STUDYING THE INFLUENCE OF FATTY ACIDS ON INFLAMMATORY BOWEL DISEASES

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ИЗУЧЕНИЕ ВЛИЯНИЯ ЖИРНЫХ КИСЛОТ НА ВОСПАЛИТЕЛЬНЫЕ ЗАБОЛЕВАНИЯ КИШЕЧНИКА

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Annotation. Fatty acids, as essential food components, have anti-inflammatory, immunoregulatory, modulating intestinal microbiota and supporting the intestinal barrier effect in pathological intestinal processes. However, the mechanisms of action of specific fatty acids, such as medium- and very long-chain fatty acids, in inflammatory bowel diseases require further clarification. The article presents the results of studies in which different classes of fatty acids are used as biomarkers of disease activity, predictors of complicated course, development of exacerbation, as well as for the purpose of differential diagnosis of inflammatory bowel diseases.

Key words: fatty acids, inflammatory bowel diseases, anti-inflammatory effect, necrotizing ulcerative enterocolitis.

Аннотация. Жирные кислоты, как незаменимые пищевые компоненты, оказывают противовоспалительное, иммунорегулирующее, модулирующее кишечную микробиоту и поддерживающее кишечный барьер действие при патологических процессах кишечника. Однако механизмы действия специфических жирных кислот, таких как средне-и очень длинноцепочечные, при воспалительных заболеваниях кишечкика требуют дальнейшего уточнения. В статье представлены результаты исследований, в которых разные классы жирных кислот используются как биомаркеры активности заболевания, предикторы осложненного течения, развития обострения, а также в целях дифференциальной диагностики воспалительных заболеваний кишечника.

Ключевые слова: жирные кислоты, воспалительные заболевания кишечника, противовоспалительное действие, язвенно-некротический энтероколит.

Introduction. Inflammatory bowel diseases (IBD) are chronic inflammatory diseases primarily of the intestine, characterized by disruption of the intestinal mucosal barrier, dysbiosis, and immune dysregulation. The main IBDs include ulcerative colitis (UC) and Crohn's disease (CD). Genetic predisposition and numerous environmental factors play a significant role in the pathogenesis of IBD [1, 20]. There is growing evidence that a high-fat Western diet is closely associated with the risk of onset and progression of IBD [2, 13]. This may be due to the effects of fatty acids (FAs), which are important components of dietary and endogenous lipids, on the regulation of inflammation, the mucosal barrier and the intestinal microbiota.

Fatty acids are a class of molecules consisting of hydrocarbon chains of varying lengths and degrees of desaturation. Based on the length of the carbon chain, FAs are divided into short-chain (SCFA), medium-chain (MCFA), long-chain (LCFA) and very long-chain FAs (VLCFA) [3]. LCFAs and VLCFAs mainly enter the body with food, while SCFAs are formed as a result of the conversion of nutrients that are not digested by the macroorganism's enzymes by specific intestinal bacteria. The anti-inflammatory effect of representatives of LCFAs - Omega-3-unsaturated FAs - is known, while omega-6-unsaturated FAs are pro-inflammatory agents [4–6]. SCFAs support the mucosal barrier and regulate immunity. Polyunsaturated fatty acids have an anti-inflammatory effect, omega-6 fatty acids are involved in the pathogenesis of IBD [2, 7].

Short-chain fatty acids (SCFAs) provide nutrition to the epithelium of the intestinal mucosa and have a powerful anti-inflammatory effect through the regulation of immune functions. Dietary fiber serves as a substrate for the production of SCFAs

by the intestinal microbiota. SCFAs exert their physiological effects by acting as ligands for G protein-coupled receptors. Data from population studies indicate lower levels of isobutyl, butyric, propionic and acetic acids in patients with acute IBD [1, 12].

In Crohn's disease, the composition of the intestinal microbiota undergoes pronounced changes, including the loss of SCFA-producing bacteria Roseburia, Eubacterium, Subdoligranulum and Ruminococcus. The reduced ability to synthesize butyrate in CD was more pronounced than in UC, probably due to insufficient dietary fiber intake and a decrease in the number of butyrate-producing bacteria. In reoperated CD patients, compared with first-time surgery patients, there was a significant reduction in levels of cyclohexanoic acid, 2-methylbutyric acid and isobutylic acid, and CD patients had lower levels of butyrate-producing bacteria [1, 6]. A. Kiasat et al. showed that changes in plasma SCFA concentrations do not differ between CD and UC [2, 8].

SCFAs, primarily butyrate, have anti-inflammatory properties in IBD. By acting on the GPR43 and GPR109a receptors, butyrate effectively suppresses the development of IBD, and an increase in its concentration reduces the expression of genes associated with inflammation in UC. Activation of the inflammasome sensor Nlrp1 triggers the synthesis of interleukin (IL)-18, which suppresses the beneficial properties of butyrate-producing bacteria, exacerbating inflammation in UC. Prophylactic administration of butyrate may reverse the decrease in cytochrome P450 2A5 activity. Addition of acetate to food reduces the level of pro-inflammatory cytokines (IL-8, tumor necrosis factor alpha (TNF-α)), while simultaneously increasing the level of hypoxia-inducible factor (HIF1α) and mucin-2 in epithelial cells in UC [2, 9].

Reduces the number of butyrate-producing bacteria, including Clostridium coccoides / Eubacterium rectale, C. leptum and F. prausnitzii in the intestinal lumen, as well as Roseburia spp. in the mucous membrane, detected in patients with UC [2, 15]. The abundance of Lachnospiraceae bacteria decreased significantly in UC. Apigenin alleviates the symptoms of colitis caused by dextran sulfate sodium by regulating the number of bacteria Akkermansia, Turicibacter, Klebsiella, Romboutsia [3, 14]. Paraclostridium bifermentans aggravates UC symptoms, potentially associated with decreased SCFA levels. Changes in the spectrum of intestinal microbiota in patients with UC can stimulate the occurrence of cancer due to the activation of T-helper type 1 and 17 cytokines [3, 13].

Butyrate reduces intestinal barrier damage induced by C. difficile, regulates autophagy of intestinal epithelial cells, modulates tight junctions due to inhibition of prolyl hydroxylase HIF, activates epidermal growth factor receptors (EGFR). Acetate maintained the epithelial barrier and reduced the levels of pro-inflammatory factors (IL-8 and TNF-α). Propionate increased the expression of tight junction proteins:

zonula occludens-1 (ZO-1) protein and occludin, which had an anti-inflammatory effect due to inhibition of macrophages and increased regulation of adhesion molecules [1, 19].

Combining F. prausnitzii, a butyrate-producing bacterium, with chitosan oligosaccharides can restore tight junction levels. Supplementation with prebiotics, probiotics, immunoglobulin G (IgG), and amino acids collectively improve intestinal barrier function in IBD. Soluble dietary fiber from quinoa bran (65%) and Panax quinquefolius polysaccharides increase SCFA production and increase tight junction protein expression.

Fecal butyrate levels decrease during the active phases of CD and UC, indicating its potential as a marker of active IBD. The reduced ability to synthesize butyrate is more pronounced in CD than in UC. In addition, isobutyrate and Verrucomicrobiota can serve as markers for diagnosing remission of UC, and hexanoate can serve as a prognostic indicator of the risk of relapse in patients with CD [1, 18].

Medium chain fatty acids are generally defined as fatty acids with a carbon chain of seven to 12 carbon atoms, they promote rapid energy supply and restoration of the intestinal mucosa, reducing inflammation. The level of MCFAs (heptanoic (C7:0), octanoic (caprylic C8:0) and nonanoic (C9:0) acids) is reduced in patients with IBD [43]. In children, higher levels of lauric acid were observed during active phases of UC compared to remission [2, 14].

Long-chain fatty acids typically include fatty acids with carbon atoms ranging from 13 to 22 and are classified as saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). Consumption through food is a common way to obtain the LCFAs (Omega-3 and Omega-6) found in fish oil.

Saturated fatty acids and trans fatty acids (TFAs) are a distinct group of SFAs that potentially regulate inflammatory responses by acting on peroxisome proliferator-activated receptor gamma (PPAR-γ) and retinoid X receptors (RXR). TFA C18, total TFA and palmitic acid are directly associated with the onset of IBD. A diet rich in TFAs may increase the degree of inflammation in IBD. A diet rich in TFAs may increase the degree of inflammation in IBD. With the consumption of large amounts of myristic acid (C14:0), the risk of relapse of UC increased in patients who were in remission.

Palmitic acid (C16:0) is a key component of EFAs that promotes inflammation by increasing intestinal epithelial permeability, activating the NF-κB pathway and cytokines, and causing endoplasmic reticulum stress, leading to lipotoxicity of intestinal epithelial cells [53]. Palmitic acid enters intestinal epithelial cells through the CD36 cluster of differentiation and participates in the palmitoylation cycle of the intracellular STAT3 metabolic pathway. Inhibition of this cycle using pharmacological inhibitors reduces the severity of inflammation caused by C16:0 [2, 11].

Oleic acid (C18:1; c9), a monounsaturated fatty acid, exerts a protective effect on intestinal epithelial cells of CD patients without increasing IL-8 levels by inhibiting the NF-κB pathway in mice with dextran sulfate sodium colitis. Excessive consumption of oleic acid-rich olive oil did not reduce symptoms in mice with dextran sulfate sodium colitis [2, 10].

Polyunsaturated fatty acids belong to the category of fatty acids, characterized by multiple double bonds. Omega-6 PUFAs include arachidonic acid (AA) (C20:4n-6) and linoleic acid (C18:2n-6), which are often associated with the progression of UC. Increased levels of AA in the colon mucosa in patients with UC are associated with the development of colorectal cancer in IBD [3, 9]. Observations indicate a positive correlation between dietary AA intake and the risk of developing UC.

Supplementation with flaxseed and omega-6 PUFA-rich fatty acids has been associated with the development of microbial dysbiosis in CD and changes in mucosal barrier function. Docosapentaene FA supplementation increased gut microbial diversity and altered microbial composition in mice with dextran sulfate sodium colitis. In addition, docosahexaenoic and eicosapentaenoic acids reduce the severity of endoplasmic reticulum stress in goblet cells by reducing the synthesis and secretion of protective mucin barriers mucin-2 (Muc2).

Eicosatetraenoic acid (ETYA, 20:4) has been shown to reduce the expression of extracellular matrix genes and reduce the severity of ileal stricture in CD through the silent information regulator protein-1 (SIRT1) pathway, reducing the expression of various pro-inflammatory cytokines and providing anti-inflammatory, antioxidant and anti-apoptotic effect. Traditional Chinese herbal remedies may influence the progression of IBD by regulating PUFA levels [2, 12].

The role of very long chain fatty acids (VLCFAs), defined as fatty acids with a carbon chain length greater than 23, in inflammation is gradually being elucidated. VLCFAs can be obtained from dietary sources and can also be endogenously synthesized from long-chain fatty acids and extended by the elongase family to very long fatty acids (ELOVL). Saturated VLCFAs can mediate necrosis and activate macrophages to generate an inflammatory response [3, 7].

The therapeutic mechanisms of biological agents, 5-aminosalicylic acid (5-ASA/5-ASA), glucocorticoids and immunosuppressive drugs are partially related to GI. Butyrate salts may synergistically enhance the therapeutic effect of treatment with anti-TNF drugs. Increased levels of SCFA-producing bacteria are one of the mechanisms by which infliximab therapy produces its therapeutic effect and serves as a biomarker of patient response to infliximab therapy. Butyrate and substrate levels correlate with the achievement of remission with infliximab treatment. Butyric acid and isobutylene acid may serve as biomarkers of patient response to vedolizumab. Prednisolone may directly reduce levels of luminal lipid mediators (PGE2 and LTB4),

reducing the severity of IBD symptoms. A recent clinical trial showed that patients with UC who received combination therapy of 5-ASA and FEEDColon, which included butyrate, had less severe subjective symptoms compared with those who received 5-ASA alone. Animal studies have shown that EPA at a dosage of 1000 mg/kg reduces colitis-associated oxidative stress, serum lactate dehydrogenase levels, colonic glucagon-like peptide-1 (GLP-1) expression, and therapeutic effects on NF- κB is comparable to sulfasalazine [2, 18].

FAs play a key role in the pathological and physiological processes in IBD by regulating the intestinal mucosal barrier, modulating the pro-inflammatory/anti-inflammatory balance, influencing immune function and regulating the homeostasis of the intestinal microbiota. Rational consumption of FA is important for both the prevention and treatment of IBD.

Increasing FA intake (usually Omega-3) is considered beneficial in IBD, which has been associated with changes in the gut microbiota of UC patients. Inclusion of a Japanese diet high in fish oil and omega-3 PUFAs is beneficial in achieving clinical remission in patients with UC. Omega-3 PUFAs exhibit an anti-inflammatory effect in postoperative patients. The use of eicosapentaenoic acid has shown promising results in reducing calprotectin levels and reducing relapses of UC, as well as improving the composition of the intestinal microbiota and reducing the severity of inflammation. Supplementation with cis-palmitoleic acid may reduce the expression of hepatocyte nuclear factor (HNF4α) and HNF4γ, potentially reducing inflammation in patients with UC. Moreover, the combination of aminosalicylic acid and Omega-3 PUFAs has been shown to effectively maintain remission in CD in children [3, 4].

The Mediterranean diet, rich in fish oil and PUFAs and low in saturated fatty acids, is considered a healthy dietary option and is recommended as part of adjunctive treatment for patients with IBD. A Mediterranean diet may increase levels of SCFA-producing bacteria, maintaining clinical remission in patients with UC and reducing IBD-related mortality. The Mediterranean diet may demonstrate greater therapeutic efficacy for mild to moderate CD compared with specific carbohydrate-based diets [3, 16].

Probiotic supplementation helps restore the balance of the gut microbiota and improves IBD symptoms by increasing MCFAs and reducing inflammation. Consumption of fermented vegetable drinks containing Pediococcus pentosaceus resulted in a reduction in diarrhea symptoms associated with increased levels of acetic, propionic and butyric acids.

Conclusions. Thus, FAs, as essential food components, have anti-inflammatory, immunoregulatory, modulating intestinal microbiota and supporting the intestinal barrier effect in the pathological processes of IBD. However, the mechanisms of action of specific FAs, such as medium- and very long-chain FAs, in IBD require further

clarification, which could potentially guide future research. When analyzing epidemiological studies studying the effect of FA on IBD, inconsistencies were identified between the results of a number of them, as well as between the results of experiments on animals. The availability of robust evidence from large-scale cohorts and RCTs is limited, and translation of findings from animal models to human populations is challenging.

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