Gastro-Duodenal Lesions and *Helicobacter pylori* Infection in Uremic Patients and Renal Transplant Recipients

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ABSTRACT

Background. Upper gastrointestinal (UGI) symptoms are common in uremic patients, and higher serum levels of urea have been suggested to be related to *Helicobacter pylori* (HP) colonization and UGI mucosal inflammation.

Aim. The aim of this study was to compare HP infection and UGI endoscopic findings between uremic patients, renal transplant (RT) recipients, and controls.

Methods. A total of 474 subjects (71 chronic renal failure [CRF], 73 hemodialysis [HD], 25 Tx, and 305 controls) from Baqyiatallah Hospital, Tehran, Iran were recruited between April 2002 and March 2004 for evaluation of dyspepsia, excluding those receiving any HP-eradication therapy. All subjects were examined for esophagus, stomach and duodenum mucosa, and infection with HP on 2 distinct tissue samples of the anthral region.

Results. Four groups of subjects (mean $\pm$ 2 se; age, 45 $\pm$ 1.6 years; 62.9% male) were studied. Duodenal ulcer in the uremic patients (CRF, 16.1%; HD, 13.7%) was more common than that in the RT-recipients (8%) and controls (6.5%); $P = .038$. Erosive gastritis and duodenal bulb deformity were also more common in the uremic subjects (CRF, 23.9%, 36.9%; HD, 30.1%, 20.5%, respectively) than those in the other subjects (RT recipients, 16%, 8%; controls, 8.2%; 0%, respectively); $P < .001$. HP infection was found to be higher in the uremic patients (CRF, 66.2%; HD, 63%) than in the RT recipients (40%) and controls (34.8%); $P < .001$.

Conclusion. Higher rates of gastric and duodenal mucosal lesions and HP infection in the uremic patients in comparison with the subjects with normal renal function may have resulted from higher serum levels of urea, anemia, and fluctuations in the gastric blood supply in the CRF and HD patients. However, more tenable evidence from controlled trials is required for the eradication of HP in all uremic patients and transplantation candidates.

HELICOBACTER *pylori* (HP) is a gram-negative spiral bacillus living in the gastric mucus adherent to mucosa, and its efficient urease protects it against acid by catalyzing urea hydrolysis to produce buffering ammonia. The prevalence of HP colonization is about 30% in the United States and other developed countries as apposed to more than 80% in most developing countries. HP is usually acquired in childhood. Other than age, the main risk factors for colonization of HP are low socioeconomic status, crowding, and low family income in childhood. Essentially, all HP-colonized persons have gastric inflammation, but this condition in itself is asymptomatic. Symptoms are due to illnesses, such as peptic ulcer or gastric malignancy, which develop in fewer than 10 percent of infected individuals.[1–3]

Several extra-gastrointestinal (GI) pathologies have been linked with HP colonization, among them chronic renal disease.[4,5]

The GI symptoms, common in patients with renal function impairment, constitute an important component of the uremic syndrome.[1] In patients undergoing hemodialysis (HD), the pathologic changes usually seen in the stomach[2] may be the result of high serum levels of gastrin, delayed gastric emptying, and HP infection.[4,5] It seems that HP infection of the gastric mucosa plays a central role in the causation of several gastro- duodenal lesions. The idea that a high level of urea in the gastric mucus in patients with advanced renal failure might predispose them to HP infection[6] stems from the notion that HP urease converts urea to ammonia and, thus, raises the local gastric pH and enhances the survival of the bacterium. The prevalence of HP infection and its relationship to upper GI pathologic changes in HD patients has been studied extensively. The prevalence of HP infection in HD patients reported in different studies is quite varied, there being a wide range of between 25% and 88%.[7–15] Most studies, however, have reported similar rates of infection. A number of these investigations have used serologic or breath-analysis methods that lack consistent sensitivity and specificity.[7–14] For all the various studies comparing upper endoscopic findings on gastro-duodenal lesions of uremic and HD patients and healthy subjects, the reports are controversial in that they show equal or higher rates of lesions, such as gastritis, duodenitis, hiatal hernia, and peptic ulcer, in these groups.[15–17] The resolution of uremia after successful renal transplantation gives rise to the hypothesis that gastric mucosa condition and HP infection status may be similar to those in subjects with normal renal function. Administration of corticosteroids and immunosuppressive drugs, however, causes concerns regarding more gastro-duodenal lesions in transplant recipients.[17,18–20]

In this study, we performed upper GI endoscopy and rapid urease test (RUT) in 3 groups of subjects with different types of renal function impairment, ie, chronic renal failure (CRF) not hemodialyzed yet, subjects undergoing HD, and renal transplant (RT) recipients and compared the results with controls, who had normal renal function status.

PATIENTS AND METHODS
Setting

Patients referred to the endoscopy division of Baqyiatallh Hospital between October 2002 and September 2004 for work-up for dyspepsia of unknown etiology were recruited.

Samples

One hundred sixty-nine patients with different levels of renal function impairments were enrolled in the study, all having dyspepsia. They were compared with 305 control patients, who had normal renal function but had been referred for an evaluation of dyspepsia. All of the 144 patients with CRF, under HD or otherwise, were older than 14 years of age and had serum creatinine (Cr) levels ≥ 1.5 mg/dL. All of the HD patients had a stable hemodynamic condition and had a history of HD for at least 4 months and 10 hours per week. Endoscopy of the HD patients was carried out on a nondialysis day. Of all of the RT recipients, having been referred for the evaluation of dyspepsia, those with serum levels of creatinine ≤1.2 mg/dL for at least 2 months before endoscopy and at least 2 months' duration of transplantation were selected (25 patients).

Exclusion Criteria

Patients with a history of smoking, alcohol consumption, abdominal surgery, and chronic liver disease; subjects with any history of receiving medication for HP eradication or any kind of antibiotics or proton pump inhibitors within a 1-month period prior to endoscopy; and subjects with an irregular consumption of nonsteroid anti- inflammatory drugs (NSAIDs) within a 2-week period before the study or any regular NSAIDs consumption during the last 2 months in each group were excluded from the study.

Main Measurements

The comparison groups were matched in terms of age, gender, and dyspepsia scores. Dyspepsia was defined as epigastric pain or discomfort (nausea, vomiting, upper abdominal fullness, or burning) lasting for at least 12 weeks. Each item of dyspepsia was scored according to the duration, intensity, and frequency of occurrence per week. The patients' latest Cr, blood urea nitrogen (BUN), and duration of HD or CRF diagnosis were assessed from their medical records. BUN and Cr levels were assessed on the day of endoscopy for the CRF, transplant and control subjects, and after the last HD session before endoscopy for the HD patients.

Upper GI endoscopy using fiberoptic endoscope (Olympus GIFQ200, Japan) was performed for all of the study subjects by one expert gastroenterologist in standard conditions. The mucosa of the subjects' esophagus, stomach, and duodenum was visualized and evaluated for erosions, ulcer, and/or deformity. The presence of multiple ptychiae and/or superficial ulcerations smaller than 5 mm was considered as erosive gastritis.[21] Two biopsy samples were obtained from each patient with biopsy forceps (Olympus FB26N, Japan) during endoscopy from the gastric antral mucosa of the greater curvature; they were considered positive for HP if the color of the urea-determinant solution (Chemenzyme Corp, Iran) changed from light yellow to violet within 24 hours after adding the specimen.

Statistical Analysis

All the data were analyzed using SPSS for Windows 11.5 (SPSS Inc., Chicago, Ill, United States), and the statistics were shown as mean ± 2 SE and frequency when necessary. Comparisons were performed with either chi-square test (or Fisher exact test when the expected count was low in more than 20% of the table cells) or one-way analysis of variance (or its correspondent nonparametric test, the Kruskal-Wallis test if necessary). Statistical significance level was considered as $P < .05$.

RESULTS

A total of 474 stable patients (62.9% male, mean age ± 2 SE: 45 ± 1.6 years) in 4 groups of subjects were studied. All of the subjects suffered from dyspepsia and had different levels of renal function status: CRF without HD (CRF, n = 71) and with HD (HD, n = 73), RT recipients (RT, n = 25), and control subjects with normal renal function (n = 305). There were no statistical differences in the study groups in

Table 1. Baseline Characteristics of Study Subjects in Different Groups

	Group				Total (n = 474)	P
	CRF (n = 71)	HD (n = 73)	RT (n = 25)	Control (n = 305)		
Age (mean ± 2 SE) y	43.9 ± 2.7	47.9 ± 3.5	39.1 ± 3.9	45.0 ± 2.3	45.0 ± 1.6	NS
Gender (m/f)	47/24	46/27	17/8	188/117	298/176	NS
BMI (mean ± 2 SE) kg/m^2	23.9 ± 0.6	23.07 ± 0.6	22.9 ± 0.6	23.7 ± 0.4	23.4 ± 0.4	NS
Cr (mean ± 2 SE) mg/dL	8.4 ± 2.7	7.3 ± 0.5	1.02 ± 0.32	0.93 ± 0.2	3.22 ± 0.5	.005
BUN (mean ± 2 SE) mg/dL	74.1 ± 5.7	67.5 ± 5.8	20.2 ± 5.6	18.5 ± 4.8	35.9 ± 4.2	.0001

Abbreviations NS, not significant.

terms of age, gender, and body mass index (BMI) distributions (Table 1). Serum BUN and Cr levels in the CRF and HD subjects were significantly higher than those in the RT recipients and the control subjects (Table 1).

The mean duration of HD for the HD subjects was 46.9 ± 10.7 months, and an average of 52.3 ± 15.6 months had elapsed from transplantation in the RT recipients.

The most common cause of renal failure in the CRF, HD, and RT subjects was diabetes mellitus (31.4%), followed by hypertension (20.1%), polycystic kidney disease (5.9%), and glomerulonephritis (2.9%). In the remaining 34.7% of the subjects, a wide range of factors had led to renal failure. There was no significant difference in the study groups regarding the etiology of renal failure (Table 2).

Upper gastrointestinal endoscopy was performed for all of the study subjects.

The control subjects showed lower rates of esophagitis than did the other 3 groups (P < .02; Table 3), but there was no significant difference in terms of the rate of hiatal hernia between the 4 study groups.

Despite higher rates of erosive gastritis in the CRF (23.9%) and HD (30.1%) subjects in comparison with those in the RT (16%) and control (8.2%) subjects, the rate of nonerosive gastritis and gastric ulcer showed no significant difference between the study groups (Table 2).

Endoscopic investigations of the duodenal area revealed that duodenal bulb ulcer and deformity were more common in the CRF and HD subjects than in the RT and control subjects; however, there was no difference regarding duodenitis, whether erosive or nonerosive, between the study groups (Table 3).

Rapid urease test for the detection of HP revealed that the CRF and HD subjects had higher rates of HP infection (66.2% and 63.0%, respectively) compared with the RT and

control subjects (40% and 34.8%, respectively); P < .001 (Table 3).

The mean serum levels of BUN and Cr in the subjects infected with HP (BUN, 49.6 ± 4.8 mg/dL and Cr, 4.9 ± 0.6 mg/dL) were higher than those in the subjects without HP infection (BUN, 24.9 ± 5.4 mg/dL and Cr, 2.4 ± 0.5 mg/dL); P < .01.

DISCUSSION

Upper GI symptoms are common among patients with CRF and patients undergoing HD. Fabbian et al[22] studied 57 HD patients, 30% of whom showed gastritis in endoscopic evaluations; nevertheless, a histological evaluation revealed that 71.5% of the patients had gastritis. Al-Mueilo,[1] in a study of 54 HD patients, demonstrated that only 18.5% of the patients had a normal gastric mucosal appearance in comparison with 33.3% in the control subjects. Our findings showed that 21.2% and 20.6% of the CRF and HD patients, respectively, had a normal gastric mucosal appearance (in comparison with 26.9% in the controls), which is in concordance with Fabbian et al and Al- Mueilo's findings.

HP has a notable relationship with CRF and HD in several ways. (1) HP contributes to development of peptic ulcer disease, esophago-gastro- duodenal erosions, and anemia due to gastro-duodenal blood loss, which is common in HD patients. (2) HP produces gastric mucosal inflammation and, hence, may contribute to dyspepsia, anorexia, and malnutrition of HD patients.[13,23,24] (3) HP may have an independent role in anemia of HD patients.[22]

We showed that erosive gastritis was common in our HD and CRF patients. A variety of factors, including NSAIDs, ethanol, biliary acids reflux, and any factor resulting in decreased gastric blood supplies, such as trauma, burn, and

Table 2. Etiology of Renal Failure in Subjects With CRF, HD Patients, and RT Recipients

	Group			Total (n = 169)
	CRF (n = 71)	HD (n = 73)	RT (n = 25)	
Diabetes	23 (32.4%)	23 (31.5%)	7 (28.0%)	53 (31.4%)
HTN	17 (23.9%)	14 (19.2%)	3 (12.0%)	34 (20.1%)
GNs	3 (4.2%)	1 (1.4%)	1 (4.0%)	5 (2.9%)
PKD	4 (5.6%)	4 (5.5%)	2 (8.0%)	10 (5.9%)
Other	24 (33.8%)	31 (42.4%)	12 (48.0%)	67 (39.7%)

Abbreviations: HTN, hypertension; GNs, glomerulonephritis; PKD, polycystic kidney disease.
Note: chi-Square P = .948.

Table 3. Upper GI Endoscopic Findings and HP Infection in Uremic Subjects, RT Recipients, and Controls With Normal Renal Function

	Group				Total (n = 474)	P
	CRF (n = 71)	HD (n = 73)	RT (n = 25)	Control (n = 305)		
Hiatal hernia	6 (8.5%)	9 (12.3%)	4 (16.0%)	34 (11.1%)	53 (11.2%)	NS
Gastric ulcer	4 (5.6%)	0 (0.0%)	0 (0.0)	10 (3.3)	14 (3.0%)	NS
Duodenal ulcer	12 (16.1%)	10 (13.7%)	2 (8.0%)	20 (6.5%)	44 (9.3%)	.038
Esophagitis						
Normal	11 (15.5%)	21 (28.8%)	3 (12.0%)	44 (62.9%)	220 (456.4%)	<.001
Mild	26 (36.6%)	22 (30.1%)	11 (44.0%)	16 (22.9%)	124 (26.2%)	.02
Erosive	30 (42.3%)	28 (38.4%)	9 (36.0%)	9 (12.9%)	114 (24.1%)	<.001
Severe erosive	4 (5.6%)	2 (2.7%)	2 (8.0%)	1 (1.4%)	16 (3.4%)	<.001
Gastritis						
Nonerosive	39 (54.9%)	36 (49.3%)	17 (68.0%)	198 (64.9%)	290 (61.2%)	NS
Erosive	17 (23.9%)	22 (30.1%)	4 (16.0%)	25 (8.2%)	68 (14.3%)	<.001
Duodenitis						
Nonerosive	15 (21.7%)	23 (31.5%)	12 (48.0%)	102 (33.4%)	152 (32.2%)	NS
Erosive	18 (26.1%)	21 (28.8%)	6 (24.0%)	60 (19.7%)	105 (22.2%)	NS
Duodenum bulb deformity	25 (36.2%)	15 (20.5%)	2 (8.0%)	0 (0.0%)	42 (8.9%)	<.001
Duodenal ulcer or deformity*	35 (49.3%)	24 (32.9%)	4 (16.0%)	40 (13.1%)	103 (21.7%)	<.001
HP	47 (66.2%)	46 (63.0%)	10 (40.0%)	106 (34.8%)	209 (44.1%)	<.001

*Either having duodenal ulcer or deformity.

sepsis, can cause gastritis.[25] However, because such factors as NSAIDs, ethanol, and other comorbidities were excluded in all of our study groups, higher rates of gastritis in the HD patients may have been due to fluctuations in the gastric blood supply during the HD sessions. This assumption is supported by the long duration of HD. Reflux of biliary acids and/or pancreatic enzymes can also be considered potential causes.

The rates of duodenal ulcer and duodenal bulb deformity in patients with impaired renal function (CRF, HD) are higher than those in subjects with normal renal function (controls and RT recipients). Karari et al, Abu farsakh et al, and Var et al[15–17] also reported similar findings in their comparative studies of uremic patients and controls.

Several investigators have reported controversial rates of HP infection in uremic patients, transplant recipients, and control subjects.[1,6–13] In our study, the rates of HP infection in the RT and control subjects were similar. That the rates of HP infection in both of the said groups were lower than those in the uremic patients (CRF, HD) can confirm the hypothesis[13,15] about the relationship between uremia and HP infection. Higher serum levels of BUN in the HP-infected subjects can be further evidence for this hypothesis.

Long periods of HD in our HD subjects (46.9 ± 10.7 months) are a marker of prolonged uremia; nonetheless, the long period of time after transplantation (52.3 ± 15.6 months) indicates enough time for the resolution of uremia and near-normal renal function in the RT recipients. A lack of information about the HD duration before transplantation in the RT recipients as a marker of the uremic period and its impact on gastritis is the major drawback of this study.

The high susceptibility of uremic patients to erosive mucosal lesions and colonization of HP necessitates that these lesions be screened and HP be eradicated in such patients. Considerable risk of complicated upper GI lesion in uremic patients despite its rarity is another reason for intensive screening.

Transplant candidates' high susceptibility to upper GI lesions, which result from pretransplantation conditions and posttransplantation stresses, such as corticosteroid therapy, makes pretransplantation evaluations and therapy advisable.[26]

We found that after transplantation, the endoscopic feature of the RT recipients became similar in comparison with the controls, who had normal renal function. Sarkio et al showed similar findings in a study of 500 RT recipients in a 6-year follow-up. Anemia resulting from CRF can be considered another potential risk factor for the colonization of HP and gastric and/or duodenal mucosal lesions.

The etiology of renal failure in a large proportion of our subjects has been reported as "others," which may be due to the fact that our criteria do not consider diabetes mellitis or hypertension diagnosed simultaneously with renal failure as etiologic factors.

In conclusion, we suggest that the eradication of HP in uremic patients and RT candidates be considered; however, the efficacy and efficiency of this approach should be evaluated in randomized controlled trials.

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