INFLUENCE OF INTESTINAL MICROFLORA ON THE DEVELOPMENT OF IRON DEFICIENCY ANEMIA

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ВЛИЯНИЕ КИШЕЧНОЙ МИКРОФЛОРЫ НА РАЗВИТИЕ ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИИ

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Annotation. The article is devoted to the study of the influence of the composition of the intestinal microbiota in the development of iron deficiency anemia, as well as the influence of iron on the microflora of the large intestine. Despite the large number of publications on this topic, additional research is required into the effectiveness of the use of drugs in this group in standard iron therapy, as well as the use of metabiotics in preventing the development of iron deficiency.

Key words: iron deficiency anemia, intestinal microbiota, prebiotics, probiotics.

Аннотация. Статья посвящена исследованию влияния состава кишечной микробиоты в развитии железодефицитной анемии, а также влияния железа на микрофлору толстого кишечника. Несмотря на большое количество публикаций на эту тему, требуются дополнительные исследования эффективности применения препаратов данной группы к стандартной терапии препаратами железа, а также использования метабиотиков в предупреждении развития железодефицита.

Ключевые слова: железо-дефицитная анемия, микробиота кишечника, пребиотики, пробиотики.

Introduction. Iron deficiency anemia is a condition accompanied by a decrease in hemoglobin levels against the background of serum iron deficiency, detected in almost 40% of the population in developing countries and almost 10% of residents in developed countries. The main causes of this condition are a lack of iron-rich foods in the diet, or the inability of the body to absorb iron from food due to acquired or genetic reasons. Iron deficiency causes anemia, leading to improper oxygenation of organs and tissues, which leads to disruption of the body's homeostasis [2, 5].

Due to increased iron consumption, iron requirements increase during pregnancy in more than 50% of pregnant women in developing countries [2, 14]. According to the WHO, anemia caused by iron deficiency can be classified into three stages, ranging from mild to severe anemia with low hemoglobin levels (<70 g/L for children under five years of age and pregnant women and <80 g/L for children over five years old, teenagers and adults). Severe anemia affects a person's cognitive and physical functions, leading to chronic fatigue and decreased performance in patients [1, 8], but such conditions can be corrected with diet or treatment with iron supplements. The most common causes of iron deficiency are low solubility of dietary iron and therefore low bioavailability, as well as blood loss due to bleeding [3, 9].

There are several options for getting iron into the body: eating foods rich in iron, taking nutritional supplements or medications, and, in extreme cases, receiving red blood cell transfusions. Of particular importance is the type of iron received and the mode of its absorption [2, 10]. Foods such as vegetables, meat and animal by-products are excellent sources of iron, and fermenting vegetables improves iron absorption. Lactic acid produced by lactobacilli helps increase the bioavailability of iron, so using probiotic bacteria can improve iron absorption. The increase in the global population and its well-being is directly proportional to the amount of iron consumption and largely depends on the composition of the intestinal microbiota. A significant number of studies confirm the connection between the bioavailability of iron and its absorption and the activity of microorganisms in the intestine. In addition, iron levels influence the virulence of many pathogens. More than 90% of dietary iron is excreted in feces, affecting the intestinal microflora, while only a small part is integrated into the metabolic pathways of the body [1, 18]. Dietary absorption inhibitors, such as polyphenols and phytates, inhibit the absorption of non-heme iron in a dose-dependent manner, and calcium and animal proteins indirectly affect intestinal iron binding. Vitamin C enhances the absorption of iron in the intestines, especially if ascorbic acid is included in the diet with foods with high availability of non-heme iron (foods rich in vegetables). At low gastric pH, ascorbic acid forms a chelate with ferric iron (Fe3+), which is retained and remains soluble in the alkaline environment of the duodenum [2, 13]. Thus, it is impossible to deny the importance of the influence of iron on the functioning of the body and its participation in many metabolic processes, however, the intake of iron into the body does not guarantee its absorption due to the significant influence of the microbiome on the reduction of bioavailability and absorption in dysbiosis of the large and small intestines and the predominance of opportunistic flora.

The role of iron in the human body is extremely important, as it plays a key role in metabolic processes. The most studied functions of iron are oxygen transport and storage, hormone synthesis, DNA replication, cell cycle control, nitrogen fixation and antioxidant properties. The amount of iron in the body of an adult is 3.5–4.0 g, most of which is contained in hemoglobin [1, 4].

Iron transport in the digestive system is controlled by several iron-binding proteins - transferrin, lactoferrin and bacterioferritin. In general, mucins bind to iron due to the acidic environment of the stomach, which helps maintain it in a soluble state for subsequent absorption in the alkaline conditions of the duodenum. The mucin-bound iron subsequently passes through the mucosal cell membrane and, after passing into the cells, is transported to the basolateral side by the cytoplasmic iron-binding protein mobilferrin, from where it is exported into the blood plasma. Absorption of heme and non-heme iron in the intestinal mucosa occurs due to various transport processes and regulatory proteins [2, 12 It is at this stage that the ferritin level is considered the most reliable marker of iron deficiency [2, 11].

The microbiota of the human gastrointestinal tract plays an important role in metabolism, influencing the vital functions of the human body. The balance in diet and nutrient intake is regulated by the healthy growth of the microbiota during the early years of human life. To preserve and maintain the quantitative and qualitative composition of the intestinal microbiota and to prevent dysbiosis, the administration of probiotics and prebiotics orally, as well as through fecal microbiota transplantation or other methods is indicated [3, 6].

The intestinal microbiota of adults and children depends on several factors, such as age, ethnicity, place of residence, lifestyle and diet. A diet rich in whole grains and fresh fruits, soluble and insoluble fiber, vegetables and nuts helps maintain a balanced microbiome. The physiological and neurological consequences of iron deficiency are well studied and described by many authors, but further research is needed to assess its impact on the development of the intestinal microbiota. The literature describes various options for iron absorption, most typical after diet correction or taking nutritional supplements [3, 15]. However, the key role of iron absorption has been shown to be due to the intestinal solubility of oral medications.

Bacteria typically regulate iron metabolism in response to iron availability, with this regulation mediated by the iron uptake regulator protein (Fur), which controls iron-dependent gene expression. In the presence of iron, this regulatory protein forms a complex with ferric iron, which, in turn, binds to the Fur boxes of bacterial DNA, suppressing the transcription of genes encoding proteins and involved in iron transport. In the absence of iron, the Fur protein stops gene suppression, leading to their expression. However, the set of gene regulatory functions is more diverse. Fur regulatory protein can also act as a positive regulator of gene transcription by suppressing regulatory RNA or activating gene expression, which prevents the recruitment of repressors. The protein can also directly activate gene expression and act as an activator and suppressor of transcription in the absence of iron, but this is characteristic of a limited number of pathogenic bacteria [3, 17]. In addition, the regulatory protein regulates iron storage in bacteria and is generally more than a simple suppressor of iron uptake, since it integrates several biological pathways (expression of pathogenicity factors and survival mechanisms for resistance to acid and oxidative stress), contributing to the virulence of bacterial pathogens [3, 7].

The gut microbiota consists of trillions of microorganisms belonging to hundreds of different species. The microbiota in the human body is represented by bacteria, archaea (single-celled organisms without a nucleus that are more closely related to eukaryotes than to bacteria), fungi (mainly yeast) and microbial eukaryotes and viruses/phages [1, 5]. In humans, the gut microbiome is dominated by five bacterial phyla (Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia). Less common phyla are Cyanobacteria, Fusobacteria, Lentisphaerae, Spirochetes and TM7. Bacteria in the intestine provide functional traits that humans cannot develop on their own: the synthesis of B vitamins, nonessential and essential amino acids, antimicrobial substances, short-chain fatty acids [1, 8]. Several metabolic, physiological and immunological features are interrelated with mutualistic associations and the gut microbial community. The microbiome encodes more digestive enzymes than its host, and thus helps break down indigestible macromolecules (polysaccharides, etc.) or synthesize certain vitamins. The microbiome is also involved in the development and regulation of immune system functions, epithelial cell maturation, and host defense against pathogens, providing resistance to colonization. Among the factors that influence the bacterial composition in the intestine, the presence or absence of available substrate in the environment is of decisive importance. Iron is critical for the growth and proliferation of most bacteria and has a direct impact on host-microbiota interactions.

Today, an important member of the phylum Firmicutes, class Clostridium, and family Ruminococcaceae has become the most abundant bacterium in the gut microbiome of healthy adults, representing more than 5% of the total bacterial population, and in some cases up to 15%. It is the most important butyrate-producing bacterium in the colon, which is considered a biomarker of human health, and its population decline leads to inflammation, which is correlated with inflammatory bowel disease and colon cancer [2, 12].

Thus, this bacterium is considered a valuable potential biomarker in the differential diagnosis of ulcerative colitis and Crohn's disease, and is also a potential active component of probiotics for a promising therapeutic strategy for various intestinal diseases. According to the NGS test results of one study, this species accounted for 3.17% of the total in healthy subjects, was reduced to 2.65% in patients with iron deficiency anemia, and increased to 6.12% after iron supplementation. However, NGS data showed no significant differences in the anemic group before and after iron supplementation, confirmed by PCR validation experiments.

Another clinical study showed that reduction in Faecalibacterium is an important biomarker in subjects with gestational anemia compared with controls [2, 9].

Iron deficiency is of great importance to the world's population, so it is essential to implement appropriate strategies to combat this problem. The most frequently offered are optimized nutrition programs, iron supplements to food products at the production stage, dietary supplements with iron, as well as probiotics, prebiotics and combination preparations [3, 18].

Prebiotics are functional food components that stimulate the growth and colonization of beneficial bacteria in the gut and ultimately improve the health of the body. Colonization of the intestinal microbiota plays a significant role in intestinal physiology. To effectively reduce the risk of certain diseases (cancer pathology, hypercholesterolemia), you can use prebiotics, such as galactooligosaccharides, fructooligosaccharides, inulin and pectin. These components help recreate the ideal intestinal microbiota and maintain its balance. Probiotic fructans (selective carbon sources) promote health by reducing levels of urea, uric acid, ammonia and nitrogenous compounds. Several studies have shown that fructans, such as inulin, have beneficial effects on the colon in two ways: through direct effects on the colon and gut microbiota, and indirectly by influencing metabolism and reducing the risk of disease [2, 20].

The results of work assessing the effectiveness of synbiotics, carried out over three months, showed an improvement in the absorption of iron in the body in children of primary school age (9–12 years). The children were divided into two groups: those who received iron supplements in the form of syrup (twice a week) and those who consumed a synbiotic mixture - Lactobacillus plantarum Dad 13 and fructooligosaccharide in a fermented milk product (six times a week). As a result, no significant differences were noted between patients in both groups. Perhaps due to the high socioeconomic status of the children included in the study, clinical and laboratory manifestations of iron deficiency anemia were insufficient to obtain reliable results However, the greatest presence of E. Coli was observed among those children who drank only syrup with iron supplements, and a greater number of bifidobacteria were detected in the feces of those who consumed the synbiotic mixture [1, 19].

Conclusions. Iron metabolism involves many processes, and even if genetic defects are excluded, there are several causes of iron deficiency in humans. To achieve the desired level of iron in the body, probiotics, prebiotics and synbiotics can be used. It is essential to investigate the ability of probiotics to act as iron carriers, convert iron into an available form, or create metabolites that indirectly increase iron content and absorption in the intestine. The few studies carried out in this direction already have promising results. Modulation of the gut microbiota through the use of probiotics, prebiotics and metabiotics can influence the rate of iron absorption, and the type of iron consumed has a significant impact. The cytotoxicity of unabsorbed iron on intestinal cells (enterocytes) warrants more research, and tailored foods may be an excellent option in the treatment of iron deficiency.

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