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The role of intestinal dysbiosis in liver cirrhosis

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Abstract

Background: - The overuse of antibiotics has been associated with a lot of disturbances in our gut. Moreover, gut microbiota plays a significant role in the development of cirrhosis of the liver and hepatocarcinogenesis.

Objective: to study the role of intestinal dysbiosis in liver cirrhosis and its complications

Methods: The Research is based on articles and previously made trails and analysis and it is going to be about the role of intestinal microbiota in human diseases specifically in liver cirrhosis and other liver diseases. A retrospective study was carried out and in this research 8 studies were reviewed and it was carried out in January 2022-april 2022 in the college of medicine university of Diyala, a hydrogen breath test was used to diagnose small intestinal dysbiosis in these studies and a bacteriological study of feces was used to diagnose colon dysbiosis.

Results: In the reviewed studies, the indicators were taken in the two groups, patients only with liver cirrhosis and without dysbiosis (1st group) and patients with cirrhosis and dysbiosis (2nd group).

It was found that patients with dysbiosis have higher percentage of Anemia (32%), Leukopenia (34%), Thrombocytopenia (57.4%), Increased transaminase levels (100%), Hyperbilirubinemia (74.5%), Increased alkaline phosphatase levels (40.4%), Hypoalbuminemia (69.9%), Hypergammaglobulinemia (48.9%).

2 more groups were examined; patients with liver cirrhosis and dysbiosis (1^{st} group) and patients with cirrhosis only (2^{nd} group).

It was found that patients with liver cirrhosis and dysbiosis have higher percentage of developing complications of cirrhosis which’s Peritonitis (14%) Hepatorenal syndrome (19%) Hepatic encephalopathy (20.1%) Ascites (32.9%)

Conclusion: Based on the analysis of literary sources, it was revealed that patients with liver cirrhosis have a very high incidence of intestinal biocenosis disorders and rapid phase of developing cirrhosis complications (70.3 - 82.4%). Violation of the intestinal microflora is factor that aggravates the course of liver cirrhosis and contributes to the development of the main complications of portal hypertension.

Introduction

The term "cirrhosis" has been used for two centuries to define the end-stage of chronic liver diseases with different etiologies.

Liver fibrosis and its related complications continue to represent a significant worldwide healthcare burden. Over the past decade there has been considerable improvement in our understanding of the cellular mechanisms and pathophysiology underlying hepatic fibrosis. This greater insight into the relevant basic sciences may lead to the development of novel treatment strategies designed to block the fibrogenic cascade or even enhance matrix degradation. In addition, there have been significant advances in the management of the complications of cirrhosis, with specific treatments now available for some conditions. Perhaps most notably, liver transplantation is now a highly successful treatment for end-stage liver disease and should be considered in all patients with chronic liver disease. [1].

Gut microbiota and liver diseases

More than 10 microorganisms live in the human gastroenterological tract, including > 10 bacterial species. Most of the bacteria are anaerobic and the numbers and composition of the bacteria differ according to the site of the gut. The numbers of bacteria increase from the stomach, to the jejunum, ileum and colon.

The composition of the bacterial flora also changes according to age and diet. It has been clarified that gut microbiota play a critical role in the formation of the gut immune system and that they also affect the systemic immune system [2].

Moreover, interactions between gut microbiota and the liver or brain have been analyzed. The composition of the microbiota is also associated with various diseases [3]. The maintenance of the gut flora may be based on immune tolerance to microbiota because of the formation of the repertoire of microbiota during early life after birth, when the immune system is too immature to eradicate intestinal micro-organisms [4][5][6].

The role of intestinal microbiota in liver cirrhosis [7]:

- Disorders of the gut microbiota
- inflammation of the intestinal mucosa
- violation of the permeability of the intestinal wall
- movement of intestinal bacteria and their toxins into the veins of the portal system
- contact of lipopolysaccharides of intestinal bacteria with liver macrophages (Kupffer cells) production of pro-inflammatory cytokines
- development of inflammatory reactions
- the formation of necrosis of hepatocytes
- progression of liver fibrosis

The aim of the research is to discuss the role of intestinal dysbiosis in liver cirrhosis and its complications.

Methods

The Research is based on articles and previously made trails and analysis and it is going to be about the role of intestinal microbiota in human diseases specifically in liver cirrhosis and other liver diseases. A retrospective study was carried out and, in this research, based on the analysis of literary sources. 8 studies were reviewed and it was carried out in January 2022-april 2022 in the college of medicine university of Diyala, a hydrogen breath test was used to diagnose small intestinal dysbiosis in these studies and a bacteriological study of feces was used to diagnose colon dysbiosis.

Results

A hydrogen breath test was used to diagnose small intestinal dysbiosis in these studies, and a bacteriological study of feces was used to diagnose colon dysbiosis. Based on the analysis of literary sources, it was revealed that patients with liver cirrhosis have a very high incidence of intestinal biocenosis disorders and rapid phase of developing cirrhosis complications (70.3 - 82.4%) [7].

Table. 1. Influence of intestinal biocenosis on indicators of laboratory tests

Indicators	Patients with liver cirrhosis with normal intestinal microflora (%)	Patients with cirrhosis of the liver with intensive bacterial growth in the small intestine and colonic dysbiosis (%)
Anemia	**0**	**32**
Leukopenia	**6.7**	**34**
Thrombocytopenia	**13.3**	**57.4**
Increased transaminase levels	**53.3**	**100**
Hyperbilirubinemia	**0**	**74.5**
Increased alkaline phosphatase levels	**0**	**40.4**
Hypoalbuminemia	**20**	**69.9**
Hypergammaglobulinemia	**6.7**	**48.9**

Anemia: - In accordance with the conducted research(table 2) a patient with dysbiosis and cirrhosis will have anemia due to multiple factors but we notice that only certain patient with dysbiosis will have more susceptibility to develop anemia than those with cirrhosis only that and until today, many human studies have only reported observed correlations, and more work is necessary to prove a causal relationship between iron-gut bacteria interactions and the development of gut inflammatory diseases and colorectal cancer. Experimental animal models have assisted in understanding how the gut microbiota interact with excessive amounts of unabsorbed luminal iron, and modern iron therapeutic administration methods for iron deficient populations [8].

Leukopenia cause in cirrhosis include portal hypertension-induced splenic and splanchnic sequestration. Alterations in granulocyte colony stimulating factor and granulocyte macrophage-colony stimulating factor.

Bone marrow suppression mediated by toxins and in case of cirrhosis and patient with dysbiosis we can notice 6 times more than in cirrhosis alone and that due to the associations we reveal are interpretable as potential effectors on sources and sinks of white blood cell counts in circulation. Intestinal bacteria may affect white blood cell counts in circulation by influencing either their sources in the bone marrow or their cytokine profiles and proliferation rates in the blood, their sinks in different organs, or both [9].

Thrombocytopenia the major mechanisms for thrombocytopenia in liver cirrhosis are (1) platelet sequestration in the spleen; and (2) decreased production of Thrombopoietin (TPO) in the liver. And we see patient with dysbiosis have higher incidence of thrombocytopenia.

This is still an area of active research given that the role of gut microbiota on the primary immune thrombocytopenia (ITP) remains unclear.

Increased transaminase levels in liver cirrhosis (table 2) alone are due to the inflammation and destruction of hepatocytes and we can also notice the higher incidence in patients with dysbiosis and this is due to the fact that Intestinal microbiota (IM)contributes to chronic and rapid inflammation not only through the production of endotoxins but also through cytokines and inflammasome dysfunction [10].

Hyperbilirubinemia in advanced cirrhosis, glucuronic conjugation of bilirubin and biliary excretion of conjugated bilirubin are markedly impaired and jaundice appears. The concentration of bilirubin in serum thus become a good prognostic marker for patients with uncompensated liver cirrhosis. And on the other hand, patient with dysbiosis will have increased levels of bilirubin in blood more than cirrhosis alone and that is due to the fact that microbiota closely interact with gut epithelial cells to regulate intestinal bilirubin, play a role in convergence, and

Increased alkaline phosphatase levels: smaller increases of blood ALP are seen in liver cancer and cirrhosis, with use of drugs toxic to the liver, and in hepatitis. Any condition causing excessive bone formation, including bone disorders such as Paget's disease, can cause increased Alkaline phosphatase (ALP)levels incidence in patients with dysbiosis and this is due to the fact that IM contributes to chronic and rapid inflammation not only through the production of endotoxins but also through cytokines and inflammasome dysfunction [11].

Patients with advanced cirrhosis almost always have hypoalbuminemia (table 1) caused both by decreased synthesis by the hepatocytes and water and sodium retention that dilutes the content of albumin in the extracellular space, and in dysbiosis the altered function of the gut barrier could lead to the passage of pro-inflammatory molecules which in turn lead to speeding the liver failure and that leads to hepatic dysfunction and inability to make some proteins including main protein Albumin.

Hypergammaglobulinemia (table 2) with significantly elevated levels of IgG is a common finding in patients with advanced liver cirrhosis of different etiologies. This may result in the misdiagnosis of Autoimmune hepatitis in some patients. However, in patients with dysbiosis and cirrhosis will have these indices increased more. the pathogenesis of this disease remains obscure.

Based on the analysis, patients with dysbiosis plus cirrhosis have worse prognosis and worse symptoms than those with cirrhosis alone and in this section will view how symptoms vary between these two groups.

Symptoms and complications of liver cirrhosis: -

The role of intestinal dysbiosis in the formation of symptoms of intestinal dyspepsia in patients with liver cirrhosis [12]. Symptoms similar to irritable bowel syndrome: abdominal pain syndrome, flatulence was found in all patients with impaired intestinal microflora composition [12].

Table 2. The role of intestinal dysbiosis in formation and complicating different symptoms and complications of liver cirrhosis

In the presence of bacterial overgrowth in the small intestine the clinical picture symptoms in the form of diarrhea predominated, while in colonic dysbiosis the patients' experienced symptoms of diarrhea and constipation with the same frequency [35].

The Influence of disturbed intestinal microflora on the development of complications of liver cirrhosis:-

Complications	Patient with dysbiosis and cirrhosis	Patient with cirrhosis only
Peritonitis	14%	0%
Hepatorenal syndrome	19%	0%
Hepatic encephalopathy	80.9%	20.1%
Ascites	63.8%	31.9 %

Hepatic encephalopathy in patients with liver cirrhosis with a combined violation of the microflora of the small and large intestine develops 4 times more often than in patients with cirrhosis of the liver with normal microflora (table 3) and is 80.9% [12].

Ascites develops 2 times more often in patients with liver cirrhosis with a concomitant violation of the small and large intestinal microflora than in patients with cirrhosis of the liver with normal intestinal microflora (table 3) and is 63.8%.[12].

The development of **peritonitis** is observed in 14% of patients with liver cirrhosis with a concomitant violation of the microflora of the small intestine and is not observed in patients with cirrhosis of the liver with normal microflora (table 3).

The development of **hepatorenal syndrome** is observed in 19% of patients with liver cirrhosis with a concomitant violation of the microflora of the small intestine and is not observed in patients with cirrhosis of the liver with normal microflora (table 3) [12].

Conclusion

Patients with liver cirrhosis have a very high incidence of intestinal biocenosis disorders (70.3 - 82.4%).

Violation of the intestinal microflora is a factor that aggravates the course of liver cirrhosis and contributes to the development of the main complications of portal hypertension.

Signs hypersplenism, increased transaminase levels in combination with hyperbilirubinemia, cholestasis syndrome and hypergammaglobulinemia were found much more often in patients with bacterial overgrowth in the small intestine.

The presence of dyspeptic disorders in patients with liver cirrhosis with a high degree of probability can serve as a diagnostic test of intestinal dysbiosis, which must be taken into account when developing tactics for their management.

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