Review Article

Graft cholangiopathy: etiology, diagnosis, and therapeutic strategies

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BACKGROUND: **Graft cholangiopathy has been recognized as a significant cause of morbidity, graft loss, and even mortality in patients after orthotopic liver transplantation. The aim of this review is to analyze the etiology, pathogenesis, diagnosis and therapeutic strategies of graft cholangiopathy after liver transplantation.**

DATA SOURCE: **A PubMed database search was performed to identify articles relevant to liver transplantation, biliary complications and cholangiopathy.**

RESULTS: **Several risk factors for graft cholangiopathy after liver transplantation have been identified, including ischemia/reperfusion injury, cytomegalovirus infection, immunological injury and bile salt toxicity. A number of strategies have been attempted to prevent the development of graft cholangiopathy, but their efficacy needs to be evaluated in large clinical studies. Non-surgical approaches may offer good results in patients with extrahepatic lesions. For most patients with complex hilar and intrahepatic biliary abnormalities, however, surgical repair or re-transplantation may be required.**

CONCLUSIONS: **The pathogenesis of graft cholangiopathy after liver transplantation is multifactorial. In the future, more efforts should be devoted to the development of more effective preventative and therapeutic strategies against graft cholangiopathy.**

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KEY WORDS: **liver transplantation; bile ducts; complications; ischemia/reperfusion injury; therapy**

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Introduction

Biliary tract complications have been recognized as a significant cause of morbidity, graft loss, and even mortality in patients after orthotopic liver transplantation (OLT). Because of the differences in graft type and the definition of biliary complications, the reported incidence varies greatly between different studies, ranging from 10% to 30%.[1-6] Post-transplant biliary complications may be related to various factors, including technical reasons, hepatic artery thrombosis (HAT), preservation injury, infection, and rejection. The technical factors refer to imperfect anastomosis, T-tube-related problems, and the usage of partial liver grafts, such as reduced-size, splitting, and living donor liver transplantation. Early HAT may result in bile duct ischemia and eventually necrosis, which are characterized by typical biliary strictures, dilatations, and casts. However, these biliary abnormalities may also occur in the absence of HAT, and have been termed diffuse non-anastomotic biliary strictures, intrahepatic biliary strictures, ischemic cholangitis, ischemic-type biliary lesions and most recently, ischemic cholangiopathy. The exact mechanisms of ischemic cholangiopathy remain unclear. However, several contributing factors have been identified (Table 1), such as ischemia/reperfusion injury,[7-9] infection,[10] immune-mediated injury,[11, 12] and bile salt toxicity.[13] To avoid the confusion and misunderstanding of the terminology of ischemic cholangiopathy, we propose a new term "graft cholangiopathy" that refers to a local or diffuse damage to bile ducts in liver grafts excluding technical reasons and HAT. In this review, we focus on the etiology, pathogenesis, diagnosis and treatment of graft cholangiopathy after OLT.

Etiology and pathogenesis

Ischemia/reperfusion injury

Ischemia/reperfusion injury is a complex process with many

Table 1. Risk factors for the development of graft cholangiopathy after liver transplantation

Risk factors
Ischemia/reperfusion injury
Warm ischemia in donation after cardiac death
Prolonged cold ischemia time
Secondary warm ischemia during implantation
Reperfusion injury
Disturbed blood flow in the peri-biliary plexus
Immunological factors
ABO incompatibility
Acute and chronic rejection
Development of donor-specific antibody
Autoimmune hepatitis
Primary sclerosing cholangitis
Infection
Cytomegalovirus infection
Chemokine polymorphism *CCR5 delta 32*
Bile salt-induced injury
Cytotoxic hydrophobic bile salts

pathophysiological mechanisms including impairment of microcirculation, leukocyte adhesion, platelet aggregation, increased oxygen-free radical production, lipoperoxidation, and hypoxia.[14-16] It has been well documented that prolonged warm and cold ischemia time predispose the liver grafts to the development of cholangiopathy.[1, 4, 5, 8, 17] Colonna et al[1] found that the cold ischemia time for all of the 6 patients who developed intrahepatic biliary strictures in the absence of HAT exceeded 12 hours. A study from Sanchez-Urdazpal et al[8] also showed that the incidence of biliary complications was significantly increased in liver grafts with a cold ischemia time of more than 11.5 hours. Nowadays, most centers therefore try to keep the cold ischemia time below 10 hours. Many studies[17-24] indicated that liver recipients are at an increased risk of developing cholangiopathy ranging between 25% and 60% after receiving allografts from donation after cardiac death (DCD), compared with 10% to 30% seen in donation after brain death (DBD). The main difference between DCD and DBD transplantation is the warm ischemia time of liver graft. It seems intuitive that the prolonged warm ischemia time would affect adversely tissue viability and graft function, and result in a higher incidence of ischemic cholangiopathy. Therefore, most centers are reluctant to prolong the warm ischemia time to more than 30 minutes.[25, 26]

The significant correlation between ischemia/reperfusion injury and cholangiopathy may be attributed by the direct ischemic damage of the biliary epithelium, secondary injury due to peribiliary microcirculation disturbance, and increased susceptibility of the biliary epithelium to reoxygenation injury. In a bile cytological study, Carrasco et al[27] found that prolonged cold ischemia time causes an increase in bile cell density at the expense of ductal epithelial cells, the longer the preservation time, the greater the increase. Ischemia can also lead to the change of cholangiocyte cytoskeleton. Using ischemia in intact liver and adenosine triphosphate (ATP) depletion in cultured cells to model cholangiocyte injury, Doctor et al[28] investigated the effects of metabolic inhibition on cholangiocyte viability and structure. The study indicated that cholangiocyte ATP depletion induced characteristic, domain-specific changes in the plasma membrane, and implicated alterations in the membrane-cytoskeletal interactions in the initiation of the changes. They concluded that, pending the re-establishment of the differentiated domains, the loss of specific secondary structures may contribute to impaired vectorial bile duct secretion and post-ischemic cholestasis. The bile canaliculus appears to be one of the hepatic structures most susceptible to ischemia/reperfusion injury. A morphological study showed that the appearance of bile canaliculi in human liver grafts changed dramatically after reperfusion, including significantly increased perimeter of the canaliculi and remarkable loss in the number of bile microvilli per unit of canalicular area.[29] In addition, an *in vitro* study by Noack et al[30] indicated that during anoxia, bile duct epithelial cells were significantly more resistant to cell killing than hepatocytes. The rates of cellular proteolysis were also 2.5-fold lower in bile duct cells than those in hepatocytes during anoxia. In contrast to anoxia, however, reoxygenation of anoxic cells increased the cell killing of bile duct cells and improved the viability of hepatocytes. The rate of toxic reactive oxygen species (ROS) formation by bile duct cells was 5-fold greater than that by hepatocytes during reoxygenation. The authors concluded that biliary epithelial cells are more susceptible to reoxygenation injury than to anoxia.[30]

A variety of experimental studies showed that failure of hepatic microcirculation is a major component of reperfusion injury in the liver.[14, 31, 32] It has been indicated that nitric oxide (NO) and endothelins (ETs), two potent vasoactive mediator systems in the liver, are involved in the pathogenesis of microcirculation impairment. The ET-induced constriction of hepatic microcirculation can be inhibited by NO-mediated vasodilatory action.[33] Recently, we also found that changes of intrahepatic biliary microcirculation were associated with the down-regulation of endothelial NO synthase (eNOS) expression and up-regulation of inducible NOS, ET-1 and intercellular adhesion