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Gastroesophageal Reflux Disease in Chronic Renal Failure Patients

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1. Introduction

Gastroesophageal reflux disease (GERD) is one of acid-related gastrointestinal disorders, because GERD develops when excessively acidic gastric contents reflux into the esophagus. The condition is believed mainly to be due to an increase in the number of transient 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. Chronic renal failure (CRF) is associated with an increased incidence of acid-related gastrointestinal disorders (1-3). Therefore we can predict high morbidity of GERD in CRF patients, but the association between GERD and CRF remains unclear.

In our study (4) by questionnaire for the diagnosis of reflux disease (QUEST) produced by Carlsson et al. (5), the prevalence of GERD was 24.2% in the 418 stable hemodialysis (HD) patients who did not undergo endoscopic examination. Compared to the reported prevalence of GERD in 6010 Japanese adults (16.3%) (6), the prevalence of GERD in CRF patients who underwent HD (24.2%) was increased.

In the gastroendoscopic findings of the 156 CRF patients who underwent endoscopic examination, the prevalence of GERD was 34.0%. Especially, in symptomatic cases, the prevalence of GERD was 44.0% (7).

Although we are now aware of the increasing prevalence of symptomatic GERD in HD patients, little is known about the gastroendoscopic findings and the prevalence of endoscopical GERD in CRF patients. In this chapter, I would like to explain about GERD in CRF patients.

2. Epidemiology

The overall proportion of reflux esophagitis in 6010 Japanese adults was 16.3% in prospective evaluation by gastroendoscopy (6). Several studies using endoscopic examination suggested that the overall prevalence of reflux esophagitis in Western countries was around 10%-20% (8, 9). These data indicated that reflux esophagitis is a common disease in Japan.

2.1 Evaluation by QUEST

We examined 418 stable CRF patients (257 men [62%] and 161 women [38%], mean age: 64.9 \pm 10.2 [\pm standard deviation, SD] [range: 23-91] years) who underwent HD in the HD clinics

and did not necessarily undergo gastroendoscopy (Table 1) (4). Instead of gastroendoscopy, QUEST, a structured questionnaire for the assessment of symptomatic GERD, was used to diagnose GERD in this study. We diagnosed GERD in those with a score of four points or more. In these 418 stable HD patients, the prevalence of GERD was 101 patients (24.2%) (Table 1) (4). Compared to the reported prevalence of GERD in Japan (16.3%) (6), 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 (10).

We also examined the risk factor for GERD in HD patients by using a questionnaire added to QUEST (4). The questionnaire included questions about age, sex, BMI (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. Mean age was 62.2 ± 11.4 (\pm SD) years (range: 35-85) in GERD group and 65.8 ± 12.2 (\pm SD) 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 ± 5.6 (\pm SD) (range: 14.7-28.2) in GERD group and 20.7 ± 6.2 (\pm SD) (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 ± 10.1 (\pm SD) (range: 40.5-61.8) in GERD group and 51.9 ± 10.6 (\pm SD) (range: 39.5-77.6) in non-GERD group. Mean systolic BP was 158.5 ± 16.2 (\pm SD) (range: 120-210) in GERD group and 155.7 ± 15.8 (\pm SD) (range: 90-230) in non-GERD group. Mean diastolic BP was 78.6 ± 12.1 (\pm SD) (range: 55-110) in GERD group and 78.6 ± 12.5 (\pm SD) (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, Fig. 1, 2).

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.

2.2 Evaluation by endoscopic examination

In an endoscopic surveillance study in adults, no difference was seen in the incidence of esophagitis between patients with CRF and healthy controls (11). 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.

We examined 156 CRF patients (97 men [62%] and 59 women [38%], mean age: 64.2 ± 12.3 [\pm SD] [range: 29-89] years) whose creatinine level was more than 2 mg/dl and who underwent endoscopy examination (7). This group involved 42 patients (27%) with some upper GI symptoms, 55 patients (35%) with DM and 87 patients (56%) with HT (Table 3). To investigate renal function, we classified the patients into three categories based on the creatinine level and as follows: $2 < \text{Cr.} < 5$ (44 patients [28%]), $\text{Cr.} > 5$ and patients on pre-dialysis (53 patients [34%]), $\text{Cr.} > 5$ and patients on hemodialysis (59 patients [38%]) (Table 3). As we could not examine glomerular filtration rate (GFR) of all patients, we used serum creatinine level as renal function. These clinical findings were compared with the gastroendoscopic findings retrospectively. The prevalence of GERD was highest (53 patients

Patients (n = 418)	
Mean age (years)	64.9 ± 10.2 (range: 23-91)
Sex	
Male	257 (61.5%)
Female	161 (38.5%)
BMI	20.7 ± 5.9 (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 (29.4%)
Diabetic Nephropathy	120 (29.2%)
Nephrosclerosis	75 (18.2%)
Polycystic Kidney	24 (5.8%)
Others	71 (17.3%)

Data are given as the mean ± standard deviation (SD) or as the number of patients (n)

Table 1. Clinical characteristics of 418 Stable HD Patients.

	GERD Group (n = 101)	Non-GERD Group (n=317)	
Mean age (years)	62.2 ± 11.4 (range: 35-85)	65.8 ± 12.2 (range: 23-91)	NS
Sex			
Male	64 (63%)	193 (61%)	NS
Female	37 (37%)	124 (39%)	NS
Mean Body Mass Index	20.8 ± 5.6 (range: 14.7-28.2)	20.7 ± 6.2 (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 ± 10.1 (range: 40.5-61.8)	51.9 ± 10.6 (range: 39.5-77.6)	NS
Mean Blood Pressure			
Systolic (mmHg)	158.5 ± 16.2 (range: 120-210)	155.7 ± 15.8 (range: 90-230)	NS
Diastolic (mmHg)	78.6 ± 12.1 (range: 55-110)	78.6 ± 12.5 (range: 45-110)	NS

Data are given as the mean ± standard deviation (SD) or as the number of patients (n)

NS, not significant

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

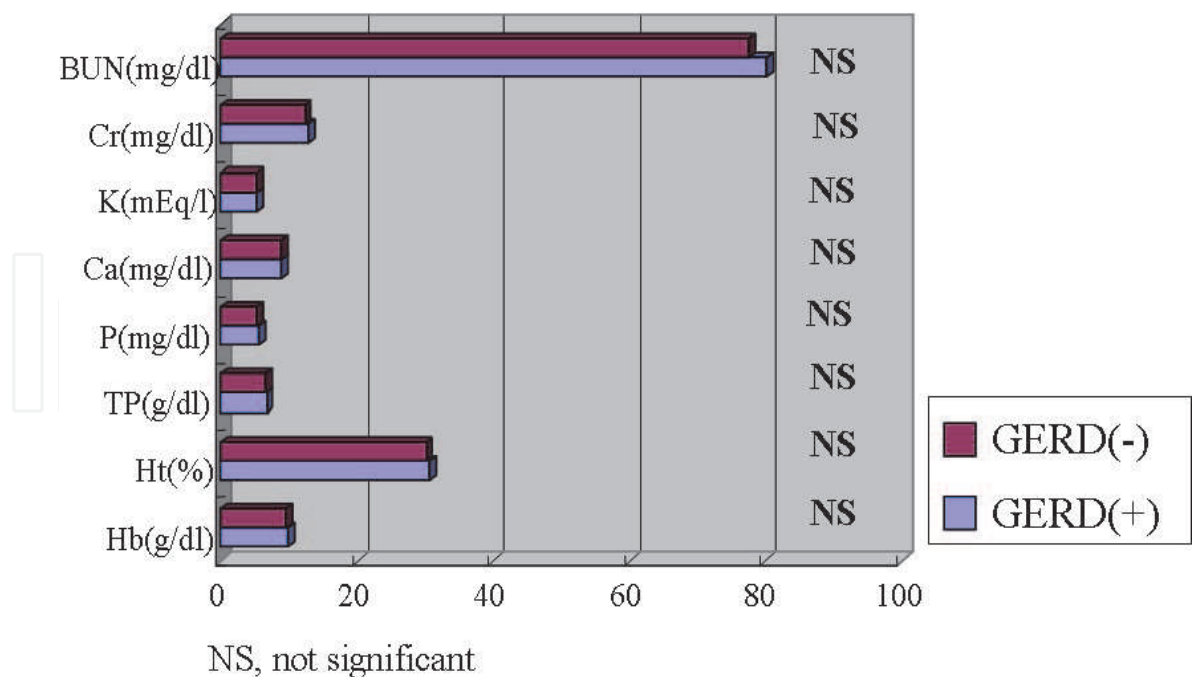


Fig. 1. Comparison of laboratory data between GERD group and non-GERD group.

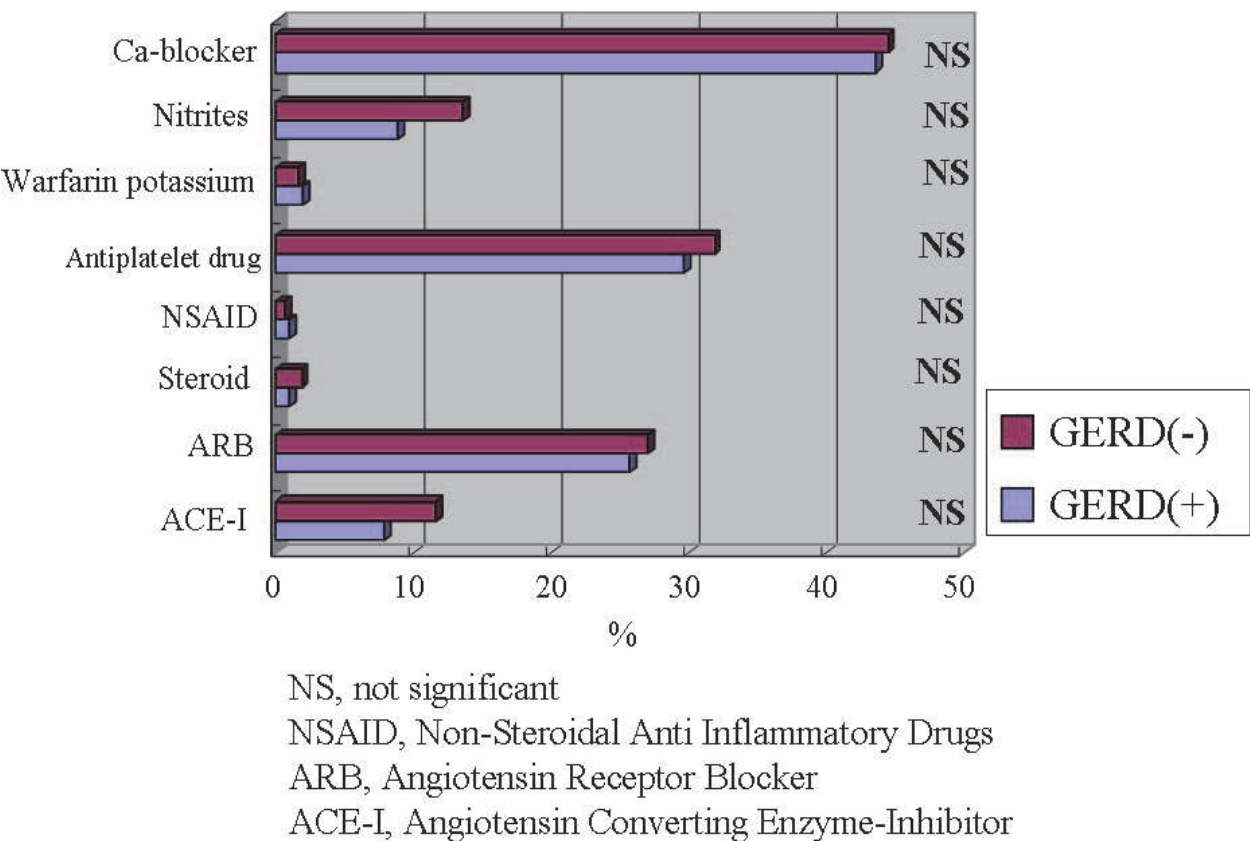


Fig. 2. Comparison of medications between GERD group and non-GERD group.

[34.0%]) in the gastroendoscopic findings of the 156 CRF patients who underwent endoscopic examination (Fig.3). Gastric ulcer and ulcer scar, erosion, hemorrhagic change (hematin), angiodysplasia and gastric antral vascular ectasia (GAVE) were seen in 39 patients (25%), 42 patients (27%), 41 patients (26%), 8 patients (5%) and 5 patients (3%), respectively (Fig.3). In the evaluation of 42 patients (27%) with some upper GI symptoms, 22 patients (52%) underwent hemodialysis, and the prevalence of GERD was highest (18 patients [44.0%]) in the gastroendoscopic findings. And in relationships between renal function and gastrointestinal symptoms, as renal function became worse, symptomatic cases tended to increase. There were statistically significant differences between the patients on hemodialysis and pre-dialysis (Fig.4). In relationships between renal function and gastroendoscopic findings, in the patients on hemodialysis the frequency of GERD and erosion increased, especially the prevalence of GERD was highest (50.0%). There were statistically significant differences between the patients on hemodialysis and pre-dialysis (Fig.5). The severity of GERD tended to be mild. In the patients with GERD, 77% was grade M or A of modified Los Angeles grading system. Esophageal herniation was seen in 19 patients (32%) (Fig.6).

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.

	Patients (n = 156)
Mean age (years)	64.2 ± 12.3 (range: 29-89)
Sex	
Male	97
Female	59
Cases with Upper GI Symptoms	42
Renal function	
2 < Cr. < 5	44
Cr. 5 < , without hemodialysis	53
Cr. 5 < , with hemodialysis	59
Complications	
Diabetes Mellitus	55
Hypertension	87

Data are given as the mean ± standard deviation (SD) or as the number of patients (n)

Table 3. Clinical characteristics of 156 CRF patients.

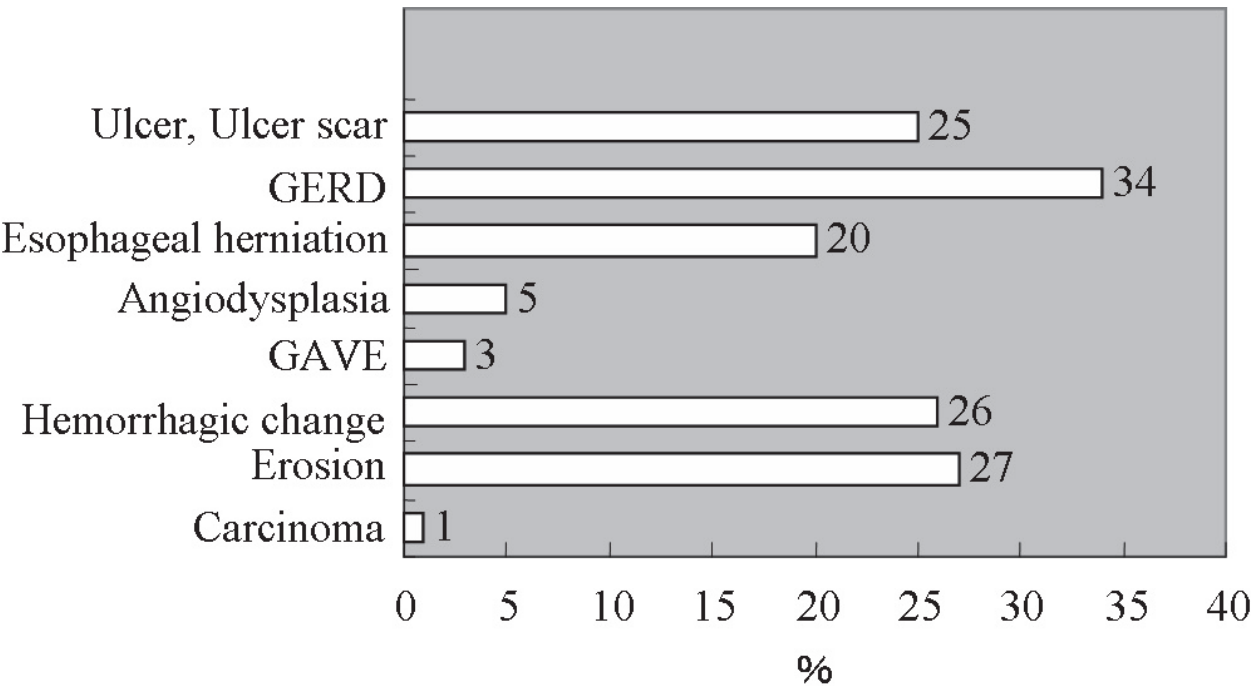


Fig. 3. Gastroendoscopic findings of 156 CRF patients who underwent endoscopic examination.

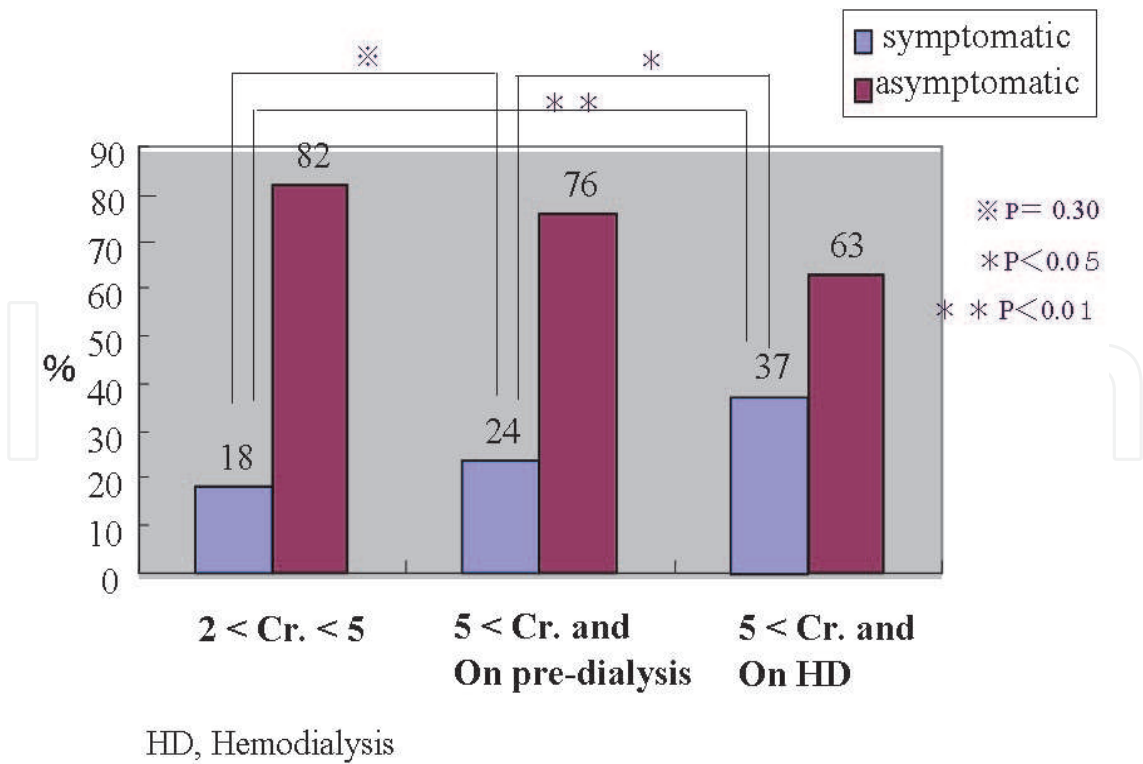


Fig. 4. Relationships between renal function and gastrointestinal symptoms.

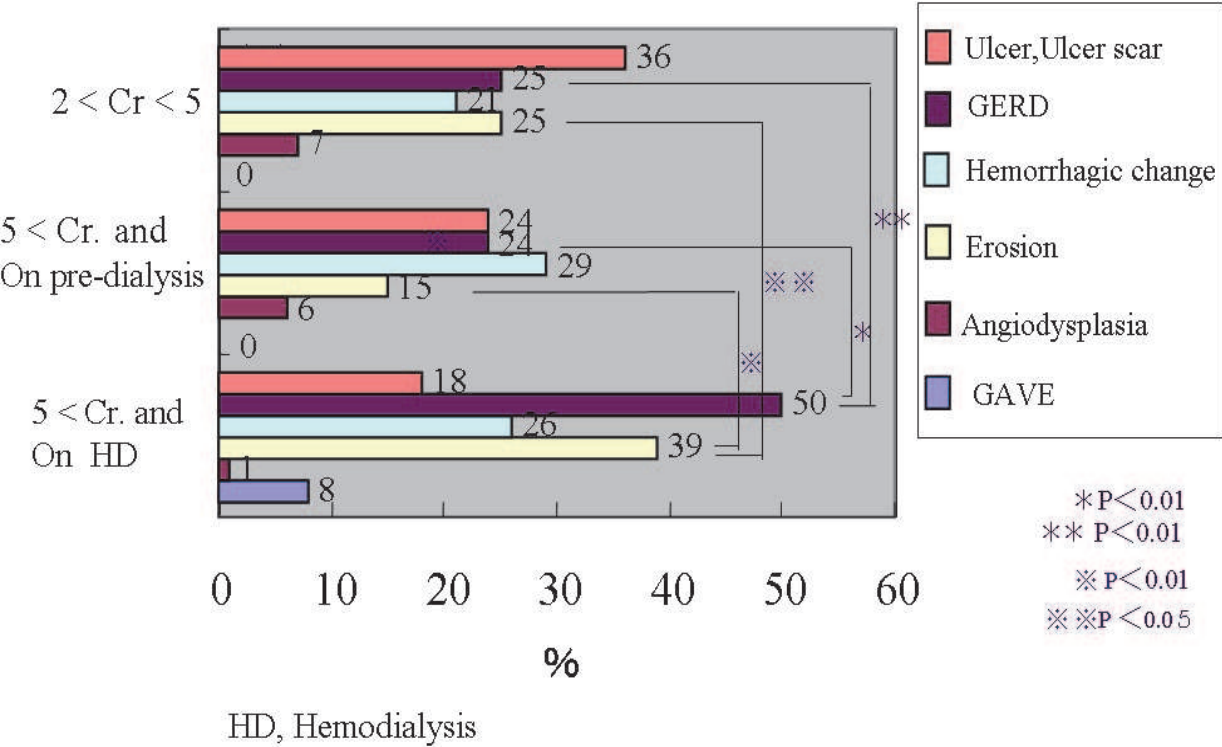


Fig. 5. Relationships between renal function and gastroendoscopic findings.

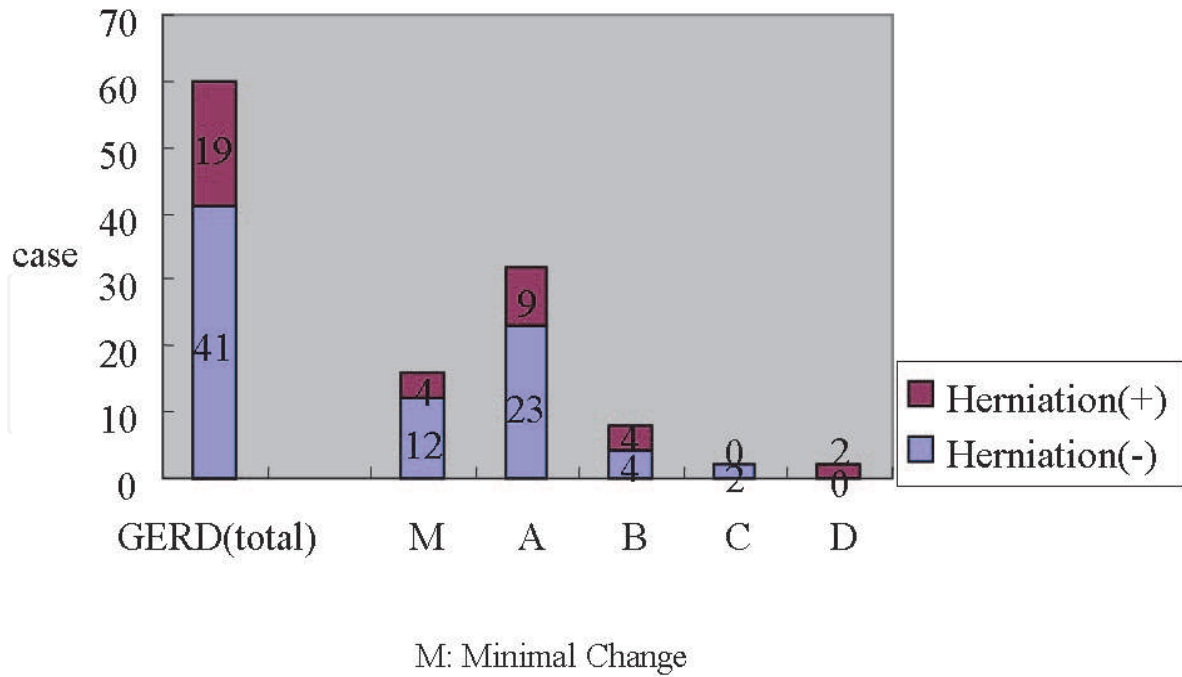


Fig. 6. Relationships between severity of GERD and esophageal herniation.

3. Pathophysiology

The pathophysiology of GERD is multifactorial and depends on interaction between aggressive factors and defensive factors. It is believed mainly that the aggressive factor is an increased gastric acid production and the defensive factor is a decreased gastric emptying.

3.1 Aggressive factors

3.1.1 Hypergastrinemia

We have to consider the association of CRF with an increased gastric acid production as an aggressive factor. Although we cannot say that increased acid production occurs in all CRF patients, some patients certainly have increase acid production. Hypergastrinemia is in fact present (12, 13) in CRF patients, and 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). And Straathof *et al.* reported that postprandial plasma concentrations of gastrin decrease lower esophageal sphincter pressure and increase the transient lower esophageal sphincter relaxations associated with reflux (14). In our study, the prevalence of GERD tended to increase as renal function become worse, although we could not examine serum gastrin level (7). But hypergastrinemia may also be in part to due increased secretion, because the density of G cells is increased in CRF patients (15, 16) 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 (17). 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.

Serum gastrin may be an important factor as both an aggressive and a defensive factor.

3.1.2 *Helicobacter pylori* infection

On the other hand several studies have shown that rates of *Helicobacter pylori* (*H. pylori*) infection in CRF are lower than expected (17-20). 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%) (19). 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. *H. pylori* infection also may be an important factor for GERD.

Some researchers reported that long-term dialysis reduced the prevalence of *H. pylori* infection (21-23), while others found no such correlation (24, 25). Nakajima *et al.* (22) 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.* (23) have shown that the prevalence of *H. pylori* infection serially decreased within 4 years in identical patients on HD, particularly among patients on HD for less than 4 years. Moriyama *et al.* (26) reported that 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.

It is widely accepted that reflux esophagitis is associated with *H. pylori* infection in the general population (27, 28). However, only two studies have investigated the correlation between *H. pylori* infection and reflux esophagitis in patients with CRF (29, 30). In a case-control study by Cekin *et al.* (30), *H. pylori* infection was found to be protective against reflux esophagitis in patients on HD; in contrast, in another study of patients prior to renal

transplantation, reflux esophagitis was found irrespective *H. pylori* infection (29). These results suggest that long-term HD is an independent risk factor of reflux esophagitis.

3.2 Defensive factors

Then we also have to consider the association of CRF with a decreased gastric emptying as a defensive factor. 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. A patient on peritoneal dialysis would be expected to have delayed gastric emptying simply due to the physical impairment caused by the peritoneal fluid. A lot of CRF patients have DM and HT as complications. We can also predict decreased gastric emptying by DM neuropathy and LES relaxations by Ca-antagonists and nitrites. CRF patients in our study also involved 55 patients (35%) with DM and 87 patients (56%) with HT, although we could not show the association of GERD with DM or HT (4). 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 (31-33). The researchers have also documented delayed gastric emptying in hemodialysis patients particularly patients who are hypoalbuminemic (32, 33). In our study, as for total protein, the differences between GERD group and Non-GERD group were not statistically significant (Fig. 1) (4). The situation is meddled by other studies that have not demonstrated decreased gastric emptying in hemodialysis patients (33-36).

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 (37). Dumitrascu et al demonstrated that patients with CRF had delayed gastric emptying if parasympathetic and sympathetic neuropathy were both present (38). DM is at increased risk of autonomic neuropathy, and they certainly constitute a large proportion of patients with CRF. In our study diabetic nephropathy was 29.2% of 418 stable HD patients (Table 1) and the differences between GERD group and Non-GERD group were not statistically significant (Fig. 1) (4). 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 (Fig. 1, 2) (4).

4. Conclusions

CRF, especially HD patients, seem to be associated with an increased incidence of GERD, though the pathophysiology of GERD is multifactorial and complicated. We should keep GERD in mind, when we see CRF patients.

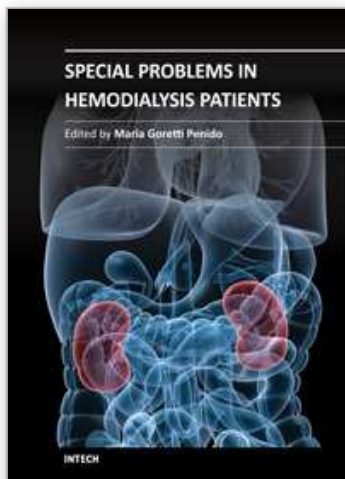
We used QUEST or endoscopy for the diagnosis of GERD. Though endoscopy is highly useful for the diagnosis of reflux esophagitis, endoscopic examination has not been used to evaluate the prevalence of reflux esophagitis in a large population of HD patients. Because many HD patients have the other diseases, we cannot undergo endoscopy easily. QUEST is thought to be accurate since upper GI symptoms in HD are correlated well with GERD (39). 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.

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Special Problems in Hemodialysis Patients

Edited by Prof. Maria Goretti Penido

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This book provides an overview of special cases in hemodialysis patients. Authors have contributed their most interesting findings in dealing with patients suffering of other diseases simultaneously, such as diabetes, cardiovascular disease and other health problems. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in these complex cases, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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