Intestinal barrier dysfunction in obstructive jaundice: current concepts in pathophysiology and potential therapies

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SUMMARY

Patients with obstructive jaundice, especially when exposed to the additional stress of an invasive diagnostic or therapeutic procedure, are prone to septic complications and renal dysfunction contributing to high morbidity and mortality rates. The key-event in the pathophysiology of obstructive jaundice-associated complications is endotoxemia of gut origin because of intestinal barrier failure. Experimental and clinical studies have shown that obstructive jaundice results in increased intestinal permeability. The mechanisms implicated in this phenomenon remain unresolved, but over the last few years mainly experimental studies have shed light on our knowledge in the field. Factors such as altered intestinal tight junctions expression, oxidative stress and apoptosis may play a key role in gut permeability alterations in cases of biliary obstruction. This review summarises the current knowledge on the pathophysiological mechanisms and the potential therapeutic strategies. Clinicians facing this very common clinical problem should not neglect protecting the intestinal barrier function, which may improve their patients’ outcome.

Key words: obstructive jaundice, intestinal barrier, intestinal permeability, endotoxiaemia, bacterial translocation, tight junctions, occludin, claudin-4, apoptosis, oxidative stress

1. INTRODUCTION

Patients with obstructive jaundice, especially when exposed to the additional stress of an invasive diagnostic or therapeutic procedure, are prone to septic complications and renal dysfunction contributing to high morbidity and mortality rates.¹ 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.²⁻⁵ 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.⁶⁻⁷ 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 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.

2. THE GUT BARRIER FUNCTION: GENERAL PRINCIPLES AND ROLE OF BILE

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 intestinal function is complex, because at the same time two opposite functions have to be served: 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
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3. INTESTINAL PERMEABILITY IN OBSTRUCTIVE JAUNDICE

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. 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. Increased intestinal permeability was evidenced in jaundiced patients either directly by the lactulose/mannitol permeability test, or indirectly by measurements of endotoxin concentrations in portal and systemic circulation, determination of anti-endotoxin core antibodies and by multiple sampling during laparotomy, demonstrating growth of translocating bacteria of primarily enteric origin in extraintestinal sites. 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. This probably reflects the magnitude of an additional “trauma” in jaundiced patients 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.

4. PATHOPHYSIOLOGY OF INCREASED INTESTINAL 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. Each of these components has different permeability properties. However, among these factors, the intestinal epithelium, consisting of the epithelial cells which are linked close to the apical surface by the tight junctions, seems to be the most important in determining intestinal permeability. Up to now, the mechanism of increased intestinal permeability in obstructive jaundice remains an enigma, but over the last few years experimental studies have shed light on our knowledge of this field.

In several studies, obstructive jaundice does not seem to induce dramatic morphologic changes in the intestinal mucosa on routine light microscopy, while in others nonspecific findings, such as subepithelial edema, lifting of the villus and sporadic mucosal denudation with exposure of lamina propria have been documented. Ultrastructural studies on intestinal mucosa revealed a certain kind of cell disruption, represented by alterations of cellular and mitochondrial membrane. In general, most studies demonstrated that obstructive jaundice increases intestinal permeability though epithelial continuity is retained and the mechanism for this was not evident.

The key event in the pathophysiology of obstructive jaundice-associated complications is gut derived endotoxin...
emia. According to its size, this molecule as well as other bacterial byproducts, could have permeated the intestinal mucosa through the paracellular pathway. 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. 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. 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. Continuing the research in this area, two years later we showed that gut barrier failure in obstructive jaundice is also associated with 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. 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, 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. A possible explanation of altered intestinal occludin and claudin-4 expression in obstructive jaundice is throught 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. These substances may produce injurious effects on TJs structure and function compromising intestinal epithelial barrier function. Specifically, it has been demonstrated that TNF-α as well as INF-γ down-regulate the human occludin promoter. Given that increased levels of both TNF-α and INF-γ have been demonstrated in obstructive jaundice, it is tempting to speculate that these cytokines may account for occludin down-regulation. Furthermore, endotoxin reduces splanic blood flow and disrupts intestinal microcirculation resulting in hypoxia of enterocytes and energy depletion. 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. An additional contributory factor might be increased bacterial adherence to the enterocyte. Obstructive jaundice results in intestinal bacterial overgrowth, mainly represented by E. coli overgrowth. Absence of bile deprives the gut from about 90% of secretory IgA, which normally prevents bacterial adherence to the intestinal mucosa. 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.

An additional crucial cellular alteration implicated in increased intestinal permeability in obstructive jaundice is increased apoptosis. Experimental studies provided evidence of increased apoptosis of enterocytes in intestinal crypts in parallel with decreased mitotic activity. 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. The responsible mechanism 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, 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.

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. Studies with experimental animals showed that obstructive jaundice induces intestinal oxidative stress evidenced by increased lipid peroxidation, protein oxidation and oxidation of non-protein and protein thiols. These findings were also confirmed in the clinical setting. The potential mechanisms of high intestinal oxidative stress in obstructive jaundice have previously been extensively reviewed. Briefly, increased levels of bile acids, systemic endotoxemia and the subsequent inflammatory response, up-regulation of...
inducible nitric oxide synthase expression, increased neutrophil chemotaxis and superoxide anion generation and decreased systemic levels of the antioxidant vitamin E contribute to the promotion of the oxidative process in obstructive jaundice. In obstructive jaundice, the presence of increased intestinal oxidative stress may be related to intestinal atrophy, since 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. In addition, given that oxidative stress disrupts the tight junction structural complex by modulating the assembly, localization, expression and function of their molecular components, this factor may underlie altered intestinal tight junctions expression in obstructive jaundice.

5. POTENTIAL THERAPEUTIC STRATEGIES

The effect of internal and external biliary drainage on the intestinal barrier function has been studied extensively in the experimental setting. Internal biliary drainage was superior to external drainage in preserving the integrity of the intestinal mucosa and preventing endotoxia when an additional “trauma” occurs. Also, internal drainage was better in improving the clearance capacity of Kupffer cells. Estimating the overall impact of preoperative internal and external drainage procedures on mortality, again only the internal drainage showed a significant positive effect. However, the effectiveness of preoperative biliary drainage in reducing postoperative morbidity is a debated issue. Clinical studies have shown that despite reduction of inflammatory mediators by the internal drainage, the postoperative morbidity was not reduced. Also, the recovery of the intestinal permeability in humans, as measured by the lactulose-mannitol test requires at least a four week period, and in most instances the interval between preoperative drainage and surgery is limited. Moreover, the insertion of an endoscopic stent is associated with an inflammatory response which may exaggerate the pathophysiological disturbances of obstructive jaundice leading to a systemic inflammatory response.

Administration of lactulose preoperatively was shown to be of benefit in experimental and clinical biliary obstruction, reducing portal and systemic endotoxia and preventing renal dysfunction. In the experimental setting lactulose was efficient in reducing endotoxin-related systemic inflammatory response and mortality in obstructive jaundice. Potential mechanisms explaining the effect of lactulose may be inactivation of gut derived endotoxin and the endotoxin-induced tumor necrosis factor production.

The importance of the presence of bile and bile salts within the intestinal lumen has been emphasized. Bile acids in the gut possess a bacteriostatic effect, promote balance of the intestina bacterial flora and neutralize endotoxin. The administration of oral bile salts in experimentally jaundiced animals reduces intestinal bacterial overgrowth, bacterial translocation, endotoxia and tumor necrosis alpha production. In jaundiced patients, oral bile salts replacement prevents endotoxia and postoperative renal failure. Among bile salts it seems that sodium deoxycholate is the most efficacious in reducing postoperative renal failure.

Immunomodulation in obstructive jaundice is another therapeutic strategy. Experimentally, anti tumor necrosis factor-alpha treatment with monoclonal antibodies may represent a potential way of intervention, since endotoxin induced cytokinemia is implicated in the pathophysiology of obstructive jaundice associated complications, but this treatment despite reduction of serum tumor necrosis factor-alpha levels does not affect mortality. Bactericidal/permeability-increasing protein is a naturally occurring endotoxin-binding protein produced in neutrophils, which binds endotoxin, neutralizing the activity and inhibiting cytokine production by mononuclear cells. Experimental studies have shown that this compound reduced endotoxin-induced mortality to a death rate comparable to that in non jaundiced animals, which may indicate its potential value in perioperative treatment in clinical obstructive jaundice. The administration of immunostimulating compounds in experimental biliary obstruction has also been tried. Muramyl dipeptide or muramyl tripeptide both restored reticuloendothelial system phagocytic function in jaundiced rats, which may prevent the “spillover” of endotoxin from portal into systemic circulation. The beneficial effects of this type of immunomodulation also included an inhibitory effect against bacterial translocation, probably by activation of mucosal macrophages.

Enteral immunonutrition using glutamine or arginine, omega-3 fatty acids, and RNA-supplemented enteral diet is an alternative approach. Experimental studies have shown that administration of these agents during both pre- and postoperative periods prevents atrophy of intestinal mucosal villi and reduces bacterial translocation. Glutamine was beneficial in preventing the increase of intestinal permeability in obstructive jaundice and also increased bacterial killing by the immune system. The enhancement of intestinal permeability by glutamine may be explained by its antiapoptotic effect on the intestinal mucosa.
Administration of intestinal trefoil agents is a reasonable strategy, since absence of bile induces intestinal mucosal atrophy. Experimental studies have shown that treatment with Growth hormone and Insulin-like growth factor I, which act on intestinal mucosal growth, development and metabolism, significantly improves intestinal barrier function and reduce portal and systemic endotoxemia in obstructive jaundice.7 Both factors beyond their trophic effect on the intestinal mucosa, exerted an antiapoptotic action, thus preserving mucosal integrity.7 Also gut regulatory peptides Bombesin and Neurtensin have been shown to beneficially affect intestinal barrier function in obstructive jaundice, preventing portal and aortic endotoxemia. The positive effect of Bombesin and Neurtensin is based on a wide spectrum of actions in the intestinal mucosa, including mitogenic, antiapoptotic, antioxidant and tight junction modulating properties.18, 32, 43

Since oxidative stress has been shown to be an important factor contributing to intestinal injury in experimental and clinical obstructive jaundice, the therapeutic trial of antioxidants for reversing gut barrier dysfunction is reasonable. Allopurinol, a xanthine oxidase inhibitor, reduced intestinal lipid peroxidation and the incidence of bacterial translocation in experimentally jaundiced rats.74 Alpha-Tocopherol (vitamin E) and ascorbic acid (vitamin C) treatment increased intestinal glutathione levels and decreased lipid peroxidation, thus improving intestinal barrier function.75 Also, several studies have demonstrated the beneficial effects of antioxidants like N-acetyl cysteine and melatonin in hepatic and renal function in obstructive jaundice, but without examining these findings under the light of their potential positive impact on the intestinal barrier function.76-80

6. CONCLUSIONS

Obstructive jaundice is a common clinical entity complicated by intestinal barrier dysfunction and endotoxemia, leading to high postoperative morbidity and mortality rates. Current advances in the pathophysiology of intestinal failure in obstructive jaundice have shown that the breakage of gut barrier is multi-factorial, involving disruption of the immunologic, biological and mechanical barrier. Factors such as altered intestinal tight junctions expression, oxidative stress and apoptosis may play a key role in gut permeability alterations in cases of biliary obstruction. Applying this knowledge in the clinical practice, there are several considerations that should be made prior to surgery in the jaundiced patient. The additional surgical trauma should be minimized, as otherwise impairment of the total host defense might increase the risk of postoperative morbidity. Before surgery, clinicians should not neglect protecting the intestinal barrier function, by applying 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. These well demonstrated clinical strategies are continuously enriched by a valuable basic research pool, which may finally lead to a better therapeutic approach and outcome for our patients. In our opinion, the key in future research is discovery of selective modulators of intestinal tight junctions in order to control intestinal permeability. Such a pharmacological intervention could for instance open the paracellular pathway to improve the intestinal absorption of a certain drug and close this gate in cases that might be complicated by gut derived sepsis, such as in critically ill patients, major trauma, burns or obstructive jaundice.

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