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Content of micro- and macroelements in patients with autoimmune thyroiditis and subclinical hypothyroidism

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Aim. To investigate the content of iodine (I), selenium (Se), zinc (Zn), magnesium (Mg), calcium (Ca) and vitamin D, the thyroid volume and thyroid functional state in patients with autoimmune thyroiditis (AIT) and subclinical hypothyroidism (SCH), to assess the elemental supply, possibilities and feasibility of preventive and therapeutic use of micro- and macronutrients in the early stages of the disease.

Materials and methods. 134 people were examined (13 men, 121 women). Within the entire sample, 2 groups were formed depending on the presence of functional and laboratory signs of the disease: 1st – control group consisted of 53 healthy individuals without endocrine pathology, average age – 37.9 ± 11.8 years, of which 8 were men (15.10 %), and 2nd group with AIT and SCH – 81 people, average age – 40.0 ± 11.1 years, of which 5 were men (6.17 %). Anthropometric parameters were determined: age, sex, height, weight, body mass index; thyroid functional state: total thyroid volume, concentration of thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), level of antibodies to thyroid peroxidase (TPOAb), level of antibodies to thyroglobulin (TgAb); level of micro- and macroelement: I in urine, Se, Mg, Ca, vitamin D in serum.

Results. In the group with AIT and SCH, a significant ($p < 0.001$) increase in thyroid volume, TSH, TPOAb and TgAb levels and a significant decrease in thyroid hormones fT4 ($p = 0.008$), fT3 ($p < 0.001$) were found compared to the control group. In both groups, a slight iodine deficiency in the urine and a deficiency of vitamin D in the serum compared to reference values were noted. In the group of patients with AIT and SCH, a significant decrease in Se ($p = 0.016$), Mg ($p < 0.001$) and total Ca ($p < 0.001$) was found compared to the control. A pronounced positive correlation of Se / I ($r = 0.691$) was found. The statistically significant Odds ratio of AIT progression and overt hypothyroidism with reduced Mg content is OR = 2.80 (95 % CI 1.29–6.09, $p = 0.0094$), with reduced Ca content – OR = 7.68 (95 % CI 2.77–21.30, $p = 0.0001$).

Conclusions. The group with AIT and SCH and the control group have a weak iodine deficiency in the urine and vitamin D deficiency in the blood serum compared to normal reference values, which indicates a general population deficiency. In the group of patients with AIT and SCH, a significant decrease in serum Se, Mg and total Ca was found compared to the control. A significant positive correlation Se / I ($r = 0.691$) indicates the relationship of these trace elements and confirms their combined effect on the development of autoimmune disorders and thyroid hormonal changes. A high risk of progression of AIT and overt hypothyroidism exists with reduced Mg and Ca content.

Keywords: autoimmune thyroiditis, subclinical hypothyroidism, microelements, macroelements, ioduria, Se, Mg, Ca, vitamin D.

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Вміст мікро- та макроелементів у пацієнтів з автоімунним тиреоїдитом і субклінічним гіпотиреозом

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Мета роботи – дослідити вміст йоду (I), селену (Se), цинку (Zn), магнію (Mg), кальцію (Ca) та вітаміну D, об'єм та функціональний стан щитоподібної залози (ЩЗ) у пацієнтів з автоімунним тиреоїдитом (АІТ) та субклінічним гіпотиреозом (СКГ), оцінити елементне забезпечення, можливості та доцільність превентивного та лікувального застосування мікро- та макронутрієнтів на ранніх етапах захворювання.

Матеріали і методи. Обстежили 134 осіб: 13 чоловіків і 121 жінку. У межах вибірки сформовано дві групи залежно від наявності функціональних і лабораторних ознак захворювання: до 1 (контрольної) групи залучено 53 здорових осіб без ендокринної патології, середній вік – 37,9 ± 11,8 року, із них 8 чоловіків (15,10 %), до 2 групи – 81 хворого на автоімунний тиреоїдит і субклінічний гіпотиреоз, середній вік – 40,0 ± 11,1 року, із них 5 чоловіків (6,17 %). Визначено такі антропометричні показники, як вік, стать, зріст, маса тіла, обраховано індекс маси тіла. Оцінили функціональний стан ЩЗ, зокрема визначили її сумарний об'єм, концентрацію тиреотропного гормона (ТТГ), вільного тироксину (вТ4), вільного трийодтироніну (вТ3), рівень антитіл до тиреопероксидази (ТРОАb), рівень антитіл до тиреоглобуліну (TgAb), а також рівень мікро- та макроелементів (I в сечі, Se, Mg, Ca, вітаміну D у сироватці крові).

Результати. У групі пацієнтів з АІТ і СКГ визначено істотне ($p < 0,001$) збільшення об'єму ЩЗ, рівня ТТГ, ТРОАb та TgAb та істотне зниження тиреоїдних гормонів fT4 ($p = 0,008$), fT3 ($p < 0,001$) порівняно з відповідними показниками контрольної групи. В обстежених з обох груп виявлено слабкий йододефіцит у сечі та недостатність вітаміну D у сироватці крові порівняно з референтними значеннями. У групі пацієнтів з АІТ і СКГ встановили значне зниження Se ($p = 0,016$), Mg ($p < 0,001$) та загального Ca ($p < 0,001$) порівняно з контролем. Виявили виражену позитивну кореляцію

Ключові слова: автоімунний тиреоїдит, субклінічний гіпотиреоз, мікроелементи, макроелементи, йодурія, Se, Mg, Ca, вітамін D.

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Se / I (r = 0,691). Статистично вірогідне співвідношення шансів прогресії АІТ та явного гіпотиреозу на фоні зниженої концентрації Mg становить OR = 2,80 (95 % CI 1,29–6,09, p = 0,0094), на фоні зменшеного вмісту Ca – OR = 7,68 (95 % CI 2,77–21,30, p = 0,0001).

Висновки. Обстежені з групи АІТ і СКГ, як і з контрольної, мають слабкий йододефіцит у сечі та недостатність вітаміну D у сироватці крові порівняно з нормальними показниками; це свідчить про загальну популяційну недостатність. У групі пацієнтів з АІТ і СКГ встановлено істотне зниження в сироватці крові Se, Mg і загального Ca порівняно з контролем. Значна позитивна кореляція Se / I (r = 0,691) підтверджує взаємозв'язок цих мікроелементів і їхній поєднаний вплив на розвиток автоімунних порушень і гормональних змін у ЩЗ. Високий ризик прогресії АІТ та явного гіпотиреозу визначено у разі зниженого вмісту Mg і Ca.

Autoimmune thyroiditis / Hashimoto's thyroiditis (AIT / HT) is one of the most common pathologies among endocrine diseases and is the most common cause of hypothyroidism. Autoimmune thyroiditis begins asymptomatically, is associated with damage to thyrocytes, and the synthesis of autoantibodies is the final stage of the immune response to the autoantigens TPO (thyroid peroxidase) and Tg (thyroglobulin). The prevalence of thyroid antibodies – TPOAb (11.3 %) and TgAb (2.0 %) in euthyroid subjects was observed in 15.3 % of individuals [1]. Over time, latent AIT progresses to subclinical and manifest thyroiditis with hypothyroidism. Subclinical hypothyroidism (SCH) is a persistent increase in the level of thyroid-stimulating hormone (TSH) with normal values of thyroid hormones (TG). Subclinical hypothyroidism is relatively common disorder, and most population studies have demonstrated a prevalence of approximately 5–10 % of the population [2]. In Ukraine, the incidence of AIT in the population is 43.1 cases per 100 thousand population, the prevalence is almost 10 times higher (421.2 cases per 100 thousand population) [3].

The implementation of genetic factors of autoimmune thyroid diseases (AITD) depends on various environmental influences, such as stress, smoking, bacterial and viral infections, chemical pollutants, and dietary iodine [4]. The autoimmune process in the thyroid is closely associated with oxidative stress (OS), a process that damages cellular structures, including lipids and membranes, proteins, and DNA [5]. Excessive formation reactive oxygen species (ROS) are involved in various stages of the pathogenesis of thyroid diseases and even endemic goiter [6].

As external factors, trace elements in appropriate concentrations are necessary for the proper functioning of the thyroid gland. Iodine (I), selenium (Se), zinc (Zn), iron (Fe), copper (Cu), manganese (Mn) are part of enzymes involved in the reduction of OS [7,8].

Iodine deficiency in nutrition is a global problem that affects all segments of the population and exists in many countries around the world [9]. Iodine is needed for the synthesis of TG, and I deficiency leads to insufficient production of thyroxine and related thyroid diseases [10]. Iodine deficiency in the thyroid causes an increase in the content of ROS, which is formed from hydrogen peroxide, which is involved in the synthesis TG [11]. Insufficient I intake (<100 μg/L) is associated with an increased incidence of thyroid nodules [12]. Both deficiency and excess I intake can serve as risk factors for thyroid diseases. Excessive I intake in the population due to poorly controlled iodine prophylaxis programs can cause euthyroid or subclinical hypothyroid AIT [13]. In regions with excess I intake, an increased incidence of AIT is observed, characterized by high TPOAb and TgAb titers [14].

Iodine and Se play a key role in the development of AITD. Selenium is a component of deiodinases, enzymes responsible for homeostasis and control of TG activity. Se deficiency reduces the expression and activity of antioxidant enzymes [7]. Selenoproteins prevent excessive ROS formation, which can lead to thyroiditis or chronic inflammation. Epidemiological data indicate the prevalence of thyroiditis in Se deficiency [15]. Although some authors did not note the relationship between the prevalence of HT and Se content [16].

Zinc is involved in TG metabolism by regulating the activity of deiodinases, TRH (thyrotropin releasing hormone) and TSH, and by modulating the structures of key transcription factors involved in TG synthesis [17]. There is a relationship between Zn deficiency and TG levels [18]. Zn acts as an antioxidant by inhibiting DNA / RNA and protein oxidation, as well as the inflammatory response, which leads to a decrease in ROS production [19].

Altered Ca^{2+} regulation in lymphocytes, which disrupts the control of metabolism, proliferation, differentiation, antibody secretion, cytokines and cell cytotoxicity, leads to autoimmune and inflammatory diseases [20]. Intracellular mitochondrial Ca^{2+} is a key regulator of cell apoptosis. Ca^{2+} uptake and mitochondrial metabolism underlie the survival of Treg cells under OS conditions [21]. Ca^{2+} signaling activates the proliferation and survival of B lymphocytes that produce autoantibodies [22]. The main mechanism of increased intracellular Ca^{2+} is the deficiency of intracellular Mg^{2+}, which can cause immunodeficiency, increased acute inflammatory response, decreased antioxidant response and OS. Magnesium regulates the balance of Ca and phosphorus (P) through its effect on vitamin D [23].

The active metabolite of vitamin D ($1,25(OH)_2D_3$), in addition to its main function in the body – maintaining Ca and P homeostasis, performs a number of non-classical effects, including reducing OS, antimicrobial protection, anti-inflammatory effect [24]. Vitamin D affects innate and adaptive immunity and may have an immunomodulatory effect on AIT [25].

Treatment of patients with AIT associated with SCH remains controversial today, most patients are under observation without treatment [26]. Treatment is recommended to start with levothyroxine (L-T4) with a serum TSH level ≥10 mIU/L, as this TSH level is associated with an increased incidence of cardiovascular events and cardiovascular mortality [27]. Therefore, it is important to understand the factors that influence the immune system in patients with AIT associated with SCH.

Aim

To investigate the content of iodine, selenium, zinc, magnesium, calcium and vitamin D, the thyroid volume and thyroid functional state in patients with autoimmune thyroiditis and subclinical hypothyroidism, to assess the elemental supply, the possibilities and feasibility of preventive and therapeutic use of micro- and macronutrients in the early stages of the disease.

Materials and methods

An open randomized controlled study was conducted to assess the content of micro- and macronutrients, the thyroid volume and thyroid functional indicators in a group of patients with AIT and SCH. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Bioethics Committee of the State Institution "V. P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine" (Protocol No 43/1-KE dated 06/06/2022). All subjects provided informed consent.

134 subjects (13 men, 121 women) were examined. Within the entire sample, 2 groups were formed depending on the presence of functional and laboratory signs of the disease: the 1st – control group consisted of 53 healthy individuals without endocrine pathology, average age – 37.9 ± 11.8 years, of which 8 were men (15.10 %), and the 2nd group with AIT and SCH – 81 people, average age – 40.0 ± 11.1 years, of which 5 were men (6.17 %). Anthropometric indicators were determined: age, sex, height, weight, and body mass index (BMI) was calculated.

Thyroid functional state: concentration of thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3); immunological indicators: level of antibodies to thyroid peroxidase (TPOAb), level of antibodies to thyroglobulin (TgAb), level of vitamin D in blood serum – were determined on the Cobas e 411 analyzer ("Roche Diagnostics", Germany). The total thyroid volume was determined by the Brunn method (Terason 2000 scanner with a linear sensor with a frequency of 10 MHz ("Terason Ultrasound", USA).

The concentration of I in the urine was determined by the cerium-arsenite Sandell–Kolthoff method modified by J. T. Dunn et al. on a UV-1280 spectrophotometer ("Shimadzu", Japan). The method for determining ioduria undergoes external quality control at the Center for Disease Control and Prevention (CDC) in Atlanta (USA). The Se content in serum was determined by the fluorometric method ("Hitachi MPF-4" spectrofluorometer) after acid mineralization, conjugation with 2,3-diaminonaphthene and extraction from acidic aqueous solutions with cyclohexane. The content of Mg, Ca in blood serum was determined photometrically using the Cobas 6000 C501 analyzer ("Roche Diagnostics", Switzerland). The content Zn in blood serum was determined by atomic absorption spectrometry (spectrometer "Labor Berlin", Germany). In regions with sufficient I content, the maximum range of reference values for thyroid volume by sex and body area is 4.25–20.98 cm^3 for men and 3.44–18.31 cm^3 for women. Reference values for serum TSH are 0.27–4.20 mIU/L, fT4 – 0.93–1.71 ng/dl, fT3 – 2.02–4.43 pg/ml, TPOAb – up to 34 IU/ml, TgAb – up to 115 IU/ml. Reference values for I in urine – 100.0–200.0 μg/L, Se in serum – 60–120 μg/L, vitamin D (25(OH)D) in serum in adults 30.0–50.0 ng/ml, Zn in serum – 70.0–150 μg/dl, total Mg in serum – 0.66–1.07 mmol/L at the age of 18–60, total Ca in serum – 2.15–2.5 mmol/L at the age of 18–60.

Statistical analysis was performed using the statistical software MedStat and MedCalc Software Ltd. To check the law of distribution of quantitative data, the Shapiro–Wilk test was used. For data with a normal distribution, the arithmetic mean with standard deviation was calculated. In the case of a non-normal distribution, the median (Me) and interquartile range (QI; QIII) were used. Comparisons were performed using the Student's test or the Wilcoxon W-test, respectively. In all tests, the value $p < 0.05$ was considered significant. To assess the relationships between the indicators, Pearson's correlation coefficient was applied for normally distributed variables, while Spearman's rank correlation was used for non-normally distributed ones. The calculation of the risk of AIT and SCH in the groups was carried out with the determination of the Odds ratio, confidence interval, significance level (OR, 95 % CI, p).

Results

A comparative study of anthropometric indicators and thyroid function in the group of patients with AIT and SCH revealed a significant ($p < 0.001$) increase in thyroid volume, TSH level and a significant decrease in thyroid hormones fT4 ($p = 0.008$), fT3 ($p < 0.001$) compared to the control group. Although the medians of thyroid hormones in the study group were at the lower limit of the reference norm. In the group of patients with AIT and SCH, a significant ($p < 0.001$) increase in TPOAb and TgAb titers was recorded compared to the control. In terms of age and BMI, both groups did not differ statistically *(Table 1)*.

The study of thyroid dimensions showed that in the control group as a whole, the mean value (M ± SD) of the thyroid volume was 10.9 ± 3.2 cm^3. In the majority of the examined women in this group (n = 45), the thyroid volume was 10.95 ± 3.2 cm^3. In men (n = 8), the thyroid volume was 10.87 ± 3.5 cm^3. That is, the thyroid volume in women and men of the control group did not differ ($p = 0.952$). In the research group (AIT with SCH), the mean value (M ± SD) of the thyroid volume was larger ($p < 0.001$) and was 24.7 ± 11.3 cm^3. This group also had a predominance of women (n = 76) and the thyroid volume was 24.8 ± 11.4 cm^3. In men (n = 5), the thyroid volume was 23.8 ± 10.8 cm^3, indicating no ($p = 0.850$) difference depending on sex, despite some differences in the reference values of thyroid volume (4.25–20.98 cm^3 for men and 3.44–18.31 cm^3 for women).

It should be noted that the study group (AIT and SCH) consisted of patients who had positive TPOAb (100 %) and TgAb (60 %). Among them, 59 patients (72.8 %) had signs of SCH – elevated TSH and normal TG levels, the remaining 22 patients (27.2 %) had elevated TSH and TG levels at the lower limit of reference values or decreased. In most patients in research group (76.5 %), the thyroid volume exceeded the upper limits of the reference value for men and women.

Table 1. Anthropometric and thyroid parameters in patients in the control group and in the group with autoimmune thyroiditis and subclinical hypothyroidism

Indicator, units of measurement	Control group (1st), n = 53	Research group (2nd), n = 81	p
Age, years	37.9 ± 11.8	40.0 ± 11.1	0.282
BMI, kg/m^2	25.5 ± 4.0	25.5 ± 3.8	0.992
Thyroid volume, cm^3	10.9 ± 3.2	24.7 ± 11.3	<0.001
TSH, mIU/L	1.38 (0.9; 2.1)	6,54 (5.2; 8.1)	<0.001
fT4, ng/dl	1.22 (1.01; 1.46)	1.08 (0.99; 1.24)	0.008
fT3, pg/ml	3.24 (2.98; 3.60)	2.99 (2.14; 3.19)	<0.001
TPOAb, IU/ml	7.1 (1.9; 11.7)	270.0 (164.0; 410.0)	<0.001
TgAb, IU/ml	14.0 (0.0; 57.5)	155.0 (89.0; 250.0)	<0.001

Mean values with standard deviation and medians with interquartile ranges (Q1; Q3) are presented. Comparisons were made using Student's t-test or Wilcoxon's W-test.

Table 2. Content of micro- and macroelements in the blood serum of patients in the control group and the group with autoimmune thyroiditis and subclinical hypothyroidism

Indicator, units of measurement	Control group (1st), n = 53	Research group (2nd), n = 81	p
Urine iodine, μg/L	84.0 (69.0; 120.5)	82.0 (69.8; 112.0)	0.667
Selenium, μg/L	75.0 (62.0; 85.1)	67.0 (53.0; 78.0)	0.016
Zinc, μg/dl	82.6 (72.0; 90.1)	79.0 (75.0; 86.0)	0.288
Magnesium, mmol/L	0.76 (0.14)	0.66 (0.01)	<0.001
Calcium, mmol/L	2.30 (2.21; 2.38)	2.18 (2.01; 2.33)	<0.001
25(OH)D, ng/ml	28.4 (9.8)	26.0 (7.2)	0.150

Mean values with standard deviation and medians with interquartile ranges (Q1; Q3) are presented. Comparisons were made using the Student's test or Wilcoxon's W-test.

The study of micro- and macronutrient content revealed mild iodine deficiency compared to the normal reference value (100–200 μg/L) and vitamin D (25(OH)D) deficiency in serum compared to the normal reference value (30.0–50.0 ng/ml) in both the control and experimental groups. The level of other elements was also at the lower limit of the reference values in both groups. In the group of patients with AIT and SCH, a significant decrease in serum Se ($p = 0.016$), Mg ($p < 0.001$) and total Ca ($p < 0.001$) was found compared to the control *(Table 2)*.

To determine diagnostic markers of the disease, correlation studies of micro- and macronutrients, thyroid status indicators in the groups of subjects were conducted. In the control group, Pearson's linear correlation studies revealed a strong positive relationship between thyroid volume and TSH level ($r = 0.979$) and a negative relationship between Se and TgAb ($r = -0.429$), as well as between I and TgAb ($r = -0.410$). Correlation analysis (Spearman's rank correlation) of the parameters in the group of patients with AIT and SCH revealed the expected significant positive correlation between thyroid parameters – thyroid volume / TPOAb ($r = 0.675$), thyroid volume / TgAb ($r = 0.525$), TPOAb / TgAb ($r = 0.551$) and a negative correlation between TSH and thyroid hormones – TSH / fT4 ($r = -0.472$), TSH / fT3 ($r = -0.491$). Regarding micro- and macroelements in the studied group, a pronounced positive correlation Se / I ($r = 0.691$) and moderate positive and negative correlations between different elements were established *(Table 3)*.

To assess the risk of onset and progression of AIT with SCH and AIT with overt hypothyroidism with reduced micro- and macronutrient content, the Odds ratio (OR) and confidence intervals (95 % CI) of the study groups were calculated. It was found that the risk of progression of AIT and overt hypothyroidism is significant ($p = 0.0094$) with reduced (<0.66–1.07 mmol/L) Mg content (OR = 2.80; 95 % CI 1.29–6.09), and also significant ($p = 0.0001$) with reduced (<2.15–2.50 mmol/L) Ca content (OR = 7.68; 95 % CI 2.77–21.30) in serum *(Table 4)*.

Discussion

The results of the study of the group of patients with AIT and SCH revealed a significant increase in the mean value of the thyroid volume, TSH level, TPOAb and TgAb titer and a significant decrease in the median of the thyroid hormones fT4, fT3 (within the lower reference range) compared to the control, which indicates the presence of SCH, activation of the autoimmune process in the thyroid gland. Both in the control and in the AIT and SCH groups, a mild degree of iodine deficiency was found compared to the normal reference value (100–200 μg/L), which indicates a general population iodine deficiency.

Our results on the increase in thyroid volume, TSH level with a decrease in the concentration of I in urine and Se in serum in patients with AIT and SCH are consistent with studies that have shown that insufficient I intake (<100 μg/L) is associated with an increased frequency of thyroid nodules and autoimmune pathology [12]. Iodine deficiency is considered to be much more harmful than excess I, as it affects entire populations, while excess I affects only a small percentage of individuals susceptible to AITD, as it can impair thyroid function through OS [28]. The possible early increase in thyroid antibodies after I consumption is mostly transient, varies between populations under the influence of genetic and environmental factors, and does not always coincide with the presence or subsequent development of AITD. The use of I supplements in the general population should not be limited by the possible increase in the prevalence of AITD. I consumption at a concentration not exceeding 300 μg/L is safe and outweighs the risk of autoimmune disorders [29].

The study of correlations between the content of micro- and macroelements, thyroid status indicators revealed in the group of patients with AIT and SCH the expected significant positive correlation between thyroid indicators – thyroid volume / TPOAb, thyroid volume / TgAb, TPOAb / TgAb and a negative correlation between TSH and thyroid hormones – TSH / fT4, TSH / fT3. The results of the study established a negative relationship between Se / TgAb and I / TgAb in both studied groups, which indicates the significance of the deficiency of these essential microelements in the occurrence and development of AIT with SCH.

In the group of patients with AIT and SCH, a significant decrease in serum Se, Mg and total Ca was found compared to the control. The level of other elements is at the lower limit of reference values in both groups. In the study group, a strong positive correlation of Se / I and moderate positive and negative correlations between different elements were noted, in particular – a positive relationship of Zn with I, Se, Mg, Ca. The positive correlation of Se / I in the AIT and SCH group indicates the relationship of these trace elements and confirms their combined effect on the

development of autoimmune disorders and hormonal changes in the thyroid. The ratio of trace elements, in particular Se / I, can be considered a diagnostic marker of AIT with SCH and AIT with hypothyroidism.

Other researchers have also reported on the reduced content of micro- and macroelements in SCH, hypothyroidism and AIT, as well as ways to compensate for their deficiency and influence on pathophysiological processes. Thus, insufficient Se intake increases susceptibility to thyroid diseases associated with OS [30]. Se supplementation in patients with euthyroid, subclinical or overt hypothyroid HT not only reduces the level of thyroid autoantibodies, TSH, fT4 / fT3, but also reduces OS and inflammatory state, and improves the structure and thyroid volume [12,31]. The use of microelements Se and Zn has been proposed to reduce oxidative thyroid damage in HT [12,32].

The results of the study of the content of micro- and macroelements in the group of patients with AIT and SCH correspond to the study of patients with latent AIT with high titer. Significantly lower serum concentrations of Mg and Fe were in HT patients with positive TPOAb and TgAb [33]. Lower serum Ca and higher serum P levels have been reported in hypothyroidism compared with SCH [34]. In patients with hypothyroidism, mean serum Ca and Mg levels are decreased, while serum P levels are increased. A statistically significant negative correlation between Ca, Mg, and TSH was observed among hypothyroidism cases [35]. The calculation of Odds ratios (OR) and confidence intervals (95 % CI) of the study groups revealed a significant risk of progression to AIT and overt hypothyroidism with decreased (<0.66–1.07 mmol/L) Mg content (OR = 2.80; 95 % CI 1.29–6.09) and with decreased (<2.15–2.50 mmol/L) Ca content (OR = 7.68; 95 % CI 2.77–21.30) in serum. A similar prediction has been made in studies by other authors. Thus, very low serum Mg levels are associated with an increased risk of TgAb, HT, and hypothyroidism. The risks of SCH and hypothyroidism in the group with the lowest Mg level (≤0.55 mmol/L) were higher than in the group with normal Mg levels [36].

The literature on the relationship between vitamin D levels and AITD is somewhat contradictory. The mechanisms of vitamin D's effect on AITD are still unknown, but may be related to its anti-inflammatory and immunomodulatory properties [25]. There is a study that failed to find a relationship between vitamin D deficiency and a higher prevalence of HT [37]. No effect of vitamin D on the levels of TSH, fT3, and fT4 hormones was found [38]. This ambiguity regarding the relationship between vitamin D and TSH, TG, and the prevalence of HT is likely due to the fact that susceptibility to AITD may be influenced by polymorphisms in some vitamin D-related enzymes and proteins, such as CYP28B1, CYP2R1, CYP24A1, VDBP, and VDR [39].

The data obtained in our study showed that both the control and AIT and SCH groups had a deficiency of 25(OH)D in serum compared to the normal reference value (30.0–50.0 ng/ml), indicating a deficiency of vitamin D at the population level. The results of our study on the level of 25(OH)D in serum were confirmed by the works of scientists who believe that the population needs to maintain 25(OH)D concentrations above 40 ng/ml in the range of 40–80 ng/ml, which is optimal for disease prevention and reducing the severity of various conditions, such as cardiovascular and metabolic diseases, autoimmune diseases, infections and cancer, as well as mortality without side effects [24]. In addition, in patients with HT, reduced levels of vitamin D were found, negatively correlated with TSH and positively with fT3 and fT4 [25,40]. HT is more closely associated with vitamin D deficiency than with its insufficiency. However, additional treatment with cholecalciferol is associated with a decrease in TPOAb and TgAb levels in patients with AITD with both insufficiency and deficiency of vitamin D [11].

According to our data in the AIT and SCH group, vitamin D showed a weak positive relationship with I, Se and Ca, which does not contradict the literature data on the

Table 3. Correlation coefficients of the content of micro- and macroelements, indicators of thyroid status in the groups of examined

Correlation between indicators	Control group		Research group	
	r (Pearson)	p	r (Spearman)	p
Thyroid volume / TSH	0.979	<0.001	–	–
Thyroid volume / TPOAb	–	–	0.675	<0.001
Thyroid volume / TgAb	–	–	0.525	<0.001
TSH / fT4	–	–	-0.472	<0.01
TSH / fT3	–	–	-0.491	<0.01
TPOAb / TgAb	–	–	0.551	<0.001
Se / TgAb	-0.429	<0.01	-0.239	<0.05
Se / I	–	–	0.691	<0.001
Se / Zn	–	–	0.317	<0.05
Se / 25(OH)D	–	–	0.273	<0.05
I / TgAb	-0.410	<0.01	-0.227	<0.05
I / Zn	–	–	0.396	<0.05
I / Mg	–	–	0.227	<0.05
I / 25(OH)D	–	–	0.252	<0.05
Zn / Thyroid volume	0.274	<0.05	–	–
Zn / Mg	–	–	0.246	<0.05
Zn / Ca	–	–	0.349	<0.05
Mg / TSH	0.273	<0.05	–	–
Ca / Thyroid volume	–	–	0.236	<0.05
Ca / 25(OH)D	–	–	0.331	<0.05

Control group: pairwise correlation coefficients (Pearson); **study group:** rank correlation coefficients (Spearman); values of coefficients that differ from 0 ($p < 0.05$) are given;
–: the absence of correlation.

Table 4. Calculation of Odds ratio of progression of autoimmune thyroiditis or overt hypothyroidism with reduced content of micro- and macroelements

Micro-, macronutrient	Control group, n	Research group, n	OR (95 % CI)	p
Urine iodine, decreased	31	56	–	–
norm	22	25	1.59 (0.77–3.27)	0.2081
Selenium, decreased	12	30	–	–
norm	41	51	2.01 (0.92–4.41)	0.0816
Zinc, decreased	9	7	–	–
norm	44	74	0.46 (0.16–1.33)	0.1523
Magnesium, decreased	11	36	–	–
norm	42	45	2.80 (1.29–6.09)	0.0094
Calcium, decreased	5	36	–	–
norm	48	45	7.68 (2.77–21.30)	0.0001
25(OH)D, decreased	33	60	–	–
Norm	20	21	1.73 (0.82–3.65)	0.1488

enhancement of the effect of vitamin D by the use of Se in patients with HT. Thus, daily intake of vitamin D (4000 IU) for 6 months increased the level of 25-hydroxyvitamin D, reduced serum TPOAb and TgAb titers in women with HT. The effect on antibody titers was more pronounced in women with HT who received daily selenomethionine (200 μg) for 12 months before the start of the study [38]. The presence of element deficiencies in AIT patients with SCH, the high risk of SCH transitioning to overt hypothyroidism, and the absence or limited treatment with L-T4 suggest the use of these elements for the prevention of the next stage of AIT with overt hypothyroidism.

Conclusions

1. In the group with autoimmune thyroiditis and subclinical hypothyroidism, a significant ($p < 0.001$) increase in thyroid volume, TSH level, TPOAb and TgAb titer and a significant decrease in thyroid hormones fT4 ($p = 0.008$), fT3 ($p < 0.001$) were found compared to the control group.

2. Mild iodine deficiency in urine and vitamin D deficiency in serum compared to normal reference values were found in the group with autoimmune thyroiditis and subclinical hypothyroidism, as well as in the control group, which indicates a general population deficiency.

3. In the group of patients with autoimmune thyroiditis and subclinical hypothyroidism, a significant decrease in serum Se ($p = 0.016$), Mg ($p < 0.001$) and total Ca ($p < 0.001$) was found compared to the control.

4. The pronounced positive correlation Se / I ($r = 0.691$) indicates the relationship of these trace elements and confirms their combined effect on the development of autoimmune disorders and thyroid hormonal changes.

5. A significant risk of progression of autoimmune thyroiditis and overt hypothyroidism exists with a reduced serum Mg content (OR = 2.80, 95 % CI 1.29–6.09, $p = 0.0094$) and with a reduced Ca content (OR = 7.68, 95 % CI 2.77–21.30, $p = 0.0001$).

Prospects for further research are to continue studying the micro-macronutrient composition in patients with autoimmune thyroiditis and subclinical hypothyroidism. For individuals with insufficiency / deficiency of micro-, macronutrients, changes in functional and sonographic thyroid indicators, to continue studying the possibility and feasibility of prophylactic use of drugs / food supplements to reduce the risk of disease onset and progression.

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