 mmol/L (AUC=0.75; 95% CI 0.53-0.97; sensitivity 0.79 and specificity 0.75); LDL-C ≥3.21 mmol/L (AUC=0.72; 95% CI 0.55-0.89; sensitivity 0.82 and specificity 0.54); and non-HDL-C ≥4.20 mmol/L (AUC=0.72; 95% CI 0.54-0.89; sensitivity 0.74 and specificity 0.61).

We also determined serum lipid panel data which affected the relative risk (odds) of MVC in patients with T2DM, HT and DNTG comorbidity: TC ≥4.89 mmol/L (AUC=0.88; 95% CI 0.71-1.00; sensitivity 0.82 and specificity 0.54); TG ≥1.56 mmol/L (AUC=0.76; 95% CI 0.60-0.90; sensitivity 0.82 and specificity 0.46); LDL-C ≥2.93 mmol/L (AUC=0.95; 95% CI 0.83-1.00; sensitivity 0.79 and specificity 0.75); non-HDL-C ≥4.04 mmol/L (AUC=0.95; 95% CI 0.83-1.00; sensitivity 0.79 and specificity 0.75); and RC ≥1.14 mmol/L (AUC=0.75; 95% CI 0.53-0.97; sensitivity 0.79 and specificity 0.75) (Table 3). Analysis of the cut-off points obtained for the studied lipid profile parameters showed that the combination of T2DM with HT or DNTG was accompanied by lowering of those lipid panel values which are crucial for macroangiopathy development.

Table 1. Serum lipid panel data of patients meeting and failing target lipid levels

Lipid level n		T2DM		T2DM + HT		p	OR (95% CI)	T2DM + DNTG		p	OR (95% CI)	T2DM + HT+ DNTG		p	OR (95% CI)
		%	n	%			n	%			n	%			
TC	Target level	59	11.78	0	0	0.025*	10.08 (0.61-166.40)	0	0	0.015*	10.89 (0.66-179.47)	0	0	0.246	4.98 (0.30-83.64)
	High level	442	88.22	37	100.00			40	100.00			18	100.00		
HDL-C	Target level	253	51.32	9	24.32	0.002*	3.28* (1.52-7.09)	14	35.00	0.049*	1.96* (1.00-3.84)	2	11.11	0.001*	8.43* (1.92-37.07)
	Low level	240	48.68	28	75.68			26	65.00			16	88.89		
TG	Target level	235	46.91	9	24.32	0.010*	2.75* (1.27-5.94)	17	42.50	0.625	1.20 (0.62-2.29)	2	11.11	0.003*	7.07* (1.61-31.06)
	High level	266	53.09	28	75.68			23	57.50			16	88.89		
LDL-C	Target level	48	9.58	1	2.70	0.236	3.81 (0.51-28.45)	1	2.50	0.161	4.13 (0.56-30.75)	2	11.11	0.687	0.85 (0.19-3.80)
	High level	453	90.42	36	97.30			39	97.50			16	88.89		
Non-HDL-C	Target level	141	28.14	3	8.11	0.006*	4.44* (1.34-14.69)	2	5.00	<0.001*	7.44* (1.77-31.26)	2	11.11	0.177	3.13 (0.71-13.80)
	High level	360	71.86	34	91.89			38	95.00			16	88.89		

*statistically significant results; T2DM = diabetes mellitus type 2; HT = hypothyroidism; DNTG = diffuse non-toxic goiter; 95% CI = 95% confidence interval; OR = odds ratio; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-HDL-cholesterol

Table 2. Serum lipid panel data and macrovascular involvement in patients with T2DM only and those with T2DM and comorbid thyroid dysfunction

Variable	T2DM		T2DM + HT		p_1, p_2	T2DM + DNTG		p_3, p_4	T2DM + HT + DNTG		p_5, p_6
	MVC +	MVC –	MVC +	MVC –		MVC +	MVC –		MVC +	MVC –	
TC, mmol/L	5.14 (4.44; 5.85)	4.80 (4.02; 5.74)	5.90 (5.16; 6.19)	4.96 (4.33; 5.20)	p_1=0.003* p_2=0.672	5.70 (5.19; 6.46)	4.96 (4.72; 5.52)	p_3=0.002* p_4=0.246	5.60 (5.33; 5.90)	4.90 (4.35; 4.96)	p_5=0.044* p_6=0.806
p	<0.001*		0.040*			0.036*			0.026*		
HDL-C, mmol/L	1.09 (0.95; 1.22)	1.13 (0.97; 1.31)	0.88 (0.76; 1.13)	1.10 (0.94; 1.21)	p_1<0.001* p_2=0.366	0.94 (0.79; 1.21)	1.09 (0.83; 1.24)	p_3=0.006* p_4=0.242	0.84 (0.78; 0.98)	0.98 (0.74; 1.22)	p_5<0.001* p_6=0.307
p	0.039*		0.037*			0.453			0.671		
TG, mmol/L	1.94 (1.17; 2.92)	1.74 (1.05; 2.64)	2.45 (1.68; 2.92)	2.03 (1.54; 2.19)	p_1=0.049* p_2=0.369	2.21 (1.53; 2.86)	2.03 (1.54; 2.19)	p_3=0.421 p_4=0.657	2.53 (2.51; 2.56)	2.77 (2.54; 2.92)	p_5=0.028* p_6=0.135
p	0.047*		0.229			0.292			0.137		
LDL-C, mmol/L	3.13 (2.54; 3.91)	2.87 (2.09; 3.66)	3.69 (3.15; 4.16)	2.80 (2.41; 3.08)	p_1=0.005* p_2=0.893	4.00 (3.26; 4.49)	3.23 (2.88; 3.68)	p_3<0.001* p_4=0.128	3.34 (3.09; 4.26)	2.60 (2.29; 2.77)	p_5=0.174 p_6=0.474
p	<0.001*		0.031*			0.091			0.008*		
Non-HDL-C, mmol/L	3.67 (2.85; 4.43)	3.99 (3.38; 4.69)	4.91 (4.17; 5.31)	3.74 (3.25; 4.26)	p_1<0.001* p_2=0.567	4.65 (4.08; 5.44)	4.03 (3.74; 4.59)	p_3<0.001* p_4=0.118	4.58 (4.55; 5.30)	3.74 (3.43; 3.92)	p_5=0.003* p_6=0.981
p	<0.001*		0.017*			0.029*			0.008*		
RC, mmol/L	0.76 (0.46; 1.22)	0.72 (0.41; 1.09)	1.05 (0.74; 1.31)	0.89 (0.85; 1.14)	p_1=0.005* p_2=0.142	0.99 (0.69; 1.29)	0.91 (0.69; 0.99)	p_3=0.048* p_4=0.269	1.25 (1.14; 1.31)	1.14 (1.13; 1.15)	p_5=0.002* p_6=0.060
p	0.158		0.357			0.285			0.137		

*statistically significant results; MVC = macrovascular complications; MVC+ = presence of macrovascular complications; MVC- = absence of macrovascular complications; p = difference between groups with and without MVC; p_1 = difference between T2DM only and T2DM + HT with MVC; p_2 = difference between T2DM only and T2DM + HT without MVC; p_3 = difference between T2DM only and T2DM + DNTG with MVC; p_4 = difference between T2DM only and T2DM + DNTG without MVC; p_5 = difference between T2DM only and T2DM + HT + DNTG with MVC; p_6 = difference between T2DM only and T2DM + HT + DNTG without MVC; T2DM = diabetes mellitus type 2; HT = hypothyroidism, DNTG = diffuse non-toxic goiter; TC = total cholesterol, TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-HDL-cholesterol; RC = remnant cholesterol.

Table 3. Cut-off points for serum lipid panel data as predictors of macrovascular complication development in type 2 diabetic patients with comorbid thyroid dysfunction

Variable	Study group	Cut-off point	Sensitivity	Specificity	AUC	95% CI AUC	p
TC (mmol/L)	T2DM+HT	≥5.11	0.79	0.67	0.73	0.52-0.94	<0.05
	T2DM+ DNTG	≥4.97	0.82	0.54	0.71	0.53-0.89	<0.05
	T2DM+HT + DNTG	≥4.89	0.93	0.50	0.88	0.71-1.00	<0.05
HDL-C (mmol/L)	T2DM+HT	≤0.95	0.39	0.33	0.22	0.07-0.36	>0.05
	T2DM+ DNTG	≤0.84	0.67	0.31	0.43	0.22-0.63	>0.05
	T2DM+HT+ DNTG	≤0.76	0.86	0.50	0.43	0.00-0.86	>0.05
TG (mmol/L)	T2DM+HT	≥2.03	0.79	0.78	0.77	0.62-0.94	<0.05
	T2DM+ DNTG	≥2.54	0.79	0.75	0.75	0,53-0.97	<0.05
	T2DM+HT+ DNTG	≥1.56	0.82	0.46	0.76	0,60-0,90	<0.05
LDL-C (mmol/L)	T2DM+HT	≥2.97	0.86	0.67	0.74	0.51-0.97	<0.05
	T2DM+ DNTG	≥3.21	0.82	0,54	0.72	0.55-0.89	<0,05
	T2DM+HT+ DNTG	≥2.93	0.79	0.75	0.95	0.83-1.00	<0.05
Non-HDL-C (mmol/L)	T2DM+ HT	≥4.29	0.75	0.78	0.77	0.56-0.98	<0.05
	T2DM+ DNTG	≥4.20	0.74	0.61	0.72	0.54-0.89	<0.05
	T2DM+HT+ DNTG	≥4.04	0.79	0.75	0.95	0.83-1.00	<0.05
RC (mmol/L)	T2DM+HT	≥0.91	0.67	0.56	0.60	0.42-0.79	>0.05
	T2DM+ DNTG	≥0.99	0.52	0.77	0.63	0.46-0.80	>0.05
	T2DM+HT + DNTG	≥1.14	0.79	0.75	0.75	0.53-0.97	<0.05

95% CI = 95% confidence interval; AUC = area under the ROC curve; T2DM = diabetes mellitus type 2; HT = hypothyroidism; DNTG = diffuse non-toxic goiter; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-HDL-cholesterol; RC = remnant cholesterol

Discussion

Diabetes mediators such as chronic hyperglycemia, dyslipidemia, and insulin resistance (IR), as well as end-products of glyco- and lipoxidation are all among factors producing vascular complications, the major morbid consequence of T2DM[9,10,34,35]. Dyslipidemia results in chronic accumulation of plaque in arteries, making it a crucial risk factor in the development of atherosclerosis. Dyslipidemia is defined as unhealthy levels of one or more circulatory lipid types, such as elevated levels of TG and TC, high levels of LDL particles, and low levels of HDL-C. While some individuals with T2DM may have high levels of LDL-C, it is the elevated low density LDL particles that produce a strong atherogenic effect[34,36]. Studies of diabetic patients demonstrate a significant association between several elevated levels, such as the TC/HDL-C ratio, non-HDL-C, and TG with arterial stiffness, which leads to the development of atherosclerosis and subsequent higher CVD mortality compared to non-diabetic controls[37,38]. For instance, 100 T2DM patients were enrolled in a cross-sectional study on the prevalence of dyslipidemia in South Africa. The patients who were within the 19-68 age range, had serum lipid abnormalities in 89% of the cases. In the study cohort, 56%, 64%, 61% and 65% of subjects had high TC, high TG, elevated LDL-C, and reduced HDL-C levels, respectively[12]. Dyslipidemia in T2DM is particularly common in patients older than 65 years[39,40]. Age-dependent changes of lipid metabolism may arise both as a result of mechanisms of biological aging and factors influencing age-dependent changes[41-43]. After age 20, serum LDL levels increase markedly in both men and women. At ages of 50-60 years (men) and 60-70 years (women), serum LDL levels remain at a plateau. Women have lower TC levels than men throughout their lives, but levels increase sharply after menopause and are higher than in men at age >60 years[44,45].

Our study compared serum lipid panel data in T2DM patients without thyroid dysfunction and T2DM patients with comorbid HT or/and DNTG, with a focus on macrovascular involvement. We showed that patients with comorbid thyroid dysfunction had a more pronounced dyslipidemia; the levels of TC and non-HDL-C were significantly higher in patients with comorbid HT, DNTG and their combination, while LDL-C levels were significantly higher in patients with comorbid HT and in those with comorbid HT and DNTG.

In the analysis of serum lipid panel data in the context of achieving normal target levels in T2DM patients without thyroid dysfunction and T2DM patients with comorbid HT or/and DNTG, we found significant differences between the respective levels of TC, HDL-C, TG, non-HDL-C in patients with comorbid HT; TC, non-HDL-C in patients with comorbid DNTG; and HDL-C, TG in patients with comorbid HT and DNTG. These lipid panel values can be used to evaluate the risk of MVC development in patients with T2DM and comorbid thyroid dysfunction. Furthermore, we found the following ROC curve optimal cut-off points for the serum lipid panel data, which determine the relative risk of MVC development in patients with T2DM and comorbid thyroid dysfunction: TC >5.11 mmol/L, TG ≥2.03 mmol/L, LDL-C ≥2.97 mmol/L and non-HDL-C ≥4.29 mmol/L in patients with comorbid HT; TC ≥4.97 mmol/L, TG ≥2.54 mmol/L, LDL-C ≥3.21 mmol/L and non-HDL-C ≥4.20 mmol/L in patients with comorbid DNTG; and TC ≥4.89 mmol/L, TG ≥1.56 mmol/L, LDL-C ≥2.93 mmol/L, non-HDL-C ≥4.04 mmol/L and RC ≥1.14 mmol/L in patients with comorbid HT and DNTG.

Previous studies showed a positive relationship between the severity of thyroid dysfunction and T2DM[46]. The available biochemical and clinical evidence suggests that both of these endocrine diseases can exacerbate each other in a feedback loop. For instance, diabetic patients with thyroid dysfunction tend to have poorer glycemic control, while their increased risk of lipid disorders, high blood pressure, and atherosclerosis contribute to the development and aggravation of vascular complications[47]. Mohamed *et al.* showed that T2DM patients with comorbid HT had a significantly increased incidence of dyslipidemia (p=0.017), diabetic nephropathy (p=0.003), diabetic retinopathy (p=0.004) and coronary heart disease (CHD) (p=0.011), compared to the group of euthyroid T2DM patients[48]. The same authors pointed out that serum lipid profiles of T2DM patients with comorbid HT had significantly higher TC and LDL-C levels compared to patients with only T2DM. In a study by Du *et al.* on the prevalence of cardio-cerebrovascular disease (CCVD) among patients with diabetes or prediabetes and with different severity of thyroid dysfunction, the authors showed

that CCVD prevalence was significantly different between the groups of diabetic patients with comorbid thyroid disease and those with diabetes only (34.12 *vs.* 26.50%; p<0.05)[49]. However, in prediabetic patients, no differences in CCVD prevalence was detected between those with and without thyroid disorders (16.60 *vs.* 15.86%; p=0.564). Furthermore, in patients with thyroid disorders, the prevalence of CCVD was significantly higher in diabetic compared to prediabetic patients (34.12 *vs.* 16.60%; p<0.01). Sarfo-Kantanka *et al.* showed the Framingham Risk Score of CHD in T2DM patients with comorbid thyroid disorder to be significantly higher compared to euthyroid T2DM patients (p<0.0001)[50]. The authors detected a strong positive correlation between elevated CHD risk and several serum markers including HbA1c (r=0.51, p<0.04), TC (r=0.49, p<0.0001), LDL-C (r=0.37, p<0.0001), and TSH (r=0.27, p=0.01)[50]. Molla *et al.* examined a total of 92 cases of T2DM patients with thyroid dysfunction and 183 cases of T2DM euthyroid patients. The mean LDL-C was significantly different between the study and control groups (116.92±45.9 *vs.* 102.34±43.97, p=0.016)[47]. Such elevated levels would predispose the patients to acceleration of atherosclerosis and subsequent development of cardiovascular events. On the other hand, Mehalingam *et al.* in their cross-sectional study on 311 T2DM patients failed to find a correlation between thyroid dysfunction and nephropathy or CVD. Notably, in that study HT was diagnosed in 13.9%, and hyperthyroidism in 3.6% of the subjects[51].

Although recent evidence suggests that TSH can mediate hyperlipidemia, while IR and subclinical HT are considered components of the metabolic syndrome, the underlying mechanism remains unclear[52,53]. Yan *et al.* showed in mice that TSH receptors expressed in hepatocytes could be stimulated by TSH to increase hepatic TG and induce hepatic steatosis, which is mediated by sterol response element-binding protein 1c (SREBP-1c)[54]. TSH also represses hepatic bile acid synthesis *via* the SREBP-2/HNF-4α/CYP7A1 signaling pathway[55]. In turn, cholesterol homeostasis is known to be regulated through modification of the rate-limiting enzyme of cholesterol synthesis, HMG-CoA reductase (HMGCR). AMP-activated protein kinase (AMPK) phosphorylates HMGCR, inactivating it. Zhang *et al.* suggest that this process could be regulated by TSH, proposing a potential mechanism for how a direct action of TSH in the liver can reduce hypercholesterolemia[56].

A cross-sectional study by Park *et al.* involving 132 346 subjects in a health checkup program aimed to determine the relationship between thyroid dysfunction and metabolic risk factors. The participants had TSH, fT4 and fT3 levels within the institutional reference ranges. While TSH levels were positively associated with the fT3/fT4 ratio within the euthyroid range, the higher fT3/fT4 ratio was associated with an increased risk of metabolic syndrome and IR; and the fT3/fT4 ratio was a better predictor of metabolic syndrome than TSH[57]. Jia *et al.* showed that CHD prevalence was significantly higher in the group of T2DM with subclinical HT compared to euthyroid diabetic patients (22.2% and 15.0%, respectively; p=0.039)[58]. Subclinical HT was found to be a nephropathy and CVD risk factor in T2DM patients[59]. In T2DM patients with subclinical hypothyroidism, the risk of cardiovascular events was significantly elevated after adjustment for age, sex, HbA1c, or other standard cardiovascular risk factors and medication (hazard ratio, 2.93; 95% CI, 1.15-7.48; p=0.024); however, it became nonsignificant after subsequent adjustment for urine albumin-to-creatinine ratio (hazard ratio, 2.06; 95% CI, 0.67–6.36; p=0.211). A study of T2DM patients with high cardiovascular risk failed to find association between plasma TSH levels in the normal range and the risk of myocardial infarction, vascular death, or all-cause mortality[60].

Our study had some limitations, i.e., sample size in study groups 2, 3 and 4 was small, follow-up period was short, the study was cross-sectional, and it did not follow the effects of thyroid dysfunction treatment on MVC risk reduction. Further studies with larger samples assessing the predictive value of TC, TG, LDL-C, non-HDL-C and RC for the development of MVC in patients with T2DM and comorbid HT and DNTG need to be considered.

Conclusion

We found that serum levels of TC >5.11 mmol/L, TG ≥2.03 mmol/L, LDL-C ≥2.97 mmol/L and non-HDL-C ≥4.29 mmol/L in T2DM patients with comorbid HT; TC ≥4.97 mmol/L, TG ≥2.54 mmol/L, LDL-C ≥3.21 mmol/L and non-HDL-C ≥4.20 mmol/L in T2DM patients with comorbid DNTG; TC ≥4.89 mmol/L, TG ≥1.56 mmol/L, LDL-C ≥2.93 mmol/L, non-HDL-C ≥4.04 mmol/L and RC ≥1.14 mmol/L in T2DM patients with a

combination of comorbid HT and DNTG could be used for stratification of patients into the category of increased risk of MVC development and to prevent further disability. Future studies on the interactions between THs and lipid variability in diabetic patients are needed to confirm the findings.

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.

Acknowledgments

The authors thank all the study participants.

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Sažetak

PROGNOSTIČKE VRIJEDNOSTI PODATAKA DOBIVENIH IZ PANELA LIPIDA ZA RAZVOJ MAKROVASKULARNIH KOMPLIKACIJA U BOLESNIKA S DIJABETESOM TIP 2 I SUPOSTOJEĆOM DISFUNKCIJOM ŠTITNJAČE

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Cilj ovog istraživanja je bio procijeniti prognostičke vrijednosti podataka dobivenih iz panela lipida u serumu za razvoj makrovaskularnih komplikacija (MVC) u bolesnika samo s dijabetesom tip 2 (T2DM) te u onih sa supostojećim hipotireodizmom (HT), difuznom netoksičnom strumom (DNTG) ili s kombinacijom ovih bolesti. U istraživanje je uključeno 596 bolesnika liječenih u bolnici. Analiza ROC (*receiver operating characteristic*) primijenjena je kako bismo utvrdili prognostički značajne vrijednosti ukupnog kolesterola (TC), triglicerida (TG), kolesterol lipoproteina visoke gustoće (HDL-C), kolesterol lipoproteina niske gustoće (LDL-C), ne-HDL kolesterola (ne-HDL) i ostatnog kolesterola (RC). Utvrđene su sljedeće prijelomne vrijednosti kao relativni rizik za razvoj MVC: TC >5,11 mmol/L, TG ≥2,03 mmol/L, LDL-C ≥2,97 mmol/L i ne-HDL-C ≥4,29 mmol/L u bolesnika s T2DM i supostojećim HT; TC ≥4,97 mmol/L, TG ≥2,54 mmol/L, LDL-C ≥3,21 mmol/L i ne-HDL-C ≥4,20 mmol/L u bolesnika s T2DM i supostojećom DNTG; i TC ≥4,89 mmol/L, TG ≥1,56 mmol/L, LDL-C ≥2,93 mmol/L, ne-HDL-C ≥4,04 mmol/L i RC ≥1,14 mmol/L u onih s istodobno postojećim HT i DNTG. Dakle, serumske razine TC, TG, LDL-C, ne-HDL-C i RC mogu se rabiti za grupiranje bolesnika s T2DM i supostojećom disfunkcijom štitnjače u kategoriju s povećanim rizikom od razvoja MVC.

Ključne riječi: *Dijabetes melitus tip 2; Hipotireodizam; Difuzna netoksična struma; Dislipidemija; Makrovaskularne komplikacije*