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ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS (LITERATURE REVIEW)

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Ключевые слова: *сахарный диабет 2 типа, кишечная микробиота, метаболиты кишечной микробиоты, инкретины, субклиническое воспаление*

Abstract. Role of gut microbiota in the pathogenesis of type 2 diabetes mellitus (literature review). Koval S.M., Snihurska I.O. *Type 2 diabetes mellitus is an extremely common disease that leads to the development of life-threatening complications but its pathogenesis remains poorly understood. One of the promising directions in this area is the study of disorders of gut microbiota. Literature data indicate that a number of quantitative and qualitative changes in the composition of the gut microbiota are the most important factors in the pathogenesis of type 2 diabetes mellitus. Bacteria of the genera Ruminococcus, Fusobacterium and Blautia are most involved in the pathogenesis of this disease. The participation of the gut microbiota in the pathogenesis of type 2 diabetes mellitus is due to its*

metabolites, which play an important role in the regulation of the permeability and integrity of the intestinal wall, the expression of specific intestinal receptors, incretin secretion, gluconeogenesis activity, chronic subclinical inflammation, and even in adipose tissue remodeling. Further in-depth study of gut microbiota disorders is promising in order to develop fundamentally new approaches to the treatment and prevention of type 2 diabetes mellitus.

Реферат. Роль кишечной микробиоты в патогенезе сахарного диабета 2 типа (обзор литературы). Коваль С.Н., Снегурская И.А. *Сахарный диабет 2 типа – чрезвычайно распростарненное заболевание, которое приводит к развитию жизнеопасных осложнений, однако его патогенез остается не достаточно выясненным. Одним из перспективных направлений в этой области является изучение нарушений кишечной микробиоты. Данные литературы свидетельствуют о том, что целый ряд количественных и качественных изменений состава кишечной микробиоты является важнейшими факторами патогенеза сахарного диабета 2 типа. В наибольшей степени в патогенез данного заболевания вовлечены бактерии родов Ruminococcus, Fusobacterium и Blautia. Участие кишечной микробиоты в патогенезе сахарного диабета 2 типа обусловлено ее метаболитами, которые играют важную роль в регуляции проницаемости и целостности стенки кишечника, экспрессии специфических рецепторов кишечника, секреции инкретинов, активности глюконеогенеза, хронического субклинического воспаления и даже в ремоделировании жировой ткани. Перспективным является дальнейшее углубленное изучение нарушений кишечной микробиоты с целью разработки принципиально новых подходов к лечению и профилактике сахарного диабета 2 типа.*

Type 2 diabetes mellitus (DM) is a highly common multifactorial disease that leads to the development of life-threatening complications and premature death of patients [46]. Given the great medical and social importance of the problem of type 2 diabetes, intensive studies of the main mechanisms of its pathogenesis are carried out, including genetic predisposition to type 2 diabetes and candidate genes associated with this disease [1, 4], insulin resistance (IR) [1, 4], disorders of glucagon, incretins [4, 41], cytokines and adipokines [20, 26, 27, 37], various neurohumoral factors [4, 35, 41]. However, despite this, the pathogenesis of type 2 diabetes remains unclear.

One of the promising areas of research on the pathogenesis of type 2 diabetes is the study of the role of gut microbiota (GM) disorders.

The purpose of this work is to review the literature on the problem of studying the role of GM disorders in the pathogenesis of type 2 diabetes.

The search for literature was carried out in scientometric databases Google Scholar, PubMed, Web of science, Scopus. Relevant scientific publications for the period 2014-2020 were selected to determine the state of GM in patients with type 2 diabetes and changes in GM at the stage of prediabetes. The search terms were: "gut microbiota", "sequencing", "type 2 diabetes", "pathogenesis".

GM, due to its multifaceted impact on the entire metabolic system of the body, is recognized as a full-fledged functional "organ" that plays an important role in digestion, nutrition, immune regulation and metabolism. It was found that more than 90% of GM of a healthy person is represented by *Bacteroidetes* and *Firmicutes*, including representatives of the genera *Lactobacillus*, *Clostridium* and *Ruminococcus. Actinobacteria*, *Verrucomicrobia* and *Fusobacteria* are also part of GM, but in much smaller quantities [3, 41].

To date, the role of GM in the development of a number of diseases and, above all, diseases of the gastrointestinal and urogenital tract, skin, nasopharynx, allergic, autoimmune and cancer diseases, as well as obesity, atherosclerosis, hypertension and many others received evidence [2, 3, 5, 41]. In recent years this list also includes type 2 diabetes [10, 11, 16].

Studies show that already at the stage of prediabetes the following changes in the composition of GM are observed in comparison with healthy individuals: decrease in the total content of bacteria of the *Clostridiales* series against the background of increasing content of such representatives as *Dorea, Ruminococcus, Sutterella* and *Streptococcus*; reduction in the number of bacteria that decompose mucin - *Akkermansia muciniphila*, belonging to the type *Verrucomicrobia* [6]. Most studies on changes of GM in patients with type 2 diabetes have reported an increase in bacteria of the genera *Ruminococcus, Fusobacterium*, and *Blautia,* and a decrease in the number of bacteria of the genera *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia, and Roseburia* in the gut of these patients [11, 13, 33, 36]. However, there are conflicting data regarding the association of *Blautia* bacteria with type 2 diabetes. Thus, in the work of Tong X. et al. (2018) it is shown that the number of *Blautia* bacteria in patients with type 2 diabetes increases after a significant improvement in carbohydrate and lipid metabolism under the influence of antidiabetic therapy [42].

A number of studies has shown a positive correlation between *Bacteroidetes / Firmicutes* and *Bacteroides-Prevotella / Clostridium Coccoides-Eubacterium rectale* with plasma glucose levels [10]. At the same time, the analysis of data from 42 studies did not confirm the association of the ratio of *Bacteroidetes / Firmicutes* with type 2 diabetes [36].

Of interest are studies of the association of bacteria of the genus *Lactobacillus* with impaired carbohydrate homeostasis and type 2 diabetes. These bacteria are gram-positive rod-shaped ones, facultative anaerobes are the main part of the group of lactic acid bacteria that convert sugar into lactic acid. An increase in the number of these bacteria in the gut of patients with prediabetes and type 2 diabetes compared to healthy individuals has been shown [36]. However, the results of the research are not homogeneous. Thus, in patients with type 2 diabetes there is, on the one hand, an increase in the number of *Lactobacillus acidophilus, Lactobacillus gasseri*, *Lactobacillus Salivarius*, and on the other – a decrease in the number of *Lactobacillus amylovorus* [36]. There are also conflicting data on the testing of some species of *Lactobacillus* as probiotics and their effect on carbohydrate metabolism. Thus, *Lactobacillus sporo¬genes, Lactobacillus casei Shirota* and *Lactobacillus reuteri* improve carbohydrate metabolism in patients with type 2 diabetes [18, 19, 21, 41], but in most cases in combination with bacteria of the genus *Bifidobacterium* [36]. In addition to studies examining changes in the quantitative composition of various bacteria, information on the main mechanisms by which GM affects carbohydrate metabolism is important for understanding the role of GM disorders in the pathogenesis of type 2 diabetes.

Bacterial production of short-chain fatty acids (SCFA), which are produced in the human colon and cecum after anaerobic fermentation of indigestible dietary fiber with the help of sugar bacteria can be one of the significant mechanisms of this effect of GM. Their main representatives – acetate, propionate and butyrate make up 95% of SCFA and are one of the most common compounds obtained with the participation of GM. Studies show that the deficiency of SCFA synthesis is associated with the development of type 2 diabetes [16, 36]. However, there is evidence that butyrate induces the expression of genes involved in intestinal gluconeogenesis, and propionate itself is a substrate of gluconeogenesis [16]. Zhao L. et al. (2018) showed that not all, but only a small number of microbial strains are involved in the production of SCFA [17].

An important feature of SCFA is the ability to affect the permeability of the intestinal wall. It has been suggested that increased intestinal permeability may lead to damage to pancreatic β-cells due to increased absorption of exogenous antigens. Experimental studies prove the ability of butyrate to improve the integrity of the intestinal wall [16]. Thus, Xu Y.H. et al. (2018) showed that oral administration of butyrate significantly reduced the levels of HbA1c, inflammatory cytokines and lipopolysaccharides in plasma in db/db mice, and after treatment with butyrate, local infiltration of inflammatory cells decreased, intestinal integrity increased and intercellular adhesion elevated [40].

The discovery of their receptors was important for understanding the role of SCFA, which allowed us to consider SCFA as important signaling molecules. Two GLC-activated G protein-coupled receptors have been described and identified as modulators of host-microbiota interaction: GPR41 and GPR43. These receptors are also known as free fatty acid receptors: FFAR3 and FFAR2, respectively. They have been found in the gut, sympathetic nervous system, liver, white adipose tissue, skeletal muscle, pancreas and immune tissues [16, 25, 41].

Experimental studies have shown that SCFA, mainly through GPR43 receptors (FFAR2), are able to stimulate the secretion of a number of intestinal peptide hormones, including incretin-glucagon-like peptide-1 (GLP-1) [16, 44].

Incretins play an important role in the regulation of insulin secretion and appetite. Incretins, in addition to GLP-1, include gastric inhibitory polypeptide (GIP). These hormones, released from enteroendocrine cells, are secreted into the bloodstream and rapidly stimulate insulin secretion from β-cells in response to food intake [4].

Faerch K. et al. (2015) in a clinical study of 1462 people showed a decrease in GLP-1 secretion in response to oral glucose loading in patients with type 2 diabetes, as well as in patients with prediabetes and obesity, compared with normal body mass and normal glucose tolerance, which indicates a disorder of GLP-1 secretion at the stage of prediabetes [14].

It has also been shown that type 2 diabetes mellitus develops specific dysbiosis that induces resistance to GLP-1 [9].

One of the ways in which GM affects the secretion of incretins is the increase in the number of enteroendocrine L-cells in the gut. Experimental studies have shown that the number of enteroendocrine L-cells doubled in the proximal colon of rats treated with oligofructose, which contributed to higher production of endogenous GLP-1 [10]. It has also been shown that the addition of indigestible carbohydrates, such as oligofructose, improves glucose tolerance, reduces IP and food consumption, which has been associated with increased plasma GLP-1 levels [16].

There is also evidence that some GM bacteria may affect the secretion of incretins through the products of their own metabolism. Thus, it was found that sulfate-reducing bacteria produce

hydrogen sulfide (H_2S) in the colon, which can directly stimulate the secretion of GLP-1 [33]. At the same time, there is evidence of an inhibitory effect of H_2S on the release of GLP-1 in vitro [35], which indicates the need for further research to clarify the role of sulfate-reducing bacteria in complex glucose metabolism.

As shown by experimental studies, another metabolite of GM – indole, formed during the dissimilation of tryptophan in GM, is able to regulate the secretion of GLP-1 from enteroendocrine L-cells of the mouse colon: to increase – in case of short-term exposure, but reduce – in the long term, i.e. to play the role of a signaling molecule through which GM can interact with enteroendocrine cells and change the glycemic control of the host [16].

One of the mechanisms of GM's effect on incretin secretion is mediated by its effect on the intestinal nervous system – on nerve cells of the myenteric plexus, which leads to decreased expression of GLP-1 receptor and stimulation of gastrointestinal motility [24].

Thus, the regulation of incretin production by modulating the parameters of GM can open a new direction in the treatment of type 2 diabetes [9]. In this regard, the possibility of direct effects on insulin secretion and β-cell proliferation through FFA2 and FFA3 receptors is very promising [15, 38].

Analyzing the possible ways of GM influence on glucose metabolism in the human body, it is also necessary to dwell on the bacterial metabolism of bile acids (BA). It is known that primary BA (choleic and chenodeoxycholic) are formed in the liver from cholesterol, and secondary BA (deoxycholic, lithocholic, alocholic and ursodeoxycholic) are formed in the colon from primary ones under the influence of GM. Thus, *Bifidobacterium* and *Lactobacillus* produce bile salt hydrolases, which convert primary conjugated bile salts into deconjugated (primary) BA, which are subsequently converted into secondary ones [10].

BA regulate their own hepatic synthesis through a negative feedback mechanism, which involves a direct interaction between the BA and the farnesoid X-receptor (FXR – farnesoid X receptor) in hepatocytes and enterocytes of the ileum. The expression of fibroblast growth factor-19 (FGF-19) is induced in the ileum, which enters the circulation and further inhibits the synthesis of BA [10, 16]. FXR is expressed in a variety of metabolically active tissues, including the liver, intestines, and white adipose tissue. Conjugated and unconjugated BA can interact with FXR, with henodeoxycholic acid being their strongest activator, while other BA are likely to be FXR antagonists [10, 16].

BA are potent signaling molecules, mainly due to their interaction with the FXR receptor and the membrane-G protein-coupled receptor TGR5 [10]. It has been shown that BA, by activating FXR and TGR5, are involved in the regulation of glucose homeostasis and energy metabolism - activation of intestinal FXR can both reduce and increase IR in obesity [22, 23, 39]. In addition to FXR and TGR5, FGF19, which stimulates glycogen synthesis in the liver in the postprandial state, may be an important regulator of blood glucose levels [10, 16].

The effect of GM on glucose metabolism can also be carried out through the regulation of inflammatory processes, in particular in adipose tissue [12, 45]. The association of chronic inflammation of adipose tissue in obesity, IR and type 2 diabetes has now been proven [16]. There is a strong and unique metabolic interaction between the intestine and peripheral white adipose tissue through compounds and metabolites produced or induced by GM, which affect the state of carbohydrate metabolism of the host [45]. An association between intestinal bacteria and inflammation has been identified through the identification of intestinal bacterial lipopolysaccharide, an inflammatory factor that plays an important role in the development of IR, obesity and type 2 diabetes [10]. A number of studies have shown that some representatives of GM are able to inhibit the production of large amounts of proinflammatory cytokines and chemokines. Thus, *Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus casei* can reduce the level of interleukin (IL)-1β, protein-1 chemoattractant monocytes, intercellular adhesion molecules-1, IL-8 and C-reactive protein [8, 29]; *Lactobacillus paracasei* and *Bifidobacterium fragilis* inhibit the expression of IL-6 [28, 36]; *Lactobacillus, Bacteroides* and *Akkermansia* inhibit the production of tumor necrosis factor-α [7, 28, 36]; *Lactobacillus paracasei, Faecalibacterium prausnitzii* and bacteria that produce butyrate – *Roseburia intestinalis* and *Faecalibacterium,* inhibit the activity of nuclear factor NF-κB [28, 30, 36]; *Lactobacillus casei* and *Roseburia intestinalis* reduce the production of the proinflammatory cytokine interferon (IFN)-γ [17] and, in addition, *Roseburia intestinalis* inhibits the synthesis of IL-17 [37].

There are also papers indicating the induction of anti-inflammatory IL-10 synthesis by such bacterial species as *Roseburia intestinalis, Bacteroides fragilis, Akkermansia muciniphila, Lactobacillus plantarum, Lactobacillus casei,* which is associated with improved glucose metabolism [36]. Increased expression of this cytokine in the muscles of mice

has been shown to prevent the development of aging-related IR [20].

Of great interest are the data that the components of GM can regulate the energy metabolism of the host by remodeling adipose tissue. Thus, Kim M. et al. (2017) in an experimental study showed that KetoA [10-oxo-12 (Z) -octadecenoic acid], a metabolite of linoleic acid produced by intestinal lactic acid bacteria, activates genes involved in the functioning of brown adipocytes, including transmembrane protein thermogenin-1 in white adipose tissue. This further increases energy expenditure in mice and thus reduces metabolic disorders associated with obesity [43].

Another experimental study [31] showed an increase in the amount of brown adipose tissue under the action of GM products, which increased tissue sensitivity to insulin, as well as reducing the size of white fat and adipocytes in lean mice and in various models of mice obesity. A significant contribution to the above processes is made by the LCDs described above, probably through the TGR5 receptor [16].

CONCLUSIONS

Thus, the data accumulated in the literature suggest that a number of quantitative and qualitative changes in the composition of the intestinal microbiota are the most important factors in the pathogenesis of type 2 diabetes. Bacteria of the genera *Ruminococcus, Fusobacterium* and *Blautia* are most involved in the pathogenesis of this disease. The participation of intestinal microbiota in the pathogenesis of type 2 diabetes is primarily due to its metabolites, which play an important role in regulating the permeability and integrity of the intestinal wall, expression of specific intestinal receptors, secretion of incretins, gluconeogenesis, chronic subclinical inflammation and chronic subclinical inflammation. adipose tissue remodeling. Further in-depth study of GM disorders is promising in order to develop fundamentally new approaches to the treatment and prevention of type 2 diabetes.

Conflict of interest. The authors declare no conflict of interest.

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