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The role of gut microbiota in patients with autoimmune thyroid diseases – current status and future perspectives

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Abstract

Introduction: Autoimmune diseases constitute a significant clinical problem, due to the increasing incidence, that is why the potential causes that determine their occurrence are sought. Intestinal microbiota greatly outnumber the all of human body's cells. Its metabolic activity and

disorders in the structure, resulting from, for example, antibiotic therapy, lead to homeostasis dysregulation, and in this way gain a new meaning in the etiology of autoimmune diseases.

Aim of the study: This article summarizes the current knowledge about gut microbiota in patients with autoimmune thyroid diseases as well as discussed the alterations in the gut microbiota and their potential relationship with thyroid cancer.

Description of knowledge: The analyzed scientific literature revealed a relationship between the occurrence of autoimmune diseases and intestinal flora disorders. It is believed that the microbiota that colonized the entire human body, due to diversity, co-formation of the intestinal barrier, its own metabolic activity and participation in many metabolic processes, plays an important role in regulating the immune system functioning. Many data indicate, that the changes in the composition of the intestinal flora in many autoimmune diseases can also be influenced by individual factors, environmental conditions, genetic predisposition, and diet.

Conclusions: Gut microbiota is an important element of the immune system and due to the demonstrated changes in its composition in various disease processes and its significant effects on metabolism, the researchers are still underway to clarify all pathogenetic mechanisms of microbiota influencing human homeostasis. Therefore, further studies are required to determine the effect of microbiota and its role in the pathogenesis of autoimmune diseases.

Key words: Hashimoto's disease, Graves' disease, gut microbiota, immune system

Introduction

Microbiota, which consists of numerous different microorganisms, including bacteria, viruses, archea, fungi colonizing our bodies, is dominated by bacteria and plays an important role in the individual life of each person [1]. According to scientific sources, the average number of all bacteria in a person is estimated at 39 trillion and exceeds the number of cells building the body of an adult [1]. It is worth noting that the above organisms are metabolically active and it is assumed that 20% of all metabolites present in blood are derived from commensal bacteria [1]. To the best of current knowledge, it is considered that the total intestinal bacteria mass is estimated approximately 1,5-2 kg [2], consisting of 2000 species, in which there are mainly Firmicutes and Bacteroides [1]. They play a very immensely role in proper functioning of immune system.

In the context of the analyzed links between bacterial flora disorders and the occurrence of autoimmune diseases, gut microbiota has special significance, due to the metabolic activity of microorganisms. As everyone knows, the intestine is the largest human immune system, consisting of subsequent lymphoid structures: lymphatic tissue, called Gut Associated Lymphatic Tissue (GALT), which is organized in the Payer's patches, lamina propria, the epithelium layer and gut microbiota, which is an essential integral component of the above-mentioned structures [1,3]. The basic defense function is a mechanical barrier, which is formed by epithelium cells. Intestinal epithelial cells are integrated with each other by tight junctions (TJs) and adherens junctions and also junctional adhesion molecules [1]. Tight junctions are multiparticulates protein complexes, among which we distinguish claudins, occludins, and junctional adhesion molecules [1]. An important function of gut barrier is played by the goblet cells, which secrete glycoproteins, both inside and outside the intestinal lumen, and interact with potentially pathogenic bacteria [1]. Furthermore, epithelial cells can secrete defensin, cathelicidins and C-type lectins, the importance of which cannot be overlooked in immune system [1].

Also, there is another defense system in addition to the mechanical barrier, which is represented by the lymphatic system. A noteworthy fact is that the GALT normally protects the naturally occurring intestinal flora against the effects of external pathogenic microorganisms, and separates immune cells from the microbiota. It is worth mentioning, that if it is composed of proper bacterial flora, it can inhibit the adhesion of pathogenic microorganisms to the intestinal epithelium, supported by dendritic cells as well as IgA antibodies produced by the cells of the immune system [3]. However, when the GALT is damaged as a result of the disease process, it becomes permeable to many pathogens and its own microbiota, which interacts with the lymphatic system. It can provide to the activation of the immune system, which lead to the formation of antibodies and subsequent to the inflammatory process [3]. The aforementioned pathomechanism is considered as one of the possible cause of autoimmune diseases resulting from cross-reactions of antibodies with their own tissues, due to the structural similarity to bacterial antigens. Moreover, in some cases it may lead to thyroiditis, inflammation, which etiology has not been established, and for which changes in microbiota may be responsible [3]. The significant clinical fact is that the ulcerative collitis can coexist on the path of various pathomechanisms, with thyroid dysfunction, such as Hashimoto's and Grave's diseases (GD), which are presented below [26].

However, there is still the lack of data showing unequivocally the effect of microbiota on various immune processes.

Aim of the study

The aim of this review was to present the role of gut microbiota in patients with autoimmune thyroid diseases, such as Hashimoto's and Graves' diseases. Moreover, we also discussed the current knowledge about the potential effect of microbiota on the metabolism of iodine, thyroid hormones, and thyroid enzymes activity as well as the effect of microbiota composition on iodine treatment.

Materials and methods

The available literature was subjectively selected due to its usefulness in showing clinical approach to the role of gut microbiota in patients with autoimmune thyroid diseases. Furthermore, data which reveals inconsistency in results was shown as well. Eligible articles in English obtained from the EBSCO and the PubMed database have been analyzed using key words in various combinations: Hashimoto's disease, Graves' disease, gut microbiota, immune system.

Description of knowledge

Nowadays, with the advancement of science, diseases, which etiology could not be determined, especially the ones with an autoimmune background, in the light of today's research, are strongly suspected to be caused by disorders of the bacterial flora, which plays a crucial role in the mechanisms of immunity. Microbiota constitutes an immensely significant issue in proper immune system function [4].

Intestinal bacteria can modulate the functioning of the immune system by the secretion of metabolites, including short-chain fatty acids (SCFAs), as a result of the fermentation of non-digestible carbohydrates, such as cellulose or inulin. They are processed in organic acids-butyrate as an energy substrate, and acetate or propionate are used for gluco- and lipogenesis [1]. SCFAs together with thyroid hormones may also, induce the enterocyte differentiation and enhance intercellular tight junctions [5]. If any alterations occur in composition of gut microbiota, some pathogenic mechanisms as like as receptors stimulation, modification of proteins structure and increasing in Th2 helper cell levels may appear, that finally lead to intercellular junctions damage, and then to many changes, including metabolic disorders [5].
Microbiota can affect thyroid functions at many levels through various mechanisms [5]. Some authors suggested that alterations in the composition of the intestinal microbiota can cause autoimmune thyroid diseases, both Hashimoto's and Grave's diseases, However, not only the microbiota itself can affect the functioning of the thyroid gland, but also the environmental

factors, eating habits, age, and sex with a great importance can influence on the microorganisms [5,23].

Immunological pathways leading to the activation of autoimmune diseases are potentially associated with the microbial metabolism. In the analyzed literature, the study on the animal model that involving the administration of butyric acid, revealed increased production of IL-10 and IL-12 cytokines due to the stimulation of Treg lymphocytes with simultaneous decreased collection of IL-17 and IL-23, reduced the nuclear factor-kappa B (NF-kB) levels, proteins that have an impact on inflammatory response, and decreased production of inflammatory factors inducing IL-6 and tumor necrosis factor (TNF-alpha) [1].

The significant role in pro-inflammatory process plays IL-17, which is produced by subpopulation of CD4+ lymphocytes, Th17 lymphocytes. They are responsible for the development of many inflammatory processes, primarily autoimmune diseases: thyroid diseases, type 1 diabetes, rheumatoid arthritis, multiple sclerosis, tick-borne disease, and systemic lupus erythematosus [28]. IL-17 induces releasing of inflammatory reaction mediators from macrophages, fibroblasts and epithelial cells [6]. That is why, novel drugs were invented to neutralize pathological effect of above-mentioned interleukin, such as monoclonal antibodies (secukinumab, ixekizumab and bimekizumab) and biologic agent inhibitors of IL-17 receptor – brodalumab as well [6].

In the case of Hashimoto's disease, it is suggested that thiamine supplementation plays an important role in reducing the symptoms of fatigue. Its bioavailability increases the intestinal microflora by the improving the functioning of enzymes or intracellular transport, what was not observed in individuals, who were treated with levothyroxine [3].

Heat shock proteins (HSP) belong to family of chaperone proteins that stabilize the structure of proteins and play an important role in presenting antigens by transporting peptide antigens to the class I and class II molecules of the major histocompatibility complexes [3]. Recent data showed, that the concentration of HSP 60 was increased in the blood of patients with Hashimoto’s disease and its presence has been demonstrated in both thyreocytes and oncocytes in thyroid tissue [3]. Moreover, HSP 60 protein has some structural similarities to thyroglobulin (TG) and thyroid peroxidase molecules (TPO). Both anty-TG and anty-TPO antibodies can cross-react with above-mentioned molecules [3].

Cross-talk between gut microbiota and thyroid hormones in Hashimoto’s disease

Hashimoto’s thyroiditis is a chronic lymphocytic thyroiditis, caused by production of autoantibodies against thyroid peroxidase (TPO) and thyroid globulin (Tg), and infiltration of

the thyroid gland by lymphocytes, which provide to hypothyroidism correlated with a typical ultrasound image [7,23,25,27]. The recent study evaluated fecal samples from 50 patients with Hashimoto's disease and 27 healthy individuals demonstrated the relationship between Hashimoto's disease and dysbiosis [7]. This study revealed that patients with thyroid dysfunction, have greater gut microbiota diversity and multiplicity than healthy individuals, but without any significant titer [7]. In this research, the greater levels of Firmicutes with decreased Bacteroides species was also found in sick patients compared to healthy individuals. To the best of our knowledge, the Firmicutes to Bacteroides ratio is representative for healthy status [7].

Potential effect of microbiota on the metabolism of iodine, thyroid hormones and thyroid enzymes activity

In many studies performed so far, it has been proved that the proper functioning of thyroid hormones depends on many mechanisms based on the enzymes, ionic pumps, transporters activity, regulated by thyroid hormones and bioavailability of iodine as well as selenium [8-10].

For many years, the effect of microbiota on the absorption of micronutrients was sought, which was proved in the study on rat model. It showed the reduced uptake of radioiodine in rats before the inception of antibiotic therapy compared to the state after treatment with that therapy (kanamycin) in remote observation lasting up to 72 days after treatment [8]. However, clinical trials conducted in patients with short bowel syndrome, fed parenterally, did not confirm the reduction in urinary iodine excretion beside to control group [8]. So far, there is no unambiguous data indicating the relationship between microbiota and iodine absorption.

The other micronutrient, selenium is greatly important for the proper functioning of the thyroid gland. There are known, both organic-selenomethionine and selenocysteine as well as the inorganic chemical compounds. The absorption of selenium takes place in the duodenum and cecum. It occurs that the concentration of selenium per gram of tissue in the thyroid gland is the highest of the whole body [8]. There is more scientific evidences for the relationship between the composition of the intestinal microbiota and selenium bioavailability compared to another elements [8]. This micronutrient is a component of selenoprotein enzymes, such as glutathione peroxidase, which plays a role in peripheral metabolism of thyroid hormones [8].

What is more, it is estimated that a quarter of bacteria possesses the genes encoding selenoproteins. Some of them, even potentially pathogenic, such as Escherichia coli, Clostridia or Enterobacteria are commonly found in the digestive tract [8]. One of the recent study revealed a competition for the selenomethionine, between the microbiota and the host. It is

known, that selenomethionine is used as a substrate for metabolic processes by intestinal inhabitants, resulting in reduced selenium bioavailability and decreased expression of above-mentioned enzymes [8].

Another important function of intestinal microbiota is participation in the deconjugation of iodothyrosins as well as T3 reabsorption, that lead to the complementation of the reserve for hormone synthesis as a consequence, especially in patients with deiodinase and selenium deficiency [8, 11].

SIBO and its association with hypothyroidism and levothyroxine therapy

SIBO (small intestinal bacterial overgrowth) is commonly defined as an increase in the number of bacteria in gastrointestinal tract, however, its etiopathogenesis is still unclear. It is suspected, that impaired motor capabilities may affect the dysregulation of the protective role of immune mechanisms and structural irregularities. The relationship between hypothyroidism treated with levothyroxine and SIBO is well known. Nevertheless, the mechanisms, which will explain the association with hypothyroidism and the levothyroxine therapy effect to the development of SIBO are not fully understood [12].

The recent studies suggest, that microbiota is important for the etiopathogenesis of fibromyalgia by affecting to the thyroid hormone metabolism, but further researches concerning the above subject are necessary [13].

Cross-talk between gut microbiota and thyroid hormones in Grave's disease

Graves' disease is one of the most common cause (60-90% of all cases) of hyperthyroidism, which occurs due to the presence of autoimmune dysregulation associated with the induction of antibody secretion, directed against the TSH receptor [14]. This disease most often appears in the age of 30 to 60 years, with about 1-2 cases per 1,000 population per year in England, and more often affecting women than men [15].

The most common extra-thyroidal clinical manifestation of Grave's disease is Grave's orbithopathy (GO), which occurs in 20.1% of patients with GD as at least one or more of the typical symptoms, such as periorbital edema, eyelid retraction, proptosis, conjunctival redness and strabismus [14-15,22].

It is generally known, that the genetic predisposition, the mutation in the AIRE (autoimmune regulator) gene, which causes the loss of self-recognition ability as well as polymorphism of the gene encoding the protein tyrosine phosphatase non-receptor type 22 (PTPN 22), lymph

dysfunction, environmental factors, smoking, sex, drugs, humoral or viruses factors and gut microbiota play the role in the etiology of GO [15].

According to the current knowledge, the development of GD induced by Yersinia enterocolitica (YE) is permissible by its porins and may cause the induction of B cells, which leads to the production of cross-reactive antibodies to the TSH receptor [15].

Helicobacter pylori (HP) is another pathogen, that is important in GD etiopathogenesis. The HP infection can lead to gastritis, especially in genetically predisposed individuals with the negative expression of HLA-DQ1A1 0201 gene and the positive one of HLA-DQA1 0501 gene, with coexisting overexpression of cytotoxin-associated gene A antigen (CagA) [15].

Moreover, neurotoxin produced by Clostridium botulinum is the other factor, which can induce GD on the basis of immunological mimicry – the homology in HLA-DR3 and/or HLA-DR7 regions with thyroid autoantigens [15].

Furthermore, *Shi TT. et al.* suggested that patients with GO, have more often a disrupted proportion between several strains of bacteria. It is characterized by an increase in population of Bacteroides with reduced numbers of Firmicutes compared to healthy individuals. The patients with GO more frequently have a predominance of Prevotellace versus Blautia, Fusicatenibacter, Butyricicocus, Anaerostipes and Collinsella, whose levels are significantly lower [16].

The detection of the V3 region of the 16 r3NA region by using real-time PCR revealed, that among others components of the intestinal microflora, the amount of Enterocuus strain is more abundant compared to Bifidobacterium and Lactobacillus in people with hyperthyroidism than in healthy people [17]. The other medical analyzes available in the PubMed database summarize the significant relationship between eye's and throat dysbiosis and autoimmune thyroid disease [18].

Alteration in the gut microbiota and their potential relationship with thyroid cancer

Actually, thyroid cancer is the fifth most common cancer in women and according to the latest data, a systematic increase in its prevalence in the American population, estimated on 3% per year over the past four decades is observed [19]. It is suggested that, due to the metabolic activity of the intestinal microbiota, which leads to an increase in the concentration of various metabolites in the blood serum, such as linolenic acid, phospholipids, gamma-aminobutyric acid in people with thyroid cancer, the risk of this cancer development increases [19]. Therefore, some metabolites including phenol and gamma-aminobutyric acid have an diagnostic significance [19].

Zhang J. et al. stated that, in the group of people with thyroid cancer, the number of opportunistic bacteria – Prevotella, Roseburia, Coprococcus, Anaerostripes, Ruminococcus, Neisseria, Streptococcus and Porphyromonas was increased in relation to the control population, where the predominance of Bacteroides, Sutturella and Butyricimonas was observed [20].

Analysis of the effect of microbiota composition on iodine treatment and its relationship with diet

The diet can obviously change the composition of the intestinal flora. It can be serve as an example the fact, that even the increase in protein intake may cause an enlargement of Bacteroidetes with Bacteroides population.

The western diet together with the high-fat and high-sugar one can lead to the predominance of Firmicutes. One of the study, conducted in animal model, showed the significant changes in the microbiota structure in mice receiving a high fat diet (HFD), a high fat diet with iodine supplementation, opposed to a control group of mice receiving only iodine [21]. The gut microbiota changed after 9 weeks of feeding with HFD [21]. The Firmicutes phylum increased from 45% to 49% and Bacteroides one decreased from 42% to 30% after HFD treatment [21].

Conclusions

Summarizing, it is worth to emphasize that microbiota, through its metabolic activity, enormous population and participation in the body's immune processes, is an important link in the etiopathogenetic chain of the autoimmune diseases. However, all the mechanisms of interaction with human body have not been fully understood, therefore, further researches are necessary.

References:

1. Opazo MC, Ortega-Rocha EM, Coronado-Arrázola I, Bonifaz LC, Boudin H, Neunlist M, et al. Intestinal Microbiota Influences Non-intestinal Related Autoimmune Diseases. Front Microbiol. 2018;9:432. doi: 10.3389/fmicb.2018.00432.
2. Virili C, Centanni M. "With a little help from my friends" - The role of microbiota in thyroid hormone metabolism and enterohepatic recycling. Mol Cell Endocrinol. 2017;458:39-43. doi: 10.1016/j.mce.2017.01.053.
3. Tomasello G, Tralongo P, Amoroso F, Damiani P, Sinagra E, Noto M, et al. Dysmicrobism, Inlflammatory Bowel Disease And Thyroiditis: Analysis of the Literature. J Biol Regul Homeost Agents. 2015;29(2):265-272.
4. Weil ZM, Borniger JC, Cisse YM, Abi Salloum BA, Nelson RJ. Neuroendocrine control of photoperiodic changes in immune function. Front Neuroendocrinol. 2015;37:108-118. doi: 10.1016/j.yfrne.2014.10.001.
5. Eleonore Fröhlich and Richard Wahl. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. Front Immunol. 2017; 8: 521. doi:10.3389/fimmu.2017.00521
6. Shao S, Yu X, Shen L. Autoimmune thyroid diseases and Th17/Treg lymphocytes. Life Sci. 2018;192:160-165. doi: 10.1016/j.lfs.2017.11.026.
7. Zhao F, Feng J, Li J, Zhao L, Liu Y, Chen H, et al. Alterations of the Gut Microbiota in Hashimoto's Thyroiditis Patients. Thyroid. 2018;28(2):175-186. doi: 10.1089/thy.2017.0395.
8. Virili C, Centanni M. "With a little help from my friends" - The role of microbiota in thyroid hormone metabolism and enterohepatic recycling. Mol Cell Endocrinol. 2017 ;458:39-43. doi: 10.1016/j.mce.2017.01.053. Epub 2017 Feb 4.
9. Somppi TL. Non-Thyroidal Illness Syndrome in Patients Exposed to Indoor Air Dampness Microbiota Treated Successfully with Triiodothyronine. Front Immunol. 2017;8:919. doi: 10.3389/fimmu.2017.00919.
10. Kunc M, Gabrych A, Witkowski JM. Microbiome impact on metabolism and function of sex, thyroid, growth and parathyroid hormones. Acta Biochim Pol. 2016;63(2):189-201. doi: 10.18388/abp.2015_1093.
11. Spaggiari G, Brigante G, De Vincentis S, Cattini U, Roli L, De Santis MC, et al. Probiotics Ingestion Does Not Directly Affect Thyroid Hormonal Parameters in Hypothyroid Patients on Levothyroxine Treatment. Front Endocrinol (Lausanne). 2017;8:316. doi: 10.3389/fendo.2017.00316.

12. Brechmann T, Sperlbaum A, Schmiegel W. Levothyroxine therapy and impaired clearance are the strongest contributors to small intestinal bacterial overgrowth: Results of a retrospective cohort study. World J Gastroenterol. 2017;23(5):842-852. doi: 10.3748/wjg.v23.i5.842.

13. Tomasello G, Mazzola M, Bosco V, Tomasello G, Damiani P, Sinagra E, et al. Intestinal dysbiosis and hormonal neuroendocrine secretion in the fibromyalgic patient: Relationship and correlations. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2018; 162(4):258-262. doi: 10.5507/bp.2018.051.

14. Masetti G, Moshkelgosha S, Köhling HL, Covelli D, Banga JP, Berchner-Pfannschmidt U, et al. Gut microbiota in experimental murine model of Graves' orbitopathy established in different environments may modulate clinical presentation of disease. Microbiome. 2018;6(1):97. doi: 10.1186/s40168-018-0478-4.

15. Covelli D, Ludgate M. The thyroid, the eyes and the gut: a possible connection. J Endocrinol Invest. 2017;40(6):567-576. doi: 10.1007/s40618-016-0594-6.

16. Shi TT, Xin Z, Hua L, Zhao RX, Yang YL, Wang H, et al. Alterations in the intestinal microbiota of patients with severe and active Graves' orbitopathy: a cross-sectional study. J Endocrinol Invest. 2019;42(8):967-978. doi: 10.1007/s40618-019-1010-9.

17. Zhou L, Li X, Ahmed A, Wu D, Liu L, Qiu J, et al. Gut microbe analysis between hyperthyroid and healthy individuals. Curr Microbiol. 2014;69(5):675-680. doi: 10.1007/s00284-014-0640-6.

18. Köhling HL, Plummer SF, Marchesi JR, Davidge KS, Ludgate M. The microbiota and autoimmunity: Their role in thyroid autoimmune diseases. Clin Immunol. 2017;183:63-74. doi: 10.1016/j.clim.2017.07.001.

19. Feng J, Zhao F, Sun J, Lin B, Zhao L, Liu Y, et al. Alterations in the gut microbiota and metabolite profiles of thyroid carcinoma patients. Int J Cancer. 2019; 144(11):2728-2745. doi: 10.1002/ijc.32007.

20. Zhang J, Zhang F, Zhao C, Xu Q, Liang C, Yang Y, et al. Dysbiosis of the gut microbiome is associated with thyroid cancer and thyroid nodules and correlated with clinical index of thyroid function. Endocrine. 2019;64(3):564-574. doi: 10.1007/s12020-018-1831-x.

21. Shen H, Han J, Li Y, Lu C, Zhou J, Li Y, et al. Different host-specific responses in thyroid function and gut microbiota modulation between diet-induced obese and normal mice given the same dose of iodine. Appl Microbiol Biotechnol. 2019;103(8):3537-3547. doi: 10.1007/s00253-019-09687-1.

22. Ishaq HM, Mohammad IS, Shahzad M, Ma C, Raza MA, Wu X, et al. Molecular Alteration Analysis of Human Gut Microbial Composition in Graves' disease Patients. Int J Biol Sci. 2018;14(11):1558-1570. doi: 10.7150/ijbs.24151.

23. Ishaq HM, Mohammad IS, Guo H, Shahzad M, Hou YJ, Ma C, et al. Molecular estimation of alteration in intestinal microbial composition in Hashimoto's thyroiditis patients. Biomed Pharmacother. 2017;95:865-874. doi: 10.1016/j.biopha.2017.08.101.

24. Virili C, Centanni M. Does microbiota composition affect thyroid homeostasis? Endocrine. 2015;49(3):583-587. doi: 10.1007/s12020-014-0509-2.

25. Zhao J, Chen Y, Xu Z, Yang W, Zhu Z, Song Y, et al. Increased circulating follicular regulatory T cells in Hashimoto's thyroiditis. Autoimmunity. 2018;51(7):345-351. doi: 10.1080/08916934.2018.1516759.

26. Virili C, Stramazzo I, Santaguida MG, Bruno G, Brusca N, Capriello S, et al. Ulcerative Colitis as a Novel Cause of Increased Need for Levothyroxine. Front Endocrinol (Lausanne). 2019;10:233. doi: 10.3389/fendo.2019.00233.

27. Mori K, Nakagawa Y, Ozaki H. Does the gut microbiota trigger Hashimoto's thyroiditis? Discov Med. 2012;14(78):321-326.

28. Rodríguez Y, Rojas M, Gershwin ME, Anaya JM. Tick-borne diseases and autoimmunity: A comprehensive review. J Autoimmun. 2018;88:21-42. doi: 10.1016/j.jaut.2017.11.007.