Prevalence of Asymptomatic Gastroduodenal Lesions and *Helicobacter pylori* Infection in Kidney Transplant Candidates

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Background: *Upper gastrointestinal (UGI) diseases are more common in patients with end-stage renal disease (ESRD) compared to general populations. Previous studies demonstrated that ESRD patients with UGI disease are at increased risk for developing complications following kidney transplantation (KT). Prevalence of UGI lesions and Helicobacter pylori in asymptomatic KT candidates remain unclear.*
Objective: *To evaluate the prevalence of UGI lesions and Helicobacter pylori in nondyspeptic KT candidates.*
Material and Method: *The authors retrospectively and prospectively enrolled consecutive patients with ESRD who underwent esophagogastroduodenoscopy (EGD) as part of pre-KT evaluation at a single tertiary center (Rajavithi Hospital, Bangkok) between 2008 and 2013. Patients with significant dyspeptic symptoms, known UGI disease and received PPI/NSAIDs/ antibiotics within two weeks before EGD were excluded. EGD was performed with random biopsies for rapid urease test and histology.*
Results: *In all, 107 ESRD patients were included; 53.0% were men and a median age was 38.7 (15.9-65.0) years. A total of 95% of patients had been on hemodialysis with the median duration of 2.1 (0.2-15.3) years. Significant EGD findings (defined as lesions other than normal and nonerosive gastritis) were encountered in 46% of patients; most lesions were erosive gastroduodenitis and peptic ulcers. Among several baseline demographic and laboratory parameters analyzed, only older age was significantly associated with significant EGD findings ($p = 0.026$). Helicobacter pylori infection was documented in 27.1% of patients. This prevalence tended to be lower than the prevalence of H. pylori of 39% in 105 sex- and age-matched, nonESRD patients without significant EGD findings who underwent EGD during the same time, but not statistically significant ($p = 0.08$).*
Conclusion: *The authors demonstrated a considerable prevalence of acid-related UGI diseases and H. pylori infection in nondyspeptic KT candidates. Therefore, EGD is a reasonable part of routine preKT evaluations, at least in our part of the world, to promptly detect and precisely manage the problem.*

Keywords: *End-stage renal disease, Kidney transplantation, Dyspepsia, Esophagogastroduodenoscopy, Peptic ulcers, Gastritis, Helicobacter pylori*

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Patients with end-stage renal disease (ESRD) have a high incidence of upper gastrointestinal (UGI) diseases, although the occurrence and type of symptoms may vary considerably in different individuals[1-6]. Various gastrointestinal symptoms, such as anorexia, nausea, vomiting and dyspepsia, are more common in patients with ESRD awaiting kidney transplantation (KT). These symptoms can be a manifestation of uremia, or result from medications and electrolyte imbalance, which do not reliably predict the presence of significant UGI lesion(s). On the other hand, many of ESRD patients with peptic ulcer are asymptomatic[2,7,8] and can be associated with significant complications both before and after KT, especially during the period of high immunosuppression[9-11].

Most previous studies have demonstrated a higher prevalence of UGI diseases in patients with ESRD when compared with the general population[1-7].

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Common UGI lesions that encounter esophagogastroduodenoscopy (EGD) in patients with ESRD include superficial gastroduodenitis, gastroduodenal erosions, gastroduodenal ulcers, hemorrhagic gastritis, angiodysplasia, and reflux esophagitis[1-7]. Although UGI lesions are often correlated with the presence of dyspeptic symptoms, UGI disease and complications have also been reported in patients with nondyspeptic ESRD[2,7,8,12]. The exact mechanism of increased prevalence of UGI diseases in patients with ESRD remains unclear, but it seems to be linked with pathophysiologic changes related to ESRD, e.g., uremia, hypergastrinemia and secondary hyperparathyroidism and concurrent medications that are commonly used among patients with ESRD, e.g., antiplatelets, analgesics, iron and calcium supplement. In addition, the prevalence of *Helicobacter pylori* infection (49-63%) is slightly lower or similar when compared with general populations in the same geographical regions[1-6,13].

Peptic ulcers are associated with substantial morbidity and mortality in patients with ESRD. Troppman et al[10] demonstrated that ESRD patients with peptic ulcer are up to three fold increased risk for developing UGI complications following KT. It should be noted that UGI bleeding in patients with ESRD is associated with high mortality (13%; vs. 2% in non-ESRD patients)[12] and very high if occurring during the first six months following KT (40% mortality)[11]. In addition, a three-year follow-up study reported that UGI symptoms or complications are relatively common after KT and are associated with a significantly increased risk of graft loss and death[14].

Based on such evidence, EGD before KT should be clearly considered in KT candidates with UGI symptoms or those with a history of peptic ulcer, and this recommendation is supported by the current guidelines of the American Society of Transplantation[15] and the Canadian Society of Transplantation[16]. Thus, KT should be postponed in patients with active peptic ulcer until they are fully treated and are asymptomatic[15,16]. However, no strong evidence exists regarding the role of routine EGD and *H. pylori* screening for nondyspeptic KT candidates and the local practice guidelines appear to vary among different transplant centers. For example, the local practice guideline in our center is to recommend all KT candidates to undergo EGD as part of routine pretransplant evaluation.

It is well-known that the prevalence of UGI diseases and *H. pylori* vary substantially among different geographical regions of the world; the prevalence of *H. pylori*-associated UGI diseases are higher in Asians when compared with Western countries[17]. To our knowledge, the prevalence of UGI lesions or the prevalence of *H. pylori* in asymptomatic KT candidates has never been systematically reported from Thailand, as well as from other Southeast Asian countries. Therefore, the prevalence of UGI diseases in patients with ESRD and the question whether or not a routine EGD for pre-KT evaluation is justified in this part of the world remain unclear.

The aims of the present study were to evaluate the prevalence of UGI lesions and *H. pylori* in non-dyspeptic KT candidates, as well as to determine the factors significantly associated with significant EGD findings and *H. pylori* infection.

Material and Method

Patients

The authors retrospectively and prospectively enrolled consecutive patients with ESRD aged between 15-65 years who underwent esophagogastroduodenoscopy (EGD) as part of pre-KT evaluations at a single tertiary center (Rajavithi Hospital, Bangkok, Thailand) between December 2008 and October 2013. Prospective evaluation was initiated since August 2012 and included 40 patients.

Exclusion criteria were significant dyspeptic symptoms, e.g., epigastric pain, epigastric burning, postprandial fullness, early satiety, known UGI disease or malignancy, history of UGI surgery, underwent EGD in the previous six months, recent use of medications that may cause UGI lesions or affect *H. pylori* testing (including proton pump inhibitors, NSAIDs, aspirin, clopidogrel, penicillin, sulphonamides, macrolides, doxycycline, tetracycline, corticosteroid, digoxin, potassium, bisphosphanate, and theophylline) within two weeks before EGD or patients who contraindicate or refuse to undergo EGD. The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 150/2555).

Data collection

Relevant clinical and laboratory data from hospital records were also reviewed covering demographics, clinical symptoms, comorbid disease(s), use of medications, cause of ESRD, mode and duration of renal replacement therapy (RRT) and laboratory parameters, e.g., blood urea nitrogen, creatinine, calcium, albumin and hematocrit. In a prospective cohort study, the patients were evaluated on the basis

of personal interviews and uniform questionnaires before EGD.

Endoscopic and Helicobacter pylori evaluations

EGD was performed after an overnight fast by four experienced endoscopists (each performing >200 EGD cases yearly). Informed consent was obtained from all patients before the procedure. Significant EGD findings, defined as lesions other than normal, non-erosive gastritis and at least four biopsy specimens were randomly obtained for rapid urease test and histology. Peptic ulcer included gastric ulcer, duodenal ulcer and peptic stricture. Erosive gastroduodenitis was defined as gastritis or duodenitis in which more than two erosions were detected on EGD.

Assessment for the presence of *H. pylori* infection was based on either the rapid urease test (Pronto Dry®, MIC France, Lyon, France) or histological staining (hematoxylin and eosin) of gastric biopsies. The positivity of at least one test was considered active *H. pylori* infection. In addition, we retrospectively reviewed EGD findings and *H. pylori* test results of 105 non-ESRD, sex- and age-matched, asymptomatic patients who underwent EGD for check-up (38%) and symptomatic patients who underwent EGD as part of a work-up (62%), and revealed nonsignificant findings in our center during the same time period to compare with the study population in terms of the prevalence of *H. pylori*.

Statistical analysis

The categorical variables are presented as number, percentage, whereas the continuous variables are presented as median (range) or mean (standard deviation). For the statistical method used in our analysis, the Chi-square or Fisher's exact test was used for categorical variables, whereas the Student t-test or Mann-Whitney U test was used for continuous variables, depending on the distribution of data. A *p*-value <0.05 was considered statistically significant. Data analyses were performed using the SPSS, version 17.0 (SPSS Inc. Chicago IL, USA).

Results

A total of 107 patients signed the consent for EGD and were enrolled in this study. Baseline demographics and laboratory data are summarized in Table 1. Fifty-seven patients (53%) were men, median age was 38.7 (16-65) years, and median weight was 55 (36-99) kg. The most common causes of ESRD were unknown (58.9%) and chronic glomerulonephritis (19.6%). Nearly all patients (95.3%) had undergone hemodialysis for the median duration of 2.1 (0.2-15.3) years before the study.

Table 1. Demographic data and laboratory parameters

Parameters	n = 107
Sex	
Male	57 (53.0)
Female	50 (47.0)
Age (years)	39.4±10.3
Weight (kg)	58.9±12.0
Comorbidities	
Diabetes mellitus	6 (5.6)
Hypertension	71 (66.4)
Dyslipidemia	14 (13.1)
Gout	4 (3.7)
Viral hepatitis	4 (3.7)
Causes of end-stage renal disease	
Chronic glomerulonephritis	21 (19.6)
Diabetic nephropathy	5 (4.7)
Lupus nephritis	5 (4.7)
ADPKD	6 (5.6)
Others	7 (6.5)
Unknown	63 (58.9)
Mode of RRT	
Hemodialysis	102 (95.3)
Continuous ambulatory peritoneal dialysis	4 (3.7)
No RRT	1 (0.9)
Duration of RRT (years)	3.2±3.0
Laboratory parameters	
BUN (mg/dL)	56.6±19.94
Creatinine (mg/dL)	10.8±2.89
Hematocrit (%)	32.6±4.71
Calcium (mg/dL)	9.1±1.43
Albumin (g/dL)	4.4±0.38

Values are represented as n (%) or mean ± SD
ADPKD = autosomal dominant polycystic kidney disease; RRT = renal replacement therapy; BUN = blood urea nitrogen

The endoscopic findings of the patients are illustrated in Table 2. Significant EGD findings were presented in 45.8% (49/107), whereas negative findings were observed in 54.2% (58/107); non-erosive gastritis in 46.7% (50/107) and normal findings in 7.5% (8/107). Among the significant EGD lesions detected, erosive gastritis 49% (24/49) and peptic ulcer 14.3% (7/49) were the most common. Notably, more than one type of lesion and incidental findings, including sliding hiatal hernia (9), gastric polyps (8), pseudomelanosis duodeni (3), postal hypertensive gastropathy (2), small esophageal varices (1) and gastric lipoma (1) were also encountered in some patients.

Several factors such as age, sex, duration of hemodialysis, blood urea nitrogen, creatinine, and hematocrit, were analyzed whether they could predict significant EGD findings; only older age was significantly associated with significant EGD findings (mean age 41.88±10.86 vs. 37.38±9.46 years, $p = 0.026$) (Table 3).

Table 2. Endoscopic findings

Endoscopic findings	Patients, n (%)
Significant findings	49 (45.8)
Peptic ulcer (gastric: duodenal = 3:4)	7 (6.5)
Erosive gastroduodenitis	24 (22.4)
Atrophic gastritis	5 (4.7)
Gastroesophageal reflux disease	5 (4.7)
Others	8 (7.5)
Nonsignificant findings	58 (54.2)
Normal	8 (7.5)
Nonerosive gastritis	50 (46.7)

Helicobacter pylori infection was documented in 27.1% (29/107) of patients and was not different among patients with and without significant EGD findings (30.6% vs. 24.1%, respectively; $p = 0.516$). This prevalence tended to be lower than the prevalence of *H. pylori* of 39% (41/105) in sex- and age-matched, nonESRD patients with nonsignificant EGD findings who underwent EGD in our center during the same period of time, but without significance ($p = 0.08$).

Discussion

Several mechanisms appear to contribute to an increased risk for UGI diseases in patients with ESRD, such as pathophysiologic changes from renal disease itself, e.g., hypergastrinemia, hyperammonemia, secondary hyperparathyroidism, comorbidities, effects of hemodialysis and concurrent medications. Gastrin level is often increased in patients with ESRD and can be partly explained by decreased renal metabolism of gastrin[7,18]. The higher level of urea in patients

Table 3. Analysis between patients with ESRD with significant versus nonsignificant EGD findings

	Significant EGD (n = 49)	Nonsignificant EGD (n = 58)	*p*-value
Sex (male)	59.2%	48.3%	0.331
Age (years)	41.9±10.9	37.4±9.5	0.026
Weight (kg)	60.3±11.6	57.7±12.3	0.282
Duration of RRT (years)	2.9±2.8	3.4±3.4	0.373
H. pylori infection	30.6%	24.1%	0.516
BUN (mg/dL)	60.5±20.2	53.1±19.2	0.067
Creatinine (mg/dL)	10.0±3.0	10.8±2.9	0.782
Hematocrit (mg/dL)	33.4±4.5	31.8±4.8	0.094
Calcium (mg/dL)	9.2±1.6	9.1±1.3	0.900
Albumin (g/dL)	4.4±0.4	4.4±0.4	0.613

Values are represented as n (%) or mean ± SD
EGD = esophagogastroduodenoscopy; RRT = renal replacement therapy; BUN = blood urea nitrogen

Table 4. Prevalence of *Helicobacter pylori* infection

	KT candidates study subjects (n = 107)	Non-ESRD controls controls (n = 105)	*p*-value
Sex (male) (%)	53.0	50.5	0.783
Age (years)	39.4±10.3	42.3±15.2	0.064
H. pylori infection (%)	27.1	39.0	0.082

Values are represented as n (%) or mean ± SD
KT = kidney transplantation; ESRD = end-stage renal disease

undergoing dialysis can lead to the increase in proton diffusion in the gastrointestinal lumen[7,18]. Accordingly, most previous studies demonstrated a higher prevalence of acid-related UGI diseases in patients with ESRD when compared with the general population[1,2,4-7].

Unlike previous studies that mostly evaluated patients with ESRD having dyspepsia and originating from North America, Europe, the Middle-East and Japan[1-6], the present study focused on ESRD KT candidates without significant dyspeptic symptoms and, to our knowledge, is the first report from Southeast Asia. Acid-related UGI lesions, particularly peptic ulcers and erosive gastroduodenitis, are commonly found in our patients with ESRD (46%), although this prevalence seems to be lower than that of the previous reports (prevalence of significant UGI lesions ranged 64-93%)[1-6]. This difference can be explained largely by geographical variation and by the fact that the majority (74-100%) of subjects included in most of the previous reports were dyspeptic[1-6]. Data taken from studies that mainly included asymptomatic patients (50-74%) have reported a prevalence of UGI diseases approximately 50%[2,7]. It should be noted that it may be imprecise to compare the results across different studies due to dissimilarities in the endoscopic classification scheme used.

Taken together, it appears that KT candidates with dyspepsia tend to have a higher prevalence of UGI diseases than those without symptoms. Nevertheless, UGI diseases are also detected in a significant proportion of asymptomatic KT candidates. The relatively low symptomatic rates among patients with ESRD having UGI lesions may be partly explained by a variety of peripheral motor and sensory nerve disorders in uremic patients, which may reduce visceral sensitivity[19]. In the author's view, this finding should be highlighted because some of these patients may later develop UGI complications, mainly UGI bleeding, without warning symptoms. Thus, the occurrence UGI complications mostly to peak around the first six months following KT and are associated with high mortality rates[9-11]. Therefore, EGD is a safe procedure for KT candidates (no peri- and postprocedural adverse events occurred among 107 patients who underwent EGD in the present study) and should be considered as part of routine preKT evaluations.

Helicobacter pylori have been known to play a key role in the pathogenesis of peptic ulcers, as well as many other UGI diseases. In this study, we evaluated the presence of *H. pylori* by two biopsy-based methods to minimize false negativity. *H. pylori* infection was detected in 27% of our patients and no correlation was observed between the presence of *H. pylori* and significant EGD findings. The prevalence of *H. pylori* of patients with ESRD tended to be lower than that of the non-ESRD control cohort (39%). Notably, this finding is in the same line as most earlier reports[1-5,13,20]. At least three reasons can explain a lower prevalence of *H. pylori* infection among patients with ESRD patients: (I) Patients receiving dialysis have higher levels of pro-inflammatory cytokines which activates inflammatory cells infiltrating the gastric mucosa. As a result, gastric atrophy progresses, accompanied by increased pH, creating an unpleasant environment for the existence of *H. pylori*; (II) Urea nitrogen levels in gastric secretions are higher in dialysis patients than in patients with normal renal function, and high urea levels may inhibit *H. pylori* growth in the gastric mucosa; (III) *H. pylori* infection might be cured upon antibiotic treatment that ESRD patients commonly received during their course of illness[20]. Interestingly, more than one third of patients receiving approximately four years of dialysis were naturally cured of *H. pylori* infection within the four-year observation period[1].

Due to low resources, the present study had several limitations including relatively small sample size, lack of parallel control group, evaluations for pathogenic mechanisms such as cytokines and neurohormonal changes and assessment for long-term outcomes following KT.

In conclusion, acid-related UGI diseases (prevalence 46%) and *H. pylori* infection (prevalence 27%) are commonly detected in nondyspeptic KT candidates. Therefore, EGD is reasonable as part of routine pre-KT evaluations, at least in Asia, to promptly detect and precisely manage the problem.

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Potential conflicts of interest

None.

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ความชุกโรคทางเดินอาหารส่วนบนและการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรในผู้ป่วยโรคไตวายเรื้อรังก่อนเข้ารับการเปลี่ยนไต

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ภูมิหลัง: *โรคระบบทางเดินอาหารส่วนบนเป็นโรคที่พบบ่อยในผู้ป่วยไตวายเรื้อรังระยะสุดท้าย ซึ่งมีความเสี่ยงในการเกิดภาวะแทรกซ้อนหลังจากการปลูกถ่ายไต ปัจจุบันยังไม่มีรายงานความชุกของการเกิดรอยโรค ในระบบทางเดินอาหารส่วนบนและการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรในผู้ป่วยไตวายเรื้อรังระยะสุดท้าย โดยไม่มีอาการปวดท้องจากประเทศไทย*

วัตถุประสงค์: *เพื่อประเมินความชุกของโรคในระบบทางเดินอาหารส่วนบน และการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรในผู้ป่วยไตวายเรื้อรังระยะสุดท้ายโดยไม่มีอาการปวดท้องก่อนการการปลูกถ่ายไต*

วัสดุและวิธีการ: *เป็นการศึกษาข้อมูลไปข้างหลังและข้างหน้าเชิงวิเคราะห์ในผู้ป่วยไตวายเรื้อรังระยะสุดท้ายที่ทำการส่องกล้องทางเดินอาหารส่วนบนเพื่อประเมินร่างกายก่อนเข้ารับการปลูกถ่ายไตที่โรงพยาบาลราชวิถีในช่วงปี พ.ศ. 2552 ถึงปี พ.ศ. 2556 ซึ่งเกณฑ์ในการคัดออกผู้ป่วยในกลุ่มดังกล่าวได้แก่ ผู้ป่วยที่มีอาการทางระบบทางเดินอาหารส่วนบน, ผู้ป่วยที่มีประวัติโรคทางระบบทางเดินอาหารส่วนบน ผู้ป่วยที่ได้รับยาลดกรดหรือยาที่อาจระคายเคืองทางเดินอาหารส่วนบนในระยะเวลา 2 สัปดาห์ก่อนทำการส่องกล้องทางเดินอาหารส่วนบน การส่องกล้องทางเดินอาหารส่วนบนทำร่วมกับการทดสอบการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรโดยวิธี rapid urease test ร่วมกับส่งชิ้นเนื้อตรวจทางพยาธิวิทยา*

ผลการศึกษา: *ผู้ป่วยไตวายเรื้อรังระยะสุดท้ายจำนวน 107 ราย ที่เข้าเกณฑ์คัดเข้าของงานวิจัยมีอายุมัธยฐาน 38.7 (15.9-65.0) ปี ร้อยละ 95 ได้รับการล้างไตแบบฟอกเลือด เป็นระยะเวลามัธยฐาน 2.1 (0.2-15.3) ปี พบว่าร้อยละ 46 ของกลุ่มการศึกษาเป็นโรคในระบบทางเดินอาหารส่วนบนอย่างมีนัยสำคัญ ซึ่งส่วนใหญ่พบว่าเป็นกระเพาะอาหารและลำไส้เล็กส่วนต้นอักเสบชนิดเยื่อบุกร่อน (erosive gastroduodenitis) และแผลในทางเดินอาหาร (peptic ulcer) และพบว่าอายุที่มากขึ้นมีความสัมพันธ์กับการพบโรคในระบบทางเดินอาหารส่วนบนอย่างมีนัยสำคัญ (p = 0.026) พบการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรในร้อยละ 27.1 ของผู้ป่วยไตวายเรื้อรังระยะสุดท้ายในการศึกษา ซึ่งความชุกของกลุ่มการศึกษามีแนวโน้มที่น้อยกว่ากลุ่มควบคุม ซึ่งไม่ใช่ผู้ป่วยโรคไตวายเรื้อรังระยะสุดท้าย และมีอายุใกล้เคียงกับกลุ่มการศึกษาและเข้ารับการส่องกล้องในระบบทางเดินอาหารส่วนบนในช่วงระยะเวลาใกล้เคียงกันจำนวน 105 ราย (พบการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรร้อยละ 39) อย่างไม่มีนัยสำคัญ (p = 0.08)*

สรุป: *โรคระบบทางเดินอาหารส่วนบนและการติดเชื้อเฮลิโคแบคเตอร์ไพโลไรมีความชุกมากพอสมควรในผู้ไตวายเรื้อรังระยะสุดท้ายที่รอปลูกถ่ายไตและไม่มีอาการทางระบบทางเดินอาหาร ดังนั้นการส่องกล้องทางเดินอาหารส่วนบนเพื่อประเมินร่างกายก่อนเข้ารับการปลูกถ่ายไตน่าจะมีความเหมาะสมเพื่อการวินิจฉัยและรักษาโรคทางเดินอาหารส่วนบนอย่างเหมาะสมก่อนการเปลี่ยนไต*