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Combined endocrine pathology under conditions of chronic stress of war

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Abstract. In patients with diabetes mellitus (DM), compared to normoglycemic individuals, pathology of the thyroid gland is more common, patients with combined endocrinopathies have worse glycemic control and are more prone to the development of complications. Thyroid hormones affect glucose metabolism through their effect on peripheral tissues; in turn, with type 2 diabetes mellitus (T2DM), the conversion of thyroxine into triiodothyronine in tissues decreases, and insulin resistance (IR) and hyperinsulinemia contribute to proliferation of thyroid tissue, nodule formation, and thyroid gland growth in size. Vitamin D deficiency is observed in 70% of people with DM. Considering the stress load of recent years, it is relevant to study the dynamics of the combination of T2DM and hypothyroidism, including on the background of vitamin D deficiency as an aggravating factor. **The aim:** to evaluate the dynamics of the proportion of elevated thyroid-stimulating hormone (TSH) levels in T2DM patients, patients with IR, and patients without DM and IR during the period from 2021 to 2024, inclusive, and the average level of vitamin D provision as of 2024. **Material and methods.** In the period 2021-2024 a prospective study was conducted, which included patients with T2DM and a glycated hemoglobin level ≥7%, patients with IR without DM, and patients without DM and IR aged 19-75 years. As part of the study, the TSH level was determined in 649 patients with T2DM (group 1) aged 19-75 from different regions of Ukraine. 690 patients with IR without DM (group 2) and 665 patients without DM and IR (group 3) were included in the comparison group. Examination for TSH was carried out annually. The results for 2021-2024 were compiled in 3 groups of patients. The assessment of the level of 25-hydroxyvitamin D (25(OH)D) was carried out in 2024. Laboratory assessment of the level of vitamin D and TSH was carried out by chemiluminescent immunoassay. **Results.** In the studied group of patients with T2DM, a significant increase in the proportion of patients with elevated TSH was found in 2022. In patients with IR, there is a trend of a progressive increase in the proportion of elevated TSH from 2022 to 2024, the changes are not reliable. In the group of patients without DM and IR in the 3rd year of the war (2024), the proportion of elevated TSH significantly increased compared to the pre-war period. The average level of 25(OH)D in patients with T2DM and elevated TSH is significantly lower (48.6 nmol/L) than in patients without DM and IR (72.6 nmol/L). **Conclusions.** Taking into account the increase in the number of cases of elevated TSH among patients with T2DM, patients with IR on the background of chronic stress, it is necessary to actively identify this category of people, with the aim of clarifying the thyroid gland pathology and for correction of hypothyroidism in time. The level of vitamin D supply in patients with combined endocrine pathology remains within the limits of vitamin D deficiency, which increases the risks of developing of chronic complications of DM and autoimmune pathology. It is necessary to supply sufficient correction of vitamin D deficiency in terms of duration and dose.

Keywords: type 2 diabetes mellitus, combined endocrine pathology, vitamin D deficiency, hypothyroidism, chronic stress.

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Among endocrine diseases, DM and thyroid pathology are the most common in the population, their association is often observed in clinical practice. In patients with DM, compared to individuals with normoglycemia, thyroid pathology is more common, patients with both endocrinopathies have worse glycemic control and they are more prone to the development of complications [1]. The range of prevalence of thyroid pathology in patients with T2DM ranges from 9.9 to 48% according to researches [2-4].

Thyroid hormones affect glucose metabolism through their effect on peripheral tissues (the gastrointestinal tract, the liver, the skeletal muscles, the adipose tissue, the pancreas). In T2DM, the conversion of thyroxine into triiodothyronine in peripheral tissues decreases, and insulin resistance and hyperinsulinemia contribute to the proliferation of thyroid tissue, nodulation, and thyroid growth [5]. Insulin resistance can develop in subclinical hypothyroidism as a result of a decrease in the rate of insulin-stimulated glucose transport caused by the translocation of the glucose transporter type 2 (GLUT 2) gene, which plays a crucial role in the pathogenesis of both T2DM and thyroid dysfunction [6]. The connection between thyroid hormones and T2DM is based on a number of biochemical and molecular events, gene polymorphism, disruption of gene expression and regulation, as well as disruption of glucose absorption in the intestines, reduction of peripheral utilization of glucose in tissues, changes in the process of hepatic gluconeogenesis [7].

Among the features of combined endocrine pathology like T2DM and thyroid pathology, it should be noted that some observational studies indicate a connection between thyroid cancer and T2DM, especially in women, as well as an increased risk of medullary carcinoma of the thyroid gland after treatment with glucagon-like peptide receptor agonists-1, hyperinsulinemia directly enhances cancer progression through overexpression of insulin receptors or indirectly through IGF-1 signaling [1]. Han C. et al. conducted a systematic review of the correlation between subclinical hypothyroidism and T2DM and estimated the prevalence of subclinical hypothyroidism in DM at 10.2%, compared with the general population, where the prevalence of subclinical hypothyroidism varies from 4% to 9% according to different authors, and the prevalence of overt hypothyroidism was 5.7% in patients with T2DM compared to prevalence 1.8% in individuals with normal glycemia, which indicates the existing correlation between T2DM and hypothyroidism [8, 9]. A large-scale cross-sectional study by Gu Y. et al. demonstrated that levels of TSH, free thyroxine (T4), and triiodothyronine (T3) correlate with the risk of T2DM, even when they are within the normal range [10].

The effect of DM on thyroid function is realized by changing the level of TSH and inhibiting the peripheral tissue conversion of T4 into T3. In patients with DM and normal thyroid function, the nocturnal peak of TSH is absent or weak, and the response of TSH to thyrotropin-releasing hormone is impaired [11]. In obese patients, elevated leptin levels stimulate the hypothalamus-pituitary-thyroid axis and lead to increased TSH levels. Vitamin D deficiency occurs in 70% of individuals with DM, and under this condition deiodinase II inactivation leads to decreased transcription of glucose transporter 4 (GLUT4) in skeletal muscle and adipose tissue, thus causing IR and thyroid carcinogenesis [12, 13]. Taking into account stress in the recent years (formation of the post-Covid syndrome, the distress of the russian-Ukrainian war), it is relevant to study the dynamics of the combination of T2DM with hypothyroidism, on the background of vitamin D deficiency, since such a combination mutually aggravates the course of the pathology.

The aim of the work was to evaluate the dynamics of the proportion of elevated TSH levels in T2DM patients, patients with IR, and patients without DM and IR during the period from 2021 to 2024, including the average vitamin D status in 2024 year.

Material and methods

In the period 2021-2024 a prospective study was conducted, which included patients with T2DM and glycated hemoglobin level ⩾7%, patients with IR without DM, and patients without DM and IR aged 19-75 years. Exclusion criteria were: T2DM with severe chronic complications, glycated hemoglobin level <7%, acute inflammatory processes, oncological diseases, body mass index ⩾40 kg/m^2, taking antidepressants, vitamin D drugs less than 2 months before the study.

As part of the study, the TSH level was determined in 649 patients with T2DM aged 19-75 (group 1). 690 patients with IR without DM (group 2) and 665 patients without DM and IR (group 3) were included in the comparison group. The groups were comparable in terms of age and sex. General characteristics of patients are presented in **Table 1**.

Table 1. Characteristics of 3 groups of patients included in the study

Indicators	Before war	2022	2023	2024
		T2DM		
n	164	142	172	171
Age, years	40.2±2.5	42.2±4.0	38.4±3.2	41.2±2.5
Gender, M/F	49/115	40/102	45/127	43/128
BMI, kg/m^2	32.4±4.4	33.6±5.1	32.5±3.2	34.6±4.0
HbA1c,%	8.4±1.6	8.5±1.7	8.8±1.5	7.9±2.1
HOMA index	6.4±1.8	5.9±3.5	4.5±2.5	5.8±3.0
		IR without DM		
n	126	184	191	189
Age, years	39.1±3.3	41.2±2.8	43.2±3.1	41.5±3.5
Gender, M/F	42/84	55/129	50/141	45/144
BMI, kg/m^2	33.4±3.5	35.3±2.8	36.8±5.6	35.2±4.5
HbA1c,%	5.7±0.7	5.6±0.4	5.9±0.5	5.5±0.6
HOMA index	7.2±3.8	6.2±3.5	4.9±2.0	5.7±2.2
		Without DM and IR		
n	172	160	156	177
Age, years	41.0±2.6	40.6±3.2	37.8±4.7	39.1±3.1
Gender, M/F	58/114	50/110	42/114	41/136
BMI, kg/m^2	27.4±3.7	26.6±6.4	29.1±3.5	31.1±4.5
HbA1c,%	5.4±0.2	4.9±0.6	5.2±0.4	5.2±0.3
HOMA index	2.1±0.3	1.9±0.4	1.6±0.3	1.9±0.5

In 2024, vitamin D status was determined in patients whose TSH level exceeded 4.0 mIU/L.

TSH research was carried out annually. The results for 2021, 2022, 2023, 2024 were compiled in 3 groups of patients. The assessment of the 25(OH)D level was carried out in 2024.

The following methods and criteria were used in the statistical evaluation of the results: the xi-square test was used for comparison, posterior comparisons were carried out according to Fisher's exact test, taking into account the Bonferroni correction. Statistical calculations were performed using the Statistical software EZR v. 1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Austria).

Laboratory evaluation of vitamin D level was carried out in the morning fasting using «25-hydroxycalciferol» test, which was performed by CLIA – chemiluminescent immunoassay method. Determination of TSH was also carried out by chemiluminescent immunoassay, by highly sensitive, biotin-independent method.

According to the conclusion of the Ethics Committee of O.O. Bogomoletz National Medical University (protocol No. 18 dated June 6, 2023), the study fully complied with ethical, moral and legal requirements in accordance with the Order of the Ministry of Health of Ukraine No. 281 dated November 1, 2000, the Declaration of Helsinki of the World Health Organization on the Ethical Principles of Conducting Scientific Medical Research with Human Participation.

Results and discussion

In the examined T2DM patients of study group, a significant increase in the proportion of patients with elevated TSH was found in 2022 ($p<0.05$). In patients with IR, there is a trend of a progressive increase in the proportion of elevated TSH from 2022 to 2024, the changes are not reliable. In the group of patients without DM and IR in the 3rd year of the war (2024), the proportion of elevated TSH significantly increased compared to the pre-war period ($p<0.05$) (**Table 2**).

TSH levels are distributed taking into account the reference values: 0.4-4.0 mIU/L.

The average levels of 25(OH)D in 3 compared groups with elevated TSH were for T2DM group 48.6±5.4 nmol/L, for IR group 61.2±7.5 nmol/L and for group without T2DM and IR 72.6± ±8.4 nmol/L. A significantly lower 25(OH)D was observed in the group of patients with T2DM compared to the group without T2DM and IR ($p<0.05$).

Thus, based on previous scientific data, the analysis of thyroid function indicators in patients with DM is very important and contributes to the early diagnosis of disorders that are clinically asymptomatic or may be masked by other diseases. This is evidenced by the data obtained, which demonstrated a significant increase in plasma TSH levels in 28.6% of cases of T2DM [5,7].

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Table 2. Distribution of TSH in the groups of patients in the period 2021-2024, abs. (%)

TSH level, mIU/L	Before war	2022	2023	2024	p
			T2DM		
	n=164	n=142	n=172	n=171	
<0.4	3 (1.6%)	14 (9.5%)	5 (2.8%)	3 (1.9%)	
0.4 до 4	148 (90.6%)	101 (71.4%)	150 (87.5%)	152 (89.0%)	0.018
>4	13 (7.8%)	27 (19%)*	17 (9.7%)	16 (9.1%)	
			IR without DM		
	n=126	n=184	n=191	n=189	
<0.4	4 (3.1%)	3 (1.8%)	4 (2.1%)	5 (2.7%)	
0.4 до 4	110 (87.6%)	162 (88.0%)	165 (86.5%)	160 (84.6%)	0.234
>4	12 (9.4%)	19 (10.2%)	22 (11.4%)	24 (12.7%)	
			Without DM and IR		
	n=172	n=160	n=156	n=177	
<0.4	6 (3.3%)	4 (2.6%)	3 (2.1%)	4 (2.1%)	
0.4 до 4	157 (91.4%)	145 (90.4%)	139 (89.1%)	158 (89.0%)	0.019
>4	9 (5.4%)	11 (7.0%)	14 (8.8%)	16 (8.9%)*	

*Note. xi-square test was used for comparison; * p<0.05 compared to the before war.*

The proportion of cases of elevated TSH among T2DM in our study ranged from 7.8% to 19%, which compared to literature data on concomitant hypothyroidism is higher (an average of 5.7%), and the proportion of cases of elevated TSH among patients without T2DM and IR ranged from 5.4% to 8.9%, which is also higher compared to literature data (1.8% on average), which may indicate an additional consolidated negative effect of chronic stress on the pathogenesis of T2DM and hypothyroidism, since the IR state affects the function of the hypothalamus-pituitary-thyroid axis [8, 9]. Chronic stress also affects this axis: due to an increase in the level of cortisol, changes in the processes of excitation/inhibition in the cerebral cortex and subcortical structures [14]. Generally, data from other researchers indicate that the diagnosis of hypothyroidism in patients with diabetes was not always established in time due to the fact that typical hypothyroidism complaints of dry skin, memory impairment, muscle weakness, fatigue, etc. were long associated with the presence of diabetes and its complications [5,12].

In all groups of patients, the proportion of elevated TSH increased in 2022, which could be associated with a violation in the provision of hormone replacement therapy (L-thyroxine), stress and stimulation of the development or exacerbation of existing thyroid autoimmune pathology, decompensation of DM, development of IR and chronic complications of DM.

The results of the study of vitamin D levels of supply in patients were assessed according to the criteria of the Ukrainian experts consensus statement «Diagnosis, prevention and treatment of vitamin D deficiency in adults» [15]. According to the Statement, the body is sufficiently supplied with vitamin D when the level of 25(OH)D in the blood reaches 100-125 nmol/L. A decrease in the indicator to less than 75 nmol/L is considered as vitamin D deficiency, as a result of which the protective functions of the body decrease and chronic diseases get worsened. Vitamin D deficiency is diagnosed when the level of 25(OH)D in the blood is less than 50 nmol/L.

The average level of 25(OH)D in group of patients with T2DM and increased TSH, was significantly lower (48.6 nmol/L) than in patients without DM and IR (72.6 nmol/L), which confirms the results of previous studies, according to which in T2DM there is a larger proportion of patients with vitamin D deficiency, compared to the population without DM, where a milder form of vitamin D insufficiency prevails. Besides, previous studies revealed a negative correlation between the degree of vitamin D supply in the body and the level of TSH in the blood; the more pronounced vitamin D deficiency in the body was accompanied by worse thyroid gland function [12]. Patients with IR in our study showed the higher level of 25(OH)D (61.2 nmol/L), it was in the range of vitamin D insufficiency.

Conclusions

Taking into account the increase in the number of cases of elevated TSH among patients with T2DM, patients with IR on the background of chronic stress, it is necessary to actively identify this category of people, with the aim of clarifying the thyroid gland pathology and for correction of hypothyroidism in time.

The level of vitamin D supply in patients with combined endocrine pathology remains within the

limits of vitamin D deficiency, which increases the risks of developing of chronic complications of DM and autoimmune pathology. It is necessary to supply adequate (sufficient in duration and dose) correction of vitamin D deficiency in patients, which will improve their quality of life and postpone the development of complications.

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Abbreviations

DM – diabetes mellitus
IR – insulin resistance
TSH – thyroid-stimulating hormone
T2DM – type 2 diabetes mellitus
25(OH)D – 25-hydroxyvitamin D

Поєднана ендокринна патологія в умовах хронічного стресу війни

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Вступ. У пацієнтів із ЦД, порівняно з особами з нормоглікемією, патологія ЩЗ є більш поширеною, пацієнти з поєднаними ендокринопатіями мають гірший контроль глікемії та більш схильні до розвитку ускладнень. Тиреоїдні гормони впливають на метаболізм глюкози через дію на периферичні тканини, своєю чергою за ЦД2 зменшується перетворення тироксину в трийодтиронін у тканинах, а резистентність до інсуліну та гіперінсулінемія сприяють проліферації тканин ЩЗ, вузлоутворенню, росту ЩЗ у розмірах. Дефіцит вітаміну D спостерігається в 70% осіб із ЦД. Враховуючи стресове навантаження останніх років, актуальним є дослідження динаміки поєднання ЦД2 з гіпотиреозом, зокрема на тлі дефіциту вітаміну D, як обтяжувального фактора. **Мета**: оцінити динаміку частки підвищеного рівня ТТГ у пацієнтів із ЦД2, пацієнтів з ІР та пацієнтів без ЦД і ІР протягом періоду з 2021 до 2024 року включно і середній рівень забезпечення вітаміном D станом на 2024 рік. **Матеріал та методи.** За період 2021-2024 рр. було проведено проспективне дослідження, в яке включалися пацієнти з ЦД2 і рівнем глікованого гемоглобіну ≥7%, пацієнти з інсулінорезистентністю (ІР) без ЦД і пацієнти без ЦД і ІР віком 19-75 років. У рамках дослідження рівень ТТГ визначено в 649 пацієнтів із ЦД2 (група 1) віком 19-75 років із різних регіонів України. У групи порівняння були включені 690 пацієнтів з ІР без ЦД (група 2), і 665 пацієнтів без ЦД і ІР (група 3). Обстеження на ТТГ проводилося щорічно. Формувалися результати за 2021, 2022, 2023, 2024 рр. у 3 групах пацієнтів. Оцінка рівня 25-гідроксивітаміна D була проведена у 2024 році. Лабораторна оцінка рівня вітаміну D і ТТГ проводилася методом хемілюмінесцентного імуноаналізу. **Результати.** В обстежених пацієнтів досліджуваної групи ЦД2 виявили вірогідне підвищення частки хворих із підвищеним ТТГ у 2022 році. У пацієнтів з ІР спостерігається тенденція проградієнтного росту частки підвищеного ТТГ з 2022 до 2024 року, зміни не вірогідні. У групі пацієнтів без ЦД і ІР на 3-му році війни (2024 рік) вірогідно збільшилася частка підвищеного ТТГ, порівняно з довоєнним періодом. Середній рівень 25(OH) D у пацієнтів ЦД2 і підвищенням ТТГ вірогідно нижчий (48,6 нмоль/л), ніж у пацієнтів без ЦД і ІР (72,6 нмоль/л). **Висновки.** Враховуючи ріст частки випадків підвищеного ТТГ серед ЦД2, пацієнтів з ІР на тлі хронічного стресу, необхідно проводити активне виявлення цієї категорії осіб, із метою уточнення патології ЩЗ і своєчасної корекції гіпотиреозу. Рівень забезпеченості вітаміном D пацієнтів із поєднаною ендокринною патологією залишається в межах дефіциту вітаміну D, що підвищує ризики розвитку хронічних ускладнень ЦД, автоімунної патології. Необхідно проводити достатню за тривалістю і дозою корекцію дефіциту вітаміну D.

Ключові слова: цукровий діабет 2-го типу, поєднана ендокринна патологія, дефіцит вітаміну D, гіпотиреоз, хронічний стрес.

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