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Helicobacter pylori Status and Esophagogastroduodenal Mucosal Lesions in Patients with End-Stage Renal Failure on Maintenance Hemodialysis

Short title: Upper GI lesion in patients on HD

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Abstract

Objectives: The aim was to clarify the impact of *Helicobacter (H.) pylori* infection on esophagogastroduodenal mucosal lesions in patients with end-stage renal failure on maintenance hemodialysis (HD).

Methods: Upper endoscopy and ^{13}C-urea breath test were performed in 198 patients on maintenance HD. Clinical features, serum pepsinogen levels and esophagogastroduodenal mucosal lesions were compared between *H. pylori*-positive and -negative patients. Risk factors associated with esophagogastroduodenal mucosal lesion were determined by multivariate analyses.

Results: Upper endoscopy revealed that gastric erosion was the most frequent (58%) followed by duodenal erosion (18%), gastric ulcer (14%), gastroesophageal reflux disease (10%), and duodenal ulcer (7%). 81 patients were positive and 117 patients were negative for *H. pylori* infection. Time duration after the introduction of HD was significantly longer and serum pepsinogen I/II ratio was significantly higher in *H. pylori*-negative patients than in *H. pylori*-positive patients. Multivariate analyses revealed *H. pylori* infection to be an independent, protective factor for gastric erosion (odds ratio 0.38; 95% confidence interval 0.21-0.70), while the infection was unrelated to other mucosal lesions.

Conclusions: Gastric erosion seems to be a mucosal lesion commonly seen in patients on maintenance HD. The high prevalence may be explained partly by the cure of *H. pylori* infection during the clinical course of maintenance HD.

Key words: end-stage renal failure, hemodialysis, *Helicobacter pylori*, ulcers, upper gastrointestinal tract.

Introduction

Dyspeptic symptoms are common in patients with end-stage renal failure (ESRF), who undergo maintenance hemodialysis (HD).[1] Because anti-coagulant therapy is inevitable during HD procedures, upper gastrointestinal bleeding occurs frequently in patients with ESRF on maintenance HD.[2] However, there have been conflicting data on the prevalence of gastroduodenal mucosal lesions in patients on maintenance HD.[3,4] Doherty et al.[3] reported that most of the patients with chronic renal failure had gastrointestinal complications, while others found that the prevalence of peptic ulceration is only 2% in patients with chronic renal failure.[4]

It is widely accepted that *Helicobacter pylori* (*H. pylori*) plays an important role in the pathogenesis of chronic gastritis and gastric ulcer.[5] While the prevalence of gastroduodenal mucosal lesion in patients with chronic renal failure has been shown to be equivalent to or higher than healthy patients,[3,4] it still remains controversial as to the prevalence of *H. pylori* infection in patients undergoing HD.[6-10] We thus attempted a multi-center, prospective and observational investigation for patients on maintenance HD to determine the prevalence of esophagogastroduodenal mucosal lesions and the impact of *H. pylori* infection on those lesions.

Materials and Methods

Patients and protocol

This study was conducted prospectively for ESRF patients on maintenance HD at 23 institutions or clinics in Fukuoka City during a period from March 2002 to August 2004. Patients who had been on maintenance HD for more than 1 month were asked to participate this endoscopic surveillance program. After being informed of the aim and the protocol of the investigation by the attending nephrologists, patients who agreed with the participation were recruited for the following examination.

After obtaining written informed consent, patients were examined at one of the institutions or clinics, where gastroenterologists performed esophagogastroduodenoscopy

(EGD) and other examinations. It is well known that proton pump inhibitor intake cause false-negative result on urea breath test.[11] Since one of the main objectives of the investigation was the prevalence of *H. pylori* infection, we excluded patients who had been taking proton pump inhibitor or who had a history of gastric surgery. The protocol of this investigation was conducted in accordance with the Helsinki Declaration.

Endoscopic examination

All patients underwent EGD, using a forward-viewing endoscope (Olympus, Tokyo, Japan) on the day not scheduled for HD. Endoscopic examinations were performed by endoscopists who had participated in consensus meetings for the determination of endoscopic findings prior to the study. The mucosal lesions were classified according to the 'minimal standard terminology' established by World Organization of Digestive Endoscopy (OMED)[12]. After an overnight fast, patients were prepared by topical anesthesia with 8% lidocaine solution. Under endoscopy, the subjects were assessed with respect to the presence and the location of reflux esophagitis, gastric ulcer, gastric erosion, duodenal ulcer, duodenal erosion, cancer and other types of lesions. Reflux esophagitis was regarded to be positive when at least one or more areas of reddish mucosa or mucosal defects were seen at the esophagocardial junction.[13] Thus, esophagitis greater than grade M in modified Los Angeles classification for reflux esophagtis[13,14] was regarded to be positive for reflux esophagitis. An ulcer was defined as an area of mucosal break with obvious whitish exudate, which was measuring more than 5 mm in its largest size. The size of each ulcer was determined in comparison with biopsy forceps. Ulcers, which were obviously larger than the size of the opened forceps, were regarded to be >5mm in size. Other mucosal breaks with reddened areas in the stomach or in the duodenum were judged to be erosions. In principle, biopsy specimens were not obtained from mucosal lesions. However, sampling of one or two biopsy specimens was permitted for a lesion, which was suspected of being malignant tumor.

Assessment of H. pylori infection

H. pylori infection was determined using ^{13}C-urea breath test (^{13}C-UBT) on the day of

and just prior to EGD. Granular powder or a tablet of 100 mg ^{13}C-urea was administered orally with 100 ml tap water. Exhaled breath samples were taken at baseline and 20 minutes after consumption of the urea. The ^{13}C enrichment in breath was measured by isotope ratio mass spectrometer. The ^{13}C-UBT was considered positive if the ∂-value at 20 minutes was > 2.5‰ when compared to the baseline value. In this study, we did not apply rapid urease test for the diagnosis of *H. pylori* infection in order to minimize the number of tissue sampling.

Other clinical variables

Clinical variables of each patient on the day of endoscopy were verified on the basis of the clinical records at the referral nephrology institution. The variables included, age, gender, duration of HD, and medications for ESRF, cardiovascular system, and upper gastrointestinal tract. The medications included anti-hypertensive drugs (angiotensin converting enzyme inhibitors, calcium antagonists, beta-blockers and diuretics), calcium and vitamin supplements, phosphate binders (calcium acetate and calcium carbonate), and gastroprotective drugs (histamine-2 receptor antagonist [H2RA] and mucosal protective drugs). In addition, possible use of non-steroidal anti-inflammatory drugs (NSAIDs) and prednisolone was also verified.

We also measured fasting serum pepsinogens (PGs) I and II on the day of endoscopy. Blood samples were obtained just prior to endoscopy and stored at 4°C in a refrigerator until assay for PG I and II. The measurement of serum PG concentration was carried out by immunoradiometric assay (PG I/II RIA BEAD; Dainabot Co. Ltd., Tokyo, Japan), in accordance with the procedure described elsewhere.[15]

Statistical analysis

Comparisons between the groups were performed, using the chi-squared test, Fisher's exact test or Mann-Whitney's U test. Logistic regression analysis was carried out to evaluate the independent influence of each variables (sex, age, duration of HD, drug consumption and *H. pylori* infection) to upper gastrointestinal lesions in patients undergoing maintenance HD. Probabilities less than 0.05 were considered to be significant.

Results

Demographic data

During the investigation period, 220 patients on HD were listed up as the possible participants to the study. After excluding patients who had been taking proton pump inhibitor, informed consent was obtained from 198 patients. All these patients successfully underwent EGD, breath test and blood sampling for PG. The patients comprised 116 males and 82 females with ages ranging from 16 to 88 years (61.3±11.6 years, mean±SD). Their primary renal disease was chronic glomerulonephritis (n=118), diabetic nephropathy (n=54), hypertensive nephropathy (n=12), and polycystic kidney disease (n=5), while it was unknown in the remaining nine patients. Mean duration of HD until the entry ranged from 1 month to 49 years (7.6±7.3 years).

Endoscopically, esophagogastroduodenal mucosal lesion was detected in 148 (75%) patients. In addition, there were three cases of malignant neoplasm (gastric cancer in two cases and malignant lymphoma in a case) and a case of gastric antral vascular ectasia. Durations of HD in three patients with gastric malignant neoplasm were 10 months, 20 months and 84 months. Serum concentrations of PG I ranged from 22.2 to 944.0 pg/ml (266.0±160.1 pg/ml) and PG II from 4.9 to 160.0 pg/ml (31.4±26.3 pg/ml). The PG I/II ratio ranged from 1.4 to 22.7 (9.9±4.5). Among the 198 patients, 81 patients (41%) were positive and 117 (59%) were negative for *H. pylori* infection.

Comparison of clinical features between H. pylori-positive and negative patients

Table 1 summarizes the comparison of clinical findings between *H. pylori*-positive and negative patients. Age and gender were no different between the two groups. Duration of HD was significantly longer in *H. pylori*-negative patients than in *H. pylori*-positive patients. There was no difference in the prescription of H2RA, mucosal protective drugs, NSAIDs and prednisolone between *H. pylori*-positive and negative patients. Although serum level of PG I was not different between the two groups, *H. pylori*-positive group had significantly higher serum level of PG II and a significantly lower PG I/II ratio than *H. pylori*-negative group.

Comparison of endoscopic findings between H. pylori-positive and negative patients

Endoscopic findings of *H. pylori*-positive and negative patients are shown and compared in Table 2. The prevalence of neither duodenal erosion, gastric ulcer, duodenal ulcer, gastric antral vascular ectasia nor malignant neoplasm was statistically different between the two groups. However, all the patients with malignant neoplasm belonged to *H. pylori*-positive group. In contrast, gastric erosion was found in 79 *H. pylori*-negative patients, while it was detected in 34 *H. pylori*-positive patients (68% vs. 42%, p=0.0004). Although the difference did not reach a statistical significance, there was also a trend towards higher prevalence of reflux esophagitis in *H. pylori*-negative patients than in *H. pylori*-positive patients (p=0.0552).

Relationship among H. pylori infection, endoscopic findings and duration of HD

Figure 1 compares duration of HD between any two groups classified by the presence or absence of esophagogastroduodenal mucosal lesions. Duration of HD was not different between patients with and without gastric erosion, gastric ulcer or duodenal erosion. On the other hand, patients with reflux esophagitis had a longer duration of HD than those without (11.9±9.7 years vs. 7.1±6.8 years).

Figure 2 indicates the prevalence of *H. pylori* infection and the prevalence of gastric erosion among four groups of patients classified by every four-year duration of HD (≤4, >4 and ≤8, >8 and ≤12, and >12 years). As shown in the figure, the prevalence of *H. pylori* infection tended to decrease according to the increase in the duration of HD (p=0.055), while the prevalence of gastric erosion was slightly and insignificantly higher in patients with longer period of HD.

Multivariate analysis for esophagogastroduodenal mucosal lesions

Adjusted odds ratios (OR) for esophagogastroduodenal mucosal lesions were calculated by using logistic regression analyses. The results are shown in Table 3. As shown in the table, *H. pylori* infection was protective against gastric erosion (OR 0.38; 95% confidence interval 0.21-0.70) in our patients on HD. In contrast, the longer duration of HD was an independent risk factor for reflux esophagitis (OR 1.09; 95% confidence interval 1.02-1.15). In addition,

NSAIDs intake was calculated to be a marginal risk factor for gastric ulcer (OR 2.67; 95% confidence interval 1.00-7.14).

Discussion

The results of our investigation indicated that in patients on HD, 1) the duration of HD was shorter in patients with *H. pylori* infection than in those without, 2) the infection was protective against gastric erosion, and 3) long-term HD was a risk factor for reflux esophagitis in patients on HD. Although it has been shown that chronic renal failure, either prior to renal transplantation or on HD, is a predisposing factor for gastroduodenal mucosal lesions,[16,17] it still remains controversial as to the role of *H. pylori* infection in the pathogenesis of the lesions. Furthermore, a possible contribution of HD on *H. pylori* status has not yet been concluded.[17-20] We believe our investigation to be the largest study, which evaluated esophagogastroduodenal mucosal lesions and *H. pylori* infection simultaneously in patients on HD.

The role of *H. pylori* in the pathogenesis of gastric erosion still remains unclear. Some investigators reported that *H. pylori* infection was associated with gastric erosion,[21,22] while others found no such correlation.[23,24] It is widely accepted that gastric erosion occurs after successful eradication of *H. pylori*.[25] Miyake et al.[25] suggested that the pathogenesis of gastric erosions involves a recovery of acid secretion after eradication of *H. pylori*. Our present study revealed that the absence of *H. pylori* infection is unequivocally a risk factor for gastric erosion in patients on maintenance HD, suggesting that gastric erosion is closely associated with the enhanced gastric acid in patients on HD. However, despite the decrease in the prevalence of *H. pylori* infection, the increase in the prevalence of gastric erosion remained insignificant according to the duration of HD in the present investigation. It thus seems likely that in addition to *H. pylori* infection humoral abnormalities, such as hypergastrinemia and high ammonia levels induced by renal insufficiency, damage gastric mucosa in patients on HD.[26,27]

Although *H. pylori* eradication leads to a decrease in the recurrence of peptic ulcer in general population,[28] there have been no follow-up studies investigating the clinical

implication of *H. pylori* eradication in patients on HD. Our current results seem to suggest that eradication of *H. pylori* increase the risk of developing gastric erosion in patients on HD. Some investigators reported that gastric erosions are the cause of overt upper gastrointestinal bleeding in up to 16-23% of patients examined by endoscopy.[29,30] A follow-up study of 117 patients with gastric erosions for 17 years by Toljamo et al.[24] revealed that peptic ulcer developed in 20% of the patients. Because gastrointestinal bleeding can be a life-threatening complication of ESRF,[2] our data would suggest eradication of *H. pylori* to be hazardous for patients on HD.

Both *H. pylori* and NSAIDs are major causative factors for gastroduodenal mucosal lesions.[5,31,32] Our present study showed that *H. pylori* status did not affect the prevalence of gastric ulcer, duodenal ulcer or duodenal erosion in patients on HD. These observations, together with the fact that H2RAs were protective against mucosal lesions, strongly suggest metabolites other than gastric acids to play a role in the occurrence of gastroduodenal mucosal lesion in patients on HD. This hypothesis is supported by experimental studies showing an increase in acid back-diffusion and nitric oxide overproduction in the gastric mucosa of uremic rats.[33,34] In addition, dysregulation of endocrine or paracrine peptides, such as cholecystokinin, neurotensin and glucagons, and alterations in electrolytes including hypercalcemia and hypokalemia during the uremic state seem to be related to the mucosal lesions.[35]

There have been descriptions that long-term dialysis reduced the prevalence of *H. pylori* infection,[36-38] while others found no such correlations.[39,40] Nakajima et al.[37] reported that in Japanese patients on HD the mean duration of HD was significantly longer in *H. pylori*-negative patients than in *H. pylori*-positive patients. More recently, Sugimoto et al.[38] have shown that the prevalence of *H. pylori* infection serially decreased within four years in identical patients on HD, and this was especially the case for patients on HD for less than four years. In our investigation, such an inverse association between *H. pylori* and HD was again confirmed, and such a trend was obvious in patients on HD for more than 8 years. Even though spontaneous disappearance of *H. pylori* does occur in general population with a rate of 0.6%

per patient-year,[41] patients on HD are more likely to be in a condition of *H. pylori* eradication, because those patients are prone to be at higher serum concentrations of antibiotics than general population.

In a cross sectional study of patients with ESRF, Moustafa et al.[42] showed a close association of *H. pylori* with atrophic gastritis. However, the investigators failed to show any significant correlation between endoscopic mucosal lesions and histological grade of atrophy. Although serum PGs have been shown to be excellent markers for *H. pylori* infection and gastric mucosal atrophy in general population,[43,44] few studies have measured serum PG levels in patients on HD.[45-47] In our patients on HD, those with *H. pylori* infection had a higher serum PG II level and a lower PG I/II ratio than those without the infection. Our results thus suggest that PG II and PG I/II ratio is predictive of gastric mucosal atrophy even in patients on HD, and that there may be an inverse correlation between the atrophy and mucosal lesions in patients on HD.

It is widely accepted that reflux esophagitis is associated with *H. pylori* infection in general population.[48,49] However, there have been only two studies that investigated the correlation between *H. pylori* infection and reflux esophagitis in patients with ESRF.[16,50] In a case-control study by Cekin et al.,[50] *H. pylori* infection has been shown to be protective against reflux esophagitis in patients on HD, while reflux esophagitis was found regardless of *H. pylori* infection in another study of patients prior to renal transplantation.[16] From the results of the present investigation, it was suggested that long-term HD was an independent risk factor of reflux esophagitis. This result may be a consequence of a decrease in *H. pylori* infection rate, because there was a trend towards lower prevalence of reflux esophagitis in *H. pylori* positive patients than in *H. pylori* negative patients.

UBT is one of the most accurate procedures for the diagnosis of *H. pylori* infection, with the sensitivity, specificity, positive and negative predictive values of 97.7%, 98.4%, 98.5% and 97.6%, respectively.[51] However, we may have underestimated the prevalence of *H. pylori* infection in the present investigation, because we did not apply another diagnostic procedure

for our subjects. It thus seems possible that false negative *H. pylori* infection might have contributed to the insignificant difference in the prevalence of acid-related esophagogastroduodenal mucosal lesions in the present investigation.

In conclusion, our endoscopic analysis of 194 patients on HD indicated that gastric erosion is a mucosal lesion commonly occurs in patients on HD and that long-term HD increases the risk of reflux esophagitis. The high prevalence of gastric erosion may be explained partly by decrease in *H. pylori* infection during the clinical course of maintenance HD. Our results thus suggest *H. pylori* infection to be protective against esophagogastric mucosal lesions in patients on HD. However, it should also be noted that malignant neoplasm of the stomach was found exclusively in patients with *H. pylori* infection, which has been confirmed to be predisposing to gastric cancer and malignant lymphoma.[52,53] Because our investigation was based on a cross-sectional analysis, prospective and interventional studies are further needed to discuss the appropriateness of *H. pylori* eradication in patients on HD.

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Table 1. Comparison of clinical features between two groups

	HP-positive (n=81)	HP-negative (n=117)	P value
Age (yrs)	62.4 ± 10.1	60.5 ± 12.6	NS
Gender (male/female)	52/29	64/53	NS
Duration of hemodialysis (yrs)	6.1 ± 5.8	8.6 ± 8.0	0.0277
Medication			
Histamine-2 receptor antagonist	38 (47%)	55 (47%)	NS
Mucosal protective drugs	29 (36%)	52 (44%)	NS
Non-steroidal anti-inflammatory drugs	14 (17%)	24 (21%)	NS
Prednisolone	2 (3%)	9 (8%)	NS
Pepsinogen I (pg/ml)	277.6 ± 181.3	257.9 ± 144.0	NS
Pepsinogen II (pg/ml)	45.0 ± 33.6	22.0 ± 13.2	<0.0001
Pepsinogen I/II	6.9 ± 3.9	12.0 ± 4.1	<0.0001

NS; not significant

Table 2. Comparison of endoscopic findings between two groups

Esophagogastroduodenal mucosal lesion	HP-positive (n=81)	HP-negative (n=117)	P value
Gastric erosion	34 (42%)	79 (68%)	0.0004
Duodenal erosion	12 (15%)	23 (20%)	NS
Gastric ulcer	12 (15%)	16 (14%)	NS
Duodenal ulcer	5 (6%)	9 (8%)	NS
Reflux esophagitis	4 (5%)	16 (14%)	0.0552
Gastric antral vascular ectasia	0 (0%)	1 (1%)	NS
Malignant neoplasm	3 (4%)	0 (0%)	NS

NS; not significant

Table 3. Adjusted odds ratio (95% confidence intervals) of independent predictors for esophagogastroduodenal mucosal lesions

	Reflux esophagitis	Gastric ulcer	Duodenal erosion	Gastric erosion
Age	0.99 (0.95-1.03)	1.00 (0.96-1.04)	0.98 (0.95-1.01)	1.00 (0.98-1.03)
Gender	1.72 (0.63-4.69)	0.68 (0.28-1.65)	0.98 (0.45-2.12)	1.18 (0.64-2.17)
Duration of hemodialysis	1.09* (1.02-1.15)	1.01 (0.95-1.07)	0.98 (0.93-1.04)	1.02 (0.98-1.07)
Non-steroidal anti-inflammatory drugs	0.34 (0.59-1.92)	2.67† (1.00-7.14)	1.31 (0.49-3.51)	1.14 (0.51-2.54)
Prednisolone	ND	0.43 (0.05-3.94)	ND	0.93 (0.25-3.51)
Histamine-2 receptor antagonist	0.72 (0.25-2.06)	1.99 (0.83-4.78)	1.20 (0.56-2.60)	0.86 (0.47-1.59)
Mucosal protective drugs	1.96 (0.67-5.72)	1.76 (0.73-4.22)	0.85 (0.83-1.89)	1.66 (0.88-3.14)
H. pylori infection	0.41 (0.13-1.32)	1.15 (0.50-2.73)	0.66 (0.30-1.45)	0.38* (0.21-0.70)

*P<0.05, by logistic regression analysis, for analysis of odds ratio for independent predictors

†P=0.05, by logistic regression analysis, for analysis of odds ratio for independent predictors

ND; not determined

Figure 1. Relationship between endoscopic findings and duration of hemodialysis ((A) gastric erosion, (B) gastric ulcer, (C) duodenal erosion, (D) reflux esophagitis)

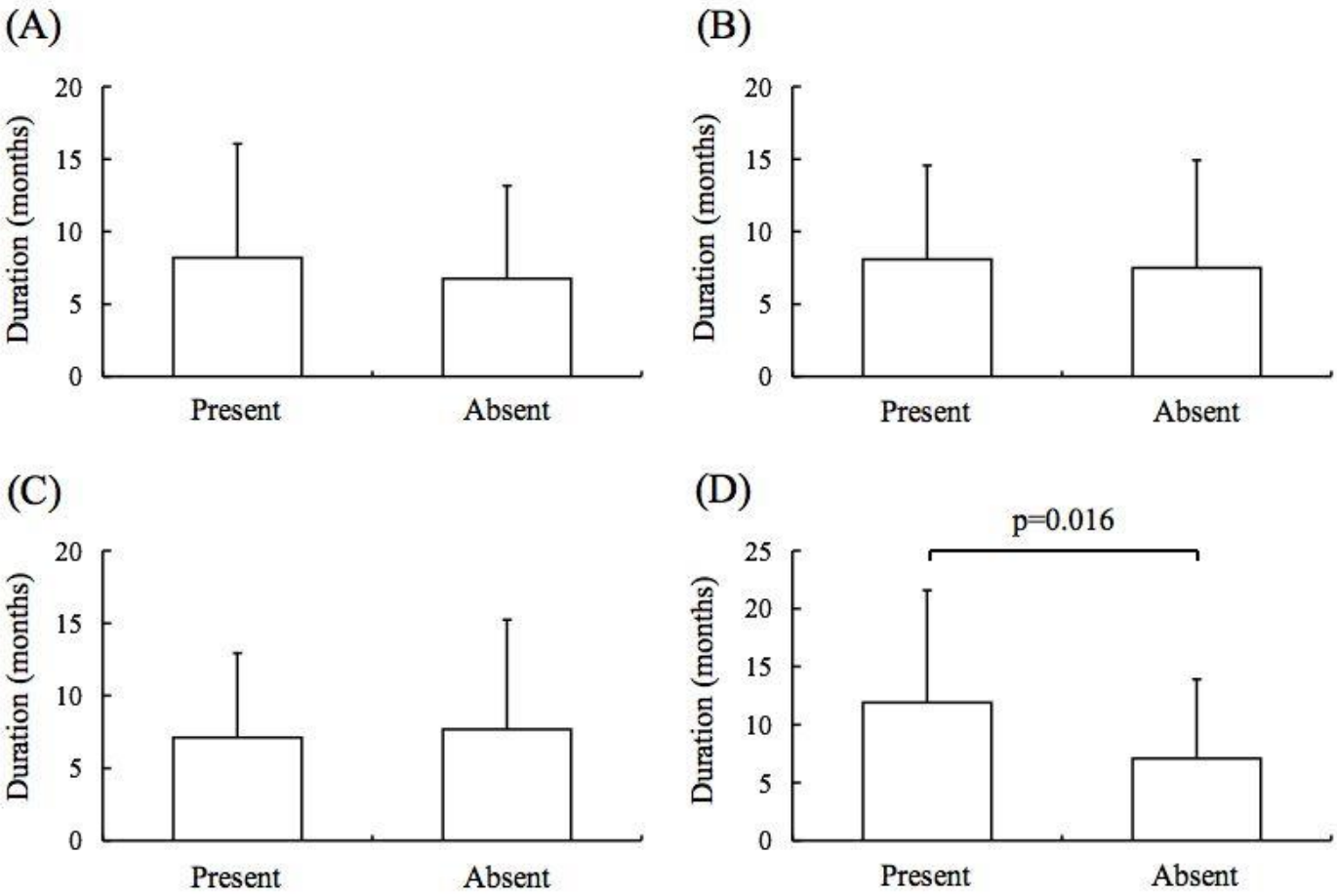
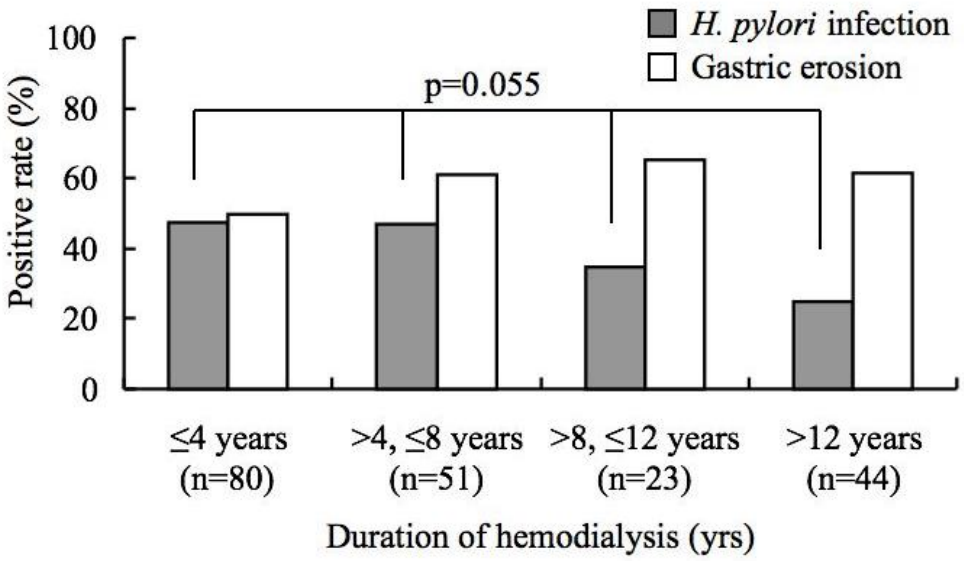
Figure 2. Relationship among *H. pylori* infection, gastric erosion and duration of hemodialysis