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RAPID COMMUNICATION

Incidence of reflux esophagitis and *Helicobacter pylori* infection in diabetic patients

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Abstract

AIM: To investigate the incidence of reflux esophagitis (RE) and *H pylori* infection in the diabetic patient.
METHODS: The incidence of RE and *H pylori* infection were investigated in 85 patients with diabetes mellitus and the results were compared with controls.
RESULTS: The incidence of RE in diabetic patients was 17.6%. Although this tended to be higher in diabetic patients, there were no statistically significant differences between diabetic patients and controls. The incidence of *H pylori* infection in diabetic patients was 53.7% but no statistically significant difference was seen between diabetic patients and controls in the incidence of *H pylori* infection.
CONCLUSION: No significant differences could be seen between diabetic patients and controls in the incidence of RE and *H pylori* infection.

Key words: Diabetes mellitus; Reflux esophagitis; *Helicobacter pylori*

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INTRODUCTION

At present, the frequency of lifestyle-related illnesses such as diabetes mellitus and obesity is increasing due to the westernization of the Japanese diet. Diabetic patients are now estimated at 7 400 000 in Japan[1] and diabetes is showing a world-wide tendency to increase[2].

In gastroesophageal reflux diseases (GERD), frequent gastroesophageal acid reflux causes such symptoms as heartburn, water brash, chest pain, and esophageal discomfort, lowering the quality of life of patients. Also, GERD damages the esophageal mucosa through erosion and the development of ulcers, mainly in the lower esophagus, leading to reflux esophagitis (RE). The incidence of RE has been on the rise in recent years, and today, it is one of the most common chronic diseases for adults in Europe and the United States[3]. While the incidence of RE in Japan is considered low as compared with Europe and the United States, the incidence of RE in Japan has increased due to the westernization of the Japanese diet, the rapidly growing elderly population, and lower *H pylori* infection rates[4].

Some investigators have reported that the incidence of RE is high in diabetic patients[5,6], although few reports have examined the incidence of RE in diabetic patient in Japan. There are some reports that hiatal hernia, age, *H pylori* infection and body mass index (BMI) are considered to affect the outbreak of RE[7,8]. Recent studies have reported that *H pylori* infection was less prevalent in patients with RE than those without RE, and was considered to suppress the onset of RE by inducing gastric mucosal atrophy and lowering gastric acid secretion[9,10].

Some investigators have reported that the incidence of *H pylori* infection in diabetic patients is higher than controls[11-14], though other investigators have reported

no such significant differences between these groups[15,16].

The objective of the present study is to examine the incidence of RE and *H pylori* infection in diabetic patients.

Patient demographics, incidence of GERD, incidence of columnar lined esophagus (CLE), serum gastrin concentration, and pepsinogen (PG) Ⅰ / Ⅱ (an index of gastric mucosal atrophy based on serologic finding) were also evaluated.

MATERIALS AND METHODS

Study design

A total of 85 consecutive patients with diabetes mellitus who visited the Department of Diabetes and Metabolic Diseases at Tohoku University Hospital from December 2002 to September 2003 were included in the present study. Patients who had other severe complications, had taken PPI or H2 receptor antagonists within four wk, or had undergone esophagogastrectomy were excluded from the present study. Nine hundred and forty four patients who had undergone endoscopy at the same period and another 67 age and sex-matched non-diabetic subjects without upper GI tract disorders were also included. Informed consent was obtained from each patient. The study protocol was approved by the ethical committee of the Tohoku University Graduate School of Medicine.

The subjects were divided into two groups, a well glycemic controlled group and a poorly controlled group. Patient demographics, incidence of RE, incidence of GERD, incidence of CLE, incidence of *H pylori* infection, severity grade of RE, serum gastrin concentration and PG Ⅰ / Ⅱ were investigated between the good glycemic controlled and poorly controlled group. The incidence of RE, GERD, CLE and the severity grade of RE were compared with 944 patients who had undergone endoscopy at the same study period as controls.

The incidence of RE and GERD were assessed due to HbA1c, disease duration, diabetic complications, and BMI. *H pylori* infection status was investigated between DM patients and 67 age and sex-matched non-diabetic subjects without upper GI tract disorders.

Patient demographics

The following factors were investigated: gender, age, height, body weight, BMI, type of DM [insulin dependent DM (IDDM) or non insulin dependent DM (NIDDM)], duration of DM, presence of hiatal hernia, with insulin therapy, with calcium antagonists, with complications (retinopathy, nephropathy and neuropathy). All patients were examined by an ophthalmologist for retinopathy. Nephropathy was diagnosed if albuminuria was > 0.3 g/L or there was evidence of chronic renal failure. Neuropathy was diagnosed if the patients had sensory abnormalities, vibration hyposensitivity, orthostatic hypotension, or impotence.

Good and poorly glycemic controlled groups: The good glycemic controlled group had hemoglobin A1c (HbA1c) 6.4% or less, and the poorly controlled group had an HbA1c value of 6.5% or more.

Assessment of RE: Subjects were diagnosed as having RE of grade A to D by the Los Angeles Classification[17].

Diagnosis of hiatal hernia: In the present study, hiatal hernia was defined as a hernia in which the gastric mucosa could be seen by endoscopy circumferentially from the esophageal hiatus.

Diagnosis of CLE: CLE was defined as the replacement of the normal squamous lining of the lower esophagus by columnar epithelium.

Assessment of *H pylori* infection: In the present study, patients were diagnosed as having *H pylori* infection if they tested positive to at least one of the following tests: biopsy of the mucosa of the gastric body and gastric antrum along the greater curvature during endoscopy, rapid urease test, and serum *H pylori* antibody test. Patients were diagnosed as being free of *H pylori* infection if they tested negative to all tests.

PG Ⅰ / Ⅱ and gastrin level: PG Ⅰ / Ⅱ[18] and gastrin level[19] were measured to assess gastric mucosal atrophy. Each blood sample was centrifuged, and the sera were stored frozen at -20℃ until testing.

Diagnosis of GERD, incidence of reflux symptoms: GERD was diagnosed with a self-administered questionnaire (QUEST). When the sum of the scores was 4 or more, the patient was considered as having GERD[20,21]. All patients were interviewed by investigators regarding their symptoms related to RE such as heartburn, burning in the upper abdomen, gastro-esophageal regurgitation, fullness, abdominal distension, anorexia, nausea, abdominal pain, and difficulty in swallowing food.

Statistical analysis

Of the various patient background factors, gender, type of DM, presence of hiatal hernia, with insulin therapy, with calcium antagonists, with diabetic complications, incidence of RE, reflux symptoms, GERD, CLE and *H pylori* infection status were compared between diabetic patients and controls by a chi-square test. Age, height, body weight, BMI, duration of DM, sum of the QUEST score, PG Ⅰ / Ⅱ and gastrin level were expressed as mean ± SD, and a one-way ANOVA test was used to compare these parameters between diabetic patients and controls. The Mann-Whitney's *U* test was used to compare RE severity. The significance level was set at < 5%.

RESULTS

Of the 85 diabetic patients, there were 79 NIDDM and 6IDDM patients, 45 (52.9%) men and 40 (47.1%)

Table 1 Patient characteristics

	Well controlled group (%)	Poorly controlled group (%)	*P*
Gender (Male/Female)	(20/16)	(25/24)	0.84
Type of DM (IDDM/NIDDM)	(1/35)	(5/43)	0.36
Age (yr)	65.9 ± 10.3	60.0 ± 11.9	0.02
Height (cm)	160.3 ± 8.7	156.9 ± 17.6	0.29
Body weight (kg)	61.4 ± 16.5	61.1 ± 17.9	0.93
BMI	23.5 ± 5.6	23.3 ± 3.1	0.77
Duration of DM (yr)	12.9 ± 10.5	16.7 ± 10.3	0.10
Hiatal hernia	33.3 (12/36)	22.4 (11/49)	0.38
Insulin therapy	33.3 (12/36)	61.2 (30/49)	0.02
Calcium antagonist	13.9 (5/36)	24.5 (12/49)	0.35
Retinopathy	16.7 (6/36)	32.7 (16/49)	0.16
Nephropathy	2.3 (1/36)	8.2 (4/49)	0.56
Neuropathy	13.9 (5/36)	20.4 (10/49)	0.45

Table 2 Comparison between diabetic patients and controls

	Diabetic patients (%)	Controls (%)	*P*
RE	17.6 (15/85)	10.3 (97/944)	0.056
Los angeles classification			
A	80.0 (12/15)	44.3 (43/97)	0.01
B	20.0 (3/15)	48.5 (47/97)	
C	0	6.2 (6/97)	
D	0	1.0 (1/97)	
Incidence of CLE	32.9 (28/85)	37.7 (356/944)	0.45

CLE: Columnar lined esophagus.

women. The mean age ± SD was 62.5 ± 11.5 years (range 28-85 years, median 64 years). The mean durations of DM was 15.1 ± 10.5 years (range 0-44 years, median 14 years).

Thirty-six patients comprised the well glycemic controlled group and 49 patients comprised the poorly controlled group. In the poorly controlled group, age and the number of patients with insulin therapy were higher than in the well controlled group. Among each group, there were no significant differences in gender, type of DM (IDDM or NIDDM), height, body weight, BMI, duration of DM, presence of hiatal hernia, with calcium antagonists, or diabetic complications (Table 1).

In the diabetic patients, the incidence of RE was 17.6% (15/85), and in the 944 controls who had undergone endoscopy at the same period in our division, the incidence of RE was 10.3% (97/944). Though the incidence of RE tended to be higher in diabetic patients, the difference was not significant between diabetic patients and controls ($P = 0.056$). Under the Los Angeles classification, all diabetic patients were grade A or B, and the severity grade of RE was statistically lower in diabetic patients than controls. The incidence of GERD and reflux symptoms in the diabetic patients were 32.9% (28/85) and 36.6% (31/85), respectively. The incidence of CLE was 32.9% (28/85), and the length all were less than 3 cm long. In the 944 controls, the incidence of CLE was 37.7% (356/944) (more than 3 cm: 11 patients, less than 3 cm: 345 patients) (Table 2).

Table 3 Comparison between good and poorly glycemic controlled groups

	Well controlled group (%)	Poorly controlled group (%)	*P*
RE	19.4 (7/36)	16.3 (8/49)	0.93
Incidence of GERD	25.0 (9/36)	38.8 (19/49)	0.27
Symptoms	30.1 (11/36)	41.3 (20/49)	0.46
QUEST score	2.06 ± 3.16	3.37 ± 4.22	0.12
Los angeles classification			
A	85.7 (6/7)	75.0 (6/8)	0.62
B	14.3 (1/7)	25.0 (2/8)	
C	0	0	
D	0	0	
Incidence of CLE	27.8 (10/36)	36.7 (18/49)	0.52
PG Ⅰ / Ⅱ	4.07 ± 2.61	4.94 ± 2.31	0.19
Gastrin	166.0 ± 126.9	137.6 ± 122.8	0.40

CLE: Columnar lined esophagus.

Comparison between well and poorly glycemic controlled groups

The incidences of RE in the well glycemic controlled group and poorly controlled group were 17.6% (15/85) and 10.3% (97/944), respectively. The incidences of RE in patients with HbA1c under 5.7, 5.8 to 6.4, 6.5 to 7.9, and higher than 8.0 were 27.3% (3/11), 16% (4/25), 14.6% (6/41), and 25% (2/8), respectively. The incidences of GERD for the same patient groups were 36.4% (4/11), 20% (5/25), 34.1% (14/41), and 62.5% (5/8), respectively. The incidence of RE and GERD did not show any particular tendency.

Among the well and the poorly glycemic controlled groups, there were no significant differences in the frequency of RE, GERD, reflux symptoms, CLE, sum of the QUEST score, severity grade of RE, PG Ⅰ / Ⅱ or gastrin level (Table 3).

Comparison between groups receiving and not receiving calcium antagonists

The incidences of RE in patients with and without calcium antagonists were 23.5% (4/17) and 16.2% (11/68), respectively. The incidences of GERD for the same groups were 29.4% (5/17) and 33.8% (23/68), respectively. There were no significant differences between patients receiving and not receiving calcium antagonists. The incidences of RE in the well and poorly glycemic controlled groups were 16.7% (6/36) and 18.3% (9/49), respectively. The incidences of GERD were 25.0% (9/36) and 38.8% (19/49), respectively. There were no significant differences between the well and the poorly glycemic controlled groups.

The incidence of RE and GERD in patients according to disease duration

The incidences of RE in patients with disease durations of less than 6 years, 6 to 11 years, 11 to 16 years, and more than 16 years were 11.8% (2/17), 10.5% (2/19), 21.4% (3/14) and 22.9% (8/35), respectively. The incidences of GERD for the same durations were 23.5% (4/17) 42.1% (8/19), 42.9% (6/14) and 28.6% (10/35),

respectively. The incidence of RE tended to rise with increased duration of the disease. The incidence of GERD did not show any particular tendency.

The incidence of RE and GERD with and without complications

Of the diabetic patients, 22 had retinopathy, 5 had nephropathy and 15 had neuropathy. The incidences of RE in DM patients with and without complications were 20% (6/30) and 16.5% (9/55), respectively. The incidences of GERD were 33.3% (10/30), and 32.7% (18/55), respectively. There were no significant differences between patients with and without diabetic complications.

The incidence of RE and GERD in non-obese and obese patients

The incidences of RE in non-obese (BMI less than 25) and obese patients (BMI higher than 25) were 17.2% (10/58) and 18.5% (5/27), respectively. The incidences of GERD were 29.3% (17/58) and 40.7% (11/27), respectively. There were no significant differences between non-obese and obese patients. There were also no BMI-related differences between patients with and without RE (23.3 ± 2.8 *vs* 23.4 ± 4.5) and between those with GERD and without GERD (23.8 ± 6.4 *vs* 23.2 ± 2.7).

H pylori infection

Of the 85 diabetic patients, measurement of their *H pylori* infectious status could be performed in 67 patients, of whom 53.7% (36/67) had *H pylori* infection. Of the age and sex-matched controls, 68.7% (46/67) had *H pylori* infection, with no significant differences seen in *H pylori* infection status between diabetic patients and controls ($P = 0.11$).

The incidences of RE in *H pylori* (+) and *H pylori* (-) patients were 19.4% (7/36) and 9.7% (3/31), respectively. The incidences of GERD in *H pylori* (+) and *H pylori* (-) patients were 27.8% (10/36) and 35.5% (11/31), respectively. No significant differences in the incidence of RE and GERD could be demonstrated between *H pylori* (+) and *H pylori* (-) patients.

DISCUSSION

The incidence of RE has been on the rise in recent years, and today, it is one of the most common chronic diseases for adults in Europe and the United States[22].

Today, the incidence of RE is reported to be 10%-20% in Europe and the United States[23-25], and 14%-16% in Japan[26-28]. While the incidence of RE in Japan is considered low as compared to Europe and the United States, the incidence of RE in Japan has increased due to the westernization of the Japanese diet, the rapidly growing elderly population, and lower *H pylori* infection rates[26-28].

Parkman[5] has reported that the incidence of RE in patients was 20% (4/20). Antwi[6] reported an incidence of 40.7% (22/54), though in these reports, glycemic control in many of the patients was poor and many had neuropathy. In the present study, the incidence of RE in diabetic patients was 17.6% (15/85), and the incidence of RE in the 944 controls was 10.3% (97/944). The incidence of RE tended to be higher in diabetic patients, there were no significant differences between diabetic patients and controls.

In Japan, with respect to the severity of RE, most patients are reported to have mild esophagitis (Grade A or B under the Los Angeles classification[26,27]. In the present study, all patients had mild esophagitis.

In Japan, Nishida has previously reported that the incidence of GERD diagnosed with the QUEST questionnaire in diabetic patients was 25.3%, and significantly higher than that of controls[29]. In this previous study, they used the QUEST questionnaire to investigate GERD, though they did not perform gastrointestinal endoscopy to investigate RE. In the present study, we used the QUEST questionnaire and additionally performed gastrointestinal endoscopy to investigate GERD and RE. To the best of our knowledge, the present study is the first study to investigate both GERD and RE at the same time for diabetic patients in Japan. In the present study, the prevalence of GERD was 32.9%.

HbA1c is an index of DM control over some months beforehand. Complications of DM such as retinopathy, nephropathy and neuropathy occur as a result of poor control of diabetes for several years. So it is conceivable that DM-related complications are more appropriate than HbA1c as an index of the diabetic control. In the present study, there were no significant differences between patients with and without complications in the incidence of RE and GERD.

Some patients with DM, particularly those with NIDDM, are obese, which increases the intra-abdominal pressure, and may worsen RE[30]. In the present study, there were no significant differences between obese patients and non-obese patients in the incidence of RE or GERD. There were also no BMI-related differences between patients with and without RE and those with and without GERD. In the present study, obesity was not a risk factor for RE or GERD in the diabetic patient.

DM induces complications such as retinopathy, nephropathy and neuropathy. Diabetic neuropathy occurs in all sensory, motor and autonomic nerves. Some investigators have reported that in diabetic patients, RE can be induced in the presence of lowered LES pressure, abnormal esophageal motility, increased transient lower esophageal sphincter relaxation (TLESR), lowered acid clearance of the esophagus and prolonged gastric emptying time due to the dysfunction of autonomic nerves or the vagal nerve[31-35]. Prolonged gastric emptying time sometimes induces an unexpected hyper or hypoglycemic status, especially in the patients using insulin or oral hypoglycemic agents. Disorder of the sensory nerves raises the perception threshold level, and some patients cannot feel reflux symptoms, possibly leading to stricture of the esophagus. In some patients, RE can be discovered for the first time during routine endoscopy. In the present study, the incidence of RE tended to be higher in diabetic patients, although the differences between diabetic patients and controls were not significant.

It would be important to test for the presence of RE in diabetic patients during the daily examination.

The incidence of *H pylori* infection in diabetic patients has attracted some controversy. Some investigators have reported that the incidence of *H pylori* infection in diabetic patients is higher than controls[9-13]. Some investigators have reported that in DM patients, due to impaired immune function and impaired gastrointestinal motility, they were prone to *H pylori* infection[36-38]. On the other hand, some previous studies show a lower incidence of *H pylori* in diabetic patients than controls[39], whereas in other studies, there was no difference in the prevalence of *H pylori* infection between diabetic patients and controls[11,14]. In some studies, *H pylori* infection was assessed by only one or two methods taken from among a biopsy of the mucosa, the rapid urease test, and the presence of serum *H pylori* antibodies. In the present study, *H pylori* infection was investigated by all three methods, so the incidence of *H pylori* infection in DM patients the present study is considered to be accurate, being recorded as 53.7%, but with no significant differences between diabetic patients and controls.

In conclusion, our results indicated that there were no differences in the incidences of either RE or *H pylori* infection between diabetic patients and controls.

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COMMENTS

Background

Some investigators had reported that the incidence of reflux esophagitis (RE) and *H pylori* infection is high in diabetic patients. Only a few reports, however, have examined the incidence of RE and *H pylori* infection in diabetic patients in Japan. The present study was designed to investigate the incidence of RE and *H pylori* infection in the diabetic patient.

Research frontiers

We investigated the incidence of gastroesophageal reflux diseases (GERD), RE and *H pylori* infection in the diabetic patient. The present study is the first study to investigate both GERD and RE at the same time for diabetic patients in Japan.

Innovations and breakthroughs

We used the questionnaire (QUEST) questionnaire to investigate GERD and performed gastrointestinal endoscopy to investigate RE at the same time for diabetic patients.

Applications

In the present study, the incidence of RE tended to be higher in diabetic patients. It would be important to test for the presence of RE in diabetic patients during the daily examination.

Peer review

This manuscript indicated that there were no differences in the incidences of either RE or *H pylori* infection between diabetic patients and controls. The study was well performed and the conclusion was clinically useful.

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