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THE ROLE OF PROBIOTICS IN LIVER CIRROSIS

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ABSTRACT. The frequency of cirrhosis is about 20–40 cases per 100,000 populations, and this indicator is steadily increasing. At present, it is one of the six main causes of death at the age of 35–60 years in economically developed countries. Foreign and domestic scientists are working on the development and synthesis of new drugs of chemical and natural origin for the treatment and prevention of liver diseases of various origins, in particular liver cirrhosis. Many studies have shown an important pathogenic role in the occurrence and progression of some liver diseases with changes in the intestinal microbiota. Therefore, antibiotics, prebiotics and probiotics are an effective treatment for liver diseases, which can correct the intestinal microbiota.

Keywords: liver disease, probiotics, liver cirrhosis, treatment

Introduction

Liver cirrhosis (LC) is an actual topic of modern medicine. According to statistics, 40 million people die every year from viral cirrhosis of the liver and hepatocellular carcinoma, which develops against the background of the carriage of the hepatitis B virus [10]. Today, despite the wide range of drugs for hepatotherapy, foreign and domestic scientists are working on the development and synthesis of new drugs of chemical and natural origin for the treatment and prevention of liver diseases of various origins. Many studies have shown an important pathogenic role in the occurrence and progression of some liver diseases with changes in the intestinal microbiota. Therefore, antibiotics, prebiotics and probiotics are an effective treatment for liver diseases, which can correct the intestinal microbiota [16].

Purpose of the research

The purpose of the research is to study the effect of probiotics on liver function under meta-analysis in this disease. Because, cirrhosis of the liver is a progressive disease that poses a threat to life.

Materials and Methods

The research materials are the results of searches conducted in the databases PubMed, ISI Web of Science, EMBASE and the Cochrane Library. Based on a careful study of the material since the creation of suitable studies, a conclusion was drawn.

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Results and Discussion

In economically developed countries, the frequency of cirrhosis is about 20–40 cases per 100,000 populations, and this indicator is steadily increasing [3] and today is one of the six main causes of death at the age of 35–60 years [10].

Cirrhosis of the liver (from the Greek - red, amber) is a chronic disease accompanied by an irreversible replacement of the parenchymal tissue of the liver with fibrous connective tissue, or stroma. It is a progressive disease that develops over a long period and is the end stage of many liver diseases, including alcoholic and non-alcoholic fatty liver disease. Viral hepatitis B, C and D are recognized as the most common causes of liver cirrhosis [4]. Poor nutrition and lipid disorders, as well as autoimmune disorders, genetic disorders, chronic cholestasis (impaired outflow of bile), blockage of the hepatic veins can also affect liver dysfunction and the development of cirrhosis. If liver damage is detected in the early stages, the development and progression of the disease can be slowed down or stopped [13].

The main factors in the formation and progression of cirrhosis are hepatocyte necrosis and progressive fibrosis [4]. According to domestic and foreign authors, intestinal dysbiosis (dysbacteriosis) is also one of these factors. It is assumed that changes in the intestinal microflora play a decisive role in the development of cirrhosis and its complications [6, 17, 23, 27].

Dysbacteriosis (from the Greek - a prefix that denies the positive meaning of the word or reinforces the negative - and "bacteria") is a state of microbial imbalance on the body or inside it. At the same time, dysbacteriosis itself is not a disease [5], but can sometimes be a consequence of any disease.

A study conducted by Japanese authors on a mouse model showed a clear correlation between a certain type of intestinal bacteria, obesity and liver cancer. Several sectional studies have shown that gut dysbiosis may be involved in the pathogenesis of liver disease, assessing the relationship between gut microbiota and liver phenotype in patients with liver problems.

M. Masami et al. (2015) showed that in patients with liver diseases, fecal Bacteroidetes decreased, the number of Clostridium coccoides increased. Patients with various liver pathologies have increased intestinal permeability, which facilitates entry of microbial agents into the portal circulation and exacerbates pro-inflammatory and fibrogenetic effects in the liver.

According to the literature of foreign researchers, bacterial overgrowth syndrome is detected in 49-60% of patients with cirrhosis. With an increase in the class of cirrhosis according to Child-Pugh, the frequency of registration of bacterial overgrowth syndrome increases (30.8% in class A, 69.2% in B and C), while all authors report a correlation between bacterial overgrowth syndrome and severity liver disease. The presence of bacterial overgrowth syndrome in patients with cirrhosis leads to a slowdown in intestinal transit and a decrease in intestinal motility, which contributes to the absorption of toxins into the systemic and portal circulation and leads to the development of hepatic encephalopathy (HE).

Research M.A. Zocco et al. (2013) showed that the innate immune system and IL-23 (which has a direct effect on macrophage function and influences CD-4+T memory cells) are associated with certain bacterial agents in patients with HE. The authors found a correlation between cognitive impairment in patients with HE and the presence of Porphyromonadaceae and Alcaligenaceae (anaerobic and aerobic Gram-negative human pathogens). A close

relationship between HE and bacterial microflora has been established, so researchers need to focus on the possibilities of modulating the intestinal microbiota in order to effectively treat HE as a formidable complication of cirrhosis. Identification of pathogenetic mechanisms linking the intestinal microbiota and NAFLD will improve understanding of the pathogenesis of the disease, thereby contributing to the identification of new therapeutic targets, which will improve the quality of life of patients with this disease.

It is known that the normal intestinal microflora is a complete ecological system that performs diverse functions in the body. The action of various factors of endogenous and exogenous origin can possibly change the quantitative and qualitative composition of the intestinal microflora [15, 17, 21, 33]. The release of bacteria and their products from the intestinal lumen leads to a violation of the intestinal barrier, which causes strong inflammatory reactions, while various infections affect the portal and systemic circulation. The reproduction of opportunistic bacteria is a violation of the qualitative and quantitative composition of the intestinal microbiocenosis [1, 6]. In turn, an increased content of conditionally pathogenic microorganisms in the large intestine in patients with cirrhosis of viral origin is associated with the development of inflammatory-necrotic activity, which leads to the development of hepatocyte necrosis and the formation of inflammatory reactions with the progression of liver fibrosis [1, 6]. Thus, the problem of intestinal dysbiosis in patients with cirrhosis of viral origin remains open [2]. Modern medicine and pharmacology is in search of a cure that is often a combination of different therapies that include traditional therapies and natural remedies. One of the modern methods of treatment are probiotics. Studies show that probiotics may support liver health, as the gut microbiota plays a critical role in metabolic and detoxification processes [35].

Probiotics are live microorganisms that benefit the host when administered in adequate amounts [3, 7, 11, 12, 14].

Probiotics were originally defined as "microorganisms that cause the growth of other microorganisms" and later as "live microorganisms which, when consumed in adequate amounts, result in health benefits to the host" [29]. Most probiotic products today are formulated using Bifidobacteria, Lactobacilli, and other lactic acid bacteria such as Lactococcus and Streptococcus. Other promising probiotic strains include the bacterial genera Bacillus, Escherichia and Propionibacterium and several other yeast genera, mainly Saccharomyces. Probiotics are generally considered safe for human health, with limited side effects [22]. Several species and strains of Lactobacilli, including Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, and Lactobacillus helveticus, have been extensively studied in the prevention of human and animal diseases. These probiotic species are able to change the population of microorganisms in the gut microbiota and control the functioning of the gut microbiota ecosystem. In earlier studies, significant evidence has been obtained from clinical trials of probiotics in animal and human models, which have demonstrated their suitability for the treatment of various diseases.

Probiotics have been proposed as prevention and treatment of chronic liver injury, as they prevent bacterial translocation and epithelial invasion, as well as inhibit bacterial mucosal adhesion and production of antimicrobial peptides while reducing inflammation and stimulating host immunity [18, 20]. According to a review article published in 2011, high-quality preclinical studies and several randomized controlled trials supported the therapeutic use of probiotics in liver disease [24].

The University of Nottingham UK (2017) considered probiotics to be of interest in the treatment of cirrhosis due to possible beneficial effects through microflora modulation. The article states that recently damage to the intestinal microbiota, endotoxemia and inflammation have been considered as significant factors in the pathogenesis of hepatic encephalopathy. In addition, probiotics are better tolerated and more cost effective than traditionally used drugs such as lactulose, rifaximin, or L-ornithine-L-aspartate (substrates of the urea and glutamine synthesis cycle). Nineteen studies were found to meet the inclusion criteria, according to which participants are selected from the population to study. Probiotics increased beneficial microflora and reduced pathogenic bacteria and endotoxemia compared with placebo or no treatment, but no effect of probiotics on inflammation was noted. Probiotics have no additional effect on the regression of minimal hepatic encephalopathy and the prevention of the onset of severe hepatic encephalopathy compared with lactulose, rifaximin and L-ornithine-L-aspartate. Only 5 studies assessed the tolerability of probiotics, and the number of side effects was minimal [32].

According to the results of the observation, V. G. Radchenko et al. (2014) [8] it was found that during the treatment there was a positive trend and normalization of the syndrome of cytolysis and cholestasis was revealed by the end of the 6th week in 17 (80.9%) patients, and by the 8^{th} week in all patients (100.0%). The condition remained stable in all patients for 6 months after discontinuation of the drug, and 6 months after discontinuation of the drug, all patients noted a deterioration in the condition to the initial level. The disadvantage of the method chosen by the researchers as a prototype is not sufficiently high efficiency in the treatment of patients with cirrhosis of the liver. In patients with cirrhosis of the liver with intestinal dysbiosis, after taking the probiotic Linex, normalization of the intestinal microflora was noted according to the results of bacteriological examination.

For the first time, scientists have established the positive effect of Linex on the course of liver cirrhosis. In the section of the Instructions "Indications for the use of the drug Linex" [9], there is no information on the use of the drug for the treatment of patients with chronic liver diseases, including those in the stage of cirrhosis.

The above data indicate a higher efficiency of the proposed method for the treatment of patients with cirrhosis of the liver in comparison with the prototype method (use of the hepatoprotector Essentiale Forte N for the treatment of patients with cirrhosis of the liver). The probiotic Linex can be recommended for the correction of liver cirrhosis without clinical and microbiological manifestations of intestinal microbiocenosis disorders due to the fact that it has the properties inherent in hepatoprotectors [31].

According to H.M. Timmerman et al. (2006), in a study conducted by leading European experts at the laboratory of Wageningen University (Holland), evaluated the probiotic material of the Latium product. The therapeutic potential of the probiotic Latium had an impact on the macroorganism: the colonization resistance of the intestine increased, the intensity of inflammatory processes decreased, the main indicators of the general and local parts of the immune response normalized. These data are the basis for expanding the clinical use of Latium in the treatment of patients with various inflammatory liver diseases accompanied by impaired intestinal colonization resistance [34].

As these trials show, the bulk of the evidence supports the use of probiotics in a mobile genetic element. A meta-analysis of 9 relevant reports showed a positive effect of prebiotics, probiotics and synbiotics in patients with hepatic encephalopathy [19]. In fact, the guidelines of the Indian National Association for the Study of the Liver recommend the use of probiotics

with a mobile genetic element [30]. The situation is less clear for probiotic preparations in overt hepatic encephalopathy. A Cochrane review of probiotics for the treatment of hepatic encephalopathy found no evidence of improvement in clinically significant outcomes, although probiotics reduced plasma ammonia levels. However, some reports indicate that probiotics are useful in overt hepatic encephalopathy; this issue needs to be resolved in further studies before any clear recommendations can be made regarding the use of probiotics for the treatment or secondary prevention of overt hepatic encephalopathy [25].

Probiotic use has been evaluated in patients with compensated cirrhosis with at least one major complication. The multi-strain probiotic showed no benefit in these patients, except for a slight trend towards lower serum ammonia levels in patients with elevated ammonia levels [26]. Preoperative and postoperative use of probiotics in patients with cirrhosis and hepatocellular carcinoma undergoing tumor resection has been associated with lower serum TNF-α levels and faster recovery of liver function [28]. In summary, with the growing recognition of the role that changes in the gut microbiota play in causing various liver diseases and their complications, there is increasing interest in probiotics and related products for the prevention and treatment of liver diseases. At this time, probiotics cannot be recommended for the treatment of most liver diseases, with the exception of minimal hepatic encephalopathy, in a clinical setting. However, as evidence accumulates, probiotics may be more widely used to treat other liver diseases.

Conclusion

The modern pharmaceutical market has been flooded with numerous commercial drugs, creating havoc with probiotics. Our meta-analysis examining the effect of probiotics in liver cirrhosis indicates evidence-based scientific studies on the use of probiotics after appropriate experimental and clinical studies. Despite the safety of probiotics, some complications are mentioned in the publications, which lead to the conclusion that an individual approach of dosage and strain, which would have a beneficial effect on the process of therapy and prevention of liver cirrhosis.

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