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CHARACTERISTICS OF GUT MICROBIOTA IN AUTOIMMUNE DISEASES OF THE THYROID GLAND AND THE METHODS OF ITS CORRECTION

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ABSTRACT — Gut microbiota is considered as a pathogenetic factor of various diseases nowadays. The patients with autoimmune diseases are known to suffer from dysbiosis. There are studies in the modern literature that demonstrate changes in the composition of the gut microbiota in case of thyroid dysfunction. This review examines a contemporary view of the gut microbiota, its role in the development of autoimmune diseases. We investigated the interaction between the thyroid gland and the gut microbiota, its species composition in hypo- and hyperthyroidism. Possible methods of correction, including the use of pre- and probiotics and transplantation of fecal microbiota have been demonstrated.

KEYWORDS — gut microbiota, autoimmune diseases, thyroid gland, autoimmune thyroiditis, hypothyroidism.

INTRODUCTION

The prevalence of autoimmune diseases (AIDs) of the thyroid gland (TG), such as chronic autoimmune thyroiditis (AIT) and Graves' disease (GD) (diffuse toxic goiter), is estimated at about 5% [1]. AIT is a chronic inflammatory disease characterized by the production of specific autoantibodies against peroxidase (TPO-ab) and thyroglobulin (TG-ab) with the development of reduced thyroid function — hypothyroidism (HT) [1]. AIT makes about 46% of the total TG's pathology. According to the epidemiological data, the carrier state of TPO-ab is more common in the female population. There is also an increase in the incidence of TG's dysfunction with age. TG's hyperfunction is observed with GD and the main autoantigen is the thyroid-stimulating hormone (TSH) receptor [2]. At present, AIDs of TG are known to have a multifactorial etiology, including genetic, environmental factors, and food habits. Changes in the gut microbiota (GM) are one of the reasons for the development of AIDs. It has been proven that patients with AIT and GD have dysbiosis. Our review will consider the interaction between GM and the development of AIDs, the characteristics of GM composition in patients with TG's dysfunction and methods of its correction.

ROLE OF GM IN THE DEVELOPMENT OF AUTOIMMUNITY

The issue of the interaction between the composition of human GM and AIDs is actively studied nowadays. The intestine is the main site of interaction between pathogenic bacteria, food antigens and normal microflora. Epithelial cells, goblet cells producing mucous secretion, immune M-cells and lymphoid tissue are all the components of the intestinal barrier, the damage of which increases the host susceptibility to the effects of various agents [3]. The study of the intestinal wall structure showed similar changes in patients with type 1 diabetes and AIT, such as partial rarefaction of microvilli on the apical side of enterocytes, a decrease in their height [4]. A change in the GM profile can damage transmembrane proteins responsible for intestinal barrier integrity, such as ZO-1 and occludin [3]. The contact of intestinal immune cells with antigens and an increase in the intestinal permeability lead to inflammation and auto-aggression against the body's own cells.

Microbial imbalance is one of the pathogenetic factors in the development of AIDs. In dysbiosis, the ratio of regulatory Treg and inflammatory Th17 changes can also increase the susceptibility to pathogenic invasion [5]. Autoantibodies against the cell wall of Saccharomycecerevisiae have been found in patients with type 1 diabetes, rheumatoid arthritis (RA), systemic lupus erythematosus, antiphospholipid syndrome, and Crohn's disease [4]. Multiple sclerosis (MS) is an AID characterized by demyelination of nerve fibers. Analysis of the 16s ribosomal RNA gene showed the presence of dysbiosis in patients with MS. Colonization of Clostridium perfringens is associated

with a relapse of MS, and the produced toxins can cause microvascular complications leading to neuronal damage. Patients with severe dysbiosis and Sjogren's syndrome had higher disease activity and increased calprotectin level, which indicates the presence of an inflammatory process in the intestine. In the study of fecal microbiota in children with type 1 diabetes, representatives of the Blautia genus dominated, and their content positively correlated with the level of glycated hemoglobin and titers of antibodies to tyrosine phosphatase. The authors have suggested that it was the GM that influenced autoimmunity and may affect the development of type 1 diabetes [4]. C. aerofaciens may affect the pathogenesis of RA through various mechanisms, for example, by increasing the permeability of the intestinal wall, production of IL-17, and chemotaxis of neutrophils [6].

Thus, it can be assumed that changes in intestinal permeability and dysbiosis are the links in the pathogenesis of AIDs.

GM INFLUENCE ON THYROID FUNCTION. FEATURES OF GM COMPOSITION IN AIDS OF THE THYROID GLAND

In recent years, the study of the Thyroid-Gut-Axis has been of increasing interest to researchers. The formation of metabolically active triiodothyronine (T3) occurs with the participation of enzymes — deiodinases, localized in many body tissues, including the intestinal wall. The authors have suggested that in view of the large surface of the GIT, the contribution of T3 activated by the deiodinases to the total body pool is substantial. GM metabolic by-products, especially short-chain fatty acids (SCFA), together with TG's hormones, affect the differentiation of enterocytes and strengthen intercellular contacts in the intestinal wall [7]. GM participates in the metabolism of microelements, which are involved in the synthesis of hormones and the maintenance of normal TG function. With AIDs of the TG, there is a change in the levels of Lactobacillaceae and Bifidobacterium, the quantitative composition of which, in turn, positively correlates with the levels of selenium and zinc in the blood serum. It was suggested that disruption in the regulation of these microelements and GM composition could affect the course of AIT and GD [8].

There is evidence that microorganisms that are structurally homologous to human proteins through the mechanisms of molecular mimicry can cause AIDs of the TG. E.P. Kiseleva et al. have found Bifidobacteriumadolescentis, B. Longum, B. bifidum, and Lactobacillus plantarum on cells surfaces; these are the components that compete with human TPO-ab and TG-ab. The dependence between the presence of antibodies to B. bifidumand L. plantarum, and TPO-abwas also obtained [9]. Gram-positive bacteria, including strains of Lactobacillus rhamnosus, can activate the transcription factor NF-κB, which controls the expression of genes responsible for the immune response, either directly or through cytokines. In the study by Jiang W. et al. in patients with GD in GM analysis, an increase in the strains of Lactobacillus and Bacteroides was revealed, and in some patients, increased titers of TPO-ab were observed [10]. The authors have assumed that hormone imbalance in GD and changes in GM towards the predominance of Lactobacillus, which had similar amino acid sequences with TPO-ab and TG-ab led to the induction of proinflammatory signaling pathways with the development of autoimmunity.

GM can affect the predisposition to the development of HT in mouse models. As far back as in 1988, Penhale W.J. et al. demonstrated that injection of an antibiotic by sterile rats followed by injection of homogenized intestinal contents from rats raised under normal conditions increased their autoimmune susceptibility [10].

It is known that AIDs of the TG are characterized by dysbiosis. Some studies point out that there is a decrease in microbial diversity; others, on the contrary, note the small intestinal bacterial overgrowth syndrome (SIBO). The research of Yan HX. et al. showed that the species composition of GM was less diverse in patients with HT, and Phascolarctobacterium predominated [11]. In the group with GD, the diversity of microbial strains also decreased and there were changes in the GM profile in the form of an increase in the number of Bacilli, Prevotella, Lactobacillales, Megamonas, Veillonella and a decrease in Rikenellaceae, Ruminococcus, and Alistipescompared with healthy people [12]. In HT, there is a decrease in the motor function of the digestive system due to the accumulation of mucopolysaccharides and the development of the intestinal wall edema. Decreased GIT vermicular movement is one of the factors in the development of SIBO. The study involving 1809 people demonstrated that the most important factors in the development of SIBO were immunosuppression, conditions after gastric/intestinal resection and HT [13]. Lauritano E.C. et al. have found that about 54% of patients with HT suffered from SIBO [14]. Zhao F. et al. have found bacterial overgrowth and differences in the GM composition of patients suffering from HT and healthy individuals in the form of increased genera Blautia, Romboutsia, EubacteriumRoseburia, Ruminococcus, Fusicatenibacter, Dorea and Eubacterium and decreased levels of Fecalibacterium, Bacteroides,

Prevotella [15]. The change in GM correlated with clinical parameters, which could be actively used for the diagnosis of diseases. Another study also demonstrated a change in GM with a predominance of Shigella, Escherichia coli, and Parasutterella and a decrease in the content of Prevotella and Dialister [16].

It is known that GM affects the absorption of drugs. Impaired absorption of levothyroxine (LT4) can be caused by a change in the GM composition due to concomitant diseases of the GIT. There is evidence in the literature that the prevalence of coeliac disease-AID, which is characterized by gluten intolerance, with AIT, according to various sources, ranges from 5 to 24%. In the study by Bibbò S. et al. in patients with AIT and coeliac disease, a decrease in the level of Bifidobacterium was observed [17]. Virili C. et al. obtained that patients with isolated HT achieved normalization of the TSH level (on average, 1.02 mU/l) against the background of LT4 therapy at a daily dose of 1.31 μg/kg, while in patients with HT and coeliac disease during the same period of treatment with similar doses, higher TSH values (4.20 mU/l) were observed [18]. It was found that when correcting HT with concomitant coeliac disease, it was necessary to increase the daily dose of LT4, on average, to 1.96 μg/kg [19]. Patients infected with Helicobacter pylori also required large doses of LT4 to achieve compensation for HT.

CONCLUSION

GM plays an essential role in the human body, performing many functions: immunomodulatory, biosynthetic, protective, etc. With the advent of new non-culture-based research methods, it became possible to study the qualitative and quantitative composition of GM in various diseases. A change in the GM profile can be considered as one of the factors in the development of AIDs. The patients with autoimmune TG's dysfunction are known to suffer from dysbiosis. Evaluating the relevant literature data, it can be assumed that there is an interaction between hormone imbalance and GM. There is no doubt concerning the necessity for further clinical studies to identify the characteristics of the GM composition in AIDs of the TG. The detection of differences between normal and transformed GM can be considered as a diagnostic criterion for TG's diseases. Further study of GM correction methods will help to determine new strategies for the treatment and prevention of TG's diseases.

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