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The role of visceral hypersensitivity and cortisol levels in the development of intestinal dysfunction in coexisting hypothyroidism

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The increasing dysfunction of the thyroid gland, particularly hypothyroidism, and its multifaceted effects on the gastrointestinal tract, such as potential changes in hormonal receptor sensitivity, neuromuscular disorders, and myopathy caused by infiltration of the colonic wall, lead to impaired bowel function. Although constipation remains the most common gastrointestinal complaint in hypothyroidism, hypomotility may contribute to excessive bacterial growth in the small intestine and the development of diarrhea.

The aim is to study the role of visceral hypersensitivity and cortisol levels in patients with intestinal dysfunction in coexisting hypothyroidism and in those with constipation or diarrhea without thyroid dysfunction.

Materials and methods. A total of 41 patients with hypothyroidism were examined, of whom 24 were diagnosed with persistent constipation and 17 with diarrhea, along with 36 patients with irritable bowel syndrome (IBS) (control group), of whom 22 had constipation and 14 had diarrhea. In all the patients, visceral hypersensitivity was assessed using the Visceral Sensitivity Index (VSI), and serum cortisol levels were measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits from Sanguin (USA). Fecal calprotectin levels were assessed with the Human CALPE (Calprotectin) ELISA KIT by Elabscience (USA).

Results. VSI was higher in patients with hypothyroidism and diarrhea and scored 66.0 (61.0; 68.0) points. In individuals with IBS and diarrhea without thyroid dysfunction, VSI was 58.0 (54.0; 62.0) points. Meanwhile, VSI was 65.0 (60.0; 69.0) points in patients with constipation due to hypothyroidism, whereas in IBS patients without thyroid dysfunction, it was significantly lower – 24.0 (22.0; 26.0) points ($p < 0.05$). In the control group without bowel and thyroid pathology, VSI scored 15.0 (12.0; 18.0) points. The serum cortisol level in patients with hypothyroidism and diarrhea was 305.41 (270.24; 309.3) nmol/L, while in patients with IBS and diarrhea without thyroid dysfunction, it was 211.0 (205.0; 222.5) nmol/L. In patients with constipation due to hypothyroidism, the serum cortisol level was 310.625 (308.440; 337.285) nmol/L, whereas in IBS patients with constipation, it was 178.0 (172.0; 187.5) nmol/L. For healthy individuals, the cortisol level was 158.0 (152.0; 167.5) nmol/L. A direct correlation has been found between a high degree of visceral sensitivity and cortisol levels in patients with hypothyroidism and constipation, as well as an inverse correlation in patients with hypothyroidism and diarrhea. The obtained data may indicate a shift towards hypersensitivity and the development of symptoms characteristic of IBS.

Conclusions. Visceral hypersensitivity is observed both in cases of diarrhea developing against the background of hypothyroidism and in irritable bowel syndrome with a similar clinical presentation. At the same time, in cases of constipation associated with hypothyroidism, hypersensitivity is also present but tends to be less pronounced in IBS with constipation. Patients with hypothyroidism, regardless of the presence of constipation or diarrhoea, have an increase in blood cortisol levels, while in some variants of IBS, they do not differ significantly from those of healthy individuals. A direct correlation was found between a high degree of visceral hypersensitivity and cortisol levels in hypothyroid patients with constipation and the opposite in hypothyroid patients with diarrhoea.

Ключові слова: гіпотиреоз, синдром подразненого кишечника, вісцеральна гіперчутливість, кортизол, кальпротектин.

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Роль вісцеральної гіперчутливості та рівня кортизолу у розвитку порушення функції кишечника на фоні гіпотиреозу

В. Г. Міщук, Г. В. Козінчук, О. З. Венгрович, У. П. Шаламай

Посилення дисфункції щитоподібної залози, зокрема гіпотиреозу та його істотний вплив на шлунково-кишковий тракт із можливими змінами чутливості гормональних рецепторів, нервово-м'язовими розладами та міопатією, що спричинена інфільтрацією стінки товстої кишки, призводять до порушення функції кишечника. Хоча закреп залишається найчастішою скаргою щодо травної системи при гіпотиреозі, гіпомоторика може спричиняти надмірний бактеріальний ріст у тонкій кишці та виникнення діареї.

Мета роботи – вивчити роль вісцеральної гіперчутливості та рівня кортизолу у хворих із порушенням функції кишечника на фоні гіпотиреозу та у пацієнтів із закрепами або діареєю без дисфункції щитоподібної залози (ЩЗ).

Матеріали і методи. Обстежили 41 пацієнта з гіпотиреозом: у 24 хворих діагностовано стійкі закрепи, у 17 – діарею; а також 36 хворих із синдромом подразненого кишківника (СПК) (контрольна група): 22 осіб мали скарги на закрепи, 14 – на діарею. В усіх обстежених визначили вісцеральну гіперчутливість за допомогою індексу вісцеральної гіперчутливості (VSI), рівень кортизолу в сироватці крові імуноферментним методом за допомогою комерційних наборів фірми «Sanguin» (США), рівень кальпротектину в калі – Human CALPE (Calprotectin) Elisa KIT (Elabscience, США).

Результати. VSI вищий у хворих на гіпотиреоз з діареєю та становив 66,0 (61,0; 68,0) бала. В обстежених із СПК і діареєю без порушення функцій ЩЗ він становив 58,0 (54,0; 62,0) бала. У хворих із закрепами на фоні гіпотиреозу VSI дорівнював 65,0 (60,0; 69,0) бала, а при СПК без порушення функцій ЩЗ – 24,0 (22,0; 26,0) бала ($p < 0,05$). В обстежених із контрольної групи без патології кишечника і ЩЗ показник VSI становив 15,0 (12,0; 18,0) бала. Рівень кортизолу в сироватці крові хворих на гіпотиреоз і діарею становив 305,41 (270,24; 309,3) нмоль/л, а на СПК і діарею, без порушення функції ЩЗ –

211,0 (205,0; 222,5) нмоль/л. У пацієнтів із закрепами на фоні гіпотиреозу рівень кортизолу в сироватці крові становив 310,625 (308,44; 337,285) нмоль/л, а при СПК і закрепах – 178,0 (172,0; 187,5) нмоль/л (у здорових – 158,0 (152,0; 167,5) нмоль/л). Встановлено прямий кореляційний зв'язок між високим ступенем вісцеральної чутливості та рівнем кортизолу у хворих на гіпотиреоз із закрепами, а також зворотний кореляційний зв'язок у пацієнтів із гіпотиреозом і діареєю.

Висновки. Вісцеральну гіперчутливість визначили і в разі діареї, що виникла на фоні гіпотиреозу, і при синдромі подразненого кишківника з такою самою клінічною картиною. Разом із тим, у разі закрепів, що пов'язані з гіпотиреозом, гіперчутливість також виявлена, проте мала тенденцію до меншої вираженості при СПК із закрепами. У хворих на гіпотиреоз незалежно від наявності закрепів чи діареї встановлено підвищення рівня кортизолу в крові, а при окремих варіантах СПК достовірно цей показник не відрізнявся від рівня, що визначений у здорових. Встановлено прямий кореляційний зв'язок між високим ступенем вісцеральної чутливості та рівнем кортизолу у хворих на гіпотиреоз із закрепами, зворотний – у пацієнтів із гіпотиреозом і діареєю.

Changes in the status of individual hormonal systems play a crucial role in the development of functional and inflammatory gastrointestinal diseases [1]. This is particularly true for the thyroid system, as thyroid hormones are involved in the regulation of motor, evacuatory, and secretory activities of the gastrointestinal organs, as well as in cellular proliferation, differentiation, apoptosis, and the epithelial cell functional activity in the digestive system [2]. Particularly often, thyroid dysfunction leads to disturbances in intestinal motility, and thyroid hormones frequently correlate with intestinal ones and affect the brain-gut axis at various levels [3].

So, there have been a growing number of thyroid dysfunctions with the prevalence of hypothyroidism averaging 13.9 % in some countries (19.4 % in women and 6.3 % in men) [4]. According to a study by C. B. Giorda et al. [5], the prevalence of hypothyroidism has increased by 35 % in recent years, primarily due to non-iatrogenic forms. Hypothyroidism also tends to be higher among females aged ≥65 years and residents of Eastern and Southern Europe [6]. The impact of hypothyroidism on the gastrointestinal tract is multifaceted, with possible changes in hormonal receptor hypersensitivity, neuromuscular disorders, and myopathy due to colonic wall infiltration, leading to decreased intestinal peristalsis. Constipation remains the most common gastrointestinal complaint in hypothyroidism [7,8].

However, hypomotility in hypothyroidism can contribute to excessive bacterial growth in the small intestine and the development of diarrhea [9]. When the number of microorganisms in the small intestine exceeds 106 colony-forming units/mg in aspirate, it results in small intestinal bacterial overgrowth (SIBO). One of the most common causes of this phenomenon is altered small intestinal motility, which occurs in hypothyroidism. It is hypothesized that excessive bacterial growth and subsequent diarrhea may affect more than half of patients with hypothyroidism and present as a chronic form [10]. On the other hand, the microbiome influences thyroid functions, leading R. Bardiel et al. [11] to hypothesize the existence of a gut-thyroid axis. In patients with excessive bacterial growth in the small intestine, thyroid functions may be impaired due to changes in thyroxine metabolism [12,13]. As W. Jiang et al. indicate, excessive bacterial growth may be present in 50 % of patients with hypothyroidism, and these conditions can lead to increased intestinal peristalsis [14].

In recent years, several studies have examined the relationship between thyroid dysfunction, particularly subclinical hypothyroidism, and irritable bowel syndrome (IBS) [15]. According to the Rome III criteria, IBS was diagnosed in 9.0 % of patients with IBS and diarrhea and 27.8 % of those with IBS and constipation. Another study examined the relationship between euthyroid Hashimoto's thyroiditis and IBS in women [16]. No significant correlation has been found between these conditions, although thyroid antibody levels were higher in patients with Hashimoto's thyroiditis and IBS compared to those with thyroiditis without gastrointestinal symptoms. The authors concluded that IBS and IBS-like symptoms, including abdominal pain and discomfort, are likely the result of the direct effect of thyroid hormones on intestinal motility, rather than solely autoimmune effects in an euthyroid state. Furthermore, A. C. Ford et al. [17], in a sample of 23,471 patients, have not observed an association between IBS and endocrine autoimmune disorders, including Hashimoto's thyroiditis.

Currently, there is limited understanding of why many patients with thyroid dysfunction continue to experience gastrointestinal symptoms even after achieving a euthyroid state. Several factors contribute to this phenomenon, including increased intestinal permeability, microbial changes, mast cell reactivity, brain-gut dysfunction, and, notably, visceral hypersensitivity and hormonal imbalances [18]. Obesity also plays a significant role in increasing visceral hypersensitivity, even in the absence of detectable systemic low-grade inflammation, and weight gain is a hallmark of hypothyroidism [19]. Furthermore, maladaptive responses in the gut may result from alterations in neuroendocrine pathways, such as the release of adrenocorticotropic hormone (ACTH) from the pituitary, leading to increased cortisol secretion and a triad of symptoms, including fatigue, heightened stress sensitivity, and pain [20]. These symptoms can also manifest in thyroid dysfunction [18].

Studies conducted by S. Benson et al. have shown that pressure-controlled distension of the rectum, used for assessing visceral modality and its correction with hydrocortisone, reduced pain perceptions. As the authors note, however, the effects of cortisol on visceral hypersensitivity and pain have not yet been fully studied [20].

Aim

The aim is to study the role of visceral hypersensitivity and cortisol levels in patients with intestinal dysfunction in coexisting hypothyroidism and in those with constipation or diarrhea without thyroid dysfunction.

Materials and methods

The work was carried out at the Centre for Clinical Medicine of the University Clinic of Ivano-Frankivsk National Medical University. Immunoenzyme tests were performed in the

laboratory of the same clinic, and bacteriological tests were done at the Department of Microbiology, Virology and Immunology of the University.

All patients included in the study gave written consent to participate in the study. The study was conducted in accordance with the principles of bioethics set out in the World Health Organization's Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" and approved by the Bioethics Committee of Ivano-Frankivsk National Medical University.

The inclusion criteria in the study were confirmed hypothyroidism and IBS with diarrhea or constipation in patients, based on hormonal spectrum determination (TSH, T3, T4) and according to the Rome IV criteria. The study did not include patients with concomitant diabetes mellitus, neurological diseases (Parkinson's disease, stroke, inflammatory diseases of the nervous system), pathology of the anal region and rectum, and individuals over 60 years of age due to the possible development of functional constipation.

We examined 41 patients with hypothyroidism, of whom 24 (16 women and 8 men) presented with constipation and 17 patients (10 women and 7 men) – with diarrhea. The level of thyroid-stimulating hormone (TSH) in patients with hypothyroidism and constipation was 14.24 (13.39; 14.98) μIU/ml, and in those with diarrhea, it was 11.95 (11.40; 12.50) μIU/ml (in healthy individuals, it was 4.32 (3.65; 4,99) μIU/ml).

The serum level of triiodothyronine (T3) in patients with hypothyroidism in the first subgroup was 1.94 (1.77; 2.09) nmol/L and in the second subgroup – 2.35 (1.79; 2.76) nmol/L. The level of thyroxine (T4) was 0.66 (0.60; 0.73) ng/dl, and 0.75 (0.67; 0.81) ng/dl, respectively.

The study also included 36 patients with IBS, of whom 22 were diagnosed with constipation variant according to the Rome IV criteria (third subgroup), and 14 – with diarrhea (fourth subgroup). In patients with IBS and constipation, the mean TSH level was 2.91 (2.80; 3.15) μIU/ml, T3 was 2.82 (2.80; 3.05) nmol/L, and T4 was 1.18 (1.10; 1.28) ng/dl. In cases of IBS with diarrhea, the serum TSH concentration was 2.18 (2.10; 2.35) μIU/ml, T3 was 2.99 (2.80; 3.25) nmol/L, and T4 was 1.210 (1.150; 1.325) ng/dl.

The patients examined for hypothyroidism were of working age, and their number at the age of 20 to 30 years was 14.6 %, from 30 to 40 – 34.1 %, and from 40 to 50 – 34.2 %, equaling an average of 43.3 ± 1.4 years. IBS at the age of 20 to 30 years was diagnosed in 36.1 %, from 30 to 40 years – in 41.7 %, while at the age of 40 to 50 years – in 19.4 % of the subjects and the mean age was 32.6 ± 0.6 years ($p < 0.01$).

In all the patients included in the study, fecal calprotectin concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) with commercial kits, Human Calprotectin / ELISA Kit from Elabscience (USA). This was done to rule out inflammatory bowel diseases in cases of diarrhea, and calprotectin levels are often significantly correlated with visceral hypersensitivity [21]. Excessive bacterial growth was determined by culturing secretions from the postbulbar portion of the duodenum on nutrient media, followed by counting the number of colonies. The condition was diagnosed when the number of colony-forming units exceeded 10^6 CFU per mg.

Visceral hypersensitivity was assessed using the Visceral Sensitivity Index (VSI) [22], which has demonstrated reliability, good content, convergent, divergent, and predictive validity. The reliability of VSI has been established through Cronbach's alpha, construct, and discriminant validity [23,24]. The VSI is a unidimensional scale with 15 items to measure specific anxiety related to gastrointestinal symptoms. The items are rated on a Likert scale from 0 to 5.

Serum cortisol levels were measured using the solid-phase enzyme immunoassay method with kits from Sanguin (USA), while fecal calprotectin levels were assessed using the Human CALPE (Calprotectin) ELISA KIT from Elabscience (USA).

The statistical analysis of the results was performed via the software packages Statistica for Windows 10 (StatSoft Inc., No. AGFR205F354521FA-5) and the statistical software packages of Microsoft Excel. Parametric and nonparametric methods of data evaluation were used. The results were statistically analyzed using Pearson's chi-square (χ^2) with Yates' correction (for qualitative data with a small sample size). The strength of the correlation between the quantitative indicators (r) was determined using the Spearman's method. The data were presented as mean ± standard error of the mean (M ± m), median (Me) and interquartile range: lower-upper quartile (LQ; HQ). Correlations between indicators were tested using Pearson's coefficient. Differences were considered significant at a level of $p < 0.05$.

Results

The analysis of clinical symptoms in patients with hypothyroidism (Group 1) and those with excessive bacterial growth secondary to it (Group 2) has shown that symptoms such as cold intolerance were reported with similar frequency: 95.8 % and 94.1 %, respectively. Fragility and hair loss have been observed in 87.5 % and 88.2 %, respectively, and memory deterioration – in 66.7 % and 64.7 %, respectively. Symptoms such as general weakness and drowsiness have been detected in 13.4 % (95.8 % and 82.4 %) and 12.0 % (70.8 % and 58.8 %), more commonly in patients with hypothyroidism and constipation. In cases of hypothyroidism with diarrhea, symptoms such as sluggishness were somewhat more frequent by 14.9 % (94.1 % and 79.2 %), decreased tolerance to physical exertion by 7.4 % (82.4 % and 75.0 %), and abdominal bloating by 44.1 % (94.1 % and 50.0 %). Among complaints typical of patients with hypothyroidism and IBS, irritability was frequently noted in 90.9 % and 78.6 %, respectively; abdominal bloating in 81.8 % and 78.6 %; and worsening sleep quality in 72.7 % and 71.4 %, respectively.

The lowest fecal level of calprotectin was in patients with IBS and constipation, amounting to 7.87 (7.12; 8.71) μg/g. In patients with hypothyroidism and constipation, this level was 24.01 (13.92; 55.12) μg/g ($p < 0.01$). In cases of diarrhea, both in patients with hypothyroidism and those with IBS, the fecal level of calprotectin was higher, amounting to 50.14 (36.17; 64.12) and 67.48 (36.17; 64.12) μg/g, respectively, (healthy controls – 31.85 (27.97; 31.85) μg/g).

The VSI was higher in patients with hypothyroidism and diarrhea, scoring 66.0 (61.0; 68.0) points. In patients with IBS and diarrhea without thyroid dysfunction, it was 58.0

Table 1. Biochemical markers in patients with intestinal dysfunction and hypothyroidism

Indicator, units of measurement	Hypothyroidism with diarrhea (Group 1)	Hypothyroidism with constipation (Group 2)	IBS with constipation (Group 3)	IBS with diarrhea (Group 4)	Control Group (Group 5)
Calprotectin level, μg/g	24.11 (13.92; 55.12) p < 0.01	7.87 (7.12; 8.71) p < 0.01	50.14 (36.17; 64.12) p < 0.01	67.48 (36.17; 64.12) p < 0.01	31.85 (27.97; 31.85) p < 0.01
Visceral sensitivity index	66.0 (61.0; 68.0) p < 0.05	65.0 (60.0; 69.0) p < 0.05	24.0 (22.0; 26.0) p < 0.05	58.0 (54.0; 62.0) p < 0.05	15.0 (12.0; 18.0) p < 0.05
Cortisol level, nmol/L	305.41 (270.24; 309.3) p < 0.05	310.625 (308.440; 337.285) p < 0.05	177.67 (122.0; 302.6) p < 0.05	211.0 (205.0; 222.5) p < 0.05	158.0 (152.5; 167.5) p < 0.05

(54.0; 62.0) points. Meanwhile, the VSI in patients with constipation due to hypothyroidism was 65.0 (60.0; 69.0) points, while in IBS patients without thyroid dysfunction, it was 24.0 (22.0; 26.0) points ($p < 0.05$). In the control group without gastrointestinal or thyroid pathology, the VSI scored 15.0 (12.0; 18.0) points.

The serum cortisol level in patients with hypothyroidism and diarrhea was 305.41(270.24; 309.30) nmol/L, whereas in patients with IBS and diarrhea without thyroid dysfunction, it was 211.0 (205.0; 222.5) nmol/L. In patients with constipation due to hypothyroidism, the serum cortisol level was 310.625 (308.44; 337.285) nmol/L, while in IBS patients with constipation, it was 178.0 (172.0; 187.5) nmol/L (in healthy individuals – 158.0 (152.5; 167.5) nmol/L).

The study has revealed a direct correlation between high levels of visceral sensitivity and cortisol levels in hypothyroid patients with constipation, as well as an inverse correlation in patients with hypothyroidism and diarrhea (*Figs. 1, 2*). This indicates possible changes in visceral sensitivity that may be related to the development of symptoms characteristic of IBS.

Discussion

The expression and predominance of both metabolic and dermatological manifestations in patients with hypothyroidism and constipation are attributed to decreased concentration and sensitivity to thyroid hormones. This may be related to mutations in the MCT8 transporter on cell membranes for thyroid hormones, as well as disruptions in their metabolism and the synthesis of selenoproteins, including deiodinases [25]. Additionally, the occurrence of constipation is facilitated by the prolongation of the first phase of inter-digestive migrating contractions and the shortening of phases II and III of this process [26]. The cited study has also demonstrated that thyroid hormones activated motility in the upper gastrointestinal tract without involving gastrointestinal hormones such as ghrelin, cholecystokinin, and others. Simultaneously, in hypothyroidism, there has been a noted shortening of intestinal villi and thickening of the intestinal wall (muscle layer), leading to reduced intestinal peristalsis [27]. Therefore, in patients with clinical manifestations of IBS, thyroid dysfunction, specifically subclinical hypothyroidism, may be present [15].

The presence of low-intensity inflammation in the large intestinal wall is also characteristic of IBS, particularly post-infectious IBS [28]. Chosakai U. C. et al. have also suggested that inflammation in the intestinal wall may be one of the pathogenetic mechanisms involved in the IBS development [29]. However, relationships between

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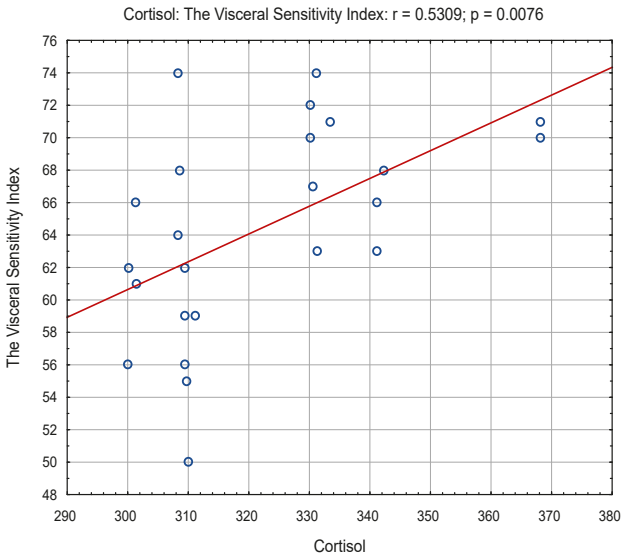

Fig. 1. Cortisol levels and visceral sensitivity index in patients with irritable bowel syndrome with constipation on the background of hypothyroidism.

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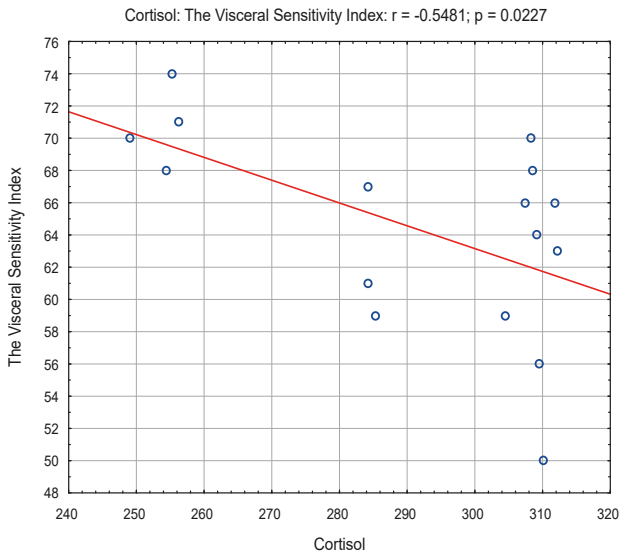

Fig. 2. Cortisol levels and visceral sensitivity index in patients with irritable bowel syndrome and diarrhea coexisting with hypothyroidism.

specific inflammatory markers and IBS subtypes remain poorly understood and require further investigation [30]. Our data have indicated that in both IBS with diarrhea and diarrhea associated with hypothyroidism, the calprotectin level was near the threshold of 50 μg/g, exceeding it only slightly, with values of 51.67 μg/g in diarrhea associated with hypothyroidism and 58.2 μg/g in patients with IBS and diarrhea. The Rome IV consensus recommends checking thyroid function in cases of diarrhea if hyperthyroidism is clinically suspected [31]. Although constipation is more common in hypothyroidism, diarrhea can develop in some cases, and it may worsen following hormone replacement therapy [15].

In cases with constipation predominance, the calprotectin level was within the range observed in healthy individuals (in constipation associated with hypothyroidism) or even 4.2 times ($p < 0.05$) decreased in IBS with constipation without thyroid dysfunction. The low calprotectin level in constipation associated with hypothyroidism, which was 1.35 times lower compared to that in healthy individuals, and the results in certain IBS subtypes with high sensitivity and specificity, allow for differentiating the presence or absence of inflammation in the intestinal wall [32].

Based on the obtained data, it should be concluded that inflammation does not play a pathogenic role in patients with hypothyroidism and constipation.

Another component that distinguishes constipation in hypothyroidism from obstipation in IBS patients is the VSI, which exceeds that of patients with functional disorders by 2.6 times ($p < 0.05$). The highest VSI values have been found in patients with diarrhea both in hypothyroidism and IBS with diarrhea, respectively, by 4.1 and 3.9 times ($p1,2 < 0.05$), which can be explained by a violation of the small intestinal microbiome.

According to K. Ustianowska et al., changes in the species composition of intestinal microorganisms are precisely what causes chronic visceral pain [34]. The positive effect of normal microbiota on reducing visceral hypersensitivity, in particular, Lactobacillus casei, is supported by the research of T. Takeda et al [35]. At the same time, in experimental animals, a decrease in plasma corticosterone levels occurred simultaneously. Hypersensitivity of visceral sensory afferent fibers and changes in the microbial spectrum of the small intestine with the subsequent development of gastroenteritis can also be considered as causes of colonic dysfunction [36].

In patients with hypothyroidism and colonic dysfunction, an increase in cortisol levels has been observed in both constipation and diarrhea, with levels rising by 2.1 and 1.9 times, respectively ($p < 0.05$), with no significant difference in cortisol levels in inflammatory bowel disease and a slight (1.3 times) increase in IBD. The interrelation between hypothyroidism and the hypothalamic-pituitary-adrenal (HPA) axis, and the crucial role of cortisol in the physiological and cognitive manifestations of hypothyroidism, has been examined by other researchers [37]. A cross-sectional observational study by the authors has confirmed the correlation between serum cortisol and TSH and T4 levels in hypothyroidism. Additionally, the authors have found that patients with severe hypothyroidism had elevated cortisol concentrations, which might act as a compensatory mechanism associated with the HPA axis. Furthermore, in primary hypothyroidism, pituitary hyperplasia and excessive secretion of TSH and cortisol can develop. As a stress hormone, cortisol exacerbates the clinical manifestations of the disease and probable affects the state of visceral hypersensitivity [38]. In cases of constipation, regardless of the thyroid gland functional state, the VSI was significantly lower (by 2.6 times, $p < 0.05$) in polycystic ovary syndrome, indicating an insufficient role of visceral hypersensitivity in the development of this functional disorder.

The results have shown a direct correlation between high visceral sensitivity and cortisol levels in cases of constipation in patients with hypothyroidism, and an inverse correlation in patients with diarrhea. This may indicate changes in gut functions associated with the development of symptoms characteristic of IBS. These findings highlight the importance of considering visceral sensitivity when studying gastrointestinal disorders in patients with hypothyroidism.

The physical and psychological stress perception, which is most pronounced in diarrhea with hypothyroidism, probable leads to the activation of ACTH release from the anterior pituitary, thereby increasing cortisol secretion from the adrenal cortex. In cases of constipation, cortisol levels are lower, and this hormonal dysregulation is reliant on the predominance of symptoms experienced by a patient, particularly visceral hypersensitivity, which, along with diarrhea, can activate the HPA axis in the central nervous system [37].

Thus, in patients with combined hypothyroidism and diarrhea, fecal calprotectin threshold values, a significantly higher VSI and blood cortisol levels, correlating with each other, have been detected. In cases of constipation with hypothyroidism, these indicators have been found to be significantly lower, except for cortisol levels, indicating other mechanisms of this comorbidity development and requiring further investigation.

Conclusions

1. Visceral hypersensitivity occurs both in cases of diarrhea with or without hypothyroidism, as well as in cases of constipation with hypothyroidism, and is somewhat less pronounced in IBS with constipation without hypothyroidism.

2. Patients with hypothyroidism, regardless of the presence of constipation or diarrhea, have increased blood cortisol levels, while in some variants of IBS, they do not differ significantly from those of healthy individuals.

3. A direct correlation has been found between a high degree of visceral hypersensitivity and cortisol levels in hypothyroid patients with constipation and an inverse one – in hypothyroid patients with diarrhea.

Prospects for further research include examining intestinal dysfunction in patients with hypothyroidism as well as in those with constipation or diarrhea without thyroid gland dysfunction.

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