

The Role of Microbiota in Chronic Liver Disease

Abstract

The intestinal microflora plays a role in local immunity, providing a barrier against harmful microbes, as well as the digestion of nutrients. Microbial translocation is the movement of live microorganisms or bacterial products (such as LPS, lipopeptides) from the intestinal lumen to the mesenteric lymph nodes and other extra intestinal locations as a result of disturbed gut flora. Recent research indicates that microbial translocation (MT) may also occur in the early stages of other liver disorders, such as alcoholic hepatopathy and nonalcoholic fatty liver disease, in addition to cirrhosis. Different factors that may favour MT include decreased immunity, greater permeability of the intestinal mucosa, and small intestinal bacterial overgrowth. Additionally, MT has been linked to the aetiology of cirrhosis complications, a major source of morbidity and mortality in cirrhotic individuals. Prokinetics and probiotics are two non-antibiotic-based therapeutic approaches that have been employed to modulate the gut flora and lower MT. Selective intestinal decontamination is an antibiotic-based therapeutic approach. Probiotics in particular can be a tempting tactic, even if bigger randomised trials are required to confirm the encouraging outcomes of animal models and small clinical investigations.

Keywords: microbial translocation • gut immune recovery • intestinal microflora • pathogenic • hepatic stellate cells • liver fibrosis • alcoholic fatty liver disease • gut barrier

Introduction

More than 500 different microbial species make up the complex ecosystem that is the intestinal microflora. In addition to aiding in the production of short-chain fatty acids and vitamins, the intestinal microflora contributes to local immunity and works in tandem with the intestinal mucosa to form a barrier against pathogens. In addition, recent lines of evidence suggest the intestinal microflora is directly involved in the induction and progression of liver damage in several chronic liver diseases, including alcoholic and non-alcoholic steatohepatitis, two common causes of cirrhosis. The pathophysiology of the problems of cirrhosis has been linked to the altered gut microbiota and enhanced microbial translocation (MT) in advanced liver disease [1].

Bacterial translocation has undergone numerous definitions since Berg and Garlington first described it as “the transit of live bacteria past the epithelial mucosa into the lamina propria and ultimately to the mesenteric lymph nodes, and perhaps other tissues.”

The current meaning of this term has expanded to include the crossing of an anatomically intact intestinal barrier by bacteria, both viable and nonviable, as well as microbial compounds such as lipopolysaccharide (LPS). The idea has recently sparked interest in the research of various infectious diseases, including leishmaniasis, hepatitis, and HIV infection. MT and widespread immunological activation are prevented and/or attenuated

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in the healthy host by a number of strategies. Contrarily, it is not surprising that numerous infectious diseases can be connected to MT and the ensuing host response given the variety of pathways that contribute to MT. A study that suggested that MT played a crucial role in HIV pathogenesis was released a few years ago [2].

According to the scientists, this phenomenon aids in the systemic immunological activation of HIV-positive individuals and hence contributes to the disease's progression. Numerous confirmatory investigations have now been carried out in response to these initial observations, sparking intense scientific discussion and prompting a reevaluation of the subject of HIV disease pathogenesis. A noteworthy result is that suppressive antiretroviral medication does not completely control MT, and that MT is linked to ineffective CD4 T-cell reconstitution. These factors make it possible to predict future mortality in the presence of on-going immune activation and inflammation despite antiretroviral therapy (ART)-mediated viral suppression [3]. Furthermore, new research suggests that MT may have a role in the pathogenesis of morbidity that is not caused by AIDS, such as dementia and cardiovascular illnesses. For these reasons, MT has become a significant problem in the present era of HIV treatment [4].

Methods and Materials

A live microorganism or bacterial endotoxin, such as bacterial lipopolysaccharide (LPS), peptidoglycan, or lipopeptides, may migrate from the intestinal lumen to the mesenteric lymph nodes (MLN) and other extraintestinal locations. This process is known as microbial translocation (MT). Enterococci, other streptococci species, and gram-negative members of the Enterobacteraceae family (such as *Escherichia coli* and *Klebsiella* spp.) are the most efficient at bacterial translocation to MLN, crossing even histologically normal intestinal mucosa. Anaerobic species, on the other hand, seldom translocate, and it has been shown that they restrict the growth of aerobic species with greater translocation potentials [5].

Both cirrhotic individuals and experimental animal models of the disease have been shown to have elevated MT. In research

on animals, the prevalence of MT, which is determined by a positive bacteriological culture from MLN that has been surgically removed, was around 50% in cirrhotic rats with ascites and up to 80% in cirrhotic rats with spontaneous bacterial peritonitis (SBP). There aren't many researches on humans because it's difficult to distinguish MT from MLN and there aren't many widely used noninvasive MT markers [6].

As many as 32% of patients with advanced cirrhosis and sterile nonneutrocytic ascitic fluid had bactDNA (mostly *E. coli*) found simultaneously in blood and ascites when it was discovered using the polymerase chain reaction (PCR), which has been considered as a sensitive surrogate sign of MT. It was significant that the similarity of the bactDNA sequences in the blood and ascites suggested a shared MT event as the genesis. The therapeutic significance of using molecular approaches to identify MT has not yet been determined due to the unfortunate lack of a correlation between the severity of liver disease and the identification of bactDNA in body fluids [7].

Discussion

The most significant health issues now are CLD and cirrhosis, according to the most recent gastrointestinal research. Patients with cirrhosis have an imbalanced nutrient and energy metabolism, which results in malnutrition and negatively, impacts their prognosis. Malnutrition in CLD is brought on by a number of processes, including insufficient food intake, problems with the gastrointestinal tract's ability to absorb and digest nutrients, and hampered hepatic synthesis of energy substrates. These anomalies eventually change the anthropometric characteristics of those patients, leading to hypoalbuminemia. The energy metabolism status in CLD is comparable to that seen in healthy persons during accelerated starvation. Reduced peripheral glucose consumption, reduced hepatic glycogen storage, and reduced glucose oxidation all contribute to reduced glucose oxidation. The loss of significant amounts of body fat mass is thought to be the cause of enhanced fat oxidation, as opposed to increased lipogenesis and subsequent fat oxidation [8].

The appetite-regulating hormone ghrelin may play a role in the complex pathophysiology of anorexia in CLD. The biologically active version of ghrelin that alters insulin sensitivity and body composition is acrylate ghrelin. Anorexia and reduced food intake, along with liver failure's effects on protein synthesis and breakdown, can result in severe protein energy deficiency. Our research showed that patients with CLD had higher serum ghrelin levels than healthy individuals, and that these levels increased as the Child's grade and liver function declined. The results, which showed that blood ghrelin levels in CLD patients were much higher than those in healthy controls and that these levels were also higher in patients with severe problems and a Child's categorization of grade C, corroborated our findings [9].

Given that Child's classification raises the risk of metabolic breakdown and clinical consequences, ghrelin may be able to address these issues in Child C cirrhosis by regulating the energy balance, arousing the hunger, and increasing food intake, among other metabolic processes. Similarly, (2010) discovered that acrylate ghrelin levels had positive correlations with total and direct bilirubin and negative correlations with serum albumin and prothrombin concentrations, suggesting that the biologically active form of ghrelin is more closely associated with the severity of CLD [10]. They therefore proposed, based on the prior premise, that an improvement in liver function and nutritional status is associated with a drop in serum ghrelin. However, other investigations indicated that plasma ghrelin levels were strongly connected to food intake in patients with disease-associated malnutrition rather than being higher in CLD patients than in healthy controls or related to the severity of liver impairment.

Although increased bioactive ghrelin secretion in cirrhotic patients may be an adaptive mechanism signalling the hypothalamus to enhance hunger and maintain energy balance in response to their low nutritional state, ghrelin does not appear to be a direct causative factor in malnutrition [11]. However, some patients with limited appetites might be resistant to ghrelin's orexigenic effects. The paradoxical response of increased ghrelin and decreased feeding leading to a malnourished state could be

partially explained by desensitisation of the hypothalamic ghrelin receptor, GHS-R, implicated in the control of food intake. Also noted was the connection between fasting ghrelin and food intake in CLD-related malnutrition. They came to the conclusion that hyperghrelinemia in anorexic patients may be a sign of a compensatory mechanism seeking to boost food intake but failing in the physiological range [12].

Conclusion

The way that chronic liver disorders develop naturally may be greatly influenced by the interaction between the host and the gut bacteria. The demand for MT surrogate markers and non-antibiotic techniques that can improve the gut environment and lessen the transit of bacteria and bacterial metabolites through the gut exists in clinical practise. Probiotics are an appealing method when outcomes from laboratory models and small clinical studies are taken into account, but they require more research in bigger controlled clinical trials.

Acknowledgments

None

Conflict of interest

None

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