

## THYROID LESION AS A MANIFESTATION OF COMORBIDITY IN PATIENTS WITH DIABETIC POLYNEUROPATHY

G. Chupryna, V. Dubynetska

Shupyk National Medical Academy of Postgraduate Education, Kyiv

The study of clinical and anamnestic and paraclinical characteristics, highlighting their dominant features in patients with DP and existing thyroid diseases occupies an important place in modern neuroendocrinology and requires more focused attention of clinicians.

**The aim of the research:** to determine the leading clinical and laboratory-instrumental parameters in patients with DP and thyroid pathology, to analyze the mutual influence of neuroendocrine pathology on the patient's somatoneurological condition.

**Materials and methods.** Was done a clinical examination of 64 patients with DP, in 27 (42%) of them was diagnosed the comorbid thyroid pathology, in 37 (58%) it was absent. All patients were divided into two groups: with DP in the background of type I, II DM and thyroid pathology (A) and with DP in the background of type I, II DM without thyroid pathology (B). During the examination of patients were used clinical-anamnestic, clinical-neurological, laboratory-instrumental, neurophysiological methods of examination. Pain characteristics were assessed using the McGill Pain Questionnaire (MPQ). Statistic calculation was done in MS Excel 2003 and using the package for statistical analysis STATISTICA 10.

**Results.** In patients of both groups comorbidly were dominated diseases of the cardiovascular system, in group A, increasingly was revealed gastrointestinal pathology. Polyneuritic disorders of sensitivity and autonomic-trophic disorders are more common in persons of group B, they have a higher frequency of comorbid pathology and longer duration of DM. In group A lack of Achilles and knee reflexes was recorded more often than in comparison group. In 18 (65%) of the examined persons of group A was detected a fatty liver dystrophy by ultrasound scanning of the abdominal organs, which exceeds the number in group B - 13 (35%). There is an inverse average dependence between the level of TSH and BMI (correlation coefficient = - 0,65). The general index of pain rating (Pain Rating Index - PRI) in group A is higher ( $30,62 \pm 2,64$  scores).

**Conclusions.** Among the thyroid diseases in the examined patients of group A hypothyroidism was most often detected, so 30% of patients had a pronounced violation of lipid metabolism in the form of obesity, besides, in this group the number of people with type II DM was prevailed. The influence of thyroid pathology on the manifestations of DP is reflected in the intensification

of neuropathic pain syndrome. There is also a significant effect on the metabolism of fats and carbohydrates, which aggravate and sometimes deepen the somatic condition of the patient.

**Keywords:** *diabetic polyneuropathy, thyroid, body mass index, comorbidities, index of pain rating.*

## **УРАЖЕННЯ ЩИТОПОДІБНОЇ ЗАЛОЗИ ЯК ПРОЯВ КОМОРБІДНОСТІ У ХВОРИХ З ДІАБЕТИЧНОЮ ПОЛІНЕЙРОПАТІЄЮ**

**Г. М. Чуприна, В. М. Дубинецька**

Національна медична академія післядипломної освіти імені П.Л. Шупика, м. Київ

Вивчення клініко-анамнестичних та параклінічних характеристик, виокремлення їх домінуючих особливостей в пацієнтів із діабетичною полінейропатією (ДП) та наявними хворобами щитоподібної залози (ЩЗ) займає важливе місце в сучасній нейроендокринології та потребує більш прицільної уваги клініцистів.

**Мета дослідження.** Визначити провідні клінічні та лабораторно-інструментальні параметри в хворих із ДП та патологією ЩЗ, проаналізувати взаємний вплив нейроендокринної патології на соматоневрологічний стан пацієнта.

**Матеріали та методи.** Проведено клінічний огляд 64 пацієнтів із ДП, із них у 27 (42%) діагностована коморбідна патологія ЩЗ, у 37 (58%) – відсутня. Усіх пацієнтів розподілено на дві групи: із ДП на фоні ЦД I, II типу та патологією ЩЗ (А) та із ДП на фоні ЦД I, II типу без патології ЩЗ (В). При огляді пацієнтів використано клініко-анамнестичний, клініко-неврологічний, лабораторно-інструментальний, нейрофізіологічний методи обстеження. Характеристики болю оцінювали за анкетною болем Мак-Гіла. Статичний обрахунок здійснювали у MS Excel 2003 та з використанням пакету для проведення статистичного аналізу STATISTICA 10.

**Результати.** В пацієнтів обох груп коморбідно переважали хвороби кардіоваскулярної системи, в групі А в більшій мірі виявлено гастроентеральну патологію. Поліневритичні розлади чутливості та вегетативно-трофічні розлади частіше зустрічаються в осіб групи В, в них і вища частота коморбідної патології та довша тривалість ЦД. У групі А відсутність ахілових та колінних рефлексів зафіксована дещо часто, ніж в групі порівняння. У 18 (65%) обстежених групи А виявлено жирову дистрофію печінки при ультразвуковому скануванні органів черевної порожнини, що перевищує кількість у групі В – 13 (35%). Існує зворотня середня залежність між рівнем тиреотропного гормону та індексом маси

тіла (коефіцієнт кореляції = - 0,65). Загальний індекс оцінювання болю (Pain Rating Index - PRI) у групі А вищий (30,62±2,64 бали).

**Заклучення.** Серед хвороб ЩЗ в обстежуваних пацієнтів групи А найчастіше виявлявся гіпотиреоз, тому 30% пацієнтів мали виражене порушення ліпідного обміну у вигляді ожиріння, крім того в даній групі кількість осіб із цукровим діабетом II типу переважала. Вплив патології ЩЗ на прояви ДП відображається в посиленні нейропатичного больового синдрому. Також суттєвим є вплив на обмін жирів та вуглеводів, які обтяжують, а подекуди й поглиблюють соматичний стан хворого.

**Ключові слова:** діабетична полінейропатія, щитоподібна залоза, індекс маси тіла, супутні хвороби, індекс оцінювання болю.

### **Патология щитовидной железы как проявление коморбидности у больных с диабетической полинейропатией**

**Г. Н. Чурьина, В. Н. Дубинецкая**

**Цель исследования:** определить ведущие клинические и лабораторно-инструментальные параметры у больных с диабетической полинейропатией (ДП) и патологией щитовидной железы (ЩЖ), проанализировать взаимное влияние нейроэндокринной патологии на соматоневрологическое состояние пациента.

**Материалы и методы.** Проведен клинический осмотр 64 пациентов с ДП, из них у 27 (42%) диагностирована коморбидная патология ЩЖ, у 37 (58%) - отсутствует. Все пациенты разделены на две группы: с ДП на фоне сахарного диабета (СД) I, II типа и патологией ЩЖ (А) и с ДП на фоне СД I, II типа без патологии щитовидной железы (В). При осмотре пациентов использовано клиничко-анамнестический, клиничко-неврологический, лабораторно-инструментальный, нейрофизиологический методы обследования. Характеристики боли оценивали по анкете боли Мак-Гиля. Статический расчет осуществляли в MS Excel 2003 и с использованием пакета для проведения статистического анализа STATISTICA 10.

**Результаты.** У пациентов обеих групп среди коморбидности преобладали болезни сердечно-сосудистой системы, в группе А в большей степени выявлена желудочно-кишечная патология. Полиневритические расстройства чувствительности и вегетативно-трофические расстройства чаще встречаются у лиц группы В, в них и высокая частота коморбидной патологии и дольше продолжительность СД. В группе А отсутствие ахиллова и коленных рефлексов зафиксировано намного чаще, чем в группе сравнения. В 18 (65%) обследованных группы А обнаружено жировую дистрофию печени при ультразвуковом сканировании органов брюшной полости, что превышает количество в

группе В - 13 (35%). Существует обратная средняя зависимость между уровнем тиреотропного гормона и индексом массы тела (коэффициент корреляции = - 0,65). Общий индекс оценки боли (Pain Rating Index - PRI) в группе А выше ( $30,62 \pm 2,64$  балла).

**Заключение.** Среди болезней ЩЗ у обследуемых пациентов группы А чаще всего наблюдался гипотиреоз, поэтому 30% пациентов имели выраженное нарушение липидного обмена в виде ожирения, кроме того, в данной группе преобладали лица с СД II типа. Влияние патологии щитовидной железы на проявления ДП отображается в усилении нейропатического болевого синдрома. Также существенным является влияние на обмен жиров и углеводов, которые обременяют, а иногда и углубляют соматическое состояние больного.

**Ключевые слова:** *диабетическая полинейропатия, щитовидная железа, индекс массы тела, сопутствующие болезни, индекс оценки боли.*

The nervous and endocrine systems are closely interconnected and play the most important role in maintaining homeostasis of the organism [5].

As of 2017 there were about 2757,7 million people with diabetes mellitus (DM) in Ukraine (Ogurtsova K. et al., 2017), which allows us to calculate the number of patients with diabetic polyneuropathy (DP) at the level of 66 thousand to 2,17 million (median - 1,627 million). Taking into account the increase of DM transmission, DP will remain one of the most important and most frequent causes of polyneuropathy (Boulton A.J., 2014; Bowling F.L. et al., 2015; Tesfaye S. et al., 2005; 2011).

Since type 1 DM occurs as a result of autoimmune disorders, the detection of thyroid diseases (thyroid), such as autoimmune thyroiditis (AIT) in such individuals, is not uncommon. In addition, patients with type 2 DM often have nodular goiter, which is diagnosed more often in the hypothyroidism phase. Some thyroid dysfunction is closely related to carbohydrate metabolism, therefore, can increase the fluctuations of glycemia, both in the direction of hyper- and hypoglycemia, and disrupt the general well-being of the patient, exacerbate the manifestations of polyneuropathy.

The prevalence of AIT and / or antibodies to the thyroid in patients' relatives with type 1 DM can reach 48% compared with 3-10% in the general population. In addition, one person has a combination of type 1 DM and autoimmune thyroid disease, the so-called polyglandular syndrome of type 3, one of the variants of autoimmune polyendocrine syndromes [8,9].

The frequency of subclinical hypothyroidism is in ranges from 4 to 20% of the adult population depending on gender (higher among women), age (over 60 years), body mass index

(BMI), race, smoking, iodine intake and other factors (Razvi S. et al., 2018; Livingston E., 2019).

In patients with DM there was a decrease in nocturnal peak secretion of thyroid-stimulating hormone (TSH) and impaired response of TSH to stimulation by thyroliberin. In patients with insufficient glycemic control (HbA1c > 10%) there is an inhibition of deiodinase type 1 activity and as a result - decrease of conversion T4 to T3, decrease serum T3 and increase concentration rT3 (reversible), which can be interpreted as a protective mechanism of the organism in response to increase of tissue catabolism and decrease of tissue oxygen consumption [3].

The deterioration of metabolic control of DM in hyperthyroidism is associated with increased concentration and activity of contrainsular hormones – glucagon and catecholamines [4].

In the general population the prevalence of thyrotoxicosis is much lower than hypothyroidism [7], but the gravity of its clinical manifestations does not give the possibility to suggest a decrease in the relevance of the study of thyroid dysfunctions, especially in connection with dysfunctions of other organs and systems [2].

In hypothyroidism reduces blood circulation in adipose tissue and muscles, which can be considered as one of the pathogenetic mechanisms of insulin resistance [6].

The study of clinical and anamnestic and paraclinical characteristics, highlighting their dominant features in patients with DP and existing thyroid diseases occupies an important place in modern neuroendocrinology and requires more focused attention of clinicians.

**The aim of the research:** to determine the leading clinical and laboratory-instrumental parameters in patients with DP and thyroid pathology, to analyze the mutual influence of neuroendocrine pathology on the patient's somatoneurological condition.

## MATERIAL AND METHODS

Was done a clinical examination of 64 patients with DP, in 27 (42%) of them was diagnosed the comorbid thyroid pathology, in 37 (58%) it was absent. According to the distribution by gender, there were 32 (50%) women and 32 (50%) men. Age gradation - from 19 to 69 years, average age is  $47,5 \pm 1,78$  years. Type I DM was verified in 38 (60%), type II - in 26 (40%) patients.

All patients were divided into two groups: with DP in the background of type I, II DM and thyroid pathology (A) and with DP in the background of type I, II DM without thyroid pathology (B).

During the examination of patients were used clinical-anamnestic, clinical-neurological, laboratory-instrumental, neurophysiological methods of examination. Pain characteristics were

assessed using the McGill Pain Questionnaire (MPQ). Statistic calculation was done in MS Excel 2003 and using the package for statistical analysis STATISTICA 10.

## RESULTS AND DISCUSSION

The average age in group A is  $50,62 \pm 2,24$  years, B –  $45,21 \pm 2,57$  years. In group A, females predominated (Fig. 1), in group B - males, which confirms data in the literature about more frequent thyroid lesion in women.

Among the thyroid pathology in patients of group A were verified: postoperative hypothyroidism 4 (15%), hypothyroidism 4 (15%), AIT 4 (15%), of which 3 patients were in the phase of hypothyroidism, multinodular goiter 1 (4%), thyrotoxicosis 5 (18%), nodular goiter 9 (33%). Besides the thyroid diseases, mentioned above, this group of patients also had diseases of the cardiovascular system (44%), urinary (7%), gastrointestinal (4%), a combination of cardiovascular and gastrointestinal pathology (11%).

In the examined patients of group B were diagnosed diseases of the cardiovascular system (38%), a combination of gastrointestinal and cardiovascular pathologies (5%), bronchopulmonary, urinary and gastrointestinal (3%), urinary and gastrointestinal (3%).

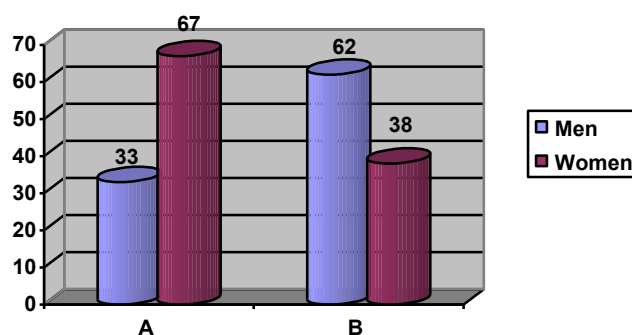
Thus, in patients of both groups comorbidly were dominated diseases of the cardiovascular system, in group A, increasingly was revealed gastrointestinal pathology.

Among the complaints in both groups the dominants were numbness in the lower extremities, headache and fatigue (table 1). Complaints of dry mouth, fluctuations of blood pressure (BP), numbness in the upper extremities, ringing in the ears and diarrhea were more often in group A.

Table 1

Frequency of complaints in patients of group A and B (absolute values)

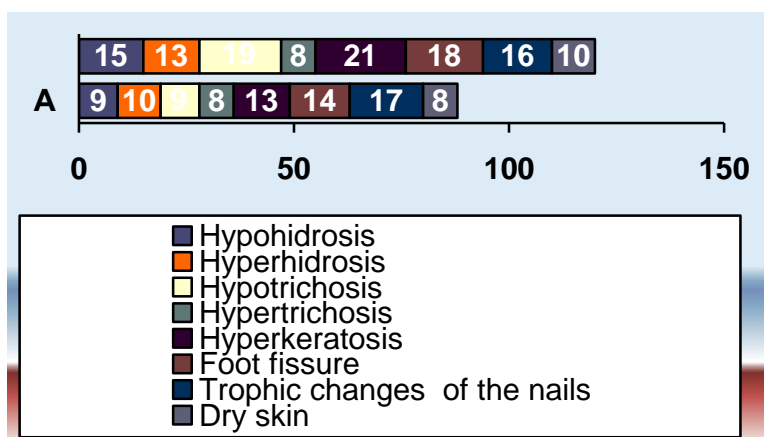
Group	Numbness of l/ex	Headache	Fatigue	Dry mouth	Fluctuations of blood pressure	Breathlessness	Impaired eyesight	Dizziness	Hypoglycemias	Heartache	Numbness of u/ex	Decrease of memory	Ringing in the ears	Diarrhea
A	23	18	14	13	12	7	7	7	6	6	4	4	2	1
B	32	22	19	11	5	10	8	11	16	9	3	6	1	0



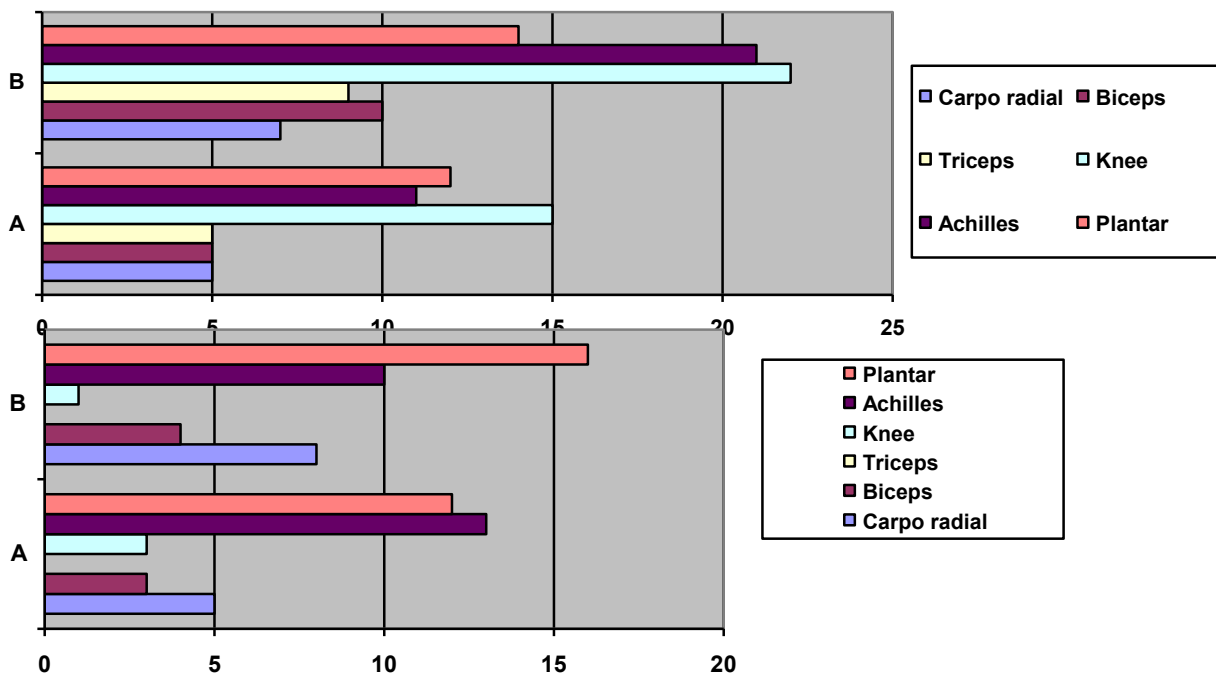
**Fig.1. Distribution of patients by gender in groups A and B.**

The average duration of DM in group A –  $11,70 \pm 1,68$  years, in group B –  $16,40 \pm 1,56$  years. Moreover, in group A of persons with type I DM - 9 (33%), type II - 18 (67%), in group B with type I DM - 29 (78%), type II - 8 (22%).

Vegetative-trophic disorders (Fig. 2) in group B are presented with greater frequency, in particular, hyperkeratosis, hypotrichosis, hypohidrosis of the distal legs, foot fissure. In group A trophic changes on the part of the nail plate are presented in a slightly larger number of individuals than in the comparison group. The predominance of trophic disorders in persons of group B is due to their longer duration of DM.



**Fig.2. Vegetative-trophic disorders in the individuals of group A and B ( absolute values)**



**Fig.3 Changes in the reflex area in the individuals of group A and B ( upper-hyporeflexia, lower-areflexia)**

In group B, checking the neurological status (Fig. 3) hyporeflexia was found in a larger number of patients, in particular it concerns most often knee and Achilles reflexes. In group A lack of Achilles and knee reflexes was recorded more often than in comparison group.

Polyneuritic sensitivity disorders with hyperesthesia of the distal extremities were recorded in 6 patients of group A and in 9 of group B, with hypesthesia -16 in group A and 26 in group B.

*Table 2*

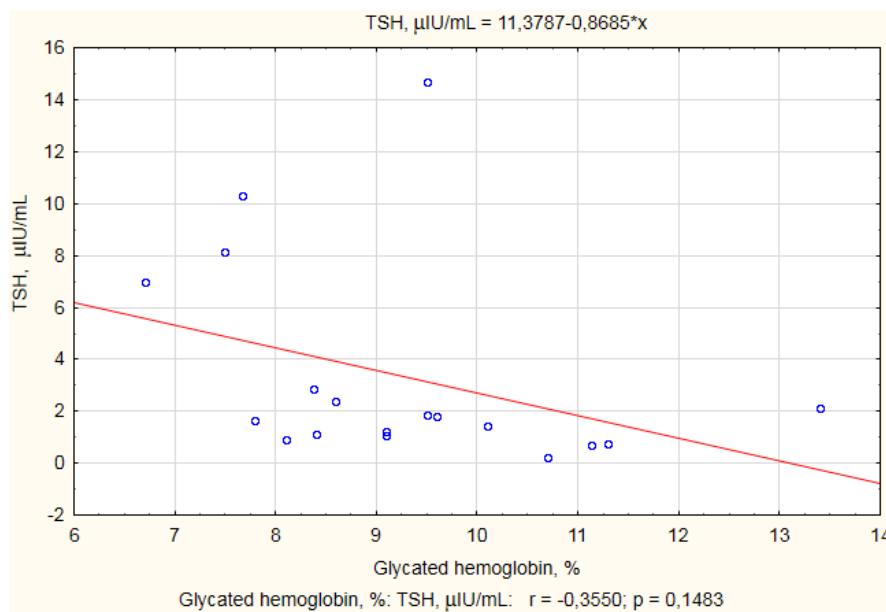
**Average values of main biochemical parameters in group A and B**

Group	Indicators of biochemical blood test												
	Total bilirubin, $\mu\text{mol/l}$	Aspartate aminotransferase, U/l	Alanine aminotransferase, U/l	Gamma-glutamyl transferase, U/l	Total protein, g/l	Urea, mmol/l	Creatinine, $\mu\text{mol/l}$	Total cholesterol mmol/l	LDL, mmol/l	HDL, mmol/l	Triglycerides, mmol/l	TSH, $\mu\text{IU/mL}$	Glycated hemoglobin, %
Norm	5-21	0-37	0-42	7-50	66-83	2,1-7,1	53-115	to 6,2	to 3,37	to 1,55	0,4-1,8	0,3-4,5	to 6%
A	15,86	26,55	29,77	76,85	71,7	6,37	87,55	5,59	2,21	1,46	1,67	3,19	9,23
B	16,37	26,16	25,99	45,70	69,48	6,15	92,02	5,27	1,40	0,90	1,60	1,28	8,90

The main laboratory parameters (table 2) in group A and B are within normal values, except the level of gamma-glutamyltransferase, the level of which is significantly increased in group A. There is a close interconnection between autoimmune thyroid pathology and functional state of the liver, that's why can consider a violation of the balance of thyroid hormones (hyper- or hypothyroidism) as a starting point for the development of insulin resistance, on the one hand, and liver pathology, on the other hand [1].

The level of glycated hemoglobin is elevated, mostly in group A, which indicates the unsatisfactory glycemic control. There is an inverse average connection (Fig. 4) (correlation coefficient= - 0,35) between the level of TSH and glycated hemoglobin. Given that TSH acts by a feedback mechanism: its decrease causes an increase in T3 and T4, and an increase - a decrease in T3 and T4, depending on whether hypo- or hyperthyroidism respectively will decrease or increase blood glucose level.





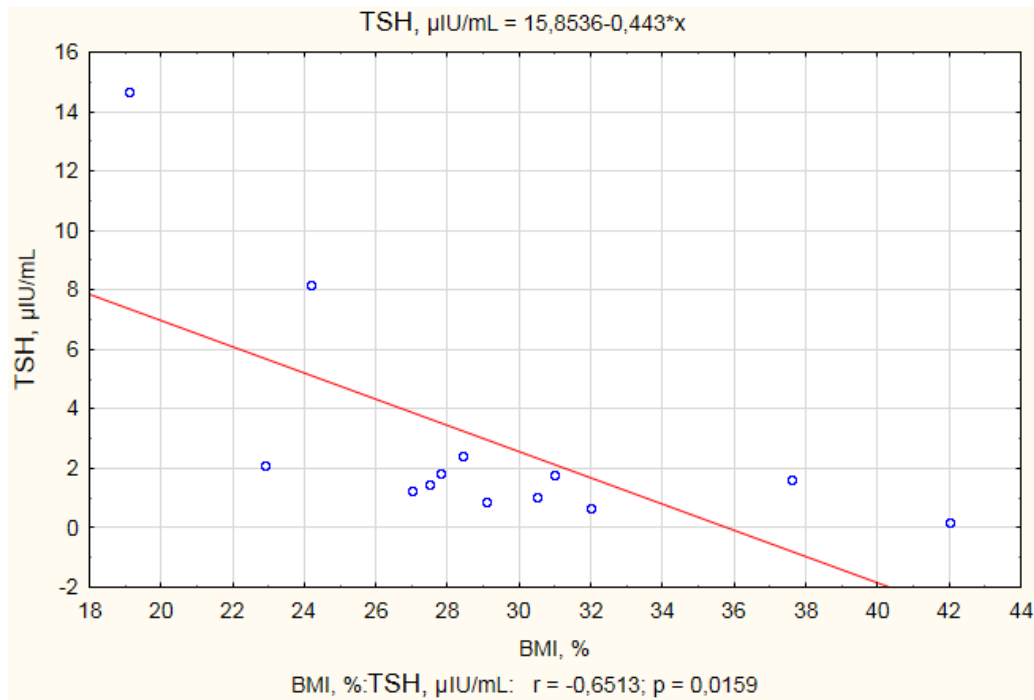
**Fig.4 Correlative connection between the level of TSH and glycated hemoglobin in persons of group A**

In 18 (65%) of the examined persons of group A was detected a fatty liver dystrophy by ultrasound scanning of the abdominal organs, which exceeds the number in group B - 13 (35%). Hypothyroidism is often accompanied by fatty liver disease (Liangpunsakul S., Chalasani N., 2003).

According to the electrocardiography (ECG) in group A, in 1 of the examined was found the prolongation of the Q-T interval, in 4 - blockade of the legs of the His bundle, while in group B conduction disturbances in the His bundles - in 6 patients.

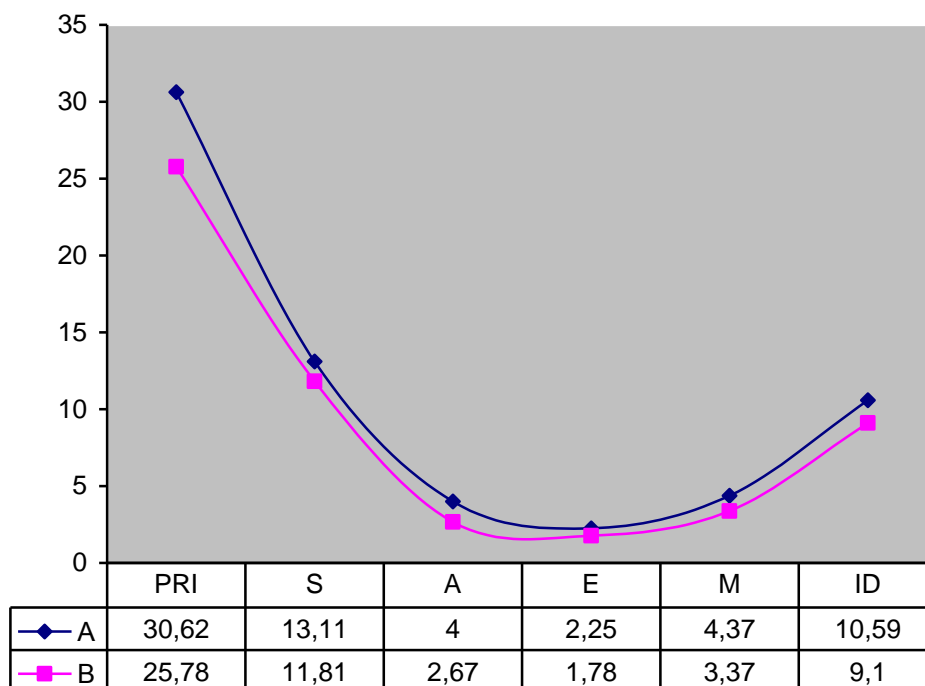
During the ultrasound scanning of the thyroid gland by the BRUNN method in group A, were revealed the following deviations : the total volume of the thyroid gland is  $19,07 \pm 2,11 \text{ cm}^3$  (norm is to  $14,0 \text{ cm}^3$ ), volume of the right share is  $10,11 \pm 1,10 \text{ cm}^3$ , left –  $11,54 \pm 1,66 \text{ cm}^3$  (norm is to  $7,0 \text{ cm}^3$ ), the presence of additional formations is in 15 (55%) patients. In group B the total volume of the thyroid gland is  $13,52 \pm 1,00 \text{ cm}^3$ , the volume of the right share is  $7,03 \pm 0,42 \text{ cm}^3$ , and that of the left share is  $6,26 \pm 0,34 \text{ cm}^3$ , in 9 (24%) were found additional formations.

BMI in group A –  $29,5 \pm 1,01\%$ , in group B –  $25,4 \pm 0,71\%$ , reflecting the presence of excess body weight - "obesity" in both groups. In group A I degree obesity is in 4 (15%) examined, II degree is in 3 (11%), III degree is in 1 (4%). Wasn't detected obesity in group B. There is an inverse average dependence between the level of TSH and BMI (correlation coefficient = - 0,65) (Fig. 5), which, in our opinion, depends on the thyroid (hypo-, hyper-) status of the patient, which affects metabolism.



**Fig.5 Correlative connection between the level of TSH and BMI in the individuals of group A**

The general index of pain rating (Fig. 6) (Pain Rating Index - PRI) in group A is higher ( $30,62 \pm 2,64$  scores). The average scores on the subscale of the Sensory Pain Rating (S), Affective (A), Evaluative (E), and Miscellaneous (M) in patients with group A are also higher than in the comparison group. The index of the number of selected descriptors (ID) among all subscales is in group A  $10,59 \pm 0,85$ , B  $9,1 \pm 0,77$ .



**Fig.6 The average score on the subscales of the McGill pain questionnaire in group A and B**

### CONCLUSIONS

1. Among the thyroid diseases in the examined patients of group A hypothyroidism was most often detected, so 30% of patients had a pronounced violation of lipid metabolism in the form of obesity, besides , in this group the number of people with type II DM was prevailed.
2. Rating of the evidence of pain syndrome on the McGill scale showed in both groups the presence of deviations, in particular, higher average scores were recorded in group A, showing a more pronounced DP degree of pain in these individuals, also due to poorer glycemic control, according to glycated hemoglobin.
3. Polyneuritic disorders of sensitivity and autonomic-trophic disorders are more common in persons of group B, they have a higher frequency of comorbid pathology and longer duration of DM. Changes in the reflex area of the lower extremities, namely areflesia are more common in group A.
4. The influence of thyroid pathology on the manifestations of DP is reflected in the intensification of neuropathic pain syndrome.
5. There is a significant effect on the metabolism of fats and carbohydrates, which aggravate and sometimes deepen the somatic condition of the patient. An important additional factor of high glycemia in such individuals is a liver damage, which is unable to deposit glycogen quickly enough, resulting in its rapid release.

## Сведения об авторах

**Чупрына Геннадий Николаевич** – Национальная медицинская академия последипломного образования имени П.Л. Шупика, 04112, г. Киев, ул. Дорогожицкая, 9; тел.: (067) 405- 78-25. E-mail: gen7chupryna@gmail.com

**Дубинецкая Виктория Николаевна** – Национальная медицинская академия последипломного образования имени П.Л. Шупика, 04112, г. Киев, ул. Дорогожицкая, 9; тел.: (096) 340-44-16. E-mail: viktorija\_md@ukr.net

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