ORIGINAL ARTICLE

CONTENTS

Dysbiosis of the large intestine and impaired barrier function of the intestine in patients with autoimmune thyroiditis

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ABSTRACT

Aim: To determine the relationship between changes in serum and fecal zonulin levels depending on the severity of colonic dysbiosis in patients with autoimmune thyroiditis.

Materials and Methods: A total of 143 patients with autoimmune thyroiditis (AIT) were included in the study. An assessment of the species and quantitative composition of the colonic microbiota (CM) was performed in the examined patients. The zonulin level was determined in blood serum and feces using enzyme-linked immunosorbent assay. The α1-antitrypsin (α1-AT) level was also determined in blood serum and feces using ELISA. Based on the results obtained, the α1-AT clearance was calculated. The level of fecal calprotectin (FC) was also assessed using the ELISA method.

Results: The data obtained indicate that the vast majority of patients had reduced thyroid hormone levels (hypothyroidism) – in 70 (49.0% of those examined). Patients with thyroid hypofunction in AIT were assigned to group 1 of the examined patients. Euthyroidism was diagnosed in 47 (32.9%) patients, who were classified as group 2. Group 3 consisted of 26 (18.1%) patients with AIT who were diagnosed with elevated thyroid hormone levels in their blood serum.

As the data show, patients with AIT and thyroid hypofunction are significantly more likely to have grade 3 colonic dysbiosis ($p<0.001$). It is in patients with AIT and hypothyroidism that grade 4 colonic dysbiosis is significantly more common (in 11.4% of cases – $p<0.01$), which is 5.0% and 7.6% more than in patients in groups 2 and 3.

Conclusions: Patients with AIT have been found to have colonic dysbiosis, the severity of which depends on the functional state of the thyroid gland. At the same time, patients with hypothyroidism in AIT are mainly diagnosed with grade 3 CD (in 57.1% – $p<0.001$), while patients with AIT and euthyroidism and hyperthyroidism are mainly diagnosed with grade 2 CD (in 55.3% ($p<0.001$) and 46.2% ($p<0.01$) of patients, respectively). CD (in 55.3% ($p<0.001$) and 46.2% ($p<0.01$) of the examined patients, respectively). In patients with AIT, impaired intestinal barrier function was established based on the levels of biomarkers such as zonulin, α1-AT in feces and blood serum, regardless of thyroid function. However, the maximum values of zonulin and α1-AT in feces were diagnosed in patients with AIT with pancreatic hypofunction (an increase in their levels to 168.73±0.51 ng/ml ($p<0.001$) and to 41.07±0.37 mg/dl($p<0.01$), respectively), which directly correlates with the severity of CD in these patients.

KEY WORDS: autoimmune thyroiditis, thyroid hormones, intestinal dysbiosis, impaired intestinal barrier function, zonulin, α1-antitrypsin, fecal calprotectin

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INTRODUCTION

Autoimmune thyroid disease (AITD) is the most common organ-specific autoimmune disease, characterized primarily by thyroid dysfunction and immune imbalance. Normal thyroid function is vital for growth, development, reproduction, and metabolism in the body. As a serious endocrine disorder, thyroid dysfunction disrupts glucose homeostasis, kidney function, and reproductive health, posing significant health risks [1-3].

Environmental factors such as radiation, smoking, and iodine intake, as well as certain endocrine disruptors such as mercury and vanadium, are considered triggers for AITD, and certain comorbidities may further increase the risk of developing AITD [4].

AITD primarily includes Graves' disease (GD) and Hashimoto's thyroiditis (HT). GD is the most common cause of hyperthyroidism in Western countries and mainly affects people between the ages of 30 and 60. In contrast, HT is the leading cause of hypothyroidism in regions with sufficient iodine intake, with a total prevalence of approximately 7.5% and a prevalence among women of 17.5% [5-7].

Recent studies show that AITD is associated with diseases such as vitiligo, alopecia areata, and celiac disease, as well as an increased risk of miscarriage and infertility in women, and may contribute to various neuropsychiatric symptoms and changes in brain function [8, 9].

The human gut microbiota consists of billions of microorganisms, such as bacteria, viruses, fungi, and pro-

tozoa. Four families of bacteria predominate in healthy gut flora, namely Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. These subpopulations of microorganisms regulate the function of gut-associated lymphoid tissue (GALT) and show a close relationship between their representatives and diet. GALT works closely with gut microbes. This is necessary to maintain proper nutrient absorption and protect the mucous membrane from harmful pathogens. Changes in the gut microbiota can weaken or destroy the integrity of the intestinal barrier. As a result, intestinal permeability increases, leading to activation of the immune system, for example, through molecular mimicry. GALT effector cells are activated, and the pro-inflammatory factors produced at this time cause subclinical inflammation. Initially, the entire process develops only in situ, but it can spread and turn into persistent generalized inflammation [10-14].

The gut microbiome ferments indigestible food components into absorbable metabolites. It is also responsible for synthesizing essential vitamins and removing toxic compounds. Short-chain fatty acids (SCFA), which are products of microbial fermentation, act as substrates for enterocytes. Therefore, they act as modulatory factors for immune cells. SCFAs form a direct link between the gut microbiome and the immune system due to their ability to induce regulatory T cells (Tregs) and regulate the balance of Tregs and Th17 cells. Thus, any state of gut microbiome dysbiosis can induce increased intestinal permeability with subsequent disruption of SCFA production and then dysregulation of the immune system [7, 15].

Therefore, identifying the factors that influence the development of AITD is extremely important for clinicians and researchers, as it helps to develop individual prevention and treatment strategies.

AIM

The aim to determine the relationship between changes in serum and fecal zonulin levels depending on the severity of colonic dysbiosis in patients with autoimmune thyroiditis.

MATERIALS AND METHODS

The study was conducted at the clinical base of the Department of Propaedeutics of Internal Diseases of the Medical Faculty of Uzhhorod National University. A total of 143 patients with autoimmune thyroiditis (AIT) were included in the study.

The examined patients with AIT were hospitalized in the endocrinology and gastroenterology departments of the Municipal Non-Commercial Enterprise "Andrii Novak Transcarpathian Regional Clinical Hospital" of the Transcarpathian Regional Council or were under outpatient follow-up by a family physician during the period from 2023 to 2026.

Among the examined women, there were 97 (67.8%), and among men, there were 46 (32.2%), aged 47.8±5.4 years. The control group consisted of 30 practically healthy individuals. Among them were 19 women (63.3%) and 11 men (36.7%), with an average age of 47.2±6.2 years.

All studies were conducted with the consent of the patients, and their methodology complied with the 1975 Helsinki Declaration on Human Rights, as amended in 1983, the Council of Europe Convention on Human Rights and Biomedicine, as well as the legislation of Ukraine and the local bioethics committee of UzhNU.

All patients included in the scientific observation were examined using general clinical examination methods. To verify the diagnosis, attention was paid to the nature of the complaints and the medical history of the disease. During the anthropometric examination, height and weight were measured, and body mass index (BMI) was calculated. According to WHO recommendations, patients were classified according to their BMI.

All patients underwent an ultrasound examination (US) of the thyroid gland (TG). Standard general and biochemical tests were performed on blood serum. All patients (for the diagnosis of AIT) had their serum thyroid hormone levels determined (free triiodothyronine (T4), triiodothyronine (T3)) and thyrotropin (TSH), and antibodies to thyroglobulin and thyroid peroxidase were also evaluated.

The diagnosis of AIT was verified taking into account the criteria of clinical guideline 00512 "Autoimmune thyroiditis", the protocol for the management of patients with AIT (E06.3).

The criteria for excluding patients from the study were: thyrotoxicosis, hypothyroidism, thyroid cancer, type 1 diabetes mellitus (DM), type 2 DM (decompensation stage), oncological diseases, psychiatric diseases that do not allow adequate assessment of the condition of patients, acute infectious diseases (including acute intestinal infections), inflammatory bowel diseases (ulcerative colitis, Crohn's disease), celiac disease, lactose intolerance, pseudomembranous colitis, intestinal lesions Clos.

The criteria for inclusion of patients in this scientific study were: patients with autoimmune thyroiditis.

An assessment of the species and quantitative composition of the colonic microbiota (CM) was performed in the examined patients. The material was cultured on a standardized set of selective and differential diagnostic nutrient media to identify aerobic and anaerobic microor-

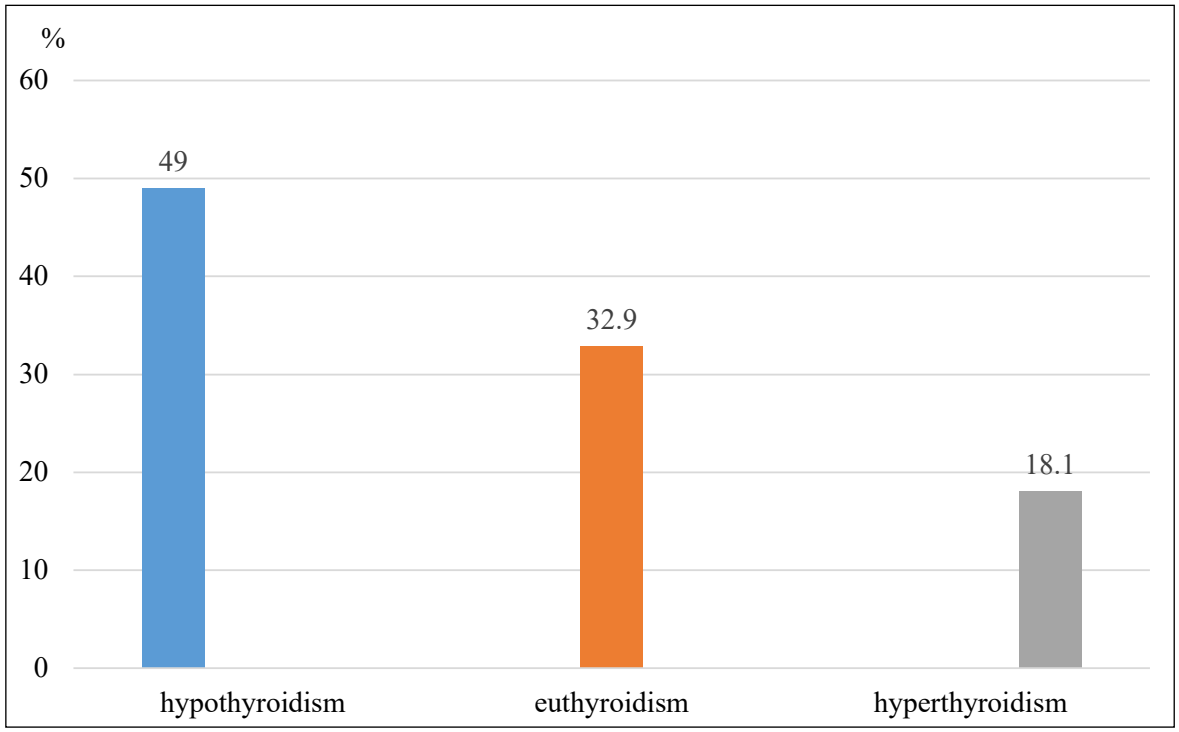

Fig. 1. Distribution of patients with AIT according to the functional state of the thyroid gland
Picture taken by the authors

ganisms using the serial tenfold dilution method (10^{-1}-10^{-9}). To determine the hemolytic forms of intestinal and coccal microflora, 5% blood agar was used; for the cultivation of bifidobacteria; identification of fungi of the genus Candida and other pathogenic fungi was carried out on Sabouraud medium; for the isolation of enterobacteria. Endo medium was used. The assessment of quantitative and qualitative composition disorders of the CM was carried out in accordance with the unified working classification of intestinal dysbiosis according to Kuvayeva-Ladodo (1991).

The zonulin level was determined in blood serum and feces using enzyme-linked immunosorbent assay (ELISA) (test systems from Elabscience, USA). The α1-antitrypsin (α1-AT) level was also determined in blood serum and feces using ELISA (test systems from Immundiagnostic AG, Germany). Based on the results obtained, the α1-AT clearance was calculated. The level of fecal calprotectin (FC) was also assessed using the ELISA method (Tecan Sunrise test system, ImmunDiagnostic, Germany).

The analysis and processing of the examination results were performed using the Statistics for Windows v.10.0 computer program (StatSoft Inc, USA) with parametric and nonparametric methods of evaluating the results obtained.

FRAMEWORK

The study was performed within the framework of the scientific topics "Clinical and Pathogenetic Features of Polymorbid Diseases in the Digestive System and Development of Differentiated Therapy Scheme in the Conditions of the COVID-19 Pandemic" (state registration number 0121U110177) researched by the Department of Propedeutics of Internal Diseases of State University "Uzhhorod National University".

RESULTS

After assessing the level of thyroid hormones in the blood serum of patients with AIG, they were divided into groups depending on the functional activity of the gland – Fig. 1.

The data obtained indicate that the vast majority of patients had reduced thyroid hormone levels (hypothyroidism) – in 70 (49.0% of those examined). Patients with thyroid hypofunction in AIT were assigned to group 1 of the examined patients. Euthyroidism was diagnosed in 47 (32.9%) patients, who were classified as group 2. Group 3 consisted of 26 (18.1%) patients with AIT who were diagnosed with elevated thyroid hormone levels in their blood serum.

We determined the quantitative and qualitative composition of the colon microflora in patients with AIT. At the same time, patients with AIT were diagnosed with a decrease in the number of bifidobacteria, lactobacilli, and E. coli with normal enzymatic properties compared to the control group. These changes were accompanied by an increase in the number of pathogenic and

Table 1. Distribution of subjects by severity of colonic dysbiosis

Severity of colon dysbiosis	Group of examined patients with AIT, %		
	Group 1 (n=70)	Group 2 (n=47)	Group 3 (n=26)
Grade 1	4.4 %	12.8 % *	26.9 % ** +
Grade 2	27.1 %	55.3 % ** +	46.2 % *
Grade 3	57.1 %	25.5 % **	23.1 % **
Grade 4	11.4 %	6.4 % *	3.8 %

Note: the difference between the indicators in patients in group 1 and groups 2-3 is significant: * – p<0.01; ** – p<0.001; the difference between the indicators in patients in groups 2 and 3 is significant: + – p<0.05; ++ – p<0.01
Source: compiled by the authors of this study

Table 2. Indicators of biomarkers of intestinal damage in the examined patients

Parameter	Patients			
	Control group (n=30)	Group 1 (n=70)	Group 2 (n=47)	Group 3 (n=26)
FC, µg/L	21,07±0,21	112.15±0.76 **	73.75±0.24 *++	84.55±0.18 *+#
Zonulin:				
in blood serum, ng/mL	13.78±0.15	118.12±0,62 **	87.23±0.41 **+	101.33±0.15 **#
in fecal, ng/mL	17.01±0.35	168.73±0.51 **	112.34±0.51 **+	134.26±0.39 **+#
α1-AT:				
in blood serum , mg/dL	115.12±0.98	241.15±2.44 *	176.15±1.71 *++	216.51±1.32 *+##
in fecal, mg/dL	13.89±0.17	41.07±0.37 *	29.09±0.18 *+	38.56±0.40 *#
clearance α1-AT, mL/day	17.28±0.41	76.18±0.45 **	47.42±0.53 *+	69.13±0.26 **+##

Note: the difference between the control group and the examined patients is statistically significant: * – p<0.01; ** – p<0.001;
The difference between the indicators in patients in group 1 and groups 2-3 is significant: + – p<0.01; ** – p<0.001;
The difference between the in dicators in patients in groups 2 and is significant: # – p<0.05; ## – p<0.01.
Source: compiled by the authors of this study

conditionally pathogenic microflora. Microbiological examination revealed hemolytic *E. coli*, fungi of the genus *Candida*, *Enterobacter*, *Citrobacter*, *Staphylococcus*, *Klebsiella*, and *Clostridium* in increased concentrations in feces compared to the control group.

After summarizing the results obtained, patients with AIT were classified according to the severity of colonic dysbiosis, as shown in Table 1.

As the data show, patients with AIT and thyroid hypofunction are significantly more likely to have grade 3 colonic dysbiosis (p<0.001). It is in patients with AIT and hypothyroidism that grade 4 colonic dysbiosis is significantly more common (in 11.4% of cases – p<0.01), which is 5.0% and 7.6% more than in patients in groups 2 and 3. In the examined patients with AIT and euthyroidism, grade 2 colonic dysbiosis was significantly more common (in 55.3% of cases – p<0.001), as well as grade 3 colonic dysbiosis (in 25.5% of cases – p<0.001). In patients of group 3 , grade 2 colon dysbiosis was also significantly more common (in 46.2% of patients), but it should be noted that it was in patients with hyperthyroidism that grade 1 colon dysbiosis was most commonly found (in 26.9% of patients).

We evaluated biomarkers of intestinal barrier dysfunction in the patients we examined (Table 2).

The data obtained indicate an increase in the level of biomarkers in dicating a violation of the intestinal barrier function (levels of zonulin, α1-AT in blood serum and feces). The maximum increase in zonulin levels in serum and feces was found in patients with AIT group 1 (patients with hypothyroidism), while the minimum deviation from the norm was found in patients with group 2 (patients with AIT, whose thyroid hormone levels indicated euthyroidism). The same dynamics can be observed in the analysis of α1-AT levels in blood serum and feces, as well as its clearance in the patients we examined.

Table 3. The relationship between the severity of colonic dysbiosis and biomarkers indicating impaired intestinal permeability

Parameter	Groups of examined patients with AIT					
	Group 1 (n=70)		Group 2 (n=47)		Group 3 (n=26)	
	Grade of colonic dysbiosis					
	Grade 2	Grade 2	Grade 2	Grade 3	Grade 2	Grade 3
Zonulin (blood)	r=0.90; p<0.01	r=0.96; p<0.01	r=0.80; p<0.01	_	r=0.84; p<0.01	r=0.76; p<0.01
Zonulin (fecal)	r=0.94; p<0.01	r=0.98; p<0.01	r=0.82; p<0.01	r=0.78; p<0.01	r=0.90; p<0.01	r=0.80; p<0.01
α1-AT (blood)	r=0.70; p<0.05	r=0.74; p<0.05	r=0.68; p<0.05	_	r=0.70; p<0.05	_
α1-AT (fecal)	r=0.92; p<0.01	r=0.96; p<0.01	r=0.72; p<0.05	r=0.70; p<0.05	r=0.76; p<0.01	r=0.68; p<0.05
FC	r=0.80; p<0.01	r=0.82; p<0.01	r=0.78; p<0.01	_	r=0.90; p<0.01	_

Source: compiled by the authors of this study

Analysis of the studies conducted also indicates a tendency toward an increase in FC levels, but the results obtained in patients in groups 2 and 3 with AIT did not exceed 5 times the norm (compared with the data obtained in the control group). The maximum increase in FC levels was observed in patients with thyroid hypofunction in AIG.

The relationship between the severity of colonic dysbiosis and changes in the levels of biomarkers indicating impaired intestinal barrier function was analyzed (Table 3).

A correlation between changes in zonulin and α1-AT levels was established mainly in the feces of patients with grade 2 and 3 CD. At the same time, a strong correlation was established mainly in patients of group I with AIT. In patients with hypothyroidism in AIT (group I), the severity of CD affects the increased levels of zonulin and α1-AT in blood serum. According to our research, the increased FC index also depends on the degree of colon dysbiosis in patients with AIT.

Thus, changes in the quantitative and qualitative composition of the colon have been established in patients with AIT, and the severity of intestinal dysbiosis affects intestinal permeability in these patients.

DISCUSSION

According to Cayres LCF et al. (2021), individuals diagnosed with TH have intestinal dysbiosis. Patient samples showed a significant increase in Bacteroides species with a concomitant decrease in Bifidobacterium among the gut microbiota [16]. Intestinal dysbiosis is associated with increased intestinal permeability [17]. Recent studies indicate that zonulin is a highly sensitive biomarker of leaky gut syndrome. Zonulin is a protein that is a potential modulator of tight junctions in the intestine [18].

Demir E. et al. indicate elevated zonulin levels in chronic thyroiditis [19]. Küçükemre Aydın B et al. (2020) examined 30 children and adolescents with HT and 30 patients with congenital hypothyroidism (CH) selected by age, sex, and body mass index (BMI). Serum zonulin, free thyroxine (fT4), thyroid-stimulating hormone (TSH), thyroglobulin antibodies, and thyroid peroxidase antibodies were measured. Zonulin levels were significantly higher in patients with TH than in patients with GHD (59.1±22.9 ng/ml vs. 43.3±32.9 ng/ml, p=0.035). In patients with HT, zonulin levels positively correlated with weight (r=0.406, p=0.03), BMI (r=0.486, p=0.006), and levothyroxine dose (r=0.463, p=0.02). In patients with CH, zonulin levels were positively correlated with age (r=0.475, p=0.008), weight (r=0.707, p<0.001), BMI (r=0.872, p<0.001), and levothyroxine dose (r=0.485, p=0.007). After adjusting for age, weight, TSH and fT4 levels, serum zonulin was associated only with levothyroxine dose in patients with HT (R2=0.36, p=0.05). In patients with CH, only weight was associated with zonulin levels (R2=0.62, p<0.001). The authors concluded that higher zonulin levels in children and adolescents with HT indicated increased intestinal permeability in these patients. In addition, the relationship between zonulin levels and levothyroxine dose may indicate an association between serum zonulin and disease severity [20].

The exact mechanism that causes autoimmunity in TH is not fully understood. Many pathologies are considered to be the cause, in particular, disruption of the intestinal epithelial barrier, which causes an inadequate immune response due to the interaction of immune cells of the submucosa with antigens. An abnormal increase in zonulin levels causes increased intestinal permeability and plays a key role in the development of autoimmune diseases. According to İşleyen ZS et al. (2022), the correlation between anti-thyroperoxidase levels, an indicator of the autoimmune process, and serum zonulin levels suggests that this molecule plays a role in the pathogenesis of TH [21].

Therefore, the gut microbiota has an undeniable impact on the integrity of the intestinal mucosa and the function of the immune system. Attempts are being made to modify the microbiome in several autoimmune

diseases, including TH. However, research findings suggest that regular use of probiotics, prebiotics, or synbiotics may have very limited benefits for patients with primary hypothyroidism [22]. Treatment with probiotics or short-chain fatty acids (SCFAs) is not commonly used in autoimmune diseases. However, studies have shown that human-derived probiotics increase SCFA production by modulating the gut microbiome in mice and humans [23]. This may indicate that this specific type of therapy could improve the gut microbiome and indirectly affect the immune system.

The results of our studies also indicate intestinal dysbiosis in patients with AIG, and the relationship between zonulin levels and thyroid dysfunction and hormone levels suggests a possible role for intestinal permeability in the development of autoimmune reactions in these patients. Further research is needed to determine the effectiveness of correcting dysbiotic changes and their possible positive effect on the functional state of the thyroid gland.

CONCLUSIONS

1. Patients with AIT have been found to have colonic dysbiosis, the severity of which depends on the functional state of the thyroid gland. At the same time, patients with hypothyroidism in AIT are mainly diagnosed with grade 3 CD (in 57.1% – $p<0.001$), while patients with AIT and euthyroidism and hyperthyroidism are mainly diagnosed with grade 2 CD (in 55.3% ($p<0.001$) and 46.2% ($p<0.01$) of patients, respectively). CD (in 55.3% ($p<0.001$) and 46.2% ($p<0.01$) of the examined patients, respectively).
2. In patients with AIT, impaired intestinal barrier function was established based on the levels of biomarkers such as zonulin, α1-AT in feces and blood serum, regardless of thyroid function. However, the maximum values of zonulin and α1-AT in feces were diagnosed in patients with AIT with pancreatic hypofunction (an increase in their levels to 168.73±0.51 ng/ml ($p<0.001$) and to 41.07±0.37 mg/dl($p<0.01$), respectively), which directly correlates with the severity of CD in these patients.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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