

## **Gut Microbiota in Inflammatory Bowel Diseases: A Possible Role in the Development of Rapidly Evolving Chronic Hepatitis and Endothelial Dysfunction with Increased Cardiovascular Risk**

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### **Background**

It is known that in various liver disorders such as hepatic steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and cirrhosis, there is a qualitative and quantitative alteration of the gut microbiota. Indeed, in such pathologies, normal intestinal flora, which is made up of lactobacilli in the healthy subject, is replaced by quantitatively significant gram-positive bacteria, probably due to the reduction of endoluminal concentration of long chain fatty acids (LCFAs). Therefore, the intraluminal production of various endotoxins increases, and among them the role of lipopolysaccharide (LPS) is notable. This results in the activation of inflammatory cells of the intestinal layer that begin to produce Tumor Necrosis Factor-alpha (TNF- $\alpha$ ). The TNF- $\alpha$  alters and destroys the tight junctions of the intestinal mucosa epithelium, so allowing translocation of intestinal bacteria and their endotoxins to the intestinal blood vessels. Through the portal circulation, endotoxins are transported to the liver and bounded to the Toll-like receptors (TLRs) present on the cytoplasmic membrane of hepatocytes, bile duct epithelial cells, Kupffer's cells, and intrahepatic stellate cells. Kupffer's cells, thus stimulated, produce pro-inflammatory interleukins (IL-1, IL-6, IL-8, IL-10), TNF- $\alpha$ , PDGF, MCP-1, while the stellate cells become able to produce collagen, that is, to trigger liver fibrogenesis. It's intuitive to understand that the whole process produces an inflammatory and pro-fibrotic liver microenvironment that is capable of causing a rapid evolution of the liver damage to necro-inflammation, fibrosis, cirrhosis and also hepatocarcinoma (HCC) at certain percentage (5 - 10%) [1-8].

Qualitative and quantitative alterations of the gut microbiota are present in Inflammatory Bowel Diseases (IBDs), where there is also an altered permeability of the intestine that facilitates the bacterial and endotoxins translocation and the subsequent cascade of events that triggers the activation of intra-hepatic Kupffer's cells and stellate cells, and the rapidly evolving liver damage to fibrosis and cirrhosis with significant risk of liver failure and HCC onset [9-13].

A possible involvement of the cardiovascular system has also been envisaged. In fact, recent evidence suggests an increased risk of acute myocardial infarction, ischemic stroke and cardiovascular mortality in patients with IBD, particularly during disease re-activation and especially in women and young people [14,15].

However, probably due to the extreme heterogeneity of the studies, the various meta-analyses have not yet provided conclusive data.

As already described, in the course of IBD, high levels of LPS induce pro-inflammatory cytokine production and this event contributes to the endothelial damage and the formation of foam cells. Endotoxemia is considered to be an important risk factor for early atherosclerosis, in fact LPS:

- Determines the oxidation of LDLs, making them toxic to the endothelial cell;
- Activates macrophages, accelerating the atherosclerotic process.

Additionally, the increased expression of Toll-like receptors 2 and 4 (TLR2 and 4) in the atherosclerotic plaques further emphasizes the role of the gut microbiota in the atherogenesis process.

Indeed, a greater expression of TLR2 and TLR4 on circulating monocytes have been shown in subjects with acute coronary syndrome than in healthy controls, and *in vitro* models studies suggest that TLR2 stimulation results in an increase in TNF $\alpha$  levels in the same monocytes.

IBD patients present also an increase in cytokines, PCR and LDL-cholesterol levels, and these factors, associated with lowering cholesterol-HDL levels, contribute to the increased risk of atherogenesis and cardiovascular disease.

Finally, patients with IBD exhibit high levels of homocysteine and coagulation factors, which are involved in the atherosclerotic process and the formation of thrombi [16-19].

### **Future Research Objectives**

Future research needs to verify:

- The prevalence of hepatic impairment in IBD patients by the study of hepatic liver function tests, abdominal ultrasound and, where necessary, abdominal CT and MRI with hepatobiliary-specific contrast agent;
- The prevalence of hepatic fibrosis, by transient elastometry (fibroscan) and liver biopsy;
- The role of qualitative and quantitative alteration of the gut microbiota by serial bacteriological examinations of feces (at diagnosis, and during therapy, remission, and re-activation of disease).

It will also have to prospect for:

- Possible pathophysiological mechanisms capable of explaining observational data, by assays of LPS and of the major cytokines involved in the activation of Kupffer's cells and stellate cells (at diagnosis, and during therapy, remission, and re-activation of disease)
- The possible links between IBD, gut microbiota alterations and cardiovascular disease.

### **Discussion and Conclusions**

In our opinion, it is a realistic hypothesis that, during IBD, a major alteration of the gut microbiota coexists, and this results in severe impairment of liver function up to rapidly evolving fibrosis and liver cirrhosis. An early recognizing and an adequate treatment of the alterations of the gut microbiota may prevent the development of chronic hepatitis and cirrhosis in subjects with IBD, thus preventing the onset of HCC.

Although the international literature shows scientific evidence confirming the role of the microbiota in hepatic conditions such as hepatic steatosis, non-alcoholic steatohepatitis (NASH) and alcoholic steato-hepatitis (ALS), it is also true that there is little "solid" data on the relationship between the alterations of gut microbiota during IBD and the rapidly evolving liver function abnormalities.

On the other hand, several studies support the hypothesis of a close association between IBD and an increased cardiovascular risk. The mechanisms through which this risk may occur are not entirely known, but most of the available data are in favour of the role of inflammation and its mediators. Endothelial dysfunction certainly has a prominent role, while the role of systemic mediators of inflammation and dyslipidaemia requires further studies to evaluate the actual mechanism.

Finding possible pathogenetic mechanisms would help to improve the knowledge of the phenomenon and would also be extremely important to anticipate possible corrective therapeutic interventions and to signal the need for careful monitoring of the gut microbiota at the time of diagnosis, during therapy, in the remission and pharmacological control phase and, if present, during exacerbations [20,21].

### **Author Contributions**

All the authors contributed to this paper.

### **Conflict of Interest Statement**

There are no potential conflicts of interest.

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