Helicobacter pylori prevalence in diabetic patients and its relationship with dyspepsia and autonomic neuropathy

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ABSTRACT. Aims: We evaluated the prevalence of Helicobacter pylori (HP) in Type 2 diabetic patients and its relationship with dyspeptic symptoms and complications of diabetes. Materials and methods: Seventy-eight Type 2 diabetic patients (54 females, 24 males, mean age: 51.9±10.6 yr) and 71 non-diabetic control subjects were involved in the study. Patients were questioned for dyspeptic symptoms. Cardiovascular autonomic neuropathy, nephropathy and retinopathy were investigated in diabetic patients. Upper gastrointestinal tract endoscopy was performed for all patients and gastric biopsies were obtained and searched for HP. Results: Helicobacter pylori prevalence was significantly higher in diabetic patients than in control subjects (75.6 *vs* 46%, $p<0.05$). No differences were found between women and men with regard to HP infection status in diabetic patients. There was no relation between HP and diabetic complications, nephropathy and retinopathy. Helicobacter pylori prevalence was significantly higher in diabetic patients with cardiovascular autonomic neuropathy than in diabetic patients without cardiovascular autonomic neuropathy (90.6 *vs* 44.0%, $p<0.02$). Forty-seven subjects with diabetes had symptoms of dyspepsia (60.3%) and the prevalence of HP was higher in these patients ($p<0.002$). Conclusion: There is a high prevalence of HP infection in diabetic patients and it is correlated with dyspeptic symptoms. Diabetic subjects complicated with cardiovascular autonomic neuropathy and dyspepsia are at high risk of HP infection and should be carefully investigated and considered for eradication therapy.

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INTRODUCTION

Gastrointestinal symptoms appear to be common in patients with Type 2 diabetes mellitus. These symptoms range from minor dyspeptic symptoms to gastroparesis. The etiopathogenesis of these symptoms are still not clear. Some studies have suggested that autonomic neuropathy and poor glycemic control may be responsible for these symptoms but other studies have yielded conflicting results (1).

Helicobacter pylori (HP) is a urease-producer bacterium considered to be the major acquired factor in the pathogenesis of chronic gastritis, gastroduodenal ulcer and gastric cancer (2). The prevalence of HP infection is about 50% in both general population and subjects with non-ulcer dyspepsia (3), and reaches up to 76% when concomitant gastrointestinal motility abnormalities are present (4). The data about the prevalence of HP in diabetic patients are scanty and controversial.

The relationship between the prevalence of HP and nephropathy and retinopathy is also controversial. Quadri et al. reported that the absence of microangiopathy may be a predisposing factor, as microvascular changes in the gastric mucosa may create an unfavorable environment for the establishment or survival of HP (5). Conversely, de Luis et al. found no relation between HP infection and retinopathy and nephropathy (6).

The aim of our study was to evaluate the prevalence of HP in Type 2 diabetic patients and its correlation with dyspeptic symptoms and complications of diabetes.

MATERIALS AND METHODS

This prospective study involved 78 Type 2 diabetic patients (54 females, 24 males, mean age: 51.9±10.6 yr) who attended the outpatient diabetes clinic of our hospital and 71 age and body mass

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index (BMI) matched non-diabetic control subjects (50 females, 21 males, mean age: 48.2±8.3 yr). All diabetic patients were under oral hypoglycemic or diet therapy. Patients with cholelithiasis, previous cholecystectomy or gastrointestinal surgery, and subjects under treatment with antiulcer drugs, antibiotics, bismuth salts and non-steroidal anti-inflammatory drugs, diuretics, antihypertensive drugs and drugs acting on the nervous system were excluded.

Glycemic control was assessed with fasting glucose, post-prandial glucose and hemoglobin A_{1c} (HbA_{1c}) levels.

Retinopathy was evaluated by fundoscopic examination performed by an experienced ophthalmologist. For assessment of nephropathy urea, creatinin levels were measured, albumin/creatinin ratio and creatinin clearance were calculated. Autonomic nerve function was documented by standardized cardiovascular reflex tests (7). Parasympathetic function was evaluated by the variation of heart rate (R-R interval) during deep breathing (an expiration:inspiration R-R ratio >1.17 is considered as abnormal) and the immediate heart rate response to standing (the R-R interval is measured at beats 15 and 30 after the patient stands and 30:15 ratio of less than 1.03 is considered as abnormal) and the Valsalva maneuver (a ratio of longest to shortest R-R interval of less than 1.2 is considered as abnormal). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The R-R interval variations were measured during the tests. The cardiovascular autonomic neuropathy classification was as follows: normal or definite autonomic neuropathy (i.e. one or more heart rate tests abnormal or orthostatic hypotension).

Patients were questioned for epigastric pain, nausea, vomiting, belching, bloating, halitosis, post-prandial fullness, symptoms of reflux and dysphagia. These symptoms were defined as present if they occurred at least once a month in the preceding 12 months. For the purpose of the study, dyspepsia was considered present if the patient had one or more of the individual symptoms.

Gastroduodenoscopy was performed by Pentax 29B flexible endoscopy for all individuals voluntarily, and gastric mucosal biopsies were obtained and searched for HP. The specimens were routinely processed and stained with hematoxylin and eosin as well as giemsa.

Informed consent was obtained from all cases according to the Helsinki Declaration, and the study was approved by the medical ethics committee of our hospital.

Statistical analyses were performed using independent samples *t*-test and Chi-square test with the statistical package for social sciences software (SPSS, version 9.0). Obtained data are presented as mean±SD. A p value <0.05 is accepted as statistically significant.

Table 1 - *Clinical and demographic information of diabetic patients and controls.*

	Diabetes mellitus (no.=78)	Controls (no.=71)	*p*
Gender (M/F)	24/54	21/50	ns
Age (yr)	51.9±10.6	48.2±8.3	ns
BMI (kg/m^2)	26±3	25±4	ns
Dyspepsia	60.3%	58.9%	ns
HP	75.6%	46.0%	<0.05

Ns: not significant; BMI: body mass index; HP: helicobacter pylori.

RESULTS

The clinical and demographic data of the patients is summarized in Table 1. Fasting glucose and post-prandial glucose levels of the diabetic patients were 185.7±60.0 and 252.6±77.3 mg/dl, respectively. No differences were found between women and men with regard to HP infection status in diabetic patients (74.1 *vs* 79.2 %, p>0.05).

When HP positive (+) and HP negative(–), diabetic groups were compared and there was no difference between mean age of diabetes, HbA_{1c} levels and BMI (Table 2). Twenty-three diabetic patients had retinopathy (29.5%). The prevalence of HP infection was not significantly different between the patients with retinopathy or without retinopathy (14/23, 60.9% *vs* 37/55, 67.3%, p>0.05). Thirty-one diabetic patients had nephropathy (39.7%). The prevalence of HP infection was not significantly different between the patients with nephropathy or without nephropathy (23/31, 74.2% *vs* 36/47, 76.6%, p>0.05). Cardiovascular autonomic neuropathy was positive in 48 HP (+) patients and in 7 HP (–) patients (84.3%, 37.0%, p<0.02). Besides, the prevalence of HP was significantly higher in patients with cardiovascular autonomic neuropathy than in patients without cardiovascular autonomic neuropathy (48/53, 90.6% *vs* 11/25, 44.0%, p<0.02). Forty-seven patients with diabetes had symptoms of dyspepsia (60.3%). HP infection was positive in 43 patients with symptoms of dyspepsia and in 16 patients without (72.9% *vs* 21.1%, p<0.02). Thirty-one diabetic subjects did not have dyspeptic symptoms, 16 with (51.6%) and 15 (48.4%) without HP infection (p>0.05). Control subjects with dyspeptic symptoms also had a higher incidence of HP than the ones without dyspeptic symptoms (89.5% *vs* 13.6%, p<0.05). Out of 59 diabetic patients with HP infection, 40 patients had both autonomic neuropathy and dyspeptic symptoms (67.8%); ten out of 78 diabetic patients had

Table 2 - *Clinical information of HP (+) and HP (–) diabetic patients.*

	HP (+) (no.=59)	HP (–) (no.=19)	*p*
Age (yr)	51.5±10.2	47.9±7.7	ns
Diabetes duration (yr)	6.9±5.9	6.7±3.7	ns
BMI (kg/m^2)	30.0±3.8	30.7±4.2	ns
HbA_{1c} (%)	8.2±1.4	7.9±2.2	ns
Retinopathy (n)	35 (60.9%)	12 (67.3%)	ns
Nephropathy (n)	23 (39.0%)	8 (42.1%)	ns
Autonomic neuropathy (n)	48 (84.3%)	7 (37.0%)	p<0.05

NS: not significant; BMI: body mass index; HP: helicobacter pylori.

atrophic gastritis (12.8%, mean age 51.4 yr), and all had HP infection. None of the non-diabetic patients had atrophic gastritis.

DISCUSSION

The present study revealed that the prevalence of HP infection was significantly higher in diabetic patients than in non-diabetics. A significant relation between cardiovascular autonomic neuropathy and HP was established in diabetic patients; HP infection had a higher prevalence in diabetic subjects with dyspeptic symptoms; and neither nephropathy nor retinopathy or glycemic control affected the HP infection status.

The data concerning the prevalence of HP infection in diabetic patients is controversial. The relationship between HP and diabetes was first reported by Simon et al. who found that the prevalence of HP was higher in diabetic patients than in the controls (62 *vs* 21%) (8). The same higher prevalence of HP in diabetic patients was also reported by some later trials but some studies found a similar prevalence or even a lower prevalence. For example, the Karakow study, based on the histological demonstration of the presence of HP, found a lower prevalence of HP in diabetic patients and attributed this finding to autonomic dysfunction that determines bile reflux in the stomach and the unfavorable conditions for HP colonization (9). Xia et al. also reported a similar prevalence of HP in diabetic patients and controls (1). Diabetic patients had a higher prevalence of gastrointestinal symptoms compared with controls, but HP infection was not associated with upper gastrointestinal symptoms (19).

In contrast to these findings, some authors found a relation between HP infection and diabetes mellitus. Quatrini et al. detected HP infection in 69% of diabetic patients and in 46% of dyspeptic controls. A high prevalence of HP infection and a relation with upper gastrointestinal lesions were demonstrated in diabetic patients. Patients with dyspeptic symptoms had a prevalence of HP infection similar to that observed in the general population, whereas the prevalence of HP was higher in diabetic patients with or without dyspeptic symptoms (10). Oldenburg et al. also indicated a higher prevalence of HP in diabetic patients (11). In the present study, HP prevalence was higher in diabetic patients than in controls (75.6 *vs* 46%), but in contrast to findings of Quatrini et al., dyspeptic diabetic patients had a significantly higher prevalence of HP than non-dyspeptic ones (91.5 *vs* 51.6%).

Persico et al. demonstrated a high prevalence of HP in diabetic patients with non-ulcer dyspepsia, and it was correlated with cardiovascular autonomic neuropathy (12). They attributed importance to the abnormalities of the migrating motor complex, considered as a putative factor responsible for the elevated frequency of HP. Quadri et al. reported a high prevalence of HP infection in diabetic women. Macroangiopathy, cardiovascular autonomic neuropathy, fasting glucose, HbA_{1c} values and BMI correlated with high prevalence of HP. Microangiopathy was higher in HP negative patients (5). In our study, there was no gender difference, no relationship between HP and fasting glucose and HbA_{1c}, and HP infection was not related to any of the glycemic control parameters. There was no relation between BMI, nephropathy or retinopathy and the prevalence of HP infection. In our study, cardiovascular autonomic neuropathy significantly correlated with HP infection ($p<0.02$).

Gastric emptying is impaired in diabetic patients with autonomic neuropathy as a consequence of vagal innervation disturbance, even when normal secretory functions of stomach are maintained. Alteration of the migrating motor complex of the stomach, prolonged pyloric activity and the atony of the duodenal bulb in diabetic patients reported by some authors may be other factors that increase the time of exposure to the pathogen (13-15). Impaired gastric motility could also be an etiological factor in diabetic gastric disorders, and a predisposing factor for HP infections. In addition to autonomic neuropathy, direct effect of hypoglycemia and hyperinsulinemia on gastric motility and altered production and secretion of intestinal hormones may also be considered as other factors in impaired gastric motility. These factors can explain the high prevalence of HP in diabetic patients with autonomic neuropathy.

The incidence of HP was higher in diabetic patients with dyspeptic symptoms than in the diabetic patients without dyspeptic symptoms. Non-diabetic patients with dyspeptic symptoms also had a higher incidence of HP than the ones without dyspeptic symptoms. Since there is a significant relationship between HP infection and dyspeptic symptoms in diabetic patients, these patients are candidates for eradication therapy. In literature, the frequency of atrophic gastritis is higher in diabetic patients and increases with age (16, 17). In our study, 10 patients had atrophic gastritis (mean age 51.4 yr), and all had HP infection. None of the non-diabetic patients had atrophic gastritis.

Person-to-person contact is considered to be the most likely transmission route of HP (18-20). Because HP has been isolated from dental plaque, saliva, feces and vomitus (21-23), the transfer of this microorganism from the stomach of one person to another is thought to be oro-fecal route (20, 24). As diabetic patients have frequent visits to hospital, they are prone to increased exposure of the pathogen HP.

As diabetes is an immunocompromised disease, the host's immunogenic condition may be another predisposing factor for HP infection.
In conclusion, our data suggest a high prevalence of HP infection in diabetic patients, and it is correlated with dyspeptic symptoms. Diabetic patients complicated by autonomic neuropathy are at high risk of HP infection: this should be carefully investigated. Furthermore, eradication of HP is essential.

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