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World J Gastroenterol 2007 December 28; 13(48): 6458-6464
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Pathophysiology of increased intestinal permeability in obstructive jaundice

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Received: July 15, 2007 Revised: August 27, 2007

http://www.wjgnet.com/1007-9327/13/6458.asp

Abstract

Despite advances in preoperative evaluation and postoperative care, intervention, especially surgery, for relief of obstructive jaundice still carries high morbidity and mortality rates, mainly due to sepsis and renal dysfunction. The key event in the pathophysiology of obstructive jaundice-associated complications is endotoxemia of gut origin because of intestinal barrier failure. This breakage of the gut barrier in obstructive jaundice is multi-factorial, involving disruption of the immunologic, biological and mechanical barrier. Experimental and clinical studies have shown that obstructive jaundice results in increased intestinal permeability. The mechanisms implicated in this phenomenon remain unresolved, but growing research interest during the last decade has shed light in our knowledge in the field. This review summarizes the current concepts in the pathophysiology of obstructive jaundice-induced gut barrier dysfunction, analyzing pivotal factors, such as altered intestinal tight junctions expression, oxidative stress and imbalance of enterocyte proliferation and apoptosis. Clinicians handling patients with obstructive jaundice should not neglect protecting the intestinal barrier function before, during and after intervention for the relief of this condition, which may improve their patients' outcome.

Key words: Obstructive jaundice; Intestinal barrier; Intestinal permeability; Endotoxemia; Bacterial translocation; Tight junctions; Occludin; Claudin-4; Apoptosis; Oxidative stress

Assimakopoulos SF, Scopa CD, Vagianos CE. Pathophysiology of increased intestinal permeability in obstructive jaundice. *World J Gastroenterol* 2007; 13(48): 6458-6464

INTRODUCTION

When mechanical biliary obstruction is diagnosed, surgical, endoscopic or radiologic intervention is usually recommended. However, despite advances in preoperative evaluation and postoperative care, intervention, especially surgery, for relief of obstructive jaundice still carries high morbidity and mortality rates, mainly due to sepsis and renal dysfunction[1-3]. The concept of preoperative biliary drainage to reduce the postoperative morbidity and mortality in patients with malignant obstructive jaundice has not proved its efficacy leading to a longstanding controversy on this issue. Studies assessing the impact of endoscopic or radiologic drainage procedures prior to surgery in jaundiced patients showed high rates of complications, highlighting the role of the factor "intervention" in general in this patient population[4]. Recently, a randomized controlled multicenter clinical trial was designed to seek evidence whether or not preoperative biliary drainage should be performed in patients with obstructive jaundice due to a periampullary tumor[4].

The reasons for the high morbidity and mortality encountered in the post operative period have been attributed to impaired immune function and the high incidence of systemic endotoxemia[5-8]. In obstructive jaundice, increased intestinal permeability has been postulated to be a key factor contributing to bacterial and endotoxin translocation to mesenteric lymph nodes, portal circulation and liver[9,10]. A suppressed clearance capacity of Kupffer cells, the main hepatic macrophage population, attributed to accumulation of bile acids into liver, permits the "spillover" of endotoxin from portal into systemic circulation, with consecutive release of proinflammatory cytokines, potentially leading to the development of the so called "gut derived sepsis". Improved knowledge and understanding of the underlying pathophysiological mechanisms explaining the failure of the gut barrier in jaundiced patients may render us with better tools for prevention, treatment and patient selection.

THE GUT BARRIER STRUCTURAL AND FUNCTIONAL COMPONENTS

Nowadays, it is accepted that the gastrointestinal tract is not only a passive organ of nutrient absorption, but it

additionally displays important endocrine, immunologic, metabolic and barrier functions. The intestinal tract contains the body's largest interface between a person and his or her external environment. The complexity of its function is obvious when thinking that at the same time the intestine has to serve two opposite functions; the selective permeability of needed nutrients from the intestinal lumen into the circulation and into the internal milieu in general, and, on the other hand, the prevention of the penetration of harmful entities including microorganisms, luminal antigens, and luminal proinflammatory factors. The latter function is known as barrier function. Gut barrier function is dependent on the immune barrier, composed of locally acting factors such as, the secretory IgA, intra-mucosal lymphocytes, Payer's nodules, mesenteric lymph nodes and of the systemic host defense represented mainly by the reticuloendothelial system, the biological barrier, which is made up of normal intestinal flora responsible for colonization resistance, and the mechanical barrier, consisting of the closed-lining intestinal epithelial cells and by the capillary endothelial cells. All these components of gut barrier integrity can be affected by biliary obstruction and the absence of bile within the intestinal lumen.

THE EFFECT OF BILE ON THE GUT BARRIER

The presence of bile and bile acids in the intestinal lumen is associated with a number of positive effects, contributing to a normal gut barrier function.

Bile and the immune barrier

Experimental studies have shown that bile affects homing and distribution of T-lymphocytes in the gut-associated lymphatic tissue (GALT) and its absence results in decreased numbers of $CD4^+$ and $CD8^+$ T-lymphocytes and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressing cells in the lamina propria[11]. In addition, bile affects the size and number of B-lymphocytes in Peyer's patches. In experimental animals, the ligation of the common bile duct induced efficient apoptosis in Peyer's patch B-lymphocytes through a Toll-like receptors-2 dependent elevation of Fas expression and/or increase in sensitivity to Fas mediated apoptosis[12]. Bilirubin has been shown to impair bactericidal activity of neutrophils attenuating bacterial clearance mechanisms[13]. Bile also contains immunoglobulin A, which enhances mucosal defense either by maintaining mucosal integrity, or by binding to bacteria and viruses[14]. Circulating polymeric immunoglobulin A (IgA) binds to the secretory component (SC) on the surface of rat hepatocytes and is internalized and transported by vesicles to the canalicular membrane where the IgA-SC complex is secreted into bile. Secretion of IgA is sensitive to bile flow and the biliary secretory pathways for IgA and SC are dissociated after brief periods of cholestasis[15]. There is also evidence that specific or nonspecific antibodies contained in bile inhibit adhesion of enteric bacteria on the intestinal mucosa or inhibit bacterial endocytosis by enterocytes, thus preventing bacterial translocation[16].

Bile and the biological barrier

Bile acids have been reported to inhibit the growth of certain bacteria such as Bacteroides, Clostridia, Lactobacillus and Streptococci[17-20]. Absence of bile salts results in a disturbed intestinal bacterial balance with overgrowth of gram negative bacteria[19,21]. Bile salts have a detergent-like activity, which can make bacterial membranes permeable and can eventually lead to membrane collapse and cell damage[22]. Alternatively, bile salts are thought to prevent intestinal endotoxin and bacterial translocation by binding directly intraluminal endotoxin and bacteria, and creating poorly absorbed detergent-like complexes[23].

Bile and the mechanical barrier

In addition, bile exerts trophic effects on the intestinal mucosa, increasing villous density and inducing hypertrophy of the intestinal wall components[21,24]. *In vitro* experiments have shown that bile acids promote intestinal epithelial cell proliferation through a c-myc-dependent mechanism and protect against apoptotic cell death through activation of NF-κB[25,26]. These data support an important beneficial role of bile salts in regulation of mucosal growth and repair. Recent studies have also shown that bile is crucial for the maintenance of the integrity of enterocyte tight junctions, regulating the expression of the essential tight junction-associated proteins occludin and ZO-1, thus preserving the intestinal paracellular barrier[27,28].

INTESTINAL PERMEABILITY IN THE JAUNDICED PATIENT

Increased intestinal permeability has been postulated to be a key factor contributing to bacterial and endotoxin translocation and the pathogenesis of septic and renal complications in patients with extrahepatic biliary obstruction[29]. Beyond several experimental studies that have repeatedly demonstrated increased intestinal permeability in obstructive jaundice, this phenomenon has been confirmed in the clinical setting as well[5,29-31]. Increased intestinal permeability was evidenced in jaundiced patients either directly by the lactulose/mannitol permeability test[29,31], or indirectly by measurements of endotoxin concentrations in portal and systemic circulation[32], determination of anti-endotoxin core antibodies[31] and by multiple sampling during laparotomy in jaundiced patients, demonstrating growth of translocating bacteria of primarily enteric origin in extraintestinal sites[33]. Clinical data also demonstrate that surgical biliary decompression in obstructive jaundice exaggerates the pathophysiological disturbances and significantly increases intestinal permeability in the immediate post operative period as compared to non-surgically treated patients[5]. This probably reflects that the magnitude of an additional "trauma" in jaundiced patients is of importance and this should be considered in order not to further aggravate the patient's condition and host defense and potentially increase morbidity and mortality.

MECHANISMS OF INCREASED GUT PERMEABILITY IN OBSTRUCTIVE JAUNDICE

Intestinal permeability is determined by interactions among several barrier components including the unstirred water layer, mucosal surface hydrophobicity, the surface mucous coat, epithelial factors (especially tight junctions) and endothelial factors[34]. Each of these components has different permeability properties. However, among these factors, the intestinal epithelium consisted of the epithelial cells which are linked close to the apical surface by the tight junctions seem to be the most important in determining intestinal permeability[35]. Up to now, the mechanism of increased intestinal permeability in obstructive jaundice remains an enigma, but in the last few years experimental studies have shed light on our knowledge in the field.

In several studies, obstructive jaundice does not seem to induce dramatic morphologic changes in the intestinal mucosa on routine light microscopy[10,36], while in others non-specific findings, such as subepithelial edema, lifting of the villus and sporadic mucosal denudation with exposure of lamina propria have been documented[9,19,37]. However, ultrastructural studies on intestinal mucosa revealed certain kinds of cell disruption, represented by alterations of cellular and mitochondrial membrane[37]. In general, most studies had demonstrated that obstructive jaundice increases intestinal permeability though epithelial continuity is retained and the mechanism for this was not evident.

Tight junctions

The key event in the pathophysiology of obstructive jaundice-associated complications is gut derived endotoxemia[7]. According to its size, this molecule as well as other bacterial byproducts, could have permeated the intestinal mucosa through the paracellular pathway[38]. Therefore, our research group investigated for the first time the expression of occludin, a bona fide integral component of the tight junction, in the intestinal epithelium of jaundiced rats. The results of this study showed that intestinal mucosal barrier dysfunction in obstructive jaundice is associated with regional loss of occludin expression in the intestinal epithelium, observed mainly at the upper part of the villi[28]. Our immunohistochemical observations were confirmed by immunoblotting by other investigators, who additionally showed that obstructive jaundice leads to decreased mucosal expression of the TJ-associated protein ZO-1 as well[27]. Those researchers applying *in vitro* experiments with enterocytic monolayers incubated in the presence or absence of graded concentrations of bile showed that the alterations of intestinal tight junctions were bile mediated, while this finding was also supported *in vivo* because gavaging mice with rat bile significantly ameliorated the deleterious effects of obstructive jaundice on intestinal permeability. Also, in a current study it was shown that intestinal electrophysiological parameters in jaundiced animals, which substantially depend on intestinal TJs' integrity, were improved after oral supplementation with bile salts[39]. Further investigaton into the role of intestinal TJs alterations on gut barrier failure in obstructive jaundice demonstrated an up-regulation of claudin-4 expression in the upper part of the villi. Claudins are the only known variable elements in TJs and different expression, combination and mixing ratios of various members of the claudin family are essential in regulation of barrier properties of TJs[40]. There is evidence that the functional role of claudin-4 in the intestinal epithelium may be associated with loosening of intercellular junctions and opening of the paracellular route[41]; therefore, its overexpression is compatible with increased intestinal permeability. The key role of claudin-4 and occludin in obstructive jaundice-associated intestinal permeability alterations is further evidenced by improvement of gut mucosal barrier after restoration of their expression by regulatory peptides administration[28,42]. Apart from the role of bile deprivation, another explanation of altered intestinal occludin and claudin-4 expression in obstructive jaundice is through endotoxin-mediated mechanisms. The excessive presence of endotoxin in portal and systemic circulation stimulates a systemic inflammatory response, characterized by the release of cytokines and other proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1, interleukin-6, interferon-gamma (INF-γ), nitric oxide and oxygen free radicals[43]. These substances may produce injurious effects on TJs structure and function compromising intestinal epithelial barrier function[44-47]. Specifically, it has been demonstrated that TNF-α as well as INF-γ downregulate the human occludin promoter[48]. Given that increased levels of both TNF-α and INF-γ have been demonstrated in obstructive jaundice[43,49], it is tempting to speculate that these cytokines may account for occludin down-regulation. Furthermore, endotoxin reduces splachnic blood flow and disrupts intestinal microcirculation resulting in hypoxia of enterocytes and energy depletion[50]. Studies in epithelial cells monolayers have shown that adenosine triphosphate depletion induces the structural perturbation of the TJ leading to loss of the permeability barrier[51]. An additional contributory factor might be increased bacterial adherence to the enterocyte. Obstructive jaundice results in intestinal bacterial overgrowth, mainly represented by *E. coli* over growth[28]. Absence of bile deprives the gut from about 90% of secretory IgA, which normally prevents bacterial adherence to the intestinal mucosa[16]. Overgrowth of *E. coli* and lack of biliary IgA may lead to increased attachment of this bacterial strain to the intestinal mucosa. *In vitro* studies have shown that attachment of the enteropathogenic *E. coli* in intestinal epithelial cells monolayers dissociates occludin from the tight junctions, thus disrupting the paracellular barrier[52].

Cell proliferation and apoptosis

Absence of bile from the intestinal lumen is known to induce intestinal mucosal atrophy[21,53]. Epithelial homeostasis is highly dependent on the balance between cell proliferation and death, and knowledge of both factors is essential when elucidating how obstructive jaundice regulates intestinal cell turnover and mucosal cellularity. Experimental studies provided evidence of increased apoptosis of enterocytes in intestinal crypts

in parallel with decreased mitotic activity[10,54]. These cellular events occurring in intestinal crypts, where the mucosal proliferation zone exists, may explain the induction of mucosal atrophy observed in cases of biliary obstruction[54].

The responsible mechanisms of increased intestinal apoptosis could reflect primary immunologic events following BDL (apoptosis has been shown to be induced by a variety of triggers, including proinflammatory cytokines such as TNF-α, IL-1 and IL-6, or by cytotoxic T lymphocytes that act through either granzyme B or Fas receptor pathways) or a direct action of bacterial toxins[43].

It is well known that bile salts exert a potent trophic effect on the intestinal epithelium. This action is based on their mitogenic effect on the enterocytes. *In vitro* studies have shown that intestinal cells exposed to physiological concentrations of the bile salt taurodeoxycholate, within 24 h are beginning to enter into S-phase of the cell cycle, while after 6 d of exposure to bile salts, cell growth is stimulated by almost 70% relative to cells grown in the absence of bile salts[26]. The proliferative effect of taurodeoxycholate is at least partly mediated by regulation of the transcription of the proto-oncogene c-myc, which has been shown to play an important regulatory role during intestinal epithelial proliferation[26].

The significant contribution of the imbalance between cell proliferation and apoptotic death in the phenomenon of gut barrier failure in obstructive jaundice is further evidenced by the improvement of gut barrier function and the reduction of gut derived endotoxemia when factors that restore intestinal homeostasis were administered. The enhancement of intestinal permeability by glutamine may be explained by its proliferative and antiapoptotic effect on the intestinal mucosa[55-57]. Administration of intestinal trefoil agents such as Growth hormone and Insulin-like growth factor I , which act on intestinal mucosal growth, development and metabolism, significantly improved intestinal barrier function and reduced portal and systemic endotoxemia in obstructive jaundice, exerting, beyond their trophic effect, a potent antiapoptotic action on the intestinal mucosa leading to preservation of mucosal homeostasis[10]. In addition, gut regulatory peptides Bombesin and Neurotensin which have been shown to prevent gut barrier dysfunction in obstructive jaundice, exerted also a combined mitogenic and antiapoptotic effect on the intestinal mucosa[54].

Oxidative stress

Altered intestinal tight junction expression and increased intestinal apoptosis are accompanied by significant alterations of the intestinal oxidative state, which represent an additional important factor in promoting intestinal injury in obstructive jaundice[21,54,58]. Studies with experimental animals showed that obstructive jaundice induces intestinal oxidative stress evidenced, not only by increased lipid peroxidation and glutathione oxidation, but also by a general imbalance between protein or non protein thiols and protein or non protein disulfides (symmetric or mixed)[21,54,59]. Specifically, in the intestine we observed increased levels of the high oxidative stress markers of thiol redox state oxidized glutathione (GSSG), non-protein mixed disulfides (NPSSR) and protein symmetric disulfides (PSSP), accompanied by the decrease of the low oxidative stress markers glutathione (GSH), GSH:GSSG ratio and protein thiols (PSH). Our findings of increased intestinal oxidative stress in obstructive jaundice were also confirmed in the clinical setting[58]. The potential mechanisms of high intestinal oxidative stress in obstructive jaundice have been extensively reviewed previously[58,60]. Briefly, increased levels of bile acids, systemic endotoxemia and the subsequent inflammatory response[61], up-regulation of inducible nitric oxide synthase expression[62,63], increased neutrophil chemotaxis and superoxide anion generation[64] and decreased systemic levels of the antioxidant vitamin E[65], contribute to the promotion of the oxidative process in obstructive jaundice.

A question raised is whether intestinal cellular and oxidative alterations could be interrelated. It has been shown that reactive oxygen species may promote cell growth arrest, *via* a mitogen-activated protein kinases dependent pathway that alters the status of growth regulatory proteins, and apoptotic cell death, *via* a cytochrome c-mediated activation of the caspase family[66]. Thus, oxidative stress may promote intestinal apoptosis and inhibition of cell proliferation, leading to mucosal atrophy in obstructive jaundice. In addition, given that oxidative stress disrupts the TJ structural complex by modulating the assembly, localization, expression and function of their molecular components[46], this factor may underlie the altered intestinal TJ expression and increased permeability in obstructive jaundice. The interrelation of oxidative stress with intestinal cellular alterations in extrahepatic cholestasis is also supported by the fact that the oral administration of the antioxidant GSH preserves the intestinal mucosal redox state and prevents intestinal histological and electrophysiological changes[39]. In line with this observation, in a recent work[59], we demonstrated that administration of different antioxidant substances (N-acetyl-cysteine, allopurinol, α-tocopherol) in ten days' cholestatic rats, induces a significant antioxidant action in the intestine, mediated by a certain influence profile on the thiol redox state by each substance, leading to improvement of intestinal barrier function and prevention of endotoxemia. In addition, administration of gut regulatory peptides bombesin and neurotensin in experimentally jaundiced rats, induces a potent antioxidant effect on the intestine, preventing all the mentioned intestinal cellular alterations (apoptosis, inhibition of cell proliferation, altered TJ expression) and improving intestinal mucosal barrier function[28,42,54]. Taken together all these data suggest that intestinal oxidative stress and the thiol redox state are important factors in the promotion of the deleterious effects of obstructive jaundice on the anatomical and functional integrity of the intestinal mucosa.

The pathophysiology of obstructive jaundice-induced gut barrier failure, endotoxemia and systemic complications, is schematically presented in Figure 1.

CONCLUSION

Clinicians handling patients with obstructive jaundice

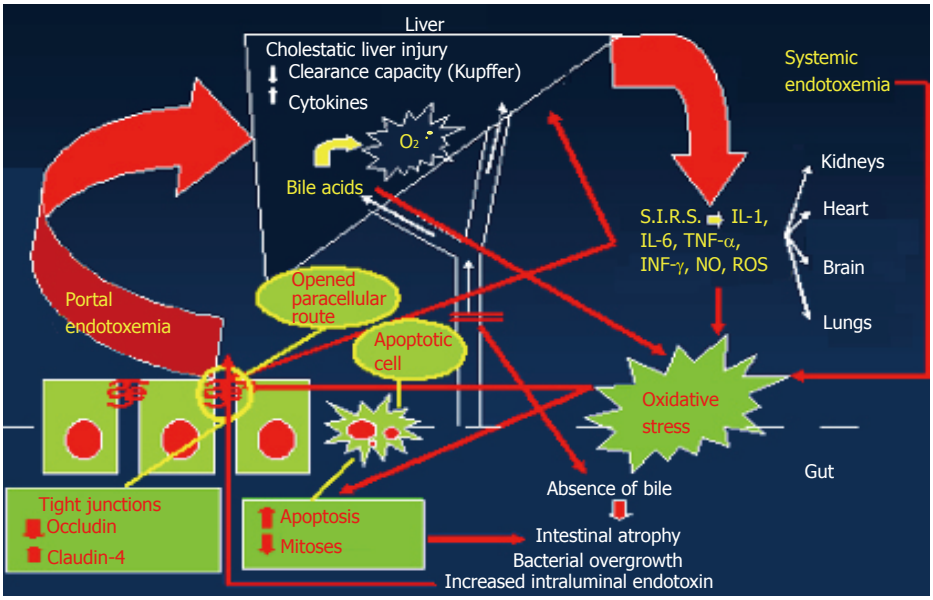

Figure 1 Pathophysiology of obstructive jaundice-induced gut barrier failure, endotoxemia and systemic complications. Absence of intraluminal bile deprives the gut from its bacteriostatic, endotoxin-neutralizing and mucosal-trophic effect leading to increased intestinal bacterial and endotoxin load and mucosal atrophy. These alterations promote bacterial and endotoxin translocation into portal circulation and subsequently, through a decreased clearance capacity of Kupffer cells because of cholestasis, into systemic circulation. Systemic endotoxemia activates a systemic inflammatory response, which is associated with dysfunction of remote organs, while it further aggravates intestinal barrier dysfunction and cholestatic liver injury. Endotoxemia, cytokinemia and increased bile acids concentrations represent important promoters of reactive oxygen species formation in diverse organs, encompassing the intestine. Increased intestinal oxidative stress in obstructive jaundice, contributes to induction of apoptosis and inhibition of cell proliferation in intestinal crypts, leading to mucosal atrophy. In parallel, intestinal oxidative stress, endotoxemia, systemic release of inflammatory mediators and absence of intraluminal bile, disrupts the integrity of enterocytes' tight junctions by altering the expression of their molecular components. As a consequence the intestinal paracellular route opens, contributing to further escape of endotoxin from the intestinal lumen into portal circulation, thus leading to a vicious cycle.

should not neglect protecting the intestinal barrier function before, during and after intervention for the relief of this condition, because failure of the intestinal barrier with consequent endotoxemia and the systemic inflammatory response may lead to serious and even life threatening complications. In this context, minimization of the additional surgical trauma, antibiotic prophylaxis, adequate fluid replacement to prevent visceral-microcirculatory disturbances, enteral nutrition to improve microcirculation, prevent mucosal atrophy and provide important nutrients for enterocytes and lactulose administration to reduce the incidence of endotoxemia are well demonstrated strategies. Growing research interest in this field has shed enough light in the pathophysiology of intestinal failure in obstructive jaundice demonstrating that the breakage of gut barrier is multi-factorial, involving disruption of the immunologic, biological and mechanical barrier. Altered intestinal tight junctions expression, oxidative stress and imbalance of cell proliferation and apoptosis may play a key role in gut permeability alterations in cases of biliary obstruction. Future studies focused on the pharmacological modulation of these factors may lead to a better control of intestinal permeability not only in obstructive jaundice, but also in diverse clinical states which may be complicated by gut-derived sepsis.

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