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Mini Review

The Role of the Microflora of the Gastrointestinal Tract and Liver in the Pathogenesis of Obesity and Type 2 Diabetes

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Abstract

Diabetes mellitus is the basis of polymorbidity. It is associated with various complications, primarily micro- and macrovascular, which often cause disability and death of patients. This disease is associated with an increased risk of developing certain types of cancer. Diabetes mellitus also causes the severe course and progression of non-alcoholic fatty liver disease, which remains an underestimated clinical problem. This pathology is usually diagnosed with severe clinical and functional disorders and the development of non-alcoholic steatohepatitis and cirrhosis of the liver.

Bile acid deficiency can lead to bacterial overgrowth syndrome, endotoxin-mediated chronic inflammation. Violation of the metabolic activity of bile acids also plays an important role in the pathogenesis of non-alcoholic fatty liver disease, which is the main reason for the ineffectiveness of treatment of many metabolic diseases, including type II diabetes mellitus.

The intestinal microbiome can interact with food components, affecting the body's sensitivity to insulin, intestinal permeability, glucose and fat metabolism. Obesity and type 2 diabetes mellitus are often characterized by changes in the intestinal microflora, inflammation and violation of the intestinal barrier. Thus, in patients with type 2 diabetes mellitus, there is an increase in the number of sulfate-reducing bacteria and a decrease in the number of Accegmapsia muciniphila - mucosal bacteria that are involved in the barrier function of the intestine. A decrease in the number of butyrate-producing bacteria may be the cause of impaired glucose metabolism.

Keywords: *Type 2 Diabetes Mellitus; Microbiota; Short-Chain Fatty Acids; Non-Alcoholic Fatty Liver Disease*

In patients with type 2 diabetes mellitus, there is an increase in the number of sulfate–reducing bacteria and a decrease in the number of *Accegmapsia muciniphila* - mucosal bacteria that are involved in the regulation of intestinal barrier function [1], in addition, patients with obesity and type 2 diabetes have a higher level of so-called metabolic infection (*Desulfovibrio* spp., *Bacteroides* spp. and *Intestinibacter* spp., *Escherichia coli*) associated with endotoxemia, inflammation and insulin resistance.

A normal gut microbiota contributes to maintaining optimal production of incretin hormones in response to food intake, signal transmission along the vagus nerve and glycemic control. Intestinal dysbiosis in type 2 diabetes leads to the development of resistance to glucagon-like peptide receptors (GLP) 1 and 2, which causes subsequent disorders of the insulin response and signal transmission through the vagus nerve [2].

The imbalance of the microbiota also leads to inflammation, impaired secretion of cytokines (interleukin 6, tumor necrosis factor α), insulin resistance and microcirculatory lesions of the colon mucosa [3,4]. Violations of the functions of the intestinal microbiota in type

2 diabetes leads to an increase in the membrane transport of sugars or branched amino acids, the activity of enzymes involved in the metabolism of xenobiotics and carbohydrates, and the restoration of sulfates, as well as a violation of the synthesis of butyrate [5-10].

Changes in the intestinal microflora cause an increased intake of endotoxin into the blood, which is considered an important link in the formation of MS and atherosclerosis. As a result of dysbiotic disorders in the large intestine, chronic circulatory disorders, in particular ischemic damage to the colon, increase. In patients with type 2 diabetes mellitus, these changes in most cases go unnoticed, as a result of which their timely diagnosis and treatment are not carried out.

Micro-ischemic colitis occurs in 54% of DM patients. An additional factor in its development is a violation of tissue metabolism caused by changes in the microbiota of the colon and metabolic dysfunction of short-chain fatty acids (SCFAs), which are metabolites of the intestinal microflora, which are formed during the processing of indigestible polysaccharides of plant fibers by microorganisms inhabiting the colon. Approximately 95% of SCLC is absorbed by the epithelium of the colon.

The main types of short-chain fatty acids include acetic, propionic, butyric and valerian acids. Each SCLC is produced by anaerobic bacteria of a certain type: acetic acid - bifido- and lactobacilli, butyric acid - butyrate-producing *Roseburia* spp., *Eubacterium hallii, Faecalibacterium prausnitzii*.

Overweight individuals have higher levels of SCLC [11], in particular propionate. It has been shown that dietary supplements with SCLC can help improve glucose homeostasis and insulin sensitivity, as well as actually prevent the development of obesity [12].

To date, the role of reducing the pool of butyrate-producing bacteria and, accordingly, butyrate deficiency in the colon in patients with diabetes and obesity is being actively studied. Analysis of human faecal samples showed that *F. prausnitzii* is the main butyrate-producing bacterium. In an experiment on fecal bacterial transplantation, patients with insulin resistance received fecal microflora from insulin-sensitive donors, which led to a significant improvement in insulin sensitivity with an increase in the number of bacteria producing butyrate [13]. According to the results of large-scale studies of metagenomic associations in various populations, the number of *F. prausnitzii* and Roseburia in the intestinal microflora in patients with type 2 diabetes was lower than in healthy individuals. In addition, the number of butyrate-producing bacteria was lower in patients with prediabetes [14], which may indicate that the absence of butyrate-producing bacteria is one of the predictors of the disease.

In the Moscow Clinical Scientific and Practical Center named after A.S. Loginov in 2019 and 2020, the authors conducted a pilot study on the content of bacterial metabolites of the colon and the concentration of SCLC in patients with type 2 diabetes and obesity. 68 patients with type 2 diabetes and 28 with obesity (body mass index more than 30 kg/m^2) were examined. The control group consisted of 20 people without carbohydrate metabolism disorders. The groups were comparable in age and gender. In addition to a thorough clinical examination, the content of short-chain fatty acids was determined in all study participants. In 45 patients with type 2 diabetes, during examination, including capsule endoscopy, endoscopic and histological changes in the SCC characteristic of previously undiagnosed micro-ischemic colitis were diagnosed. In most patients with type 2 diabetes and obesity, the concomitant disease was irritable bowel syndrome. The results of the study of the content of SCLC are presented in figure 1 and 2.

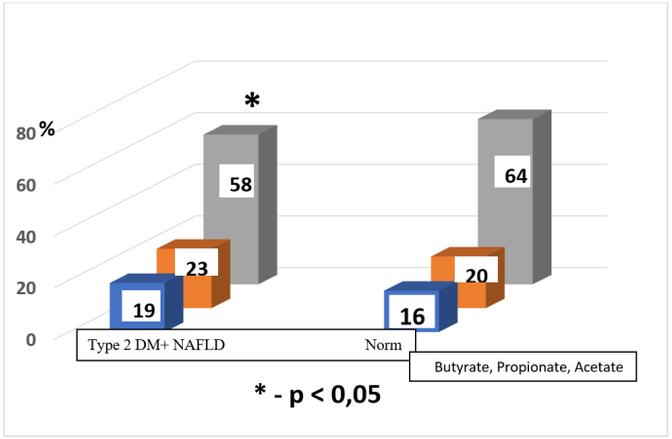

Figure 1: *The structure of the main bacterial metabolites of the colon.*

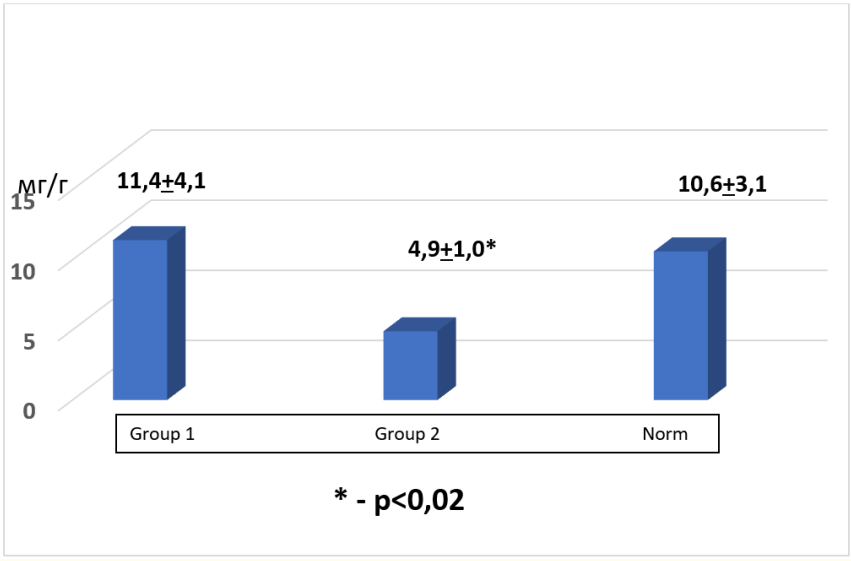

Figure 2: *The total concentration of SCLC in patients with type 2 diabetes.*

The total definition of short-chain fatty acids is often uninformative and depends on many factors. The spectrum of qualitative and quantitative content of the main SCFCS is recognized as an informative method. Figure 3 and 4 shows the results of a histological examination of the SOTK in comparison with the content of the main SCFCS. They indicate signs of a micro-ischemic lesion of the SOTK due to a deficiency of butyrate, which has a protective effect against the mucous membrane of the colon.

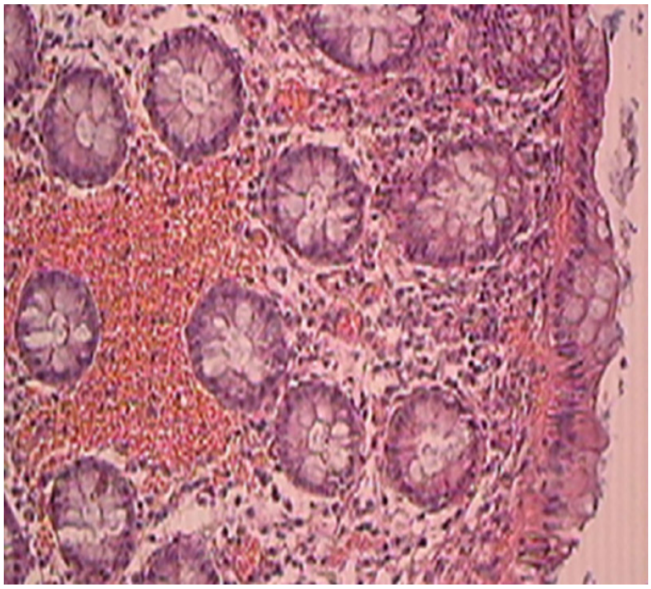

Figure 3: *Dystrophy and necrobiosis of the superficial epithelium, dilation of blood vessels, stasis of blood incapillaries, erythrocyte extravasates, edema of the own plate (staining with hematoxylin and eosin, magnification 1:300).*

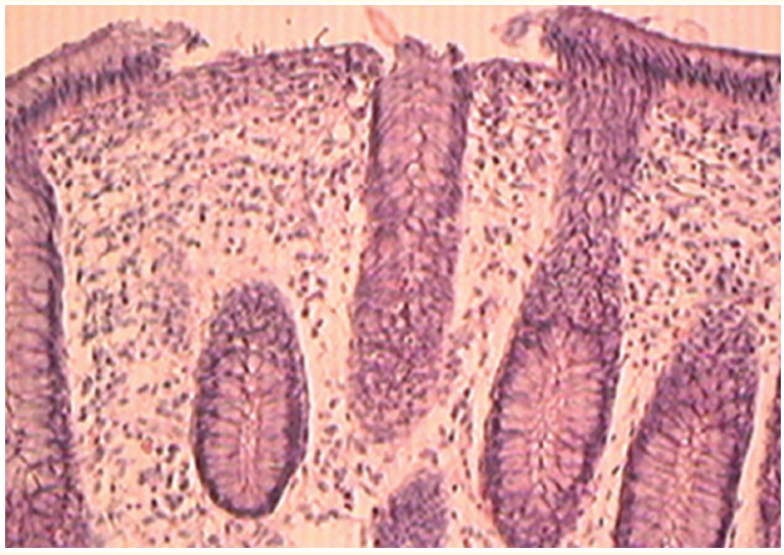

Figure 4: *Erosion of the mucous membrane, shortening of crypts, reduction in the number of goblet cells,enhanced lymphoplasmocytic infiltration of the lamina proper (staining with hematoxylin and eosin, 1:300 increase).*

Many studies have proven a close relationship between type 2 diabetes, non-alcoholic fatty liver disease (NAFLD) and cholelithiasis (GI). Thus, the correlation of the insulin resistance index (NOMA-IR) with the gastrointestinal tract (risk ratio 2.25, p = 0.03) was found. The prevalence of GI is higher among patients with type 2 diabetes. The combination of fatty hepatosis (LH) with type 2 diabetes is detected in 100% of cases, NASH and GI - in 42% of cases [15]. Our own morphological studies of the liver and the gallbladder wall in patients with type 2 diabetes and GI indicate similar changes in the gallbladder wall and elastic vessels against the background of atherosclerosis (Figure 5) [15].

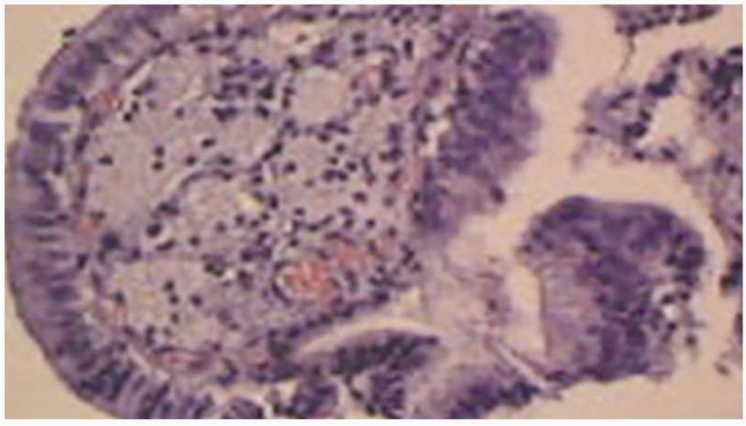

Figure 5: *Foamy cells in the submucosal layer of the gallbladder wall.*

In almost 50% of patients with type 2 diabetes, clinical manifestations of GI precede the diagnosis of NAFLD [16]. However, according to the results of our own research, the processes of stone formation, the development of NASH and liver steatosis proceed simultaneously, as evidenced by the proliferation of ductules against the background of liver steatosis (Figure 6) [17].

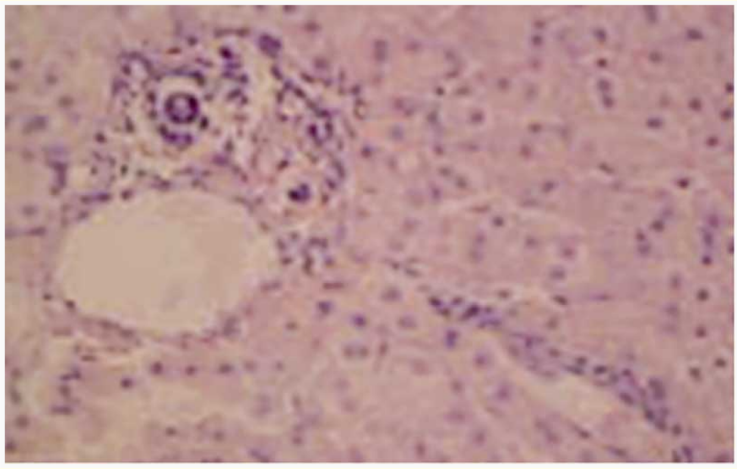

Figure 6: *Pronounced proliferation of ductules on the background of liver steatosis.*

Conclusion

Carbohydrate metabolism and the state of the intestinal microbiome are closely interrelated. The microbiota affects the sensitivity of body tissues to insulin, while type 2 diabetes itself can often lead to disorders of the intestinal microflora.

It is important to remember that violations of the properties of the intestinal microbiota entail not only an aggravation of insulin resistance, but along the chain of many mechanisms leads to the development of non-alcoholic fatty liver disease, the faster progression of which is characteristic of people with type 2 diabetes mellitus.

A study of the state of the microbiota in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease has shown that patients with a low content of SCLC develop inflammatory bowel diseases, such as micro-ischemic colitis; the protective barrier and permeability of the colon membranes decreases due to violations of the density of epithelial contacts of the colon mucosa.

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