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Review Article

Gut microbiota and probiotics in chronic liver diseases

Claudia Cesaro[a,*], Angelo Tiso[a], Anna Del Prete[a], Rita Cariello[b], Concetta Tuccillo[a], Gaetano Cotticelli[a], Camillo del Vecchio Blanco[a], Carmelina Loguercio[a]

[a] Department of Clinical and Experimental Internistica "F. Magrassi and A. Lanzara", Gastroenterology Unit, Second University of Naples, Naples, Italy
[b] Department of Experimental Medicine, Second University of Naples, Naples, Italy

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ABSTRACT

There is a strong relationship between liver and gut: the portal system receives blood from the gut, and intestinal blood content activates liver functions. The liver, in turn, affects intestinal functions through bile secretion into the intestinal lumen.

Alterations of intestinal microbiota seem to play an important role in induction and promotion of liver damage progression, in addition to direct injury resulting from different causal agents. Bacterial overgrowth, immune dysfunction, alteration of the luminal factors, and altered intestinal permeability are all involved in the pathogenesis of complications of liver cirrhosis, such as infections, hepatic encephalopathy, spontaneous bacterial peritonitis, and renal failure. Probiotics have been suggested as a useful integrative treatment of different types of chronic liver damage, for their ability to augment intestinal barrier function and prevent bacterial translocation.

This review summarizes the main literature findings about the relationships between gut microbiota and chronic liver disease, both in the pathogenesis and in the treatment by probiotics of the liver damage.

1. Introduction

There is a strong relationship between liver and gut: the portal system receives blood from the gut, and intestinal blood content activates liver functions. The liver, in turn, affects intestinal functions through bile secretion into the intestinal lumen [1,2].

The intestinal microbiota form a complex ecological system that participates, under physiological conditions, to the production of vitamins, degradation of bile acids, digestion of nutrients, and local and general immunity [3]. Finally, together with the intestinal mucosa, the endogenous intestinal flora form an important barrier against pathogens [4]. Despite the diversity of causes of liver damage (e.g., viral, toxic, metabolic), the triggered pathogenetic mechanisms responsible for various kinds of liver injury (e.g., inflammation, steatosis, fibrosis, cirrhosis) share commonalities. Alterations of intestinal microbiota seem to play an important role in induction and furthering the progression of liver damage, in addition to direct injury resulting from different causal agents. Probiotics may beneficially influence several of the functions of the intestinal microbiota and modulate several pathogenic alterations in the induction and progression of chronic liver disease [5].

This review summarizes the main literature findings on gut microbiota, probiotics, and liver.

2. Gut microbiota in chronic liver diseases

Gut flora alterations consist of overgrowth and release in the circulation of bacterial endotoxins (e.g., bacterial lipopolysaccharide [LPS], peptidoglycan, lipoproteins, and various lipopeptides) also termed pathogen-associated molecular patterns (PAMPs). Endotoxemia appears to be responsible for initiation of the liver damage, through its interaction with specific recognition receptors, the toll like receptors (TLRs). TLRs, acting as pathogen sensors, contribute to adaptive immune response and regulation of inflammation and represent a link between intestinal flora changes, endotoxemia, and liver damage [6–9]. Amongst the cells in the liver exhibiting a variable expression of TLRs, Kupffer cells play the most important role, mainly defined in metabolic and alcohol liver diseases, whilst not yet fully understood in chronic viral hepatitis. Nevertheless mechanisms through which microbiota may cause liver damage that do not include TLR activation have been suggested, they remain to be clarified [10,11].

2.1. Viral hepatitis

A direct relationship amongst endotoxemia and intralobular necrosis, regeneration of hepatocytes and Ito cell differentiation

* Corresponding author. Italy. Tel.: +39 3335225472; fax: +39 0815666718.
E-mail address: cesaro.claudia@libero.it (C. Cesaro).

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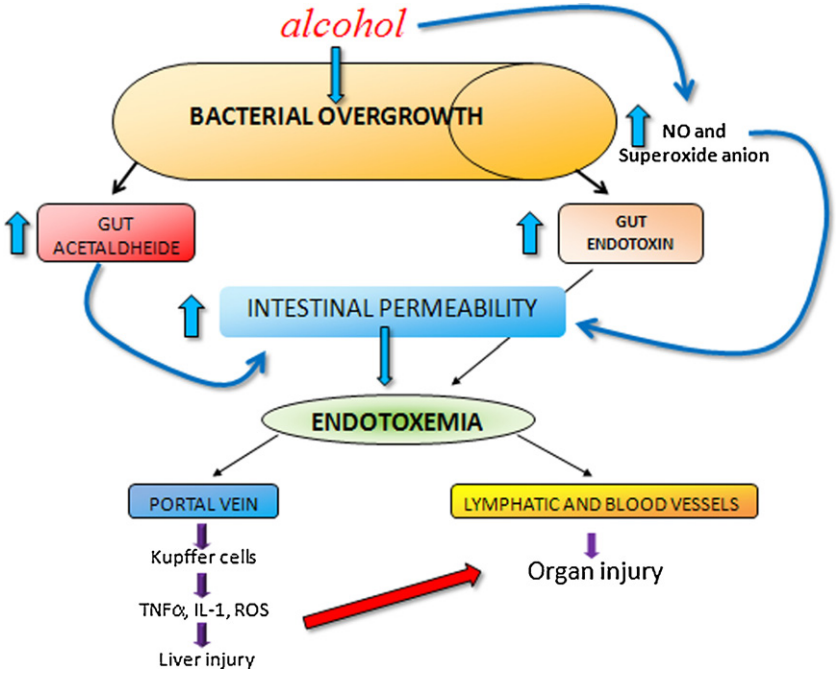

Fig. 1. Relationship between alcohol, gut, and liver: alcohol induces bacterial overgrowth and increased intestinal permeability by both direct and indirect mechanisms; the indirect mechanism is determined by acetaldehyde. NO: nitric oxide; ROS: reactive oxygen species.

was highlighted in patients with chronic viral hepatitis by hepatitis C virus (HCV) and hepatitis B virus (HBV) [12,13]. Caradonna et al. evaluated the plasma levels of endotoxin in patients with chronic C hepatitis before and after therapy (interferon [INF] and ribavirin). In responders, LPS was not detectable, whilst LPS was detectable in 42% of non-responders [14]. High levels of endotoxin in plasma of patients with hepatitis C were associated with an overproduction of the pro-inflammatory cytokines including Tumour Necrosis Factor (TNFα). This overproduction should be also caused by a loss of tolerance by TLRs arising from a combination of viral and host factors. Therefore, the outcome would be a bacterial LPS hypersensitivity, which could be involved in the persistence of inflammation in patients with chronic viral hepatitis [15].

2.2. Alcoholic hepatitis

Alcoholic liver disease ranges from simple steatosis to cirrhosis. Although the main mechanism of alcohol-induced liver damage is dependent on its metabolism in hepatocytes, also the intestine participates to its onset and progression [16]. Intestinal bacteria of the large bowel participate to the metabolism of alcohol ("bacteriocolonic" metabolism of ethanol), resulting in the introduction of high concentrations of toxic acetaldehyde into the lumen [17,18]. Acetaldehyde, per se, increases intestinal permeability (gut leakiness), indirectly changing the microbiota equilibrium, and increasing the LPS quantity that arrives at the liver [19]. Bacterial intestinal flora also produce endogenous ethanol through the fermentation of carbohydrates, a normal pathway that is strongly enhanced in the presence of gut dysmotility (e.g., from obesity, diabetes, or chronic alcohol use) or an excess of carbohydrates in the diet [20,21]. In 1984, Bode et al. first analysed the gut microflora in people with alcoholism, demonstrating both a quantitative and a qualitative significant difference in respect to the flora of a control group [22]. In 1997, Hauge et al. reported a bacterial overgrowth also in the duodenum [23], and in another study Bode et al. reported an incidence of intestinal bacterial overgrowth that was three times higher in patients with alcoholism than amongst non-alcoholic controls [24]. The intragastric administration of LPS after administration of alcohol induces an increase of intestinal permeability and this demonstrates that ethanol can drive the alteration of intestinal permeability to endotoxins [25]. Also nitric oxide (NO) has a pathogenic role in the alcohol-mediated liver disease. Tang et al., using rats gavaged daily with ethanol + inducible nitric oxide synthase (iNOS) inhibitors, demonstrated an improvement of the alcohol-induced cascade leading to gut leakiness, endotoxemia, and, at last, liver damage [26]. Finally, acute and chronic alcohol ingestion affects both the specific and unspecific immune system altering the barrier function of the gastrointestinal tract in fact, ethanol suppresses natural killer cell activity and antibody-dependent cell-mediated cytotoxicity by lymphocytes and likewise, the T cell-dependent antibody responses, leading to susceptibility to pathogen bacteria of the gastrointestinal tract [27,28]. Fig. 1 gives an overview of each of these mechanisms.

2.3. Metabolic syndrome and liver steatosis

Amongst the stigmata of the metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), the hepatic expression of metabolic syndrome, and obesity are most strongly associated with alterations of gut microbiota. In obesity there are changes in the composition and functions of the microbiota ("obese microbiota"), that can extract more energy from the diet [29,30]. Evidences suggest that gut bacteria can initiate the inflammation and insulin resistance associated with obesity through the activity of LPS. Particularly a high-fat diet favours the transport of LPS from gut to portal system [31–33] and also determines changes in the gut microbiota by reducing the numbers of bifidobacteria. This variation in the gut microbiota increases gut permeability and LPS plasma levels [34].

NAFLD is the most common cause of chronic liver injury in all industrialized countries with an increasing incidence. NAFLD includes a spectrum of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) to cirrhosis and its complications. Whilst NAFLD is a condition of simple accumulation of lipids in the liver, NASH is a more complex entity because of the overlap of a necro-inflammation component. A series of experimental findings suggest that, in the activation of inflammatory

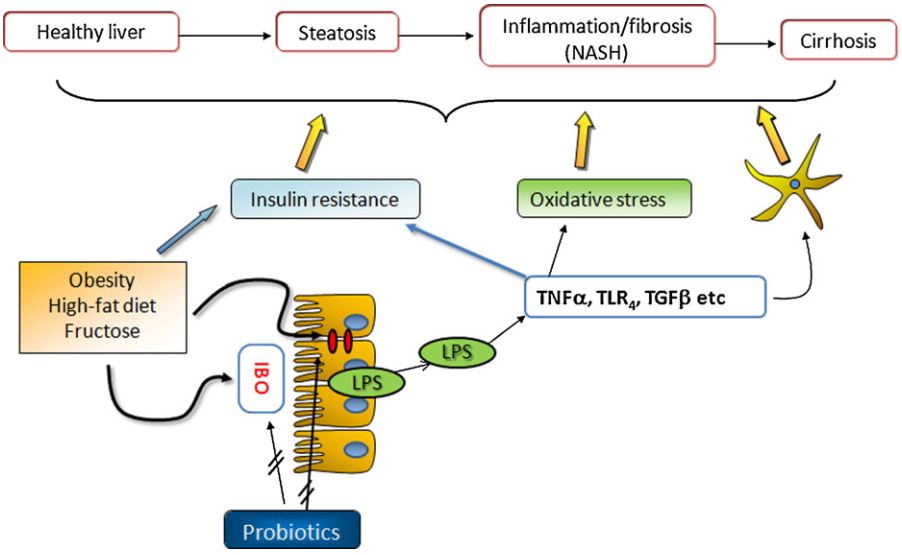

Fig. 2. Bacterial translocation: migration of aerobic pathogens or their products from gut to mesenteric lymph nodes or to other organs. LPS: lipopolysaccharide; IgA: immunoglobulin A.

processes typical of NASH, the microbiota play an important role. This theory stems from a series of observations in animal models and in humans [35–37].

There seem to be two mechanisms underlying endotoxemia and initiation of inflammation: bacterial overgrowth and alteration of intestinal permeability (leaky gut), analogous to that which occurs in alcohol-related liver damage. These changes have been demonstrated in numerous studies: Wigg et al. [38] documented the association between bacterial overgrowth and NASH, whilst Farhadi et al. [39] revealed alterations in intestinal permeability in animal models, in particular showing that altered intestinal permeability in NASH is irregular. Trigger factors not yet identified may effect a greater susceptibility to endotoxemia in a subgroup of NAFLD patients. This possibility is important because it represents an interpretation of potential differences between NAFLD and NASH, showing an increased susceptibility to endotoxemia in a latter group of patients. Tight junctions appear to have a central role in the control of intestinal permeability as evident from the work of Brun et al. [40] and from the more recent report from Miele et al. [41]. This latter provided the first evidence in humans of a relationship amongst small intestinal bacterial overgrowth (SIBO), gut permeability, and NAFLD. By comparing 35 patients with biopsy-proven NAFLD with 27 patients affected by untreated celiac disease, selected as a model of intestinal hyperpermeability, authors documented a higher prevalence of SIBO and of leaky gut in NAFLD in respect to a control group, thus demonstrating the role of increased permeability in the pathogenesis of hepatic fat deposition. Moreover, further studies have identified a relationship amongst nutrients, obesity, NAFLD, and microbiota [42–47].

2.4. Cirrhosis

Liver cirrhosis is a “vascular disease” characterized by portal hypertension and hyperdynamic syndrome [48]. The main mediator of these fundamental alterations is an over production of NO following the activation of iNOS, eNOS (endotherial NOS), and nNOS (neuronal NOS). These enzymes are mainly activated by LPS and pro-inflammatory cytokines as demonstrated in several studies [49,50]. LPS directly correlates with the severity of liver disease, and cooperates with the initiation of a complex series of interrelated events that lead to the development of cirrhosis and its complications. These complications are supported by a condition known as bacterial translocation (BT), which, in association with the presence of vascular shunts, is responsible for increased circulating levels of LPS, primarily in the portal blood [51].

BT is defined as a migration of bacteria or their products from the gut to mesenteric lymph nodes or to other organs [52,53] (Fig. 2). Bacterial DNA (bactDNA) in the circulation is also considered a marker of BT in humans [54]. In cirrhotic patients, bactDNA was found both in the circulation and in ascitic fluid, and it was correlated with plasma levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-12) as well as with the activation of iNOS [55]. LBP (LPS binding protein), synthesized by the liver, is considered another marker of BT, and it has been demonstrated that LBP increases in patients with liver cirrhosis and ascites [56]. BT may occur as a consequence of bacterial overgrowth, immune dysfunction, alteration of the luminal factors and altered intestinal permeability. Bacterial overgrowth frequently occurs in cirrhosis and it appears to be related to the degree of hepatic dysfunction [57]. It seems to be the result of an intestinal hypo-dysmotility, with a still-unknown basic mechanism [58,59]. An anomalous propagation of peristaltic waves was found in patients with portal hypertension compared with those without portal hypertension. Therefore, SIBO is directly related to the vascular abnormalities in the splanchnic area [60]. Moreover, the same bacterial overgrowth can alter intestinal motility, as demonstrated by an improvement of motility through a bowel decontamination with antibiotics [61]. In the presence of cirrhosis, there are several abnormalities of both the systemic and local immune systems. The reticular endotelium system (RES) is the main mechanism of defence against infections and bacteremia, and Kupffer cells represent the main component of the RES; however, the activities of RES are depressed in cirrhosis [62]. In rats with experimentally induced cirrhosis, there is a marked decrease of IFNγ and intraepithelial lymphocytes. The lymphatic system of the intestinal mucosa has a vital function in maintaining the balance between intestinal bacterial flora and the host. Only a few bacteria move outside the mesenteric lymph nodes under physiological conditions. The decrease in IFNγ in cirrhosis can lead to damage to the phagocytic activity of macrophages and to other cells, and thus allows the bacteria to multiply and migrate to extra gastrointestinal sites [63].

Different factors act in the intestinal lumen, such as bile acids, IgA, mucine, defensine, lysozyme, and phospholipase A2. Bile acids inhibit bacterial overgrowth, especially of anaerobic bacteria. BT

has been documented in the course of obstructive jaundice, as a consequence of the absence of bile [64]. In the presence of cirrhosis, the secretion of bile acids is decreased, which may contribute to bacterial growth and BT [65].

A great deal of evidence indicates that patients with cirrhosis could present increased intestinal permeability [66]. The factors responsible for its appearance are primarily structural (e.g., vascular congestion, muscle fibre proliferation, reduced villous ratio/crypts, thickened muscularis mucosae). Such changes appear to be related to the presence of portal hypertension and hypertensive enteropathy [67]. In addition, studies have identified a condition of altered oxide-reductive state and consequent oxidative damage to the intestinal mucosa, leading to the lipid peroxidation of the brush border membrane [68]. An overproduction of NO in the liver and splanchnic area occurs in the development of portal hypertension and results in an alteration of the integrity of the intestinal mucosa through the expansion of tight junctions, destruction of the cytoskeleton, and inhibition of the formation of adenosine triphosphate, all factors involved in the increase of intestinal permeability [69]. Our group has recently documented that intestinal permeability is altered in patients with advanced liver disease. Independent factors for this alteration were age, portal hypertension, alcohol use, and diabetes. Plasma levels of inflammatory cytokines and nitrosothiols, as an expression of overproduction of NO, were significantly higher in patients with altered permeability compared to those found in patients with normal intestinal permeability [70].

The main consequences related to portal hypertension and BT are infections and hepatic encephalopathy (HE).

Bacterial infections are present in about 15–47% of patients with liver cirrhosis; amongst these, 70–80% are determined by Gram negative bacteria, even if the incidence of infection from Gram-positive bacteria has increased in recent years. Patients who develop an infection have a higher mortality compared with those without infection, and the two factors predictive of development of infections are the severity of liver disease and gastrointestinal bleeding [71,72]. The main infections are spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia, spontaneous pleural empyema, and the so-called spontaneous bacteremia. Patients with SBP have a higher prevalence of SIBO relative to those without SBP; conversely, patients with SIBO have a higher incidence of SBP compared to those who do not have a large bacterial overgrowth. These findings further stress the close relationship between intestinal bacteria and liver disease-related complications [73]. Cirrhosis is considered per se an independent risk factor for sepsis [74]: in fact, starting from a bacterial infection, the enhanced production of pro-inflammatory cytokines and other toxic metabolites can lead to the onset and propagation of a systemic inflammatory state. This state, in turn, may induce vascular and coagulative alterations until the development of systemic inflammatory response syndrome (SIRS). The vascular alterations of SIRS, added to those of cirrhosis, induce shock and intravascular coagulopathy until death [75].

Bacterial infections are also associated with upper gastrointestinal bleeding. The risk of bleeding in cirrhotics correlates to the degrees of portal hypertension, liver dysfunction and the size of varices. BT and LPS lead to priming of monomacrophages that release NO and TNFa; this, in turn, further increases the portal pressure, the impairment of liver function and of coagulation, increasing the risk of variceal bleeding [76].

HE is a complex neuropsychiatric syndrome, defined as “disturbance of the function of the central nervous system due to liver” [77]. Ammonia and other toxic substances derived from the gut, in the presence of portal and systemic shunts as well as of reduced liver clearance capability, represent the pathogenic mechanisms of HE [78].

3. Probiotics and liver diseases

3.1. Viral hepatitis

There are few major findings regarding the beneficial effect of probiotics in viral hepatitis. Chen et al. [79], evaluated the effect of lactitol, a prebiotic, that can increase the number of beneficial bacteria, in reducing plasma levels of endotoxin in a subset of patients with hepatitis C and B, compared to a control group. Lactitol treatment decreased endotoxemia through by an increase in *Bifidobacterium* and *Lactobacillus* and an inhibition of potentially pathogenic bacteria growth. Other studies are not reported in this review because they were performed in a small number of patients, without a control group or without the direct demonstration of changes in intestinal microflora.

3.2. Alcoholic hepatitis

Modulation of the intestinal flora to increase beneficial bacteria by suppressing the growth of Gram-negative bacteria, and to reduce the amount of endotoxin has been studied in alcohol-related diseases in both animal models and in humans.

In 1994, Nanji et al. [80], compared rats fed with ethanol to rats fed with ethanol and Lactobacilli GG. The authors measured plasma endotoxin and evaluated the severity of liver damage. In the group treated with *Lactobacillus* GG, there were no pathologic changes in the liver, and the endotoxin level was significantly lower than in the other group.

In 2009, Forsyth et al. studied a rat model of alcoholic steatohepatitis, demonstrated that alcohol + *Lactobacillus* GG-fed rats had less severe alcoholic steatohepatitis than alcohol-fed rats; in fact *Lactobacillus* GG reduced alcohol-induced gut leakiness, oxidative stress and inflammation in both intestine and liver [81]. A recent study [82] found a possible beneficial effect of association probiotics/prebiotics (*Lactobacillus* GG and oats) in a rat model of alcoholic steatohepatitis. In alcohol-fed rats, there was an “intestinal dysbiosis” that was not present in rats treated with probiotics or prebiotics. In an earlier study [83], the effect of synbiotics versus metronidazole on endotoxemia and liver damage in the course of experimental acute alcoholic pancreatitis was tested. The authors fed a first group of rats with a mixture of synbiotics (*Lactobacillus acidophilus*, *Lactobacillus helveticus* and *Bifidobacterium* in an enriched medium) and a second and a third group, respectively, with metronidazole and with a standard diet. Then they induced acute pancreatitis; rats pretreated with synbiotics were protected against endotoxin and related liver damage, whilst metronidazole did not produce beneficial effects.

Treatment with *Bifidobacteium bifidum* and *Lactobacillus plantarum* 8PA3 for 5 days was comparered with a standard therapy alone (abstinence plus vitamins) in 66 patients with alcoholic psychosis and liver damage [84]. Patients treated with probiotics had a restoration of the gut flora with an increased number of both bifidobacteria and lactobacilli, compared to controls. The authors concluded that short-term supplementation with probiotics is associated with greater improvement in alcohol-induced liver injury than standard therapy.

In patients with alcoholic cirrhosis, treatment with probiotics decreased Gram-negative gut organisms and restored the deranged neutrophil function. This effect was associated with a reduced production of pro-inflammatory cytokines [85].

Therefore, the effects of probiotic treatment in alcohol-related liver disease are more consistently documented that in viral hepatitis, even if no large clinical trials have been performed in humans.

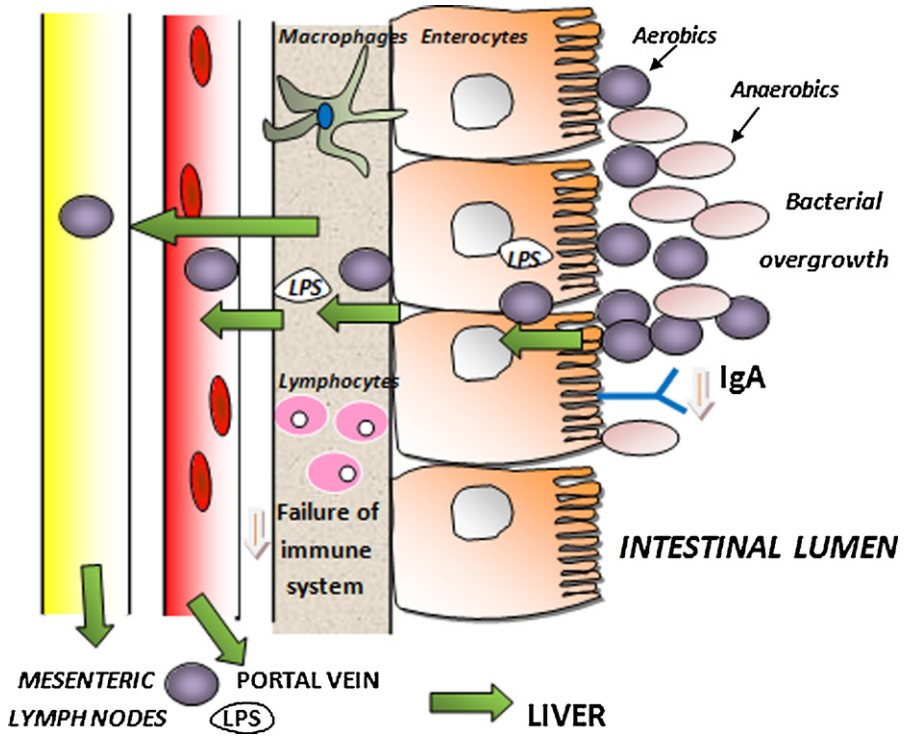

Fig. 3. Role of gut flora and other factors in progression of liver injury from steatosis to steatohepatitis and cirrhosis, and the role of probiotics. IBO: intestinal bowel overgrowth; LPS: lipopolysaccharide; TLR_4: toll like receptor 4; TGFβ: transforming growth factor beta.

3.3. Metabolic syndrome and liver steatosis

The use of probiotics in NASH is a recent addition in clinical research setting. The first study on animal model of NASH was that of Li et al. [86]. They found that VSL#3 (a mixture of probiotics) improved liver histology, reduced hepatic total fatty acid content, decreased serum ALT levels, and reduced the activity of proteins involved in regulating TNFα and insulin resistance.

In 2005, Chen et al. [87] showed the protective effect of selenium-enriched *Lactobacillus* on hepatic injury induced in mice by carbon tetrachloride (CCl_4). The effect was related to an enhancement of macrophage function and antioxidant enzyme activities, with a consequent reduction of the lipid peroxidation and the release of TNFα.

In mice with a high fat diet (HFD)-induced hepatic natural killer cell depletion, which in turn leads to insulin resistance and steatosis [88], probiotic treatment with VSL#3 improved steatosis, insulin resistance and inflammatory signalling. In a mouse model of NASH [89], the same treatment failed to prevent steatosis or inflammation but ameliorated liver fibrosis by decreasing expression of procollagen and matrix metalloproteinases (MMPs). In a third study [90], VSL#3 supplementation reduced the expression of lipid peroxidation markers, TNFα, iNOS, cyclooxygenase 2, and MMP in HFD rats (a NAFLD animal model) compared to rats fed with HFD without VSL#3 supplementation. In humans, VSL#3 ameliorated oxidative/nitrosative stress parameters in 22 patients with NAFLD and 20 patients with alcoholic liver cirrhosis, but no effects were observed in 36 patients with chronic hepatitis by HCV [91].

Fig. 3 summarizes the possible role of probiotics in NAFLD/NASH and metabolic syndrome.

Despite these encouraging data in animals and man, a recent Cochrane systematic review on the use of probiotics in patients with NAFLD/NASH concluded that the lack of randomized clinical trials makes it impossible to assess the effect probiotics and therefore neither supports nor refutes their use in clinical practise (verb)/practice (noun) [92].

3.4. Cirrhosis

The use of probiotics in patients with liver cirrhosis should be aimed at preserving the natural biological balance of the intestinal tract and modulating the growth of other groups of bacteria to stabilize the intestinal mucosal barrier, stimulate host resistance to infection, reduce the "negative" relationship between portal hypertension and both local and systemic hemodynamic alterations, and, finally, prevent and/or correct HE [93,94]. The bacterial species most used in studies have been *Lactobacilli* and *Bifidobacteria*, both anaerobic species; whilst the Gram-negative aerobic bacteria move easily through an intact epithelium, the anaerobic bacteria, which under normal conditions exceed aerobic flora in the gut, move with much more difficulty, and only when intestinal damage to the epithelium opens the way [95].

In an experimental model of pre-hepatic portal hypertension [96], bacteriotherapy with *Lactobacillus* could not drive changes in bacterial translocation because of the ineffectiveness in the modulation of bacterial flora. Indeed, bacterial translocation was not significantly different between the animals treated with probiotic (82%) and those treated with placebo (75%), either using *Lactobacillus acidophilus* or *Lactobacillus* GG. In a a rat model of experimental CCl_4-induced cirrhosis and ascites[97], *Lactobacillus* strain GG was unable to prevent both BT and infection of the ascitic fluid; however, cecal colonization was achieved in 90% of treated rats.

In the study by Chiva et al. [98], a combination of *Lactobacillus johnsonii* LA1 and antioxidants was administered in rats with CCl_4-induced cirrhosis to determine the effect on intestinal flora, endotoxemia, and BT. After 10 days of treatment, there was a decrease in intestinal enterobacteria and enterococci and in bacterial translocation compared to untreated control rats and there was a reduction in malonyldialdehyde (MDA) levels (an index of intestinal oxidative damage); however, in this study, the effectiveness alone of *Lactobacillus johnsonii* was not assessed, as the probiotic was not administered in the absence of antioxidants.

In clinical studies, the effectiveness of probiotics was rated in two areas: prevention of infections and improvement of liver function. Rayes et al., in a prospective randomized trial, enrolled patients following major abdominal surgery or liver transplantation; they evaluated the incidence of bacterial infections amongst patients receiving conventional parenteral or enteral nutrition compared to patients receiving enteral nutrition with fibre and *Lactobacillus plantarum* 299 or enteral nutrition with placebo. The incidence of bacterial infections was significantly lower in the fibre + probiotics group compared to the conventional nutrition group [99]. In a second prospective, randomized, double-blind trial undertaken in liver transplant recipients, the same authors demonstrated a decrease in infection rate after liver transplantation, using a combination of different lactic acid bacteria and fibre (symbiotic composition) in addition to antibiotic therapy; treatment with fibre only did not lead to a lower incidence of severe infections [100].

Two studies addressing liver function have been conducted. In the first, the authors identified an improvement and a reduction in Child-Pugh class in 50% of cases and an amelioration of endotoxemia [101]. In a second randomized controlled study, *Escherichia coli* Nissle was administered to a group of patients with liver cirrhosis. In the treated group, compared to a control untreated group, an improvement of endotoxemia and of liver function was found according to Child-Pugh score. This result was attributed to the restoration of normal bacterial flora in the gut, resulting in lower absorption of toxic metabolites and endotoxins in treated patients [102].

Two studies in the literature have addressed the effectiveness of probiotics in decreasing portal pressure and bleeding risk. In the first study, a group of patients was treated in two series with a probiotics combination (*Streptococcus thermophilus*, *Bifidobacteria*, *Lactobacillus acidophilus*, *L. plantarum*, *L. casei*, *L. delbrueckii bulgaricus*, *S. faecium*). Blood flow in the portal, splenic, and mesenteric veins was measured before and after therapy. At the end of the second period of treatment, an improvement in the hemodynamic parameters of portal circulation with a modification of microbiota was demonstrated [103]. In the second study [104], however, a VSL#3 probiotic used in patients with compensated or early decompensated cirrhosis resulted in no reduction in portal pressure, despite a reduction in plasma endotoxin.

The rationale for administration of probiotics in HE is based on the ability of probiotics to reduce the total amount of ammonia that reaches the portal system through various mechanisms [105]. In the literature, there are few studies addressing the role of probiotics in HE. Our group [106,107], compared the effects of *Enterococcus faecium* SF68 vs. lactulose on ammoniemia and clinical scores of HE. These randomized studies showed the ability of SF68 to yield results similar to lactulose during the treatment period and in particular the maintenance of the therapeutic effect reached even during the wash-out period only in the group treated with probiotics, suggesting the ability of SF68 to colonize the colon.

The studies of Liu et al. [101], Malaguarnera et al. [108], Bajaj et al. [109], and Dhiman and Chawla [110] have yielded results with synbiotics both in presence of overt HE, but also in minimal HE, as detected by psychometric evaluations.

Therefore, we can conclude that the studies on the use of probiotics in patients with liver cirrhosis are consistent, even if few probiotic preparations have been used.

4. Conclusions

Bacterial flora is a large component of our organism and the strong relationship between gut and liver should induce to study further the possible variations of the intestinal ecosystem both in the induction and progression of chronic liver diseases.

The role of probiotics in the context of liver disease remains controversial because the mechanisms responsible for their ability to restore the physiological bacterial flora and antagonize the effects of pathogens have yet to be identified. In our opinion, future studies should include an accurate evaluation of gut flora according to the current sophisticated microbiological methods, and a more accurate selection of potentially useful bacterial strains for the management of patients with chronic liver disease.

Conflicts of interest statement

Authors reported no biomedical financial interests or potential conflicts of interest.

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