

Changes of Intestinal Functions in Liver Cirrhosis

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Key Words

Small intestinal dysmotility · Small intestinal bacterial overgrowth · Intestinal hyperpermeability · Bacterial translocation · Endotoxemia · Liver cirrhosis

Abstract

Background: Understanding of the gut-liver axis is important for the up-to-date management of liver cirrhosis, and changes of intestinal functions form the core of this interesting research field. **Summary:** Most investigators noted small intestinal dysmotility in their patients with liver cirrhosis. Marked changes in the contraction pattern were observed in early manometric studies. The orocecal transit time, particularly small intestinal transit, has generally been reported to be prolonged, which has been demonstrated in multiple investigations to be related to the severity of the liver disease (e.g., Child-Pugh class), the presence of small intestinal bacterial overgrowth (SIBO) and hepatic encephalopathy (HE) as well as a history of spontaneous bacterial peritonitis. Bacteriologically proven SIBO in proximal jejunal aspiration

has been reported to be present in up to 59% of cirrhotic patients and is associated with systemic endotoxemia. Clinical and experimental studies suggest that delayed small bowel transit in liver cirrhosis may lead to SIBO, which could contribute to the symptoms of abdominal pain and diarrhea. In addition to autonomic neuropathy, metabolic derangements and diabetic state, SIBO itself may delay intestinal transit in cirrhotic patients. Several studies, both from the West and the East, have shown that the gut microbiota is altered in cirrhotic patients and particularly those with HE. Further, a quantitative change in *Bacteroides/Firmicutes* ratio, with a prevalence of potentially pathogenic bacteria (e.g., *Enterobacteriaceae*) and reduction in specific commensals (e.g., *Lachnospiraceae*), has been described. Structural and functional changes in the intestinal mucosa that contribute to increases in intestinal permeability for bacteria and their products have been observed in patients with liver cirrhosis, which is considered as an important pathogenic factor for several complications. The mechanism of intestinal barrier dysfunction in cirrhosis is multifactorial, including alcohol, portal hypertension (vascular congestion

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and dysregulation), endotoxemia, SIBO, local inflammation and, most likely, immunological factors and medications. **Key Messages:** This review summarizes major achievements regarding intestinal dysfunction in cirrhosis for future gastroenterology research. The question of whether this intestinal barrier dysfunction is accompanied and/or at least partly caused by structural and functional changes in the epithelial tight junction proteins is as yet unsolved. Development of new strategies to modulate gut-liver interaction is urgently needed.

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Introduction

The passage of viable bacteria from the intestinal lumen through the intestinal wall as well as to mesenteric lymph nodes and other sites, defined as bacterial translocation (BT), generally explains the cause of bacterial infections, which increase mortality 4-fold in patients with liver cirrhosis [1]. The concept of BT was later broadened to include microbial products and/or their fragments, such as endotoxin and bacterial DNA [1]. Because the gut barrier system of intestinal epithelial cells prevents the translocation of large amounts of bacteria and bacterial products, we should pay more attention to changes of intestinal functions for the management of liver cirrhosis. Small bowel dysmotility, small intestinal bacterial overgrowth (SIBO) and intestinal hyperpermeability are mutually related and finally lead to pathological increases in BT.

This review discusses intestinal dysfunction from various viewpoints. In addition, structural and functional changes to the gastrointestinal tract developing in liver cirrhosis are discussed. Specific guidelines on the topic do not exist, but the European Association has recently published a consensus statement on the diagnosis and treatment of bacterial infections in liver cirrhosis [2]. The final remark of the key points and outlook was that a development of new strategies to modulate gut-liver interaction is urgently needed.

Small Intestinal Dysmotility

We will first introduce Western studies, since almost all data concerning small intestinal dysmotility come from the Western world. Table 1 summarizes studies comparing gastrointestinal motility in patients with liver cirrhosis versus healthy controls. The methods of study-

ing intestinal motility are roughly divided into manometry and measurement of transit time. Since the first manometric motility study by Chesta et al. [3], various studies have shown small intestinal dysmotility in patients with liver cirrhosis [4]. Chesta et al. [3] investigated fasting proximal small intestinal motility in 16 cirrhotic patients and 8 healthy controls. Changes in intraluminal pressure were sensed by the external transducers connected to the perfused catheter in the small intestine. The authors analyzed the mean duration and characteristics of the migrating motor complex and found that cyclic activity – noted in all healthy controls – was absent in 2 cirrhotic patients showing a prolonged phase 2-like pattern. The duration of the cycles was significantly longer in the remaining 14 patients with cirrhosis compared with controls. Additionally, marked changes in the contraction pattern during phase 2, characterized by multiple clusters of contractions separated by quiescent periods, were noted in cirrhotic patients [3]. Madrid et al. [5] studied motility by means of perfused catheters and external transducers in 33 patients with liver cirrhosis and related the changes in the migrating motor complex to Child-Pugh classes. Absence of cycling activity was most frequently observed in Child-Pugh class C patients. In these advanced cirrhotics, increased frequencies and amplitudes of clustered contractions were noted compared to Child-Pugh class A patients. The authors thought these findings might be related to the delayed transit time observed in liver cirrhosis [5]. Gunnarsdottir et al. [6] showed with their antroduodenal pressure recordings that long clusters were more common in cirrhotics with portal hypertension than in healthy subjects. Combined with their results from bacterial cultures of jejunal aspirates, they speculated that portal hypertension per se might be significantly related to the small intestinal abnormalities observed in patients with liver cirrhosis.

Van Thiel et al. [7] showed that the orocecal transit time (OCTT) of a lactulose load was longer in cirrhotics with hepatic encephalopathy (HE) and increased as a function of HE grade. The OCTT as measured with a scintigraphic technique was also shown to be prolonged in end-stage cirrhotic patients awaiting liver transplantation [8]. Kalaitzakis et al. [9] showed by radiologic procedure that 38% of patients with cirrhosis had prolonged small intestinal transit, and that prolonged small intestinal transit was related to diarrhea and abdominal pain. A recent study utilizing a wireless motility capsule (SmartPill) [10] also revealed that decompensated cirrhotics have slower intestinal transit times than compensated cirrhotics and healthy controls.

Table 1. Studies comparing gastrointestinal motility in patients with liver cirrhosis versus healthy controls

Authors	Country	Cirrhotics, n	Healthy controls, n	Methods applied	Main results
Chesta et al. [3], 1993	Chile (W)	16	8	Manometry	Marked changes in the contraction pattern during phase 2 in cirrhosis
Gupta et al. [4], 2010	India (E)	102 (26 with cirrhosis with SIBO, 76 with cirrhosis without SIBO)	–	OCTT with the lactulose breath test	OCTT was significantly prolonged in cirrhotics with SIBO compared with those without SIBO
Madrid et al. [5], 1997	Chile (W)	33 (Child-Pugh A 8, B 12, C 13)	–	Manometry	Clustered contractions and the frequency and amplitude of contractions were increased from Child-Pugh class A to class C
Gunnarsdottir et al. [6], 2003	Sweden (W)	24 (12 with portal hypertension, 12 without portal hypertension)	32	Manometry with antroduodenal pressure recordings	Long clusters were more common in cirrhotics with portal hypertension than in healthy subjects
Van Thiel et al. [7], 1994	USA (W)	30 (10 without HE, 10 with subclinical HE, 10 with grade 1 HE)	–	OCTT by the lactulose load	OCTT was longer in cirrhotics with HE and increased as a function of the hepatic encephalopathy grade
Galati et al. [8], 1997	USA (W)	10 (advanced cirrhosis undergoing evaluation for orthotopic liver transplantation)	10	OCTT with a scintigraphic technique	OCTT was longer in end-stage cirrhotic patients awaiting liver transplantation
Kalaitzakis et al. [9], 2009	Denmark (W)	42 Child-Pugh A (24), B (15), C (3)	83	Small bowel transit with the radiologic procedure	38% of cirrhotics had prolonged small bowel transit, and that prolonged small bowel transit was related to diarrhea and abdominal pain
Chander Roland et al. [10], 2013	USA (W)	20 (10 compensated, 10 decompensated)	(Historical healthy controls)	A wireless motility capsule (SmartPill)	Decompensated cirrhotics had slower intestinal transit times as compared with compensated cirrhotics and healthy controls
Sadik et al. [11], 2003	Sweden (W)	16 (10 male, 6 female)	83	Gastrointestinal transit with a newly developed radiological procedure	Small bowel residence time was significantly longer in male patients with alcoholic cirrhosis as compared to male patients with other causes of portal hypertension
Chen et al. [12], 2000	Taiwan (E)	23 with HBV-related liver cirrhosis, 26 with chronic hepatitis B, 45 asymptomatic HBV carriers	45	OCTT with the hydrogen breath test	OCTT was delayed in patients with HBV-related liver cirrhosis but not in those with chronic hepatitis B or in asymptomatic HBV carriers
Chen et al. [13], 2002	Taiwan (E)	40 with HCC, 20 with liver cirrhosis	40	OCTT with the hydrogen breath test	HCC patients mostly with viral liver cirrhosis showed delayed gastrointestinal transit like patients with viral cirrhosis

Table 1 (continued)

Authors	Country	Cirrhotics, n	Healthy controls, n	Methods applied	Main results
Chang et al. [14], 1998	Taiwan (E)	40 (20 with a history of SBP, 20 without a history of SBP)	–	Manometry with a 3-channel solid-state manometric catheter	Small intestinal motility dysfunction was more severe in cirrhotic patients with a history of SBP
Nagasako et al. [15], 2009	Brazil (W)	32 patients with nonalcoholic cirrhosis (Child-Pugh A, B)	8	OCTT with the lactulose hydrogen breath test	OCTT values were significantly higher in Child-Pugh class B patients than in controls
Madsen et al. [27], 2000	Denmark (W)	8 (postsinusoidal hepatic pressure gradient ≥ 13 mm Hg)	8	Small intestinal transit, colonic transit rates with the gamma camera technique	No difference in small intestinal mean transit time of liquid and solid markers between patients and controls; the patients had a faster colonic transit
Chacko [28], 1997	India (E)	10 (decompensated nonalcoholic male cirrhotics)	10 (male controls)	Total and segmental colonic transit time with a radiopaque marker method	Total and left colonic transit times were shorter in cirrhotics as compared to healthy controls
Karlsen et al. [29], 2012	Denmark (W)	15 (with portal hypertension; Child-Pugh A 8, B 6, C 1)	18	Small intestinal motility with a magnet-based motility tracking system; total gastrointestinal transit time by radiopaque markers and abdominal radiographs	Cirrhotics with portal hypertension displayed a faster-than-normal transit through the proximal small intestine
Sato et al. [18], 2012	Japan (E)	30 (Child-Pugh A 14, B 11, C 5)	17	Electrogastrography and ^{13}C octanoic acid breath test	Half-time of gastric emptying was significantly increased in cirrhotics with PHG; the EGG frequency increased at baseline in all cirrhotics with PHG, particularly in those with severe PHG (more than in those with mild PHG)
Gumurdulu et al. [19], 2003	Turkey (E)	24 (Child-Pugh A 8, B 8, C 8)	25	Gastric scintigraphy	Prolonged gastric emptying half-time in cirrhotic Child-Pugh class B/C patients and/or autonomic dysfunction (being significantly improved with cisapride)
Ishizu et al. [21], 2002	Japan (E)	25	18	Gastric scintigraphy	Prolonged gastric emptying half-time
Verne et al. [24], 2004	USA (W)	20 (Child-Pugh A 5, B 8, C 7)	10 (HCV without cirrhosis)	Gastric scintigraphy	Mean percentage of gastral retention after 100 min was significantly higher in cirrhotics
Charneau et al. [25], 1995	France (W)	18 (GAVE 8, no GAVE 10)	8	Ultrasound	Antral area half-time was increased and the antral area postprandially was reduced in cirrhotics with GAVE as compared to other groups

Table 1 (continued)

Authors	Country	Cirrhotics, n	Healthy controls, n	Methods applied	Main results
Miyajima et al. [20], 2001	Japan (E)	Child-Pugh A 7, B/C 22	20	Electrogastrography	Gastric dysmotility, particularly postprandially (not basal) in Child-Pugh class B/C patients
Kalaitzakis et al. [9], 2009	Denmark (W)	42 (Child-Pugh A 24, B 15, C 3)	10	Radiopaque markers	24% of cirrhotic patients had delayed half gastric emptying time (correlated with postprandial fullness and levels of glucose, insulin and ghrelin)
Isobe et al. [17], 1994	Japan (E)	20	10	Gastric scintigraphy	Prolonged gastric emptying half-time correlated with gastrointestinal symptom score
Balan et al. [22], 1996	UK (W)	57 (Child-Pugh A 47, B 10)	16	Gastric scintigraphy	No difference in gastric emptying time
Pimpo et al. [23], 1996	Italy (W)	10	12	Ultrasound	Delayed gastric emptying in cirrhotics, which was ameliorated with cisapride

Four studies [4, 5, 7, 14] subdivided cirrhotic patients based on SIBO, Child-Pugh classes, HE and history of SBP and compared them. E = East; W = West; HCC = hepatocellular carcinoma; PHG = portal hypertensive gastropathy; GAVE = gastric antral vascular ectasia.

Sadik et al. [11] found that the small bowel residence time was significantly longer in male patients with alcoholic cirrhosis as compared to male patients with other causes of portal hypertension, while that in female patients was not different from that in healthy subjects. These findings suggest that the etiology of the liver disease and gender may influence transit in patients with portal hypertension [11].

Studies from Asia reported data on nonalcoholic cirrhosis. Using a noninvasive hydrogen breath test, Chen et al. [12] from Taiwan reported that the OCTT was delayed in patients with hepatitis B virus (HBV)-related liver cirrhosis but not in those with chronic hepatitis B or in asymptomatic HBV carriers. They further reported that hepatocellular carcinoma patients mostly with viral liver cirrhosis showed delayed gastrointestinal transit like patients with viral cirrhosis [13]. Chang et al. [14] showed that small intestinal motility dysfunction was more severe in cirrhotic patients with a history of spontaneous bacterial peritonitis (SBP). There is another study from Latin America [15] that reports delayed OCTT in Brazilian patients with nonalcoholic cirrhosis of Child-Pugh class B. The potential primary role of prolonged small intestinal transit as for BT in patients with cirrhosis can be extrapolated from

a pilot trial in the UK showing that it precedes the appearance of bacterial DNA in serum and ascites [16].

However, in liver cirrhosis not only the small intestine is affected by dysmotility but also the stomach. This deserves mentioning here, since gastric motility is physiologically closely linked to small and large intestinal motility. A significantly prolonged gastric emptying time has been reported in cirrhotic patients as compared to healthy controls in multiple independent trials from the East [17–21] and West [9, 22–25]. Delayed gastric emptying with enhanced gastric accommodation and prolonged small intestinal transit time appear to correlate with gastrointestinal symptoms (early satiety, postprandial fullness, nausea, etc.) as well as with postprandial hyperglycemia, hyperinsulinemia and hypoghrelinemia [9, 26]. These alterations may be mediated at least in part by autonomic dysfunction [24].

Although most studies have reported prolonged gastric and small intestinal transit times (as stated above), there still remain contradictory results. By means of a gamma camera, Madsen et al. [27] observed no difference in small intestinal mean transit time of liquid and solid markers between patients with well-characterized portal hypertension and healthy controls, although the patients

had a faster colonic transit. By use of a radio-opaque marker method, Chacko [28] reported from India that total and left colonic transit times were shorter in cirrhotics as compared to healthy controls and considered accelerated colonic transit as a possible pathogenetic factor for diarrhea in liver cirrhosis. Using a magnet-based motility tracking system, Karlsen et al. [29] recently reported that patients with liver cirrhosis and portal hypertension displayed faster-than-normal transit through the proximal small intestine. Finally, also with regard to gastric emptying, Balan et al. [22] did not observe any significant difference between cirrhotic patients and healthy controls. Although the reason for these discrepancies is unknown, the differences in methodology and subjects (social environment, race, disease severity, presence/absence of SIBO, etc.) may explain this.

Small Intestinal Bacterial Overgrowth

SIBO is a condition in which colonic bacteria translocate into the small bowel due to impaired microvillus function, which causes a breakdown in intestinal motility and gut homeostasis [30, 31]. In normal individuals, intestinal peristalsis, gastric acid, biliopancreatic juice and mucosal immunity (e.g., secretion of antimicrobial peptides) prevent the development of SIBO. Abnormalities in one or more of the above factors can result in SIBO [4]. SIBO, defined as a total of $\geq 10^5$ colony-forming units per milliliter of proximal jejunal aspiration, has been reported to be present in up to 59% of cirrhotic patients and is associated with systemic endotoxemia [32].

SIBO was also determined by the breath hydrogen test. Both Western [33] and Eastern investigations [14] reported that SIBO as diagnosed by this method is common in cirrhotics, especially in those with ascites and advanced liver dysfunction and in those with a history of SBP. On the other hand, in a study that estimated SIBO by more reliable quantitative cultures of jejunal aspirates, the occurrence of SBP did not correlate with the presence of SIBO [34].

Small bowel manometry disturbances and delayed gut transit may be associated with the development of SIBO [35]. The OCTT and small bowel residence time were significantly longer in patients with SIBO than in patients without bacterial overgrowth [4, 11]. Pardo et al. [36] reported that acceleration of orocecal transit by cisapride is associated with abolishment of bacterial overgrowth in 4 out of 5 cirrhotic patients with bacterial overgrowth. The authors also demonstrated that cisapride administration

to cirrhotic rats resulted in a reduction of the intestinal bacterial overgrowth, which was associated with a marked decrease in BT [36]. It is thus possible that delayed small intestinal transit in liver cirrhosis may lead to the development of SIBO, which could contribute to the symptoms of abdominal pain and diarrhea [35].

The exact etiology of delayed intestinal transit in patients with liver cirrhosis is largely unknown, but it is most likely multifactorial [4]. It could be due to complication of autonomic neuropathy, metabolic derangements and diabetic state in cirrhotic patients. In addition, SIBO itself may lead to delayed intestinal transit in patients with cirrhosis [4]. Antibiotic therapy has been shown to reduce the OCTT in cirrhotics, which makes it likely that bacterial overgrowth per se alters small intestinal motility [7].

Overall, the microbiota, as a 'new and so far underappreciated organ', exerts a wide array of physiological functions such as salvaging energy, providing vitamins, limiting access for pathogens and shaping immune function [37]. Several studies both from the West and the East show that the gut microbiota is altered in cirrhotic patients and particularly in those with HE [38]. Culture-independent techniques such as pyrosequencing analyses of fecal contents could demonstrate reductions in microbial diversity and distinct dysbiosis in both animal models and human cirrhosis [14, 39]. More specifically, a quantitative change in the *Bacteroides/Firmicutes* ratio, with a prevalence of potentially pathogenic bacteria (e.g., *Enterobacteriaceae*) [39, 40] and reduction of specific commensals (e.g., *Lachnospiraceae*) [40], has been described. In a report from China, two thirds of the cases of cirrhosis were related to HBV, while 52% of the cirrhotics in a report from the USA were alcoholic. Liu et al. [41] from China reported results on patients with cirrhosis mostly (70–80%) related to HBV or HCV and found a significant fecal overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcus* spp. in the gut microbiota of cirrhotics with minimal HE. Another investigation from China observed a majority of patient-enriched species to be of buccal origin, suggesting an invasion of the gut from the mouth in liver cirrhosis [42]. Almost 50% of the enteral consortia detectable in cirrhotics belong to the oropharyngeal inhabitants – as compared to their near absence in healthy individuals. This underlines the concept of deficient intestinal antimicrobial capacity in cirrhosis (see below). The abovementioned study from the USA [40] has shown that patients with cirrhosis and HE had higher concentrations of *Enterobacteriaceae* and *Alcaligenaceae* than control subjects and cirrhotic pa-

tients without HE [38]. In this regard, another investigation from the USA highlights the explicit clinical relevance of the mucosa-associated flora in patients with HE [43]. There was no difference in stool microbiota between patients with and those without HE, but the mucosal microbiome was different, with lower *Roseburia* and higher *Enterococcus*, *Veillonella*, *Megasphaera* and *Burkholderia* abundance in HE. Most importantly, the sigmoid mucosal microbiome differs significantly from the stool microbiome in cirrhosis. In other words, feces are most likely not the optimal target compartment in terms of immunological and metabolic impact and, hence, clinical relevance. This can be attributed at least in part to the completely different environment in mucus as compared to the intestinal lumen, explaining vast differences in bacterial proliferation and resource utilization [44]. Dietary habits, by increasing the percentage of intestinal Gram-negative endotoxin producers, may accelerate liver fibrogenesis, introducing dysbiosis as a cofactor contributing to chronic liver injury in nonalcoholic fatty liver disease [45]. However, this is beyond the scope of this review.

Intestinal Hyperpermeability

Transmucosal passage of bacteria across the intestine is the essential step for BT [46]. The gut epithelium plays an important role in immune homeostasis in the gut as the first barrier against BT [47, 48]. Because the gut barrier system of intestinal epithelial cells prevents the translocation of large amounts of bacteria and bacterial products, a very small amount of them can reach the liver in a healthy state [49]. The intestinal barrier is formed mainly by intestinal epithelial cells and their mucinous components [34]. In addition, intercellular junctions such as tight junctions and gap junctions allow a selective passage of substances [34]. Structural and functional changes in the intestinal mucosa that increase the intestinal permeability of bacteria and their products are frequently observed in patients with liver cirrhosis [34]. Portal hypertensive gastro- and duodenopathy is defined by enlarged mucosal and submucosal vessels with little or no inflammatory infiltrate or epithelial erosion [50]. This is associated with increased susceptibility to injury from noxious factors reflected in an increased prevalence of peptic ulcer in cirrhotic patients [51]. Factors mediating mucosal damage and impairing the mucosal healing response to injury in advanced cirrhosis may include a reduction of potential differences in gastric mucosa [52], impairment of bicarbonate secretion [53, 54], impairment of gastric

oxygenation [55], suppression of endogenous prostaglandin production and excessive NO production [56–58] as well as increased oxidative stress due to reduced levels of glutathione peroxidase, superoxide dismutase and catalase [59]. Endoscopic features of portal hypertensive duodenopathy are found in 8–50% of cirrhotic patients with portal hypertension, but histopathological changes are seen in many more cases, reaching 85% of assessed cirrhotic patients [60, 61].

In addition to the vascular changes stated above, also nonvascular changes such as increased apoptosis, fibromuscular proliferation, increases in intraepithelial lymphocytes and shortened and atrophic villi with a decreased villous-crypt ratio have been reported [61, 62]. Interestingly, some of these changes correlated closely with changes to brush border enzymes as well as cell and membrane enzymes [63]. Moreover, due to the introduction of capsule endoscopy, data on mucosal alterations in the whole small intestine reflecting portal hypertensive enteropathy in cirrhotic patients are accumulating. These changes include inflammation-like abnormalities (edema, erythema, granularity and friability) as well as vascular lesions [64]. In fact, portal hypertensive enteropathy has been reported to be detected in up to 63% of the capsule endoscopies performed on cirrhotic patients with chronic anemia and a history of variceal bleed [65]. The macroscopic impression of edema is mediated most likely by a rise in interstitial hydration due to marked increases in intestinal capillary filtration caused by portal hypertension. In fact, it has been proposed that in case of chronic severe portal hypertension, the intestinal interstitial fluid content may be increased by up to 40% [66]. Intestinal barrier dysfunction has also been considered to be an important pathogenetic factor for several complications of liver cirrhosis [35]. Portal hypertension, alterations in the intestinal microbiota, inflammation and oxidative stress can affect the barrier function of both the small and the large intestine and may contribute to the development of complications [67].

There has been a long-standing debate about the role of increased intestinal permeability in patients with cirrhosis [68]. Some authors have shown an association between increased intestinal permeability and severity of liver cirrhosis as assessed by the Child-Pugh classification [68–70], but others have failed to reproduce these results [71–73]. Increased permeability on hospital admission has also been related to some complications of liver cirrhosis [67], although the published studies are not always unanimous [74]. In an Italian study, intestinal hyperpermeability has been shown to be more common in patients

with a history of SBP [68]; in a Korean study, it was considered to be a predictor of bacterial infections in cirrhosis [75]. Four studies, 3 from the Western world (Spain, USA and Italy) and 1 from China [68, 70, 76, 77], reported a significantly higher intestinal permeability in cirrhotic patients with ascites, although other studies did not observe a significant difference [67, 69, 73, 78–80]. Contrasting results have been reported on the association between intestinal permeability and HE as well [67].

Methodological problems should be taken into account when interpreting these conflicting results [76, 81]. Some authors used sugars [69, 70, 82], whereas others used isotope probes [68, 71–73]; the latter are considered to be the gold standard, since these probes are not synthesized or digested in the human body [68]. However, an assessment of mucosal intestinal permeability by urinary excretion of orally administered, nonmetabolizable sugars gave us some information with regard to discrimination between transcellular and paracellular fluxes [83].

The probes appear to traverse the epithelium in one of three ways: paracellular, transcellular aqueous or transcellular lipid [84]. Villous tight junctions, reflecting the transcellular pathway, are more accessible to luminal compounds and more selective for smaller compounds than are crypt tight junctions [84]. Monosaccharides, such as mannitol, are absorbed through this transcellular pathway and reflect the extent of absorption of small molecules. Disaccharides, such as lactulose, are absorbed through the paracellular junction complex (the tight junctions) and extrusion zones of the intervillous spaces, which corresponds to the permeability of larger molecules [82, 85]. Mannitol absorption as assessed by urinary excretion can be considered as an indicator of the mucosal absorptive area, and lactulose absorption as a measure of the integrity of the intestinal mucosal tight junctions [85, 86]. The problem of using a single test substance is that premucosal (i.e., gastric emptying, bacterial degradation) and postmucosal (i.e., renal disease, volume of distribution) factors may affect urinary recovery of the test substance [84]. The urinary ratio of two probes has been used as a more accurate indicator of intestinal permeability, because the premucosal and postmucosal factors should influence the probes equally, and, therefore, the urinary excretion ratio should not be affected [84, 87, 88].

The lactulose/mannitol ratio (LMR) thus comprises an index to appraise intestinal permeability, and its increase has been used as a marker of hyperpermeability [89]; in most studies, this ratio has been reported to be elevated in patients with liver cirrhosis [67] and to be markedly elevated at an advanced stage [69, 70]. Alcoholics with

liver disease also had marked and statistically significant increases in lactulose excretion in addition to an increased LMR [89]. Pascual et al. [70] found a significantly higher lactulose excretion with a comparable mannitol excretion in patients with liver cirrhosis as compared to controls. Pijls et al. [90] showed that small intestinal permeability as determined by the lactulose/rhamnose ratio is not altered, whereas large intestinal permeability is increased in patients with stable compensated cirrhosis of mixed etiology, although the authors could not deny a tendency of increased small intestinal permeability in a small group of patients with alcoholic cirrhosis. As a larger number and diversity of bacteria are present in the large intestine, an increased permeability of this site may enhance the risk of BT [90].

Parlesak et al. [78] reported that the permeability of polyethylene glycol (PEG) with high molecular masses (PEG 1,500 and 4,000) was increased in patients with alcoholic liver diseases including cirrhosis. They discussed PEG as an appropriate probe for the assessment of gut-derived endotoxin translocation on the basis of its homogeneous chemical properties, appropriately adaptable molecular mass and linear, chain-like shape mimicking the structure of endotoxin [78]. Lee et al. [77] from China reported that intestinal permeability as determined by PEG 400 and 3,500 was significantly elevated in cirrhotics with ascites. They also reported a significantly higher permeability in patients with Child-Pugh class C versus those with Child-Pugh class A and B cirrhosis [77]. Such findings were also reported in an Italian study by Scarpellini et al. [68], who used isotope probe ⁵¹Cr-EDTA for permeability measurement. Kim et al. [75] from Korea reported that the intestinal permeability index, the percentage of permeability of PEG 3,350 to that of PEG 400, was increased on admission for active gastrointestinal bleeding in patients with liver cirrhosis and infections.

Potential Mechanisms of Intestinal Barrier Dysfunction in Cirrhosis

Figure 1 summarizes the possible mechanisms and individual influencing parameters on intestinal dysfunction in liver cirrhosis. These include not only alcohol use, portal hypertension, endotoxemia and bacterial overgrowth, but also deficits in bile and gastrointestinal secretions (e.g., antimicrobial peptides) as well as alterations in enteric innervation. In alcoholic liver cirrhosis, alcohol and its metabolites, acetaldehyde and fatty acid ethyl esters, may contribute to the disruption of tight junctions, main-

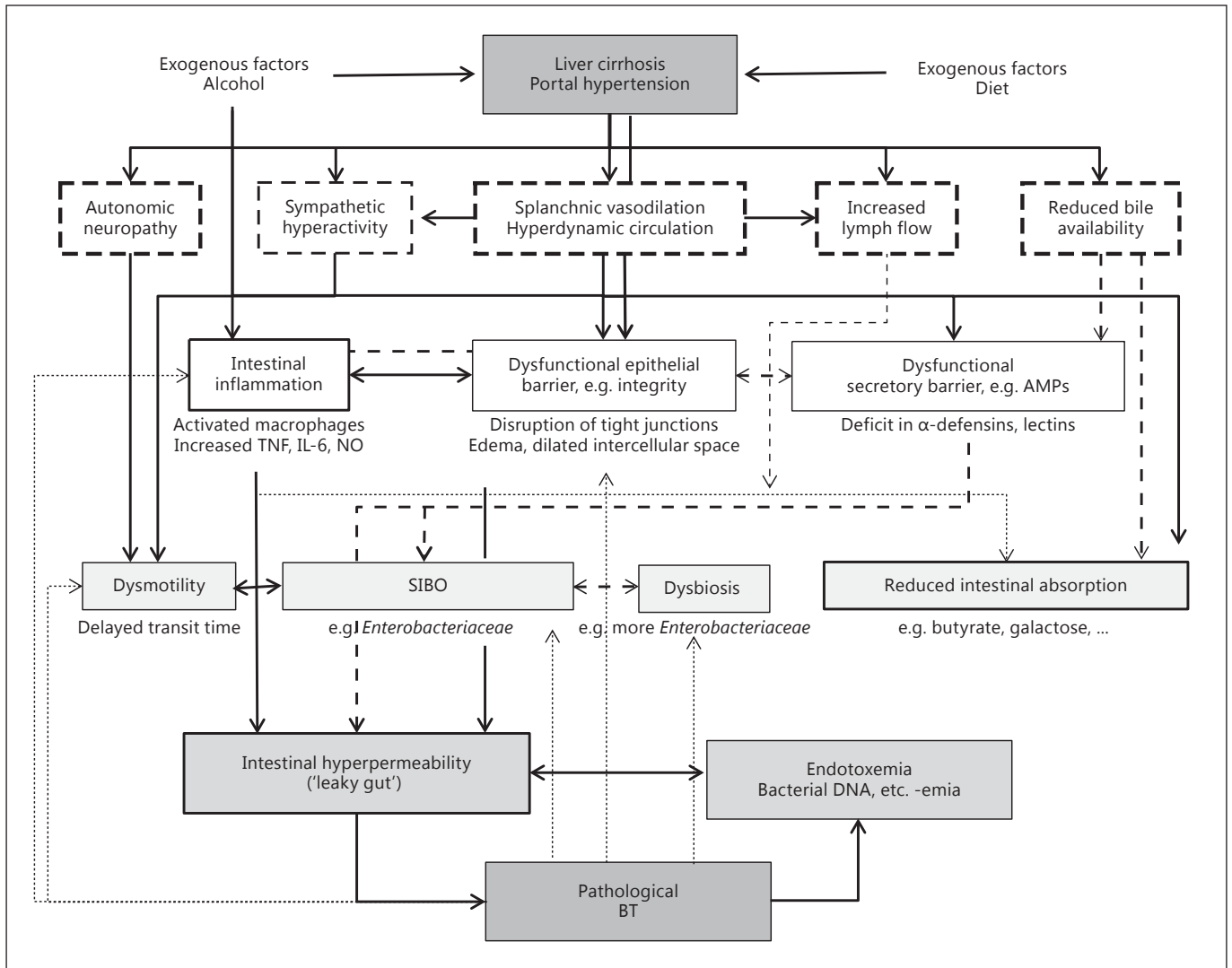


Fig. 1. Mechanism of intestinal dysfunction in liver cirrhosis. Small intestinal dysmotility, SIBO and intestinal hyperpermeability are mutually related and finally lead to BT. Dashed arrows: not clearly proven/hypothetical.

ly through nitric oxide-mediated oxidative tissue damage and alterations in the cytoskeleton, but also through direct cell damage [35, 91, 92]. Recently reported genetic mechanisms of alcohol-induced intestinal inflammation and hyperpermeability were summarized elsewhere [93]. Portal hypertension itself may affect the integrity of the intestinal barrier by causing edema in the gut wall with dilatation of the intercellular spaces [35, 94]. Fujii et al. [95] from Japan reported that the lactulose/L-rhamnose excretion ratio increased in cirrhotics, especially in those with large colonic vascular ectasia or rectal varices, and they thought that increases in lactulose intestinal permeability

in patients with liver cirrhosis reflect the effects of portal hypertension extending to the lower digestive tract. Xu et al. [96] from China reported that intestinal permeability as evaluated by LMR and portal pressure decreased significantly 2 weeks after transjugular intrahepatic portosystemic shunt (TIPS) insertion. Consistent with these findings, Reiberger et al. [97] recently reported that portal pressure (i.e., hepatic venous pressure gradient) was correlated to intestinal permeability in cirrhotics with portal hypertension (hepatic venous pressure gradient >12 mm Hg). Furthermore, qualitative or quantitative changes in the bacterial flora of the gut – and, in particular, SIBO –

may lead to disruption of the intestinal barrier [98, 99], thereby increasing permeability.

Recently, Assimakopoulos et al. [100] showed that human liver cirrhosis induces significant alterations in tight junctions of enterocytes. They found a significantly reduced expression of the tight junction proteins (TJPs) occludin and claudin-1 in duodenal biopsies of a total group of 24 patients [alcohol: n = 13; viral: n = 9; nonalcoholic steatohepatitis (NASH): n = 2] compared with 12 healthy controls, and this correlated with Child-Pugh score, the grade of esophageal varices and endotoxemia. In addition, the cirrhotic patients with ascites showed a significantly reduced expression of occludin and claudin-1 compared with those without ascites [100]. In rats with NASH-like liver fibrosis induced by a CDAA (choline-deficient L-amino acid-defined) diet, we observed increased intestinal permeability and reduced expression of the TJPs ZO-1 and claudin-4 in the intestine compared with control rats fed choline-supplemented amino acid [101]. Oral administration of antibiotics, polymyxins and neomycins improved intestinal permeability and enhanced TJP expression [101]. On the other hand, Du Plessis et al. [102] reported that the structural TJPs ZO-1, occludin and claudin-1 as well as the gap junction protein connexin 43 were not decreased at the mRNA and protein levels in cases of cirrhosis related to NASH and alcoholic steatohepatitis. In that study, electron microscopy further revealed an intact epithelial barrier in patients with decompensated cirrhosis, suggesting that the epithelial barrier is functionally altered but structurally normal in cirrhosis. General conclusions on specific TJPs or subgroups of patients cannot be drawn due to methodological differences and the relatively small number of studies/patients [67]. Intestinal mucosal mitotic counts were significantly lower in patients with compensated and decompensated cirrhosis as compared to controls, while a trend towards increased apoptosis was recorded. The mitosis/apoptosis ratio was significantly reduced in Child-Pugh class B and C cases as compared to controls [103].

Bile inhibits SIBO, has a trophic effect on the intestinal mucosa, decreases epithelial internalization of enteric bacteria, exerts detergent actions with anti-adherence effects, neutralizes endotoxins and exerts potent effects on immune cells in gut-associated lymphatic tissue [104]. In cirrhosis, marked decreases in intestinal intraluminal concentrations of bile acids have been ascribed to decreased secretion and increased deconjugation by enteric bacteria [105]. In experimental models, the absence of bile in the intestine has been shown to facilitate BT [106] and to enhance susceptibility to further translocation in

response to endotoxins [107]. Most recently, the transcription factor farnesoid X receptor (FXR), which is the nuclear receptor for conjugated bile acids, has gained much attention. FXR plays a crucial role in preserving intestinal epithelial integrity and protection from inflammation presumably by repression of NF- κ B signaling and modulation of antimicrobial peptide release [108, 109]. The commercially available FXR agonist obeticholic acid has recently been reported to improve intestinal antibacterial defense and permeability as well as to reduce gut BT in CCl₄-induced [110] and bile-duct-ligated cirrhotic rodents [111]. In addition, in two different cirrhotic animal models obeticholic acid has shown clear portal hypotensive action mediated by lowering intrahepatic vascular resistance [111, 112]. Finally, early human data using obeticholic acid have shown promising results with improvement of histological activity and even a reduction of fibrosis in various liver diseases, underscoring the gut-liver axis [113]. Principally, bile acids can be considered as a 'language' with which the liver and gut are communicating. In fact, the gut-liver axis works as cross talk in both directions, for which bile acids are the best example.

Changes in gastrointestinal secretions have not been studied extensively in cirrhosis. Nonetheless, hypo- and achlorhydria have been observed in cirrhotics independently of acid-suppressive medication, resulting in a higher pH in the small intestine and promoting SIBO [114]. Moreover, decreased fecal IgA concentrations as well as decreased secretion of mucosal IgA into the jejunum have been reported [115, 116], suggesting a potential relationship between IgA and BT. As for the secretion and function of antimicrobial peptides, compromised Paneth cell antimicrobial host defense via reduced α -cryptdin secretion and concordantly diminished intestinal tissue antimicrobial activity have been shown to predispose to BT in experimental cirrhosis [117]. Also the expression of intestinal antimicrobial lectins (Reg3b and Reg3g) has been shown to be reduced in ethanol-induced chronic liver disease, with the lowest levels being observed in the proximal small intestine, where bacterial overgrowth was most pronounced [118]. These data were also confirmed in humans, as patients with chronic alcohol intake have down-regulated Reg3b and Reg3g in the jejunum. Therefore, a deficiency in various AMPs (α -defensins, Reg3 proteins) likely leads to decreased mucosal killing activity, resulting in a shift of the bacterial composition facilitating bacterial overgrowth and increases in BT in cirrhosis.

Enteric innervation not only regulates motility but likewise affects gut-associated lymphatic tissue and modulates intestinal secretions. Intestinal autonomic dys-

function plus parasympathetic hypofunction and sympathetic hyperactivity are observed in advanced stages of cirrhosis [20, 119, 120]. Splanchnic sympathectomy has been shown to prevent endogenous BT [121]. Besides the improved bacterial phagocytosis observed after sympathectomy, additional proposed beneficial effects are an accelerated intestinal transit time, prevention of Gram-negative bacterial overgrowth and improvement in gastrointestinal permeability. Propranolol has likewise been used and found to lower rates of BT in experimental cirrhosis [122]. In fact, treatment with nonselective beta blockers has been proposed to reduce intestinal permeability as well as BT in patients with cirrhosis [97, 123].

Bacterial Translocation

BT or microbial translocation is defined as the migration of viable microorganisms or bacterial products (i.e., bacterial lipopolysaccharide, peptidoglycan and lipopeptides) from the intestinal lumen to the mesenteric lymph nodes and other extraintestinal sites [124]. Passage of viable bacteria from the intestinal lumen through the intestinal wall and their translocation to mesenteric lymph nodes and other sites is the accepted pathogenic mechanism for the development of spontaneous infections such as SBP or bacteremia in liver cirrhosis [34]. Bacterial products, such as endotoxin, or bacterial DNA can translocate to extraintestinal sites and promote an immunological response similar to that produced by viable bacteria. Pathological BT is a contributing factor in the development of complications in cirrhosis, not only in infections but also by exerting a profound inflammatory state and exacerbating the hemodynamic derangement [34, 67]. Du Plessis et al. [102] showed the presence of activated CD14(+)Trem-1(+) iNOS(+) intestinal macrophages releasing IL-6 and NO as well as increased intestinal permeability in cirrhotics related to NASH and alcoholic steatohepatitis, suggesting that these cells may produce factors capable of enhancing permeability by bacterial products. In our rat model of NASH induced by a CDAA diet, significantly increased immunostaining for TNF- α , TLR4 and macrophage/dendritic cells was demonstrated in the small intestinal submucosa, indicating the activation of innate immune response [125]. The synthesis of cytokines, particularly TNF- α , interleukins and NO, exacerbates oxidative damage to the intestinal mucosa [126], which in turn increases intestinal permeability, probably favoring BT [34]. The inflammatory response induced by BT also acts on the permeability of the

intestinal barrier, favoring translocation of bacteria and microbial products, thus creating a feedback in which BT itself perpetuates the pathogenic mechanisms that cause it [34].

Sanchez et al. [127] reported that an increase in intestinal aerobic bacteria in experimental cirrhosis is associated with translocation and is supposed to play an important role in the development of BT. Gut flora imbalances and higher levels of *Enterobacteriaceae* resulted in significant changes in BT and liver function in cirrhotic rats [128]. Further, SIBO in cirrhosis showed a high correlation with the presence of bacterial DNA fragments in peripheral blood, suggesting that SIBO could be a major risk factor for BT, especially in ascitic patients [129].

Intestinal Absorption and Nutrition in Cirrhosis

Various pathophysiological processes affect small intestinal function in cirrhosis, including increased small intestinal water secretion, enhanced lymph flow, malabsorption, intestinal protein loss and alterations in the release of gut-derived hormones. Hence, multiple parts of nutrient absorption are dysfunctional in advanced cirrhosis. By increasing intestinal capillary pressure, chronic portal hypertension enhances the capillary filtration coefficient and thus lymph flow (capillary filtration rate) up to 3–4 times as compared to healthy conditions [66]. Moreover, in portal hypertension the number of lymphatic vessels in the mesentery is vastly increased and may represent a specific adaptation to long-standing edematogenic stress [130]. Consecutively, an increased interstitial fluid pressure counterpoises the increase in intestinal capillary pressure, and the transcapillary oncotic pressure gradient remains stable. In fact, this and the compensatory increase in lymph flow may explain why diarrhea is not a prominent feature of cirrhosis despite mucosal edema.

Fecal concentrations of albumin, transferrin and α_1 -antitrypsin have been proposed as markers for intestinal protein loss and are found to be increased in cirrhotic patients [116]. TIPS insertion thus has been shown to markedly ameliorate the fecal excretion of albumin, IgG and α_1 -antitrypsin in cirrhotic patients with protein-losing enteropathy [131, 132]. Intestinal transport of sugars and amino acids is disturbed in experimental cirrhosis [133, 134], and inhibition of the activity of the membrane enzymes alkaline phosphatase and aminopeptidase as well as the activity of succinic dehydrogenase and reduced galactose transport [133] have been reported in experimen-

tal cirrhosis [135]. In contrast, an enhanced intestinal glutaminase activity is present in liver cirrhosis and may contribute essentially to the increase in ammonia following an oral glutamine challenge [136]. Glutaminase is the main glutamine-catabolizing enzyme in the small intestine, and glutamine is the main respiratory fuel of intestinal cells [137]. The mechanism by which glutaminase activity may be increased in cirrhosis remains to be delineated, but it may be due to an enhanced glutamine load associated with splanchnic hyperemia or could be activated by glucagon and/or angiotensin II [138].

Plentiful evidence on fat malabsorption in chronic liver failure exists, and steatorrhea may be present – if investigated thoroughly – in up to 50% of patients [139]. Explanations proposed for this malabsorption include: (1) a reduced pool size of bile acids, resulting in the inability to form micelles, (2) bacterial deconjugation of bile salts in the small intestine due to SIBO and (3) portal hypertension-associated edema and intestinal malfunction. In addition, triglyceride levels in the small intestine are significantly decreased in experimental as well as human cirrhosis, probably because of low intestinal apolipoprotein A-IV [140]. In cirrhosis, fatty acid transport is also altered compared to healthy conditions: portal absorption of long-chain fatty acids and their inflow into the liver are considered to be increased in advanced disease [141]. In contrast, short-chain fatty acid transport seems to be reduced. Net butyrate absorption in the rectum has been demonstrated to be significantly lower in cirrhotic patients than in controls [142]. Finally, micronutrients are malabsorbed as well. For instance, intestinal zinc absorption was significantly reduced in cirrhotics in correlation with the degree of liver dysfunction [143].

Cachexia is a prominent symptom in liver cirrhosis [144] with deleterious consequences on morbidity and mortality, as the degree of malnutrition has been shown to correlate inversely with survival and to compromise liver transplantation results [145, 146]. The pathogenesis of cachexia in advanced cirrhosis is multifactorial and may include complex metabolic disorders, catabolism and malnutrition. However, malassimilation and malabsorption are clear contributing factors. Moreover, most cachectic conditions are associated with underlying inflammatory processes mediated at least in part by increased levels of proinflammatory cytokines [144]. In liver cirrhosis, the gut is the main producer of proinflammatory agents [147, 148] overloading systemic circulation due to a lack of hepatic clearance [149]. These cytokines are associated with anorexia and depression and play a role in hypermetabolism, protein catabolism and insulin

resistance. Levels of the cytokine receptors sTNF-RI, sTNF-RII and sCD14 have been shown to be higher in patients with cachectic liver cirrhosis and to be related to resting energy expenditure corrected by body cell mass. In this context, pathological BT may play a perpetuating role as well. In animal models, starvation and malnutrition per se promote bacterial overgrowth, diminish intestinal mucin production, decrease global gut IgA levels, cause mucosal atrophy (increasing intestinal permeability), diminish T- and B-lymphocyte cell numbers and function in Peyer patches and lamina propria and accelerate oxidative stress [150–152]. Therefore, malnutrition in itself has been shown to aggravate BT [153]; thereby, it might fuel the proinflammatory process, further aggravating the cachectic process. In addition, decreased food intake is frequently observed in advanced cirrhotics and contributes to the negative energy balance in liver cirrhosis [154]. TIPS insertion has clearly been shown to increase body cell mass, evidencing an improvement in nutritional status after portal decompression [155]. This points towards a key role of portal hypertension and associated changes in intestinal nutrient absorption as well as improved food intake due to relief from abdominal symptoms and protein anabolism. In patients with liver cirrhosis, the severity of gastrointestinal symptoms is both related to recent weight loss and severity of disease and thus, not surprisingly, is associated with health-related quality of life [156]. An adequate daily energy and protein supply should be ensured in patients with liver cirrhosis, which is higher than in the normal population because of hypermetabolism and higher amino acid turnover.

Conclusions

We introduced various studies from the West and the East on the topic, as well as some experimental evidence, which support the conclusions that intestinal dysmotility, SIBO and intestinal hyperpermeability are closely related and enhance BT in liver cirrhosis. Alcohol, obesity and portal hypertension may become precipitating factors for these pathological processes. A so-called leaky gut is essential for the passage of toxins, antigens and/or bacteria as well as bacterial products into the body, and it may play a pathogenic role in advanced liver cirrhosis and its complications. Better management of intestinal dysfunction may open up new possibilities in clinical hepatology. Whereas its etiology may differ between the East and the West, the mechanisms and consequences of pathological

BT and intestinal dysfunction remain identical, since cirrhosis is the common cause. Readers interested in these topics are advised to read some recent excellent reviews [35, 67, 93, 157]. The relationship of gut dysbiosis and small intestinal dysfunction to endotoxemia, the pathophysiological backgrounds of various complications related to these abnormalities and the therapeutic approaches were discussed in our previous reviews [1, 158–160].

Disclosure Statement

We have no conflicts of interest to declare that are relevant to the subject of this review paper and any of the statements in it.

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