Gastroesophageal Reflux Disease in Hemodialysis Patients

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Background: The association between gastroesophageal reflux disease (GERD) and chronic renal failure (CRF) remains unclear. The aim of the present study is to assess the prevalence of GERD and also attempt to identify possible pathogenic factors in the development of reflux in hemodialysis (HD) patients.
Patients and Methods: This study consisted of 418 stable CRF patients who underwent HD and did not necessarily undergo gastroendoscopy. Instead of gastroendoscopy, QUEST, a structured questionnaire for the assessment of symptomatic GERD, was used to diagnose GERD. We checked the age, sex, body mass index, etiology of renal disease, QUEST score, medication, alcohol consumption, smoking and laboratory data, and compared GERD group with non-GERD group.
Results: In the 418 stable CRF patients who did not undergo gastroendoscopy, the prevalence of GERD was 24.2%. There were no statistically significant differences in age, sex, BMI, alcohol consumption, smoking, etiology of CRF, laboratory data and medication between GERD group and non-GERD group.
Conclusions: Compared to the reported prevalence of GERD in Japan (16.3%), the prevalence of GERD in CRF patients who underwent HD (24.2%), was increased. The risk factor for this increased GERD in CRF patients was not clear in the present study.

Key words: gastroesophageal reflux disease (GERD), chronic renal failure (CRF), hemodialysis (HD), QUEST

INTRODUCTION

Gastroesophageal reflux disease (GERD) develops when acidic gastric contents reflux into the esophagus. The condition is believed mainly to be due to an increase in the number of transient lower esophageal sphincter (LES) relaxations. Other major mechanisms include decreased clearance of esophageal contents and reflux owing to impaired peristalsis, decreased gastric emptying with resultant reflux into the esophagus, and increased gastric acid production with a resultant increase in the potency of the reflux.

Although the exact prevalence is difficult to determine, undoubtedly GERD is the most common esophageal disease. The typical symptoms are heartburn and acid regurgitation. The initial diagnosis of GERD is based on the history or on questionnaires such as questionnaire for the diagnosis of reflux disease (QUEST), produced by Carlsson *et al.* [1], as well as the findings at upper gastrointestinal endoscopy. Other diagnostic modalities for GERD include 24-h esophageal pH monitoring and the proton pump inhibitor (PPI) test, which is a therapeutic diagnostic method [2]. Because diagnosis on the basis of the history is the simplest and quickest method, placing no demands on the patient, it is favored by general practitioners.

CRF is associated with an increased incidence of acid-related gastrointestinal disorders [3–5]. And a lot of CRF patients have diabetes mellitus (DM) and hypertension (HT) as complications. We can predict decreased gastric emptying by DM neuropathy and lower esophageal sphincter (LES) relaxations by Ca-antagonists and nitrites. Although we are now aware of the increasing prevalence of GERD, little is known about this condition in CRF patients, especially stable HD patients. To our knowledge, no studies have examined the rate of transient LES relaxation or esophageal clearance in CRF, but some work has been done on the rates of gastroparesis or hyperacidity in uremia [3–5]. The aims of this study were to investigate the prevalence of GERD in HD patients and to identify factors associated with the development of this condition in HD patients.

PATIENTS AND METHODS

This study consisted of 418 stable CRF patients (257 men [62%] and 161 women [38%], mean age: 64.9 [range: 23–91] years) who underwent HD in the HD clinics and did not necessarily undergo gastroendoscopy between November 2004 and January 2005 (Table 1). Instead of gastroendoscopy, QUEST, a structured questionnaire for the assessment of symptomatic GERD, was used to diagnose GERD. We diagnosed GERD in those with a score of four points or more. And we made a questionnaire added to QUEST. The questionnaire included questions about age, sex, BMI

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Table 1 Clinical characteristics of 418 Stable CRF Patients, QUEST group

	Patients (n = 418)
Mean age (years)	64.9 (range: 23–91)
Sex	
Male	257 (61.5%)
Female	161 (38.5%)
BMI	20.7 (range: 14.1–30.0)
Smoker	79 (18.9%)
Alcohol Drinker	91 (22.1%)
QUEST score (more than 4)	101 (24.2%)
Etiology of Renal Disease	
Chronic Glomerulonephritis	121 (294%)
Diabetic Nephropathy	120 (29.2%)
Nephrosclerosis	75 (18.2%)
Polycystic Kidney	24 (5.8%)
Others	71 (17.3%)

Table 2 Comparison between GERD Group and Non-GERD Group in 418 Stable CRF Patients, QUEST Group

	GERD Group (n = 101)	Non-GERD Group (n = 317)	
Mean age (years)	62.2 (range: 35–85)	65.8 (range: 23–91)	NS
Sex			
Male	64 (63%)	193 (61%)	NS
Female	37 (37%)	124 (39%)	NS
Mean Body Mass Index	20.8 (range: 14.7–28.2)	20.7 (range: 14.1–30.0)	NS
Smoker	40 (51%)	39 (49%)	NS
Alcohol Drinker	49 (54%)	42 (46%)	NS
Prevalence of Diabetes mellitus	27 (27%)	92 (29%)	NS
Mean Cardiothoracic Ratio (%)	51.2 (range: 40.5–61.8)	51.9 (range: 39.5–77.6)	NS
Mean Blood Pressure			
Systolic (mmHg)	158.5 (range: 120–210)	155.7 (range: 90–230)	NS
Diastolic (mmHg)	78.6 (range: 55–110)	78.6 (range: 45–110)	NS

NS, not significant

(height and weight), presence of upper gastrointestinal symptoms, etiology of renal disease, past history, alcohol consumption and smoking habits. And we checked medications, laboratory data (BUN, Cr, K, Ca, P, TP, Hb, Ht), blood pressure (BP) and cardiothoracic ratio (CTR). As for these clinical findings, we compared the GERD group with the non-GERD group. The Ethics Committee of Yokohama City University approved this study. All participants gave informed consent to participate in this study.

For statistical analysis, the χ^2 test was used and *P*-values of <0.05 were considered statistically significant.

RESULTS

In the 418 stable HD patients who did not undergo gastroendoscopy, the prevalence of GERD was 101 patients (24.2%) (Table 1). Mean age was 62.2 years (range: 35–85) in GERD group and 65.8 years (range: 23–91) in non-GERD group. GERD group consisted of 64 males (63%) and 37 females (37%), on the other hand non-GERD group consisted of 193 males (61%) and 124 females (39%). Mean BMI was 20.8 (range: 14.7–28.2) in GERD group and 20.7 (range: 14.1–30) in non-GERD group. 79 patients (18.9%) were smoker, 51% of those were GERD group. 91 patients (22.1%) were alcohol drinker, 54% of those were GERD group. Diabetic nephropathy was seen in total 120 patients (29.2%) who consisted of 28 GERD patients (27%) and 92 non-GERD patients (29%). Mean CTR was 51.2 (range: 40.5–61.8) in GERD group and 51.9 (range: 39.5–77.6) in non-GERD group. Mean systolic BP was 158.5 (range: 120–210) in GERD group and 155.7 (range: 90–230) in non-GERD group. Mean diastolic BP was 78.6 (range: 55–110) in GERD group and 78.6 (range: 45–110) in non-GERD group. There were no statistically significant differences in age, sex, BMI, alcohol consumption, smoking, etiology of CRF, CTR, BP, laboratory data and medications between the GERD group and non-GERD group (Table 2, Figs. 1, 2).

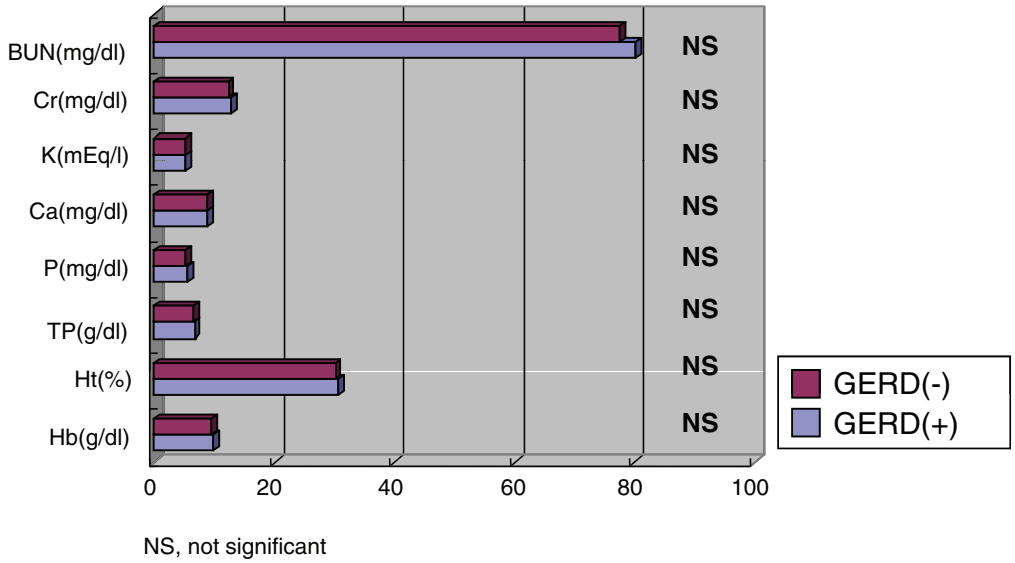

Fig. 1 There were no statistically significant differences in laboratory data between the GERD group and non-GERD group in 418 stable CRF patients.

DISCUSSION

Patients with CRF frequently develop upper GI tract complications [1–3]. But little is known about this condition in patients with CRF. In our clinical data the prevalence of GERD was highest (34.0%) in the 156 CRF patients who underwent gastroendoscopy. In HD patients the frequency of GERD and erosion increase, especially the prevalence of GERD was highest (50.0%). In the prevalence of GERD there were statistically significant differences between the patients on HD and pre-dialysis. These results suggest to us that CRF patients, especially on HD, might have specific risk factors that make them susceptible to GERD. GERD develops when excessively acidic gastric contents reflux into the esophagus. The pathophysiology of GERD is multifactorial and depends on interaction between aggressive factors and defensive mechanisms. It is believed mainly that the aggressive factor is an increased gastric acid production and the defensive mechanism is a decreased gastric emptying. On the other hand, the association between GERD and CRF remains unclear. Therefore, it is important to examine their risk factors in CRF patients. We used QUEST, a structured questionnaire for the assessment of symptomatic GERD instead of gastroendoscopy, to assess the prevalence of GERD and also to identify possible pathogenic factors in the development of reflux in stable HD patients. QUEST is thought to be accurate since upper GI symptoms in HD are correlated well with GERD [6]. And We think that GERD diagnosed by QUEST is nearly equal to symptomatic GERD. But we need to pay attention that symptomatic GERD is not always equal to endoscopic GERD. Though endoscopy is highly useful for the diagnosis of reflux esophagitis, endoscopic examination has not been used to evaluate the prevalence of reflux esophagitis in a large population of HD patients. Because many HD patients have the other diseases, we cannot undergo endoscopy easily. Therefore we think that QUEST is useful for HD patients.

Higher acid production can occur secondary to hypergastrinemia, which can be a consequence of decreased clearance of gastrin owing to a reduced glomerular filtration rate (GFR). Hypergastrinemia is in fact present [7, 8] in CRF patients, but may also be in part to due increased secretion, because the density of G cells is increased in CRF patients [9, 10], possibly owing to a hyperthyroid state. Elevated serum gastrin causes an increase in acid production by the parietal cells. However, when measured in CRF patients, large variations in the mean gastric acid production actually occur from achlorhydria to hyperchlorhydria [11]. Indeed, achlorhydria has been suggested as the stimulus for hypergastrinemia, because a feedback mechanism exists between the G cells and the low-acid state that stimulates the secretion of gastrin. Although we cannot say that increased acid production occurs in all CRF patients, some patients certainly have increase acid production.

Although we could not examine the rate of *Helicobacter pylori* (*H. pylori*) infection in this study, this also may be an important factor. Several studies have shown that rates of *H. pylori* infection in CRF are lower than expected [11–14]. Shousha *et al.* found that the prevalence of antral *H. pylori* was significantly less in patients with renal disease (24%) than in a control group (42%) [13]. These lower rates of *H. pylori*, which lead to hyperacidity state in stomach, may potentially be a mechanism by which CRF can be associated with GERD.

Nausea and vomiting are often encountered in CRF and can be caused by delayed gastric emptying. The association of CRF with delayed gastric emptying seems to depend on the type of patient. Although this study did not involve the patients on peritoneal dialysis, a patient on peritoneal dialysis would be expected to have delayed gastric emptying simply due to the

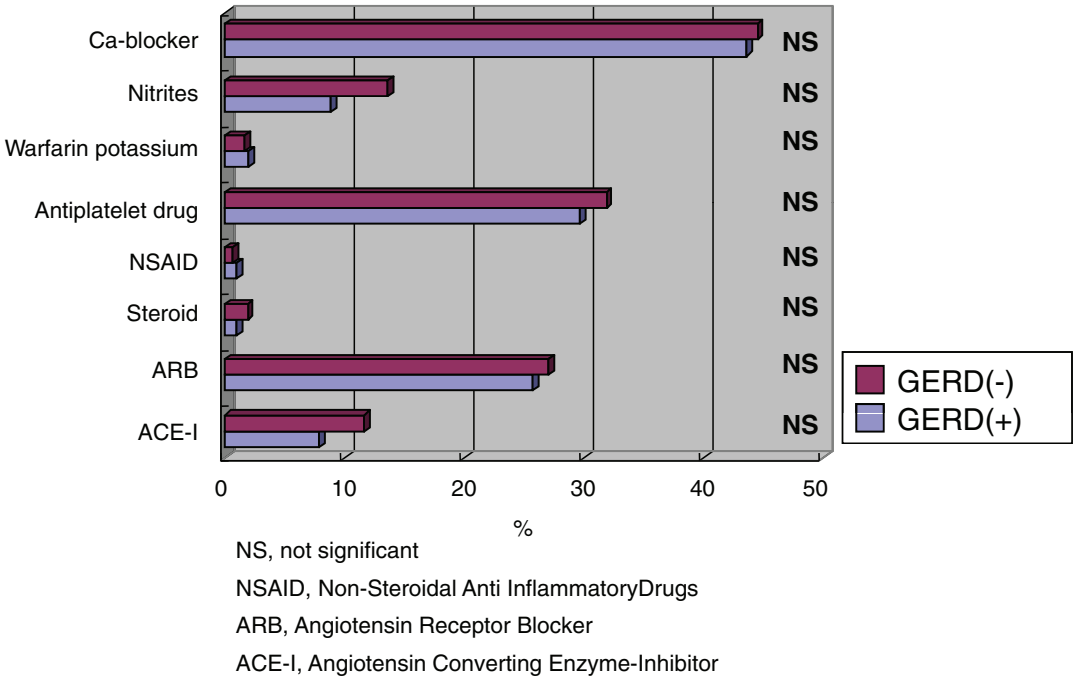

Fig. 2 There were no statistically significant differences in medications between the GERD group and non-GERD group in 418 stable CRF patients.

physical impairment caused by the peritoneal fluid [15]. Results in other CRF patients, such as patients with uremia but not on dialysis, or patients on HD, have yielded conflicting results. Three studies demonstrated delayed gastric emptying in uremic predialysis patients [16–18]. The researchers have also documented delayed gastric emptying in HD patients, particularly patients who are hypoalbuminemic [19, 20]. In this study, as for total protein, the differences between GERD group and Non-GERD group were not statistically significant (Fig. 1). The situation is muddled by other studies that have not demonstrated decreased gastric emptying in HD patients [15, 18, 21, 22].

The reasons for the discrepancy between the various results are likely multifactorial. One of the confounding factors is whether the patient is pre-dialysis, on peritoneal dialysis, or on hemodialysis. Ko *et al.* demonstrated that uremic patients undergoing dialysis had gastric rhythm disturbance that deteriorated after HD [23]. Dumitrascu *et al.* demonstrated that patients with CRF had delayed gastric emptying if parasympathetic and sympathetic neuropathy were both present [24]. DM is at increased risk of autonomic neuropathy, and they certainly constitute a large proportion of patients with CRF. In this study diabetic nephropathy was 29.2% of 418 stable CRF patients (Table 1) and the differences between GERD group and Non-GERD group were not statistically significant (Fig. 1). As the other risk factor of GERD, we examined age, sex, BMI, alcohol, smoking, etiology of renal disease, laboratory data (BUN, Cr., K, Ca, P, TP, Ht, Hb) and some medications, but the differences between GERD group and Non-GERD group were not statistically significant (Figs. 1, 2).

The overall proportion of reflux esophagitis in 6010 Japanese adults was 16.3% in prospective evaluation by gastroendoscopy [25]. Several studies using endoscopic examination suggested that the overall prevalence of reflux esophagitis in Western countries was around 10%–20% [26,27]. These data indicated that reflux esophagitis is a common disease in Japan. Compared to the reported prevalence of GERD in Japan (16.3%) [25], the prevalence of GERD in CRF patients (24.2%), especially who underwent HD, is increased. This increased prevalence of GERD in HD patients was in accordance with the results (36%) of the autopsy study of 78 HD patients [28]. The risk factor for this increased GERD in CRF patients was not clear. Evaluation of the prevalence of reflux esophagitis of HD patients needs further exploration by endoscopy.

In an endoscopic surveillance study in adults, no difference was seen in the incidence of esophagitis between patients with CRF and healthy controls [29]. On the other hand, in an uncontrolled study using 24 hour pH-metry, Ruley *et al.* found that 73% (16 of 22) of children with CRF had significant GERD. Although mechanisms exist that potentially lead to an increase of GERD in CRF, their existence would be insufficient to suggest that the incidence of GERD is increased in CRF patients without further study.

CONCLUSION

It is possible to suggest that the prevalence of GERD is increased in CRF patients, especially that underwent HD. The risk factor for this increased GERD in HD patients was not clear in this study.

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