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INTESTINAL MICROFLORA: RELATION TO INFLAMMATION AND METABOLIC DISORDERS

Bezborodov V. V.[1], Tishchenko I. Yu.[2], Dubinina N. V.[2]
[1]Sumy National Agrarian University, Sumy, Ukraine;
[2]National University of Pharmacy, Kharkiv, Ukraine
vovabezborodov117@gmail.com

Introduction. The gastrointestinal microflora has a significant impact on almost all physiological, metabolic, molecular-genetic and behavioral reactions, and this has been unequivocally proven. Scientists unanimously recognize the fact that each individual has a personal microbiota, and this specificity is strong evidence that host-related factors are of great importance in the chain of pathogenetic processes that cause microecological and functional disorders of certain gastrointestinal organs. Today, the above-mentioned relationship between dysbiosis and the development of a number of diseases associated with metabolic disorders is undeniable.

Aim. To analyze the relationship between intestinal microflora and metabolic disorders and the development of inflammatory processes.

Materials and methods. Interdisciplinary analysis of modern scientific research and literature sources in the field of microbiology and pathophysiology.

Results and their discussion. The intestine is an important component of the "vicious" cycle of the systemic inflammatory response, in which changes in metabolic processes occur, leading to disruption of the work of mediator systems. The evolution of these views has allowed us to form an idea of complex changes in the metabolism of lipids, proteins, carbohydrates that occur in the systemic inflammatory response syndrome. Spontaneous hyperglycemia most often occurs. At the same time, glucose production in the liver increases in response to the release of adrenaline, noradrenaline, glucagon and cortisol. Gluconeogenesis is observed, refractory to the introduction of exogenous glucose. Amino acids are mobilized from skeletal muscles and transported to the liver for the synthesis of glucose and mediators of systemic damage. The factor that initiates the release of mediators of systemic inflammation can be very different in origin: intestinal dysbiosis, ischemia (ischemic colitis in atherosclerosis, diabetes, obesity), etc. The most important role in the development of systemic metabolic disorders is played by mediator systems and primarily cytokines. The most pronounced metabolic effects are in interleukin-6 (IL-6) and tumor necrosis factor (TNF).

Cytokines are low-molecular proteins whose biological activity is carried out through specific receptors located on cell membranes. The most significant are TNF and IL-1, IL-6, IL-10. They are capable of exerting both local and distal effects (on distant organs and tissues). Common to the entire group is the enhancement of leukocyte adhesion and aggregation, as well as hypercatabolic and hyperdynamic effects. Cytokines are the first-line mediators, which themselves are capable of causing cascades of humoral reactions. The main cytokines responsible for stimulating the systemic response in the acute phase are IL-1, IL-6 and TNF, with IL-6 playing a dominant role. Thus, for the occurrence of inflammatory bowel diseases and rheumatoid arthritis, an increase in IL-6 and TNF is common.

Eicosanoids are the breakdown products of arachidonic acid. These include thromboxanes, leukotrienes, epoxides. The combined effects are characterized by the development of microthrombosis, adhesion, aggregation, degranulation of leukocytes, the development of bronchoconstriction, increased membrane permeability. The predominance of eicosanoids is characteristic of the initiation and progression of atherosclerosis, diabetes, obesity, and MS in general.

An increase in cytokines and eicosanoids with a subsequent cascade of chronic inflammatory reaction is the basis of all chronic non-communicable diseases. The main factors that increase the “mediator-cytokine cascade” are: hypoxia, dysoxia, profound microcirculation disorders, abnormally high concentrations of intermediate and end products of metabolism, circulating immune complexes, biogenic amines, and peroxidation products. The combined effects of damage mediators form a generalized systemic inflammatory response, or systemic inflammatory response syndrome (SIRS), a symptom complex that characterizes the severity of the inflammatory response in the endothelial cell system, and therefore the direction of the inflammatory response to damage.

The connection between intestinal microflora and obesity has been proven. An increase in body mass index (BMI) of more than 25 kg/m2 correlates with the species characteristics of the patient's intestinal microflora: obesity and metabolic syndrome (MS) are accompanied by a decrease in the species diversity of the intestinal microbiota and a change in the pool of working microbial genes. The composition of the microflora in people of different build is significantly different. In overweight patients, the predominance of *Firmicutes* bacteria in the intestinal microflora is characteristic, which contribute to the accumulation of a large number of calories and prevent adequate weight loss in such patients. In underweight people, *Bacteroidetes* predominate in the microbiota.

Obesity is associated with a decrease in bacterial diversity, a change in the level of microflora types and an altered representation of bacterial genes and metabolic pathways. Changes in the intestinal microbial ecology (decrease in *Bacteroidetes* and proportional increase in *Firmicutes*), a sharp drop in overall diversity (an increase in one class of *Firmicutes* leads to a change in metabolic potential), enrichment of phosphotransferase systems contributes to an increase in the potential for the absorption of typical carbohydrates of the “Western diet” and for the metabolism of consumed sugars. The intestinal microbiota, through the system of recognition epithelial receptors (Toll-like receptors, TLR), constantly interacts with the host immune system. It has been proven that there is an infectious intestinal component of the cascade of metabolic disorders in obesity. The fact of identifying a connection between components of the innate immune system, the predisposition to obesity and the microbiota is interesting. The gut microbiota may be important in the development of both obesity and MS in general.

Intestinal damage in obese patients is associated not only with dysbiotic changes, but also with chronic elevations in the levels of inflammatory markers in adipose tissue and pro-inflammatory cytokines in the blood (IL1, IL6, TNFα, IL17, IFNγ) and confirms that chronic low-grade inflammation is one of the main causes of insulin resistance.

The composition of the intestinal microbiota in patients with type 2 diabetes has its own characteristics. In a metagenomic case-control study (MGWAS), which evaluated DNA samples from feces of patients with type 2 diabetes and controls without diabetes, a decrease in butyrate-producing bacteria (*E. rectale*, *F. prausnitzii*, etc.) and an increase in opportunistic pathogens (*C. hathewayi*, *C. ramosum*, *E. coli*), mucin-degrading species, sulfate-reducing bacteria were found. The decrease in lacto- and bifidobacteria, typical of *E. coli*, the increase in the number of yeast-like fungi of the genus *Candida* and subsequent disturbances in the intestinal microbiota in patients already at the stage of prediabetes and in its presence lead to increased permeability of the intestinal wall, impaired detoxification processes of exo- and endogenous substrates and the body's immunity. The relationship between the intestine and the insulin-producing apparatus of the pancreas, named the “enteroinsular axis,” has been proven. There is evidence of the influence of enterohormone on insulin secretion. Intestinal dysfunction in patients with type 2 diabetes is associated with both dysregulation of EO and non-hormonal factors — morphological and functional changes in the intestine, which are caused by motility, the protective properties of its microbiota, secretion, and absorption of nutrients.

Over the past decade, many studies have shown that the intestinal microbiota is closely related to the development of atherosclerosis. In this pathology, disturbances in the intestinal microflora have been detected in 90% of patients: excessive bacterial growth and translocation of the flora contribute to the activation of a systemic inflammatory response, pathogenetically associated with heart failure. Also, patients with atherosclerosis more often have a third enterotype, which is characterized by the presence of a large number of bacteria of the genus *Ruminococcus* and *Collinsella*; more genes responsible for the synthesis of the bacterial wall component peptidoglycan - an inducer of inflammation. In healthy people, Eubacterium, *Roseburia* and *Bacteroides* predominated, the content of *Clostridium* was higher - carriers of genes encoding butyrate, which has anti-inflammatory properties. Intestinal bacteria contain many genes that ensure the production of such anti-inflammatory substances as lycopene and beta-carotene. Neuro- and angiopathies are also at the heart of intestinal damage in patients with atherosclerosis.

Conclusions. Pathologies with different pathogenetic mechanisms of development have common risk factors that are triggers for the development of both metabolically associated diseases and structural and functional changes in the intestine. At the same time, each risk factor — whether it is a violation of the intestinal microbiota, an altered anti-inflammatory profile, or intestinal dysmotility — and, presumably, their combination increase the risks of developing metabolic consequences in the form of excess body weight, impaired carbohydrate and lipid profiles, etc. Therefore, the elimination of known risk factors in patients with metabolically associated diseases should be aimed at reducing clinical manifestations from the intestine, restoring intestinal endoecology, creating prerequisites for the formation of a favorable metabolic phenotype.

Keywords: Gastrointestinal microflora, intestine, inflammation, mediators of damage, metabolic syndrome, obesity, diabetes mellitus, atherosclerosis.