ORIGINAL ARTICLE

Gut and Liver, Vol. 6, No. 3, July 2012, pp. 349-354

# Increased Incidence of Endoscopic Erosive Esophagitis in Solid Organ Transplant Recipients

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**Background/Aims:** Solid organ transplant recipients frequently report gastrointestinal symptoms, especially heartburn or dyspepsia. However, the prevalence of endoscopic erosive esophagitis (EE) and associated risk factors after transplantation are unknown. The aim of this study was to determine whether there was a high incidence of endoscopic findings of EE in solid organ transplant recipients. **Methods:** This retrospective case-control study included 256 of 3,152 solid organ transplant recipients who underwent sequential screening upper endoscopic examinations and an equal number of controls. **Results:** Forty-four (17.2%) and 16 (6.2%) cases of EE were detected in the solid organ transplant and control groups, respectively (p<0.001). In the multivariate analysis, transplantation was significantly associated with EE (odds ratio [OR], 6.48; 95% confidence interval, 2.74 to 15.35). Factors such as old age (OR, 1.17), the presence of a hiatal hernia (OR, 5.84), an increased duration of immunosuppression (OR, 1.07), and the maintenance administration of mycophenolate mofetil (OR, 4.13) were independently associated with the occurrence of EE in the solid organ transplant recipients. **Conclusions:** A significant increase in the incidence of endoscopically detected EE was observed in solid organ transplant recipients. This increased incidence was associated with the type and duration of the immunosuppressive therapy. **(Gut Liver 2012;6:349-354)**

**Key Words:** Transplantation; Erosive esophagitis; Gastroesophageal reflux; Mycophenolate mofetil; Barrett esophagus

## INTRODUCTION

According to literature, cancer is expected to surpass cardiovascular complications as the primary cause of death in transplanted patients within the next 2 decades.[1,2] A nationwide cohort study from Sweden indicated a 3-fold increased risk of *de novo* tumors after solid organ transplantation (SOT).[3] In addition, increased incidence of *de novo* esophageal cancer in the population of liver transplant recipients has been reported.[4,5] Accumulating evidence suggests that gastric acid is the major factor in the pathogenesis of gastroesophageal reflux disease and its complications, including erosive esophagitis (EE), Barrett's esophagus (BE), and esophageal adenocarcinoma.[6,7] In the case of BE, which is recognized as a complication of EE and a pre-malignant condition that may lead to the development of esophageal adenocarcinoma, the proximal level of the squamocolumnar junction no longer coincides with the gastroesophageal junction.[8,9]

Gastrointestinal complications are frequent in SOT recipients and may involve any segment of the gastrointestinal tract. These disorders may be related to stress, infections, or exacerbation of pre-existing gastrointestinal pathology.[10,11] In addition, immunosuppressive agents may cause gastrointestinal side effects, either directly or by favoring the development of bacterial or viral infection. Severe gastrointestinal disorders may develop in approximately 10% of SOT patients, eventually leading to graft loss and even patient death. Gastrointestinal complications may also result in reduction of the dose of immunosuppressant drugs and associated risk of organ rejection.[10,11] According to various studies of patient-reported gastrointestinal symptoms, the majority of patients complained of symptoms such as indigestion, abdominal pain, constipation, diarrhea, or reflux.[12,13] In particular, symptoms indicating the possibility of gastroesophageal reflux disease (heartburn or regurgitation) were reported to occur in 17% to 43% of renal transplant recipients during the post-transplant period.[14-16] Similarly, it was reported that incidence of

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Received on December 12, 2011. Accepted on January 9, 2012.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2012.6.3.349
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such symptoms rose from 3.4% to 27.6% after living donor liver transplantation.[17,18] From these results, we hypothesized that a considerable number of transplant recipients are likely to show endoscopic evidence of EE or BE after transplantation. However, to date, no study using endoscopy to screen for EE in SOT recipients, compared to a general non-transplant population, has been performed, and little is known regarding the occurrence of BE after organ transplantation. Indeed, a majority of investigations include endoscopic examination only for individuals with serious symptoms.[14,15] Furthermore, there appears to be more interest in infectious than non-infectious esophagitis in SOT recipients. To overcome these limitations, it will be essential to evaluate the endoscopic findings of the gastroesophageal junction by using upper endoscopy as a screening tool for the population undergoing SOT.

The aim of the current study was to determine whether the incidence of endoscopic findings of EE or BE is high in SOT recipients compared with a control population.

## MATERIALS AND METHODS

### 1. Patients

We performed a case-control study at the Severance Hospital in Seoul, Korea from 2005 to 2010. The study population consisted of subjects who had pre and post-transplant upper gastrointestinal endoscopy among 3,152 SOT (kidney, liver, pancreas, or heart transplantation) recipients. Patients were excluded for the following reasons: no baseline endoscopic examination prior to SOT (n=1,941), no data of follow-up endoscopy after transplantation (n=409), diagnosed of EE or BE in baseline endoscopy (n=133), previous gastric cancer or colorectal cancer (n=21), previous gastric surgery (n=9), high-risk symptoms such as occult blood, anemia, hematemesis, hematochezia, melena, vomiting, dysphagia, odynophagia, palpable mass, jaundice, or weight loss (n=70),[19] current use of nonsteroidal anti-inflammatory drugs (NSAIDs) or other ulcerogenic agents (n=99), or drug history of acid suppressive treatment within 6 months from 2nd endoscopic examination (n=214). The control group consisted of age- and gender matched patients who had undergone sequential endoscopies at intervals over 1 year as part of a health check-up during the same period and who had no endoscopically observed EE or BE in the first endoscopy. SOT patients (n=256), including 164 kidney, 85 liver, 5 pancreas, and 2 heart recipients, were selected using the procedure illustrated in Fig. 1. Patients in an age- and gender-matched screening population (n=256) were enrolled as controls. Both the groups consisted of 141 men (55.1%) and 115 women (44.9%); their mean age was 47.3±6.9 years.

### 2. Endoscopic findings

Our hospital operates a digital filing system for endoscopic images. All digital endoscopic images were independently and retrospectively reviewed by two trained endoscopists to investigate the endoscopic findings, including hiatal hernia, EE, and BE. If any inconsistency in the assessment of the digital endoscopic images occurred, a final diagnosis was decided upon by a joint review of the digital endoscopic images.

### 3. Hiatal hernia

Hiatal hernia was diagnosed when the distance between the gastroesophageal junction and the diaphragmatic hiatus was 1 cm or more.[20]

### 4. EE

EE was diagnosed based on the Los Angeles Classification and was divided into three groups: none, mild (grades A and B), or severe (grades C and D).[21]

### 5. BE

The presence of BE was diagnosed based on the C&M crite-

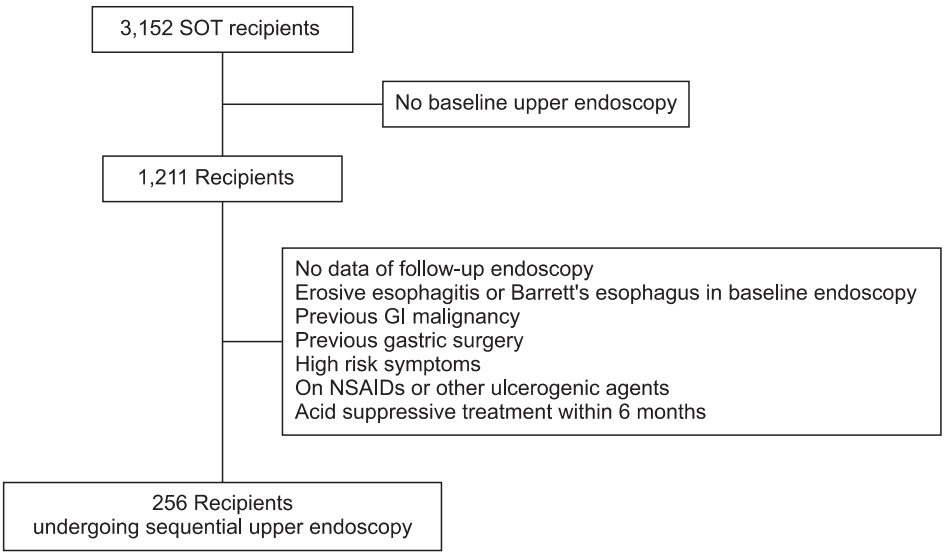


**Fig. 1.** Selection of patients for the case-control study.
SOT, solid organ transplantation; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

ria.[22] According to these criteria, BE is defined as the macroscopic identification, using a standard endoscopy examination, of abnormal columnar esophageal epithelium suggestive of a columnar-lined distal esophagus. The length of BE is measured (in centimeters) using the circumferential extent (the C extent) and the maximum extent (the M extent) above the gastroesophageal junction, identified as the proximal margin of the gastric mucosal folds.

### 6. Patient profiles

The data collected included age, gender, body mass index (BMI), medical history of diabetes or hypertension, use of tobacco, alcohol intake, date of transplantation, baseline maintenance immunosuppression (cyclosporine, tacrolimus, sirolimus, azathioprine, or mycophenolate mofetil [MMF]), reflux-related symptom, and date of upper endoscopy.

### 7. Statistical analysis

Statistical analysis was performed using a chi-square test for comparison of the discrete variables, and a t-test was used for comparison of continuous variables. The continuous variables measured in this study were expressed as the mean±SD. Significant variables in the univariate analyses ($p<0.05$) were entered into a multivariate model. Multivariate analysis was performed using logistic regression. For each variable, the odds ratio (OR) and 95% confidence interval (CI) were given. A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was conducted using PASW Statistics version 17.0 (SPSS Inc., Chicago, IL, USA).

**Table 1.** Characteristics of the Subjects

| Characteristic | SOT (n=256) | Control (n=256) | p-value |
|---|---|---|---|
| Age (SD), yr | 47.3 (6.9) | 47.3 (6.9) | 1.000 |
| Male gender, n (%) | 141 (55.1) | 141 (55.1) | 1.000 |
| Body mass index (SD), kg/m$^2$ | 22.2 (2.3) | 23.9 (2.1) | 0.031 |
| Diabetes, n (%) | 65 (25.4) | 23 (9.0) | <0.001 |
| Hypertension, n (%) | 103 (40.2) | 48 (18.8) | <0.001 |
| Smoking habit, n (%) | 24 (9.4) | 36 (14.1) | 0.145 |
| Regular drinking habit, n (%) | 37 (14.5) | 50 (19.5) | 0.136 |
| Reflux-associated symptom, n (%) | 78 (30.5) | 17 (6.6) | <0.001 |
| Endoscopic interval, mo | 23.9±7.9 | 24.9±7.8 | 0.371 |
| Erosive esophagitis, n (%) | | | |
| None | 212 (82.8) | 240 (93.8) | <0.001 |
| Total | 44 (17.2) | 16 (6.2) | |
| Grade A | 29 | 14 | |
| Grade B | 10 | 2 | |
| Grade C | 4 | 0 | |
| Grade D | 1 | 0 | |
| Hiatal hernia, n (%) | 48 (18.8) | 55 (21.5) | 0.621 |
| Barrett's esophagus, n (%) | 3 (1.1) | 4 (1.6) | 0.727 |

SOT, solid organ transplantation; SD, standard deviation.

## RESULTS

### 1. Case-control comparisons

A comparison of patient profiles and endoscopic findings between SOT and control groups is shown in Table 1. BMI was significantly lower in the patients compared to the controls ($p=0.031$), whereas the frequency of hiatal hernia was almost equal in both the groups. Thirty-seven (17.2%) and 13 (6.2%) cases of EE were detected in the SOT and control groups, respectively ($p<0.001$). A higher incidence of severe graded esophagitis was also found in the SOT group, but this difference was not statistically significant (11.4% vs 0%, $p=0.232$). In addition, there was no significant difference in the prevalence of BE between the SOT and control groups (1.1% vs 1.6%, $p=0.727$). The mean durations from baseline upper endoscopy to second endoscopy in the SOT group and control group were 23.9±7.9 and 24.9±7.8 months, respectively ($p=0.371$).

### 2. Risk factors for EE

Based on the univariate analysis for risk factors, EE was associated with age, BMI, presence of hiatal hernia, presence of BE, and transplantation (Table 2). Based on the multivariate logistic regression analyses, old age (OR, 1.12; 95% CI, 1.07 to 1.19), high BMI (OR, 1.28; 95% CI, 1.06 to 1.45), presence of hiatal hernia (OR, 4.98; 95% CI, 2.51 to 9.91), and transplantation (OR, 6.48; 95% CI, 2.74 to 15.35) were associated with an increased risk for EE (Table 3).

### 3. Characteristics of subjects with EE in the SOT group

When the characteristics of individuals with or without

**Table 2.** Clinical Characteristics of the Patients according to the Presence or Absence of Erosive Esophagitis

| Characteristic | Erosive esophagitis | | p-value |
|---|---|---|---|
| | Absence (n=452) | Presence (n=60) | |
| Age (SD), yr | 46.3 (6.3) | 53.1 (6.8) | <0.001 |
| Male gender, n (%) | 247 (53.1) | 35 (58.3) | 0.121 |
| Body mass index (SD), kg/m$^2$ | 22.4 (2.1) | 23.8 (2.3) | 0.039 |
| Diabetes, n (%) | 76 (16.8) | 12 (20.0) | 0.171 |
| Hypertension, n (%) | 128 (28.3) | 23 (38.3) | 0.078 |
| Smoking habit, n (%) | 54 (11.9) | 6 (10.0) | 0.989 |
| Regular drinking habit, n (%) | 78 (17.3) | 9 (15.0) | 0.411 |
| Reflux-associated symptom, n (%) | 50 (11.1) | 45 (75.0) | <0.001 |
| Hiatal hernia, n (%) | 78 (17.3) | 25 (50.0) | <0.001 |
| Barrett's esophagus, n (%) | 4 (0.9) | 3 (5.0) | 0.046 |
| Transplantation, n (%) | 211 (46.7) | 45 (75.0) | <0.001 |

EE within the SOT group were analyzed, age (p<0.001), BMI (p=0.001), hiatal hernia (p<0.001), duration of immunosuppression (p=0.006), and maintenance administration of MMF (p=0.006) were associated with EE, according to the univariate analysis (Table 4). Based on the multivariate logistic regression analyses, an increased risk of EE was strongly associated with the presence of hiatal hernia (OR, 5.84; 95% CI, 2.23 to 15.71; p<0.001), and MMF (OR, 4.13; 95% CI, 1.25 to 13.92; p=0.022) and more weakly with age (OR, 1.17; 95% CI, 1.09 to 1.29; p<0.001) in the SOT group (Table 5). In addition, increased duration of immunosuppression was an independent factor associated with the development of EE (OR, 1.07; 95% CI, 1.04 to 1.15; p=0.019).

**Table 3.** Multiple Logistic Regression Analysis of the Clinical Factors Associated with Erosive Esophagitis

| | OR | 95% CI | p-value |
|---|---|---|---|
| Age | 1.12 | 1.07-1.19 | <0.001 |
| Body mass index | 1.28 | 1.06-1.45 | 0.002 |
| Hiatal hernia | 4.98 | 2.51-9.91 | <0.001 |
| Barrett's esophagus | 3.19 | 0.47-22.51 | 0.241 |
| Transplantation | 6.48 | 2.74-15.35 | <0.001 |

OR, odds ratio; CI, confidence interval.

**Table 4.** Characteristics of the Subjects with Erosive Esophagitis in the SOT Group (Univariate Analyses)

| Characteristic | Erosive esophagitis | | p-value |
|---|---|---|---|
| | Absence (n=211) | Presence (n=45) | |
| Age (SD), yr | 46.1 (6.6) | 51.8 (6.1) | <0.001 |
| Male gender, n (%) | 115 (54.5) | 26 (57.8) | 0.365 |
| Body mass index (SD), kg/m$^2$ | 21.1 (2.6) | 23.5 (1.9) | 0.001 |
| Diabetes, n (%) | 53 (25.1) | 12 (26.7) | 0.731 |
| Hypertension, n (%) | 83 (39.3) | 20 (44.4) | 0.311 |
| Smoking habit, n (%) | 19 (9.0) | 5 (11.1) | 0.517 |
| Regular drinking habit, n (%) | 30 (14.2) | 7 (15.6) | 0.819 |
| Hiatal hernia, n (%) | 27 (12.8) | 21 (46.7) | <0.001 |
| Barrett's esophagus, n (%) | 3 (1.4) | 0 | 0.694 |
| Duration of immunosuppression (SD), mo | 24.9 (7.1) | 29.2 (6.5) | 0.006 |
| Maintenance immunosuppression, n (%) | | | |
| Cyclosporine | 104 (49.3) | 23 (51.1) | 0.857 |
| Tacrolimus | 94 (44.5) | 22 (48.9) | 0.611 |
| Sirolimus | 25 (11.8) | 3 (6.7) | 0.312 |
| Azathioprine | 34 (16.1) | 9 (20.0) | 0.577 |
| Mycophenolate mofetil | 85 (40.2) | 29 (64.4) | 0.006 |

SOT, solid organ transplantation; SD, standard deviation.

## DISCUSSION

The principal finding of this study is that SOT was a significant factor for the development of EE. The occurrence of this complication was found to be associated with the type of immunosuppressant and the duration of immunosuppressive therapy in SOT recipients.

Our study showed an increased incidence of EE in SOT recipients undergoing sequential screening endoscopic examinations before and after transplantation. Although this increase was largely driven by mild-grade esophagitis, it was significantly higher than the prevalence in controls. Organ transplantation was strongly associated with EE (OR, 6.48; 95% CI, 2.74 to 15.35) along with previously identified factors such as age, BMI, and hiatal hernia. There is evidence that a proportion (between 1% and 13%) of patients with EE develop BE annually, and it has been shown that patients with EE are 5 times more likely to develop esophageal cancer. Interestingly, it was reported that the risk of esophageal cancer is twice as high in transplanted patients compared with those on the waiting list.[23,24] However, no significant difference was identified between cases and controls with regard to the incidence of BE. The nonsignificant rate of severe esophagitis or BE in our analysis may be attributable to the relatively short follow-up interval. Because it is known that patients who have been affected by gastroesophageal reflux disease for 20 years have 16.4 to 40 times greater risk of developing BE than does the general population, long-term follow-up evaluation from SOT through EE to BE is clearly warranted.[25]

The genesis of SOT-related gastrointestinal complications is multifactorial. Multiple factors, including the stress of surgery, use of NSAIDs, and possible impairment of native gastroduodenal cytoprotection due to an azathioprine or MMF-induced slowing of intestinal cell turnover, contribute to ulcer formation in transplant patients.[26] Data regarding the incidence of dyspepsia and reflux symptoms with different immunosuppressive regimens are rare and inconclusive. However, preliminary data suggest that changes in immunosuppressive therapy could improve the gastrointestinal symptom burden and increase gastrointestinal specific health-related quality of life in those patients with gastrointestinal complaints.[10,27] Some independent

**Table 5.** Characteristics of Subjects with Erosive Esophagitis in the SOT Group (Multivariate Analysis)

| Characteristic | OR | 95% CI | p-value |
|---|---|---|---|
| Age | 1.17 | 1.09-1.29 | <0.001 |
| Body mass index | 1.24 | 0.99-1.53 | 0.059 |
| Hiatal hernia | 5.84 | 2.23-15.71 | <0.001 |
| Duration of immunosuppression | 1.07 | 1.04-1.15 | 0.019 |
| Mycophenolate mofetil | 4.13 | 1.25-13.92 | 0.022 |

SOT, solid organ transplantation; OR, odds ratio; CI, confidence interval.

factors influencing the development of EE after SOT were identified in our study. It has previously been shown that treatment with MMF is associated with frequent gastrointestinal adverse events. Although data from randomized-clinical trials are lacking, a substantial body of evidence from retrospective studies and registry database analyses indicates that gastrointestinal complications in renal transplant patients necessitate MMF dose reduction or discontinuation in a high proportion of cases.[27,28] Our study showed that duration of immunosuppression and maintenance of MMF was significantly associated with EE after organ transplantation. This should be considered in screening for post-transplant complications. However, it is not clear whether MMF exerts a direct effect, or whether EE developed secondary to functional gastrointestinal problems induced by MMF. It was known that MMF had the potential to cause toxic injury throughout the gastrointestinal tract. Within the upper gastrointestinal tract, MMF was associated with topical irritation and damage, leading to NSAID-like pathology, including esophageal and duodenal ulcers, and also reactive gastropathy, which appears to be a common manifestation of MMF. Within the lower gastrointestinal tract, MMF-induced pathology appears to be related mainly to its antimetabolite effects, giving biopsies from the colon and ileum Graft-versus-Host disease-like properties, including mild architectural changes with dilated damaged crypts, lamina propria edema, increased crypt epithelial apoptosis, and patchy neutrophilic inflammation.[29]

The main limitations of our investigation are the short duration of follow-up and a rather small number of cases. In addition, our study was a retrospective, observational study in which the need for screening endoscopy was determined by the endoscopist. Endoscopic diagnosis of BE was a problematic limitation of retrospective design. Nevertheless, this is the first case-control study of EE associated with SOT. The results of this study warrant a much larger prospective study to confirm these observations.

In conclusion, there was a significant increase in the incidence (OR, 6.49) of endoscopic findings of EE in SOT recipients, compared with a control population. However, we did not identify a significant association of BE with SOT. Other factors, including age, presence of hiatal hernia, duration of immunosuppression, and maintenance of MMF, had significant influences on EE in SOT recipients.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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