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Original Research

Laboratory criteria for comorbid course of type 2 diabetes mellitus and thyroid dysfunction

Volodymyr Musiienko[1,*], Ivan Lukasevych[2], Khrystyna Maksiv[1], Iryna Bandas[3]

[1] Department of Functional and Laboratory Diagnostics, I Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
[2] Department of Physical Therapy and Ergotherapy, National University of Ukraine on Physical Education and Sport, Kyiv, Ukraine
[3] Department of Medical Biochemistry, I Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

***Correspondence to:** Volodymyr Musiienko, Department of Functional and Laboratory Diagnostics, I Horbachevsky Ternopil National Medical University, Ternopil, Ukraine, Phone: +380687727054, E-mail id: musiienko@tdmu.edu.ua

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Abstract

Background and aims: Diabetes mellitus (DM) rates have reached endemic levels, which is a major challenge for the modern health care system; the vast majority are patients with type 2 diabetes mellitus (T2DM). The presence of other comorbidities drastically affects diabetic patient outcomes, treatment, and management options. The aim of our study was to analyze routine laboratory data of type 2 diabetic patients with thyroid dysfunction and search for possible markers of comorbid course of T2DM, hypothyroidism (HT), and diffuse nontoxic goiter (DNG). **Material and method:** We analyzed 596 medical records of T2DM patients without thyroid dysfunction and with comorbid HT and/or DNG. **Results and conclusions:** Type 2 diabetic patients with comorbid HT or DNG have significantly higher BMI, increased level of HbA_{1c} and increased ESR compared with patients with T2DM without thyroid dysfunction. The progression of lipid metabolism disorders in patients with a comorbid course of t T2DM and HT is characterized by a significant decrease in HDL-C level, as well as an increase of RC and TG levels compared with T2DM only, as well as the comorbidity of T2DM and DNG.

Keywords: type 2 diabetes mellitus, hypothyroidism, diffuse nontoxic goiter, laboratory data.

Background and aims

Diabetes mellitus (DM) rates have reached endemic levels, which is a major challenge for the modern health care system. The presence of other comorbidities drastically affects DM patient outcomes, treatment, and management options. Today, there are 463 million registered patients with this disease in the world, and by 2030 their number could reach 578 million. The vast majority are patients with type 2 diabetes mellitus (T2DM) (about 90%) [1–5]. If left untreated, it can lead to frequent hospitalizations and premature death. Diabetes and its complications are among the top 10 causes of death in the world. Most patients with T2DM have at least one complication [6–10]. Dysfunction of the thyroid gland, after DM, is the second most common metabolic dysfunction in the world [11]. In recent years, researchers have paid more attention to the comorbid course of T2DM with thyroid dysfunction. Among patients with T2DM, thyroid dysfunction is more common than in the general population. The prevalence of thyroid dysfunction among patients with T2DM has been reported to range from 2.2 to 17.0% [12, 13].

Hypothyroidism (HT) and diffuse nontoxic goiter (DNG) are common thyroid pathologies. In regions with sufficient iodine intake, the prevalence of primary HT ranges from 1.0 to 2.0% [14]. On the other hand, in patients with T2DM, according to various authors, the prevalence of HT ranges from 5.7 to 37.1% [15–17]. The prevalence of DNG increases with increasing iodine deficiency and becomes endemic in populations where iodine intake is insufficient [18]. Thus, in the world population, the prevalence is 15.8%, ranging from 4.7% in America to 28.3% in Africa [19]. The main risk factors for the emergence of DNG are age, sex, hereditary history, iodine levels in household salt, and socio-economic conditions [20–23]. Recently, researchers have increasingly focused on the relationship between insulin resistance (IR), which is a hallmark of T2DM, and abnormal thyroid function and morphology.

The aim of our study was to analyze routine laboratory data of type 2 diabetic patients with thyroid dysfunction and search for possible markers of comorbid course of T2DM, hypothyroidism, and DNG.

Material and method

For the purpose of retrospective analysis of medical records, the study included 596 patients with T2DM who were hospitalized in the Endocrinology department of the municipal nonprofit enterprise "Ternopil University Hospital" of Ternopil Regional Council in 2019. Patients were divided into 4 groups: group 1 (501 patients with T2DM without comorbid thyroid dysfunction), group 2 (37 patients with T2DM and comorbid HT), group 3 (40 patients with T2DM and comorbid DNG), and group 4 (18 patients with comorbid T2DM, HT, and DNG).

The diagnosis of T2DM was confirmed according to the recommendations of the American Diabetes Association. The diagnosis criteria use the level of glycated hemoglobin (HbA_{1c}) (≥6.5%), which was determined using an automatic biochemical analyzer COBAS 6000 (Roche Hitachi, Germany) and plasma glucose level, which was determined on an automatic biochemical analyzer BAS INTEGRA® 400 (Roche Diagnostics) using a standard set [24]. HT was diagnosed according to the criteria of the European Thyroid Association: elevated levels of thyroid-stimulating hormone (TSH) in combination with a decrease in free thyroxin (T4) [25]. If T4 values were within normal limits, subclinical hypothyroidism (SCH) was diagnosed. The diagnosis of DNG was confirmed according to the WHO guidelines [26]. The 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 or nodular alteration(s) occurred in the enlarged or normal thyroid gland.

Patients with a history of other thyroid diseases (than HT and DNG), patients which were prescribed thyroid hormone-related drugs, patients with pregnancy or lactation, as well as with cancer, infectious diseases, neurological or mental diseases (depression, anxiety, and schizophrenia) were excluded from the study.

Thyroid sonography was performed for all participants including transverse and longitudinal locations. Maximal width (w), depth (d), and height (h) of each lobe were measured and each lobe volume was calculated by Brunn J. et al. method [27]:

$$V\ (cm^3) = 0.479 \times d \times w \times h\ ,\ \text{where}$$

w, d, h – mutually perpendicular dimensions of thyroid gland; 0.479 – coefficient.

Total volume of the thyroid was estimated as both lobes volumes sum.

A complete blood count (CBC) was performed using a Yumizen H500 CT automatic hematology analyzer. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in blood serum were determined using a standard kit with a COBAS INTEGRA® Diagnostics automatic biochemical analyzer.

Fasting venous blood (5 ml) was collected from each individual after an overnight fast of over 10 hours. Serum lipid panel values were determined by the Biochemical Laboratory of Ternopil University Hospital; total cholesterol (TC), triacylglycerol (TG), and high-density lipoprotein cholesterol (HDL-C) were determined with commercially available kits on a Cobas 6000 analyzer (Roche Hitachi, Germany).

Friedewald equation was used to calculate low-density lipoprotein cholesterol (LDL-C) levels (if serum TG <4.5 mmol/l): LDL-C (mmol/l) = TC – HDL-C – (0.45 × TG).

Non-HDL-C was calculated using the following formula (if serum TG >4.5 mmol/l): non-HDL-C (mmol/l) = TC – HDL-C.

Remnant cholesterol (RC) was calculated using the following formula: RC (mmol/l) = TC – (HDL-C + LDL-C).

Plasma insulin level was determined with the help of enzyme-linked immunosorbent analyzer "Thermo Scientific Multiskan FC" using a DRG set (Germany). HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) index was used to determine IR. It was calculated using the formula: HOMA-IR= (fasting plasma glucose, mmol/l × fasting plasma insulin, μIU/ml)/22.5 [28].

Body mass index (BMI) was calculated using the formula: body weight (kg) / height (m^2).

Study results were analyzed using STATISTICA 7.0. The Kolmogorov–Smirnov test was used to compare probability distributions. Quantitative values, due to their non-parametric distribution, are presented as the median, lower, and upper quartiles, and compared using the Mann–Whitney test.

Results

Analysis of the data of type 2 diabetic patients included in the study (Table 1) showed that the average age of patients in the group T2DM was 56 (50; 62) years, 56 (52; 61) years in the group T2DM + HT, 58 (55; 64.3) years in the group T2DM + DNG and 58 (57; 68) years in the group T2DM + HT + DNG. BMI in the group T2DM + HT + DNG was significantly higher by 15.9% compared with the group T2DM without thyroid pathology, by 11.8% compared with the group T2DM + HT, and by 12.4% compared with the group T2DM + DNG.

The evaluation of the CBC data revealed a significantly higher level of ESR (p = 0.038) in patients with a comorbid course of T2DM, HT, and DNG compared with patients with only T2DM. The level of hemoglobin and RBC count in the group of T2DM + HT + DNG was 4.4% and 4.6% lower, respectively, compared with only T2DM (Table 2).

The evaluation of glucose metabolism (Table 3) revealed significantly higher levels of HbA_{1c} by 20.4% in the group T2DM + HT + DNG compared with only the T2DM group. Comparing data on insulin, fasting glucose, and HOMA-IR index, no significant differences were found between the study groups.

Evaluating the data of the lipid panel (Table 4), we found significantly higher levels of RC by 64.0% and 23.6% lower levels of HDL-C in the group T2DM + HT + DNG compared with only

Table 1: Characteristics of the study groups.

Group	Age (years)	BMI (kg/m²)	Sex	
			Male n (%)	Female n (%)
T2DM	56 (50; 62)	30.5 (26.3; 34.2)	274 (54.7)	227 (45.3)
p_1	0.176	<0.001*	<0.001*	
T2DM + HT	56 (52; 61)	31.6 (27.4; 34.7)	4 (10.8)	33 (89.2)
p_2	0.163	0.035*	0.987	
T2DM + DNG	58.0 (55.0; 64.3)	31.4 (28.1; 35.4)	4 (10)	36 (90)
p_3	0.630	0.020*	0.911	
T2DM + HT +DNG	58 (57; 68)	35.3 (30.4; 36.7)	2 (11.11)	16 (88.89)

Note: p_1 – T2DM vs. T2DM + HT + DNG, p_2 – T2DM + HT vs. T2DM + HT + DNG, p_3 – T2DM + DNG vs. T2DM + HT + DNG; *Statistically significant difference.

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Table 2: The indices of CBC in type 2 diabetic patients with comorbid thyroid dysfunction.

Group	Hemoglobin (g/l)	Red blood cells (RBC) (10^{12})	Color index	Erythrocyte sedimentation rate (ESR) (mm/hour)
T2DM	138 (127; 149)	4.4 (4; 4.7)	0.9 (0.9; 1)	11 (6; 20)
p_1	0.044*	0.026*	0.956	0.038*
T2DM + HT	126 (116; 139)	4.2 (4.0; 4.6)	0.9 (0.9; 1)	13 (10; 22)
p_2	0.302	0.596	0.701	0.602
T2DM + DNG	130 (127; 145)	4.3 (4; 4.6)	1.0 (0.9; 1)	18 (12; 24)
p_3	0.333	0.216	0.245	0.730
T2DM + HT +DNG	132 (122; 138)	4.2 (3.95; 4.3)	0.9 (0.9; 1)	14.5 (10.25; 23.5)

Note: p_1 – T2DM vs T2DM + HT + DNG, p_2 – T2DM + HT vs T2DM + HT + DNG, p_3 – T2DM + DNG vs T2DM + HT + DNG; *Statistically significant difference.

Table 3: The indices of glucose metabolism in type 2 diabetic patients with comorbid thyroid dysfunction.

Group	Glucose, mmol/l	HbA1c, %	Insulin, µIU/ml	HOMA-IR
T2DM	9.4 (7.5; 12.1)	8.1 (7.0; 9.3)	13.9 (9.9; 17.3)	5.6 (4.6; 6.8)
p_1	0.975	0.005*	0.312	0.138
T2DM + HT	9.9 (8.0; 12.4)	9 (7.5; 10.0)	14.3 (10.3; 17.2)	6.1 (4.5; 7.7)
p_2	0.622	0.154	0.500	0.809
T2DM + DNG	8.5 (7.8; 10.2)	8.7 (7.6; 10.1)	15.0 (10.8; 18.7)	5.9 (4.6; 6.7)
p_3	0.444	0.160	0.886	0.187
T2DM + HT +DNG	9.4 (7.9; 10.7)	9.8 (8.1; 11.1)	16.3 (11.7; 17.3)	6.4 (5.9; 7.1)

Note: p_1 – T2DM vs. T2DM + HT + DNG, p_2 – T2DM + HT vs. T2DM + HT + DNG, p_3 – T2DM + DNG vs. T2DM + HT + DNG; *Statistically significant difference.

Table 4: The lipid panel data in type 2 diabetic patients with comorbid thyroid dysfunction.

Group	TC, mmol/l	HDL-C, mmol/l	LDL-C, mmol/l	RC, mmol/l	non-HDL-C, mmol/l	TG, mmol/l
T2DM	5.0 (4.3; 5.9)	1.1 (1.0; 1.2)	3.1 (2.4; 3.9)	0.8 (0.4; 1.2)	3.9 (3.2; 4.7)	1.8 (1.1; 2.8)
p_1	0.833	<0.001*	0.494	<0.001*	0.279	0.008*
T2DM + HT	5.3 (4.8; 6.0)	1.0 (0.8; 1.2)	3.3 (2.6; 3.9)	1.1 (0.7; 1.3)	4.5 (3.7; 4.9)	2.5 (1.9; 2.9)
p_2	0.169	0.187	0.097	0.093	0.346	0.164
T2DM + DNG	5.3 (4.7; 6.0)	1.0 (0.8; 1.3)	3.2 (2.8; 4.1)	1.0 (0.6; 1.2)	4.1 (3.6; 4.8)	2.1 (1.4; 2.7)
p_3	0.415	0.071	0.150	0.014*	0.769	0.014*
T2DM + HT +DNG	5.0 (4.8; 5.6)	0.8 (0.8; 1.0)	2.9 (2.6; 3.3)	1.2 (1.1; 1.3)	4.0 (3.7; 4.6)	2.7 (2.5; 2.9)

Note: p_1 – T2DM vs. T2DM + HT + DNG, p_2 – T2DM + HT vs. T2DM + HT + DNG, p_3 – T2DM + DNG vs. T2DM + HT + DNG; *Statistically significant difference.

the T2DM group. There was also a 49.7% increase in TG level in patients with comorbid T2DM, HT, and DNG compared with T2DM patients without thyroid pathology. Significantly higher levels of RC (p=0.014) and TG (p=0.014) were also found in the group T2DM + HT + DNG compared to T2DM + DNG group.

During the study of biochemical profile parameters, we found significantly higher levels only of AST activity in the group T2DM + HT + DNG 25.2 (22; 30.6) U/l compared to T2DM + DNG 18.2 (13.3; 24.7) U/l (p=0.028) and with only T2DM 18.1 (14.2; 25.8) U/l (p = 0.014). No statistically significant difference was found between other studied biochemical parameters.

Table 5: Thyroid hormone levels in type 2 diabetic patients with comorbid thyroid dysfunction.

Group	TSH (mIU/l)	T4 (pmol/l)
T2DM	1.9 (1.6; 2.8)	16.0 (15.0; 17.2)
p_1	<0.001*	<0.001*
T2DM + HT	4.6 (2.5; 8.4)	9.9 (8.8; 12.6)
p_2	0.647	0.424
T2DM + DNG	1.7 (0.9; 3.5)	14.8 (12.4; 17.6)
p_3	0.003*	<0.001*
T2DM + HT + DNG	4.0 (2.8; 5.1)	10.4 (9.7; 12.4)

Note: p_1 – T2DM vs. T2DM + HT + DNG, p_2 – T2DM + HT vs. T2DM + HT + DNG, p_3 – T2DM + DNG vs. T2DM + HT + DNG; *Statistically significant difference.

When evaluating the level of thyroid hormones (Table 5), significantly lower TSH levels were obtained in the group of patients with only T2DM compared to the group of T2DM + HT + DNG (p<0.001) and significantly higher by 64.9% T4 levels (p<0.001), respectively. There are also higher levels of TSH (p<0.001) and lower T4 (p<0.001) in the group T2DM + HT + DNG compared with T2DM + DNG.

When comparing the measurements of thyroid ultrasound, it was revealed significantly higher size of the thyroid gland in the group T2DM + HT + DNG compared with only T2DM and T2DM + HT. Thus, the total thyroid volume was 47.4% and 51.3% higher in the group T2DM + HT + DNG compared with the groups only T2DM and T2DM + HT, respectively (Table 6).

Discussion

Thyroid dysfunction, obesity, and T2DM are among the most common endocrine disorders and they are often concomitantly present in the same patient [29–31]. The frequency of thyroid dysfunction among T2DM patients is higher than that of the general population. There are data available that the prevalence of HT in T2DM patients ranges from 6.0 to 20.0% across different ethnic groups [12, 15]. On the contrary, Smithson reported lower prevalence rates for thyroid dysfunction in T2DM patients [32]. These inconsistencies could be explained by differences

Table 6: Thyroid gland ultrasound parameters in type 2 diabetic patients with comorbid thyroid dysfunction.

Group	Total volume (cm^3)	Right lobe (cm^3)	Left lobe (cm^3)	Isthmus (mm)
T2DM	11.6 (9.1; 15.2)	6.1 (4.5; 7.2)	6.1 (4.6; 8.0)	5 (3.7; 5.5)
p_1	0.018*	0.047*	0.048*	0.739
T2DM + HT	11.3 (9.6; 14.1)	5.4 (4.4; 7.2)	6 (4.8; 6.7)	4.3 (3.7; 5.2)
p_2	<0.001*	0.003*	<0.001*	0.102
T2DM + DNG	15.6 (12.7; 20.1)	8.1 (6.6; 10.1)	8.0 (5.6; 9.5)	5 (4.3; 6.2)
p_3	0.775	0.980	0.410	0.562
T2DM + HT +DNG	17.1 (14.4; 18.6)	8.9 (6.7; 9.5)	7.9 (6.8; 10.6)	5.1 (4.4; 5.4)

Note: p_1 – T2DM vs. T2DM + HT + DNG, p_2 – T2DM + HT vs. T2DM + HT + DNG, p_3 – T2DM + DNG vs. T2DM + HT + DNG; *Statistically significant difference.

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in age, sex, and iodine intake in the populations surveyed [33]. Undiagnosed thyroid dysfunction may affect metabolic control and enhance cardiovascular, and other chronic complication risks in diabetic patients [34], therefore, it is very important to determine risk factors for thyroid dysfunction development among T2DM patients.

Obesity or overweight, according to the WHO, occurs in 44% of patients with diabetes [35]. Patients with HT are also often found to be overweight [36, 37]. In a study by Nair et al. [38] BMI was significantly higher in patients with a comorbid course of T2DM and HT ($p \leq 0.001$) compared with euthyroid T2DM patients. Patients with a BMI> 35 kg/m2 were 20 times more likely to develop T2DM [39]. There were 16 females and 2 males in the group T2DM + HT + DNG in our study. Women suffer from HT 10 times more often than men [14]. Also, according to Gebremichael et al. women are almost twice as likely to develop goiter as men [40].

The evaluation of the CBC data revealed significantly higher ESR, lower levels of hemoglobin and RBC in the group of T2DM + HT + DNG compared with T2DM without thyroid dysfunction. It should be noted that the results of our previous studies of the comorbid course of T2DM and HT showed in patients laboratory signs of anemia (decreased hemoglobin and RBC). We also found previously that the combination of T2DM and HT significantly increases the level of ESR [4, 41].

The evaluation of glucose metabolism revealed significantly higher levels of HbA_{1c} in the group T2DM + HT + DNG compared with T2DM only. There are data that thyroid dysfunction is more common in patients with HbA_{1c} levels above 8% [42]. Barmpari et al. reported higher levels of HbA_{1c} in patients with T2DM and HT compared with patients without HT [17]. The results of our previous studies have shown that the combination of T2DM and HT significantly increases the level of HbA_{1c} in patients with T2DM [41].

Evaluating the data of the lipid panel, we found significantly higher levels of RC and lower levels of HDL-C in the group T2DM + HT + DNG compared with T2DM only. There was also an increase in TG levels in patients with comorbid T2DM, HT and DNG compared with T2DM without thyroid dysfunction. Significantly higher levels of RC and TG in the group of T2DM + HT + DNG were also found in comparison with T2DM + DNG. Dyslipidemia is observed in patients with T2DM and thyroid dysfunction. So, Du et al. [43] identify low levels of HDL-C in T2DM patients as a risk factor for thyroid dysfunction. Elgazar et al. [42] also reported in their study a significant increase in TG levels in T2DM patients and thyroid dysfunction compared with only T2DM patients. During the study of T2DM and HT, we also found the progression of dyslipidemia compared with only T2DM patients [4, 41].

Studies of thyroid function in other researches show higher levels of TSH and T4 in patients with a comorbid course of T2DM and thyroid dysfunction compared with only T2DM patients [14, 40]. The obtained results indicate a bidirectional relationship between thyroid function and T2DM, which is subject to complex interactions and indicates common mechanisms of HT and DNG in the case of T2DM [44].

Conclusions

Type 2 diabetic patients with comorbid hypothyroidism or DNG have significantly higher BMI, increased level of HbA_{1c}, and increased ESR compared with patients with T2DM without thyroid dysfunction. The progression of lipid metabolism disorders in patients with a comorbid course of T2DM and hypothyroidism is characterized by a significant decrease in HDL-C level, as well as an increase in RC and TG levels compared with T2DM only, as well as the comorbidity of T2DM and DNG.

Conflict of Interest

The authors declare no conflict of interest.

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