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ORIGINAL ARTICLE

Consequences of Living-Donor Liver Transplantation for Upper Gastrointestinal Lesions: High Incidence of Reflux Esophagitis

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Abstract There is little information available regarding the consequences of living-donor liver transplantation (LDLT) for upper gastrointestinal lesions. We retrospectively compared the pre- and posttransplant incidences of noninfectious reflux esophagitis, portal hypertensive gastropathy (PHG), esophageal varix, gastroduodenal ulcer, *Helicobacter pylori* infection, and abnormal gastroesophageal valve in 29 adult patients (16 males, 13 females) who underwent LDLT for end-stage liver disease. Here we present four findings from this study. First, the posttransplant incidence of noninfectious esophagitis was significantly higher than the pretransplant incidence (27.6% vs. 3.4%; $P < 0.001$), irrespective of postoperative use of standard-dose H2RA. Second, PHG and esophageal varix, which were noted in 65.5% and 96.6% of pretransplant recipients, respectively, spontaneously resolved postoperatively in all cases. Third, *H. pylori* infection, which was observed in 50.0% of preoperative recipients, decreased to 5.6% postoperatively, although no significant difference was observed between the pre- and the posttransplant incidences of gastroduodenal ulcer (6.9% vs. 6.9%). Finally, the incidence of abnormal gastroesophageal valve did not change following LDLT (34.5% vs. 34.5%). In conclusion, this study suggests that noninfectious reflux esophagitis occurs more frequently following LDLT. Although the disease is the results of a very complex interaction of various factors, spontaneous resolution of PHG and serendipitous *H. pylori* eradication might have contributed to increased incidence of postoperative esophagitis, possibly through gastric acid hypersecretion. In contrast, morphological change of the gastroesophageal valve was not considered to be the cause of this disease. Because this study was a retrospective analysis of a small population of LDLT recipients, prospective randomized controlled studies of a sufficient number of cases are required to substantiate these conclusions.

Keywords Reflux esophagitis · Living-donor liver transplantation · Portal hypertensive gastropathy · *Helicobacter pylori*

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Introduction

The long waiting time and high incidence of death during this time are a serious problem in countries where cadaveric liver transplantation is routinely performed [1]. Living-donor liver transplantation (LDLT) provides an alternative source of organs for patients with end-stage liver disease. This procedure was initially introduced to overcome organ shortage for pediatric patients [2, 3]. Recent advances in LDLT have led to its wide acceptance as the only realistic option in countries where cadaveric organ harvesting is limited for cultural, social, and historic reasons [4, 5]. This is particularly the case in Asian countries. Gastroesophageal endoscopic features in patients with advanced liver disease have been well-documented [6–10]. However, there is little information available in this respect following LDLT. Therefore, we aimed to evaluate the consequences of LDLT on the upper gastrointestinal lesions.

Patients and methods

We retrospectively examined the pre- and posttransplant findings from upper gastroesophageal endoscopy in 29 adult patients (16 males, 13 females) who underwent LDLT for end-stage liver disease at the Department of Surgery, Keio University Hospital, between June 1997 and February 2005. We compared the pre- and posttransplant incidences of reflux esophagitis, portal hypertensive gastropathy (PHG), esophageal varix, gastroduodenal ulcer, *Helicobacter pylori* infection, and abnormal gastroesophageal valve. These patients underwent upper gastrointestinal endoscopy within 2 weeks before LDLT and 2 to 24 weeks (median, 8 weeks) following LDLT. Endoscopic procedures were performed by several experienced endoscopists according to a fixed protocol. During each procedure, the esophagus and stomach as well as the first two portions of the duodenum were carefully examined. Patients afflicted with fungal or CMV esophagitis were excluded from this study. To prevent postoperative stress ulcers, standard-dose histamine receptor antagonist (H2RA) was given to all patients.

Esophagitis was evaluated by such endoscopic findings as mucosal break, which was graded according to the Los Angeles (LA) classification [11]. Grade A is one or more mucosal breaks confined to the mucosal folds, each no longer than 5 mm. Grade B is at least one mucosal break more than 5 mm long confined to the mucosal folds but not continuous between the tops of two mucosal folds. Grade C is at least one mucosal break continuous between the tops of two or more mucosal folds but not circumferential.

The endoscopic grade of PHG was assessed according to McCormack *et al*. [12]. Mild gastropathy includes a fine pink speckling or scarlatina-type rash, a superficial reddening particularly on the surface of the rugae giving a striped appearance, and a fine white reticular pattern separating areas of raised red edematous mucosa resembling a snake skin. Severe gastropathy includes discrete red spots analogous to the cherry red spots described in the esophagus and a diffuse hemorrhagic gastritis.

The diagnosis of *H. pylori* infection was made by histological examination of gastric mucosal biopsy specimens, rapid urease test, and detection of serum IgG antibodies.

The valvular appearance of the cardia visualized from below using the retroflexed endoscope was evaluated according to the V-grades, as reported by Ismail *et al*. [13]. V0 is no hiatus hernia and a normal valve appearance. V1 is a small hiatus hernia, and the cardia is closed around the endoscope. V2 is an open cardia with minimum distention and no hiatus hernia.

The pre- and posttransplant incidence data were compared by the chi-square test. Differences were considered significant at $P < 0.05$.

Results

Patient characteristics

The median age was 50 years (range, 27 to 63 years). The causes of liver disease were primary biliary cirrhosis in seven, primary sclerosing cholangitis in two, hepatitis B in four, hepatitis C in six, alcoholic hepatitis in three, fulminant hepatic failure in three, biliary atresia in one, Wilson disease in one, familial amyloid polyneuropathy in one, and Caroli's disease in one. Postoperatively, tacrolimus ($n = 15$) or cyclosporine ($n = 14$) was given to these patients.

Upper gastrointestinal lesions

The pre- and posttransplant incidences of noninfectious reflux esophagitis, PHG, esophageal varix, gastroduodenal ulcer, *H. pylori* infection, and abnormal gastroesophageal valve are listed in Table 1. Preoperatively, only 1 of 29 (3.4%) was diagnosed as having reflux esophagitis (grade A). Following LDLT, the number of cases increased to eight (27.6%) (Figs. 1A and B). Of these, four patients (13.8%) had grade A, 2 (6.9%) had grade B, and two (6.9%) had grade C. Five of eight patients had clinical symptoms (including nausea, heartburn, chest pain, and epigastric pain) from these lesions. The posttransplant incidence was significantly higher

Table 1 Upper gastrointestinal lesions before and following living-donor liver transplantation

	Pretransplant (%) ($n = 29$)	Posttrasplant (%) ($n = 29$)	*P* value
Reflux esophagitis			<0.001
Normal	96.6	72.4	
Grade A	3.4	13.8	
Grade B	0	6.9	
Grade C	0	6.9	
PHG			<0.001
Normal	34.5	100	
Mild	62.1	0	
Severe	3.4	0	
Esophageal varix			<0.001
Yes	96.6	0	
No	3.4	100	
Gastroduodenal ulcer			NS
Yes	6.9	6.9	
No	93.1	93.1	
H. pylori infection			<0.001
Yes	50	5.6	
No	50	94.4	
Gastroesophageal valve			NS
V0 (normal)	65.5	65.5	
V1	13.8	13.8	
V2	20.7	20.7	

Note. PHG, portal hypertensive gastropathy; NS, not significant.

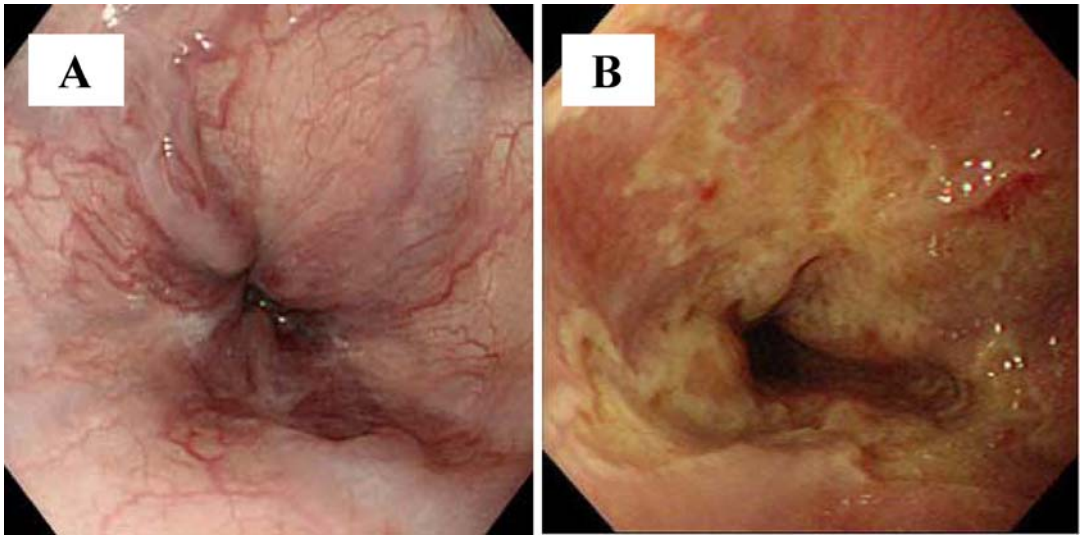

Fig. 1 Representative endoscopic pictures of the hiatus before (A) and following (B) living-donor liver transplantation. Grade C Reflux esophagitis occurred postoperatively

than the pretransplant incidence ($P < 0.001$). No complicated pathologies of the esophagus (such as stenosis and bleeding) were observed. With proton pump inhibitor (PPI) therapy, control of the disease was achieved in all cases. Before transplantation, 19 of 29 (65.5%) were diagnosed as having PHG, of which only 1 (3.4%) was severe. Nonetheless, PHG spontaneously resolved postoperatively in all cases (Figs. 2A and B). Esophageal varix was observed in 28 of 29 pretransplant cases (96.6%), and it also resolved spontaneously following LDLT in all cases. Gastroduodenal ulcer was noted in 2 of 29 pretransplant recipients (6.9%), and it did not increase following LDLT. The incidence of *H. pylori* infection significantly decreased following LDLT (50.0% vs. 5.6%; $P < 0.001$). Ten of 29 (34.5%) had abnormal findings for the gastroesophageal valve before LDLT: V1, 4 (13.8%); V2, 6 (20.7%). The other 19 (65.5%) had a normal valve (V0). Postoperatively, 10 of 29 (34.5%) had abnormal findings: V1, 4 (13.8%); V2, 6 (20.7%).

Discussion

This paper reports four major findings. First, the incidence of noninfectious esophagitis significantly increased following LDLT, irrespective of postoperative use of standard-dose H2RA. Second, PHG and esophageal varix, which were noted in the majority of pretransplant recipients, respectively, spontaneously resolved postoperatively. Third,

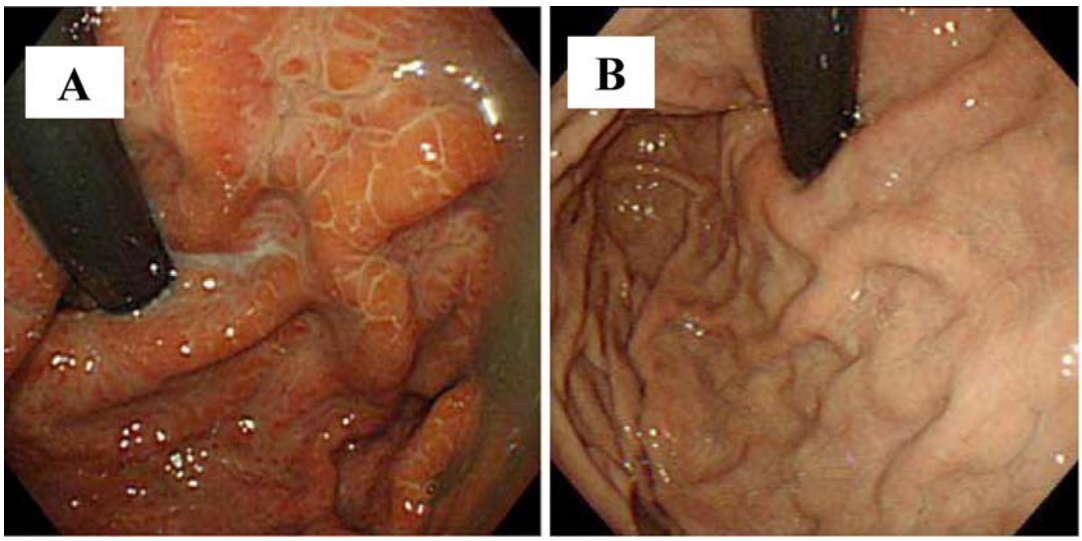

Fig. 2 Representative endoscopic pictures of the proximal stomach before (A) and following (B) living-donor liver transplantation (LDLT). PHG characterized by sneak skin appearance was observed before LDLT, resolving spontaneously postoperatively

H. pylori infection, which was observed in 50.0% of preoperative recipients, decreased to 5.6% postoperatively. Finally, the incidence of abnormal gastroesophageal valve did not change following LDLT.

The reported incidence of reflux esophagitis in cirrhotic cases ranges from 5% to 12% [6–10]. However, in the present study, we found that the incidence rose from 3.4% to 27.6% following LDLT. Because little information is available regarding this issue, specific reasons why patients seem more likely to develop reflux esophagitis following LDLT remain unclear. Although the pathophysiology of this disease is complex and multifactorial, it results from an imbalance between defensive factors protecting the esophagus (lower esophageal sphincter [LES] and esophageal acid clearance) and aggressive factors from the stomach contents (gastric acid and refluxate).

Normally, reflux of gastric acid and refluxate from the stomach into the esophagus is prevented by the LES. Hiatus hernia is frequently identified in patients with reflux esophagitis, and is considered to impair LES function [14–16]. Patients with hiatus hernia clear esophageal contents into the hernia, which is subject to intrathoracic pressure. During inspiration, negative thoracic pressure may draw such content back into the esophagus. However, in the present study, the incidence of abnormal gastroesophageal valve did not increase postoperatively. Therefore, the morphologic change of the gastroesophageal valve was not considered to be the cause of this disease.

The primary importance of gastric acid is indisputable in the development of reflux esophagitis. Its mechanism may involve activation of pepsin rather than direct damage from gastric acid alone [17–19]. In the present study, in order to prevent gastroduodenal ulcers, we routinely administrated H2RA to all patients postoperatively. As a result, the incidence of gastroduodenal ulcer did not increase postoperatively. However, reflux esophagitis did occur more frequently following LDLT. Patients with reflux esophagitis who respond poorly to acid suppressive therapy have more gastric acid secretion than control patients [19]. In the present study, esophageal varix and PHG were noted in the majority of pretransplant recipients (96.6% and 65.5%, respectively). However, both lesions spontaneously resolved postoperatively. LDLT resolves the congestion of the splanchnic viscera and improves portal hypertension. PHG is associated with diminished acid secretion [20, 21]. Therefore, it is possible that resolution of PHG following LDLT might have resulted in gastric acid hypersecretion.

Additionally, in the present study, the prevalence of *H. pylori* infection decreased significantly, from 50.0% to 5.6%, postoperatively. The reported incidence of *H. pylori* infection in cirrhotic cases ranges from 40% to 52% [22, 23]. Recent studies have shown that *H. pylori* infection prevents reflux esophagitis by decreasing gastric acid secretion [24, 25]. Therefore, serendipitous *H. pylori* eradication might have contributed to the occurrence of esophagitis by increasing gastric acid production.

Patients with reflux esophagitis often have impaired clearance of refluxate, which is demonstrated in 24-hr pH monitoring studies. Esophageal dismotility is observed in 25% of cases with mild esophagitis and in approximately 50% of cases with severe disease [26]. In transplant recipients, it is possible that some postoperative medications (such as immunosuppressive drugs) might be related to esophageal dismotility.

In conclusion, this study suggests that noninfectious esophagitis occurs more frequently following LDLT. Although the disease is the result of a very complex interaction of various factors, spontaneous resolution of PHG and serendipitous *H. pylori* eradication might have contributed to the increased incidence of postoperative esophagitis, possibly through gastric acid hypersecretion. In contrast, morphological change of the gastroesophageal valve was not considered to be the cause of this disease. Because this study was a retrospective analysis of a small population of LDLT recipients based on random endoscopies, prospective randomized controlled studies of a sufficient number of cases are required to substantiate these conclusions. Careful follow-up and adequate acid suppressive therapy are mandatory for the prevention of posttransplant reflux esophagitis.

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