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Helicobacter pylori, Gastrointestinal Symptoms, and Metabolic Control in Young Type 1 Diabetes Mellitus Patients

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ABSTRACT. *Objective.* The role of *Helicobacter pylori* infection in metabolic control and gastrointestinal symptoms in type 1 diabetes mellitus (DM1) patients has been debated. The aim of this study was to investigate the prevalence of *H pylori*, of the more cytotoxic Cag-A-positive strains, and the effects of infection on gastrointestinal symptoms and metabolic control in young DM1 patients.

Research Design and Methods. *H pylori* infection was investigated by using the ¹³C-urea breath test in 121 DM1 patients (65 males, 56 females; mean age: 15 ± 6 years) and 147 matched controls. In positive patients, an assay for specific immunoglobulin G against Cag-A was performed. Glycosylated hemoglobin A, daily insulin requirement, and duration of illness were established; a questionnaire concerning the presence of dyspeptic symptoms was administered.

Results. No difference in *H pylori* infection rate between patients and controls was observed. Thirty-four (28.1%) of 121 patients and 43 (29.25%) of 147 controls were infected. Twenty-one patients and 24 controls were positive for Cag-A. Glycosylated hemoglobin A, daily insulin requirement, and duration of illness were not affected by infection nor by Cag-A status. Among gastrointestinal symptoms, only halitosis was related to *H pylori* infection, but this association disappeared after correction for age. Positive patients with halitosis showed a worse glycemic control than uninfected patients with halitosis.

Conclusions. *H pylori* infection and Cag-A-positive strains do not affect metabolic control in DM1 patients. With regard to gastrointestinal symptoms studied, *H pylori* infection, when present in participants with halitosis, seems to predict a worse metabolic control than in *H pylori*-negative patients with halitosis. *Pediatrics* 2003; 111:800–803; type 1 diabetes mellitus, children, *Helicobacter pylori*, Cag-A.

ABBREVIATIONS. DM1, diabetes mellitus type 1; BMI, body mass index; HbA1c, glycosylated hemoglobin A; DIR, daily insulin requirement; ¹³C-UBT, ¹³C-urea breath test.

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During infections, patients with type 1 diabetes mellitus (DM1) often show poor glycemic control and need higher doses of insulin. *Helicobacter pylori*, one of the most common chronic infections worldwide,^{1,2} is the main etiologic agent of chronic gastritis and peptic ulcer, and it is also related to gastric cancer and type B low-grade mucosa-associated lymphoid tissue lymphoma.^{3,4}

Several studies have investigated the prevalence of *H pylori* in diabetic patients and a possible role of the infection in their metabolic control with discordant results.^{5–14} Some studies did not find a higher prevalence of *H pylori* in diabetics patients and did not support any correlation between metabolic control and infection, while others have demonstrated a higher seroprevalence of the infection in diabetic participants and a reduced glycemic control in infected DM1 patients when compared with uninfected diabetic patients. Moreover, a link between *H pylori*, insulin, and fasting serum glucose levels has recently been demonstrated.¹⁵ These different results could be explained by considering the evidence that some strains of *H pylori* are considered more virulent; in particular, Cag-A-positive strains have been presumed to have a higher pathogenic effect on gastric mucosa and they have been related to duodenal ulcer and gastric cancer. More specifically, Cag-A-positive strains are associated with the increased production of cytokines such as tumor necrosis factor, interleukin-1, -6, and -8 that might alter the control of glycemia in diabetic patients.

A prospective study was performed to evaluate prevalence of *H pylori* and of Cag-A-positive strains in a cohort of children and adolescents with DM1 and in a group of age, sex, and social class-matched controls. A possible influence of the infection on metabolic control and on gastrointestinal symptoms was also observed.

RESEARCH DESIGN AND METHODS

One hundred twenty-one consecutive patients (66 males and 55 females; mean age: 14.8 ± 5.6 years; range: 6–21) affected by DM1 were enrolled between November 2001 and June 2002 in the Pediatric Diabetology Center of the Catholic University in Rome. None of the participants had known peptic ulcer disease and no patient presented complications attributable to diabetic vasculopathy. Written informed consent was obtained from each participant or from related parents and the study was approved by the Ethical Committee of the Catholic University. Demographic (age and gender), socioeconomic (annual family income and number of individuals per room) and clinical information (body mass

TABLE 1. Demographic, Clinical, and Socioeconomic Information in Patients With Type 1 Diabetes Mellitus and Controls

	Patients	Controls
Age (y)	14.8 ± 5.6	15.1 ± 5.3
Females (%)	45 (55/121)	45 (67/147)
Males (%)	55 (66/121)	55 (80/147)
BMI (kg/m ²)	20.9 ± 3	21.4 ± 2
HbA1c	8.2 ± 1.4	—
DIR (IU/kg/d)	0.7 ± 0.3	—
Duration of illness (mo)	79.7 ± 55.5	—
Annual family income* (%)		
<15 000	33.9 (41/121)	34 (50/147)
15 000–30 000	35.5 (43/121)	35.4 (52/147)
30 000–45 000	19 (23/121)	18.4 (27/147)
>45 000	11.6 (14/121)	12.2 (18/147)

* In Euro.

TABLE 2. Prevalence of *H pylori* Infection (%) in Different Socioeconomic Groups

Annual Family Income (Euro)	DM1 Patients (%)	Controls (%)	<i>P</i>
a) <15 000	36.6 (15/41)*	38 (19/50)†	NS
b) 15 000–30 000	25.6 (11/43)	30.8 (16/52)†	NS
c) 30 000–45 000	21.7 (5/23)	18.5 (5/27)	NS
d) >45 000	21.3 (3/14)	16.6 (3/18)	NS
Total	28.1 (34/121)	29.2 (43/147)	NS

NS indicates not significant.

* *P* < .05 when compared with b–d.

† *P* < .05 when compared with c and d.

index [BMI], number of months since the diagnosis of DM1, glycosylated hemoglobin A [HbA1c] levels and daily insulin requirement [DIR]; IU/kg/d) were obtained from patients. HbA1c serum levels, disease duration, and the DIR of diabetic patients are shown in Table 1. Demographic (age and gender), socioeconomic (annual family income), and clinical information (BMI) for patients and controls are described in Table 1.

A validated questionnaire to evaluate the prevalence and the intensity of gastrointestinal symptoms (epigastric pain, halitosis, bloating, postprandial fullness, nausea and vomiting), extra-digestive symptoms (Raynaud's phenomenon, asthma) or coexisting diseases (celiac disease, thyroiditis, Addison's disease, Down's syndrome) was administered. One hundred forty-seven healthy participants matched for sex, age and social class were recruited as controls (80 males and 67 females, mean age: 15.1 ± 5.3 years; range: 6–21 years).

The prevalence of *H pylori* infection was investigated by a ¹³C-urea breath test (¹³C-UBT).^{16,17} A sample serum was obtained from each participant in the study for the evaluation of specific immunoglobulin G against CagA using a commercially available enzyme-linked immunosorbent assay kit (RADIM, Pomezia, Italy). History of peptic ulcer and treatment with antibiotics, proton pump inhibitors, H₂-receptor blockers, sucralfate- or bismuth-containing compounds, nonsteroidal antiinflammatory drugs, or antacids in the 2 months before testing were considered exclusion criteria.

Data were evaluated using STATA 6.0 software (Stata Corporation, College Station, TX). Comparisons between data of categorical type were performed with the χ^2 test for proportions or, if necessary, with the Fisher exact test. Normality was evaluated with the Shapiro-Francia test for continuous numeric data. If data distribution was compatible with Gauss' normality, parametric tests were performed comparing average and standard deviations of the two groups (T test); when incompatible, evaluation of ranks was performed according to nonparametric techniques. The Mann-Whitney *U* test was used for the comparison of the mean data in the 2 groups of diabetic patients and controls. Logistic regression was used to correct for age. Correlation between intensity of gastrointestinal symptoms (measured as score: 0–4) and disease duration was studied using Kruskal-Wallis test. A *P* value <.05 was considered statistically significant.

TABLE 3. Prevalence of *H pylori* Infection (%) in Different Socioeconomic Groups

Individuals/Rooms	DM1 <i>H pylori</i> -Positive (%)	DM1 <i>H pylori</i> -Negative (%)	<i>P</i>
<.7	6 (17.6%)	40 (46%)	<.05
.7–1	14 (41.2%)	29 (33.3%)	NS
>1	14 (41.2%)	18 (20.7%)	<.05

NS indicates not significant.

TABLE 4. Prevalence of Gastrointestinal Symptoms Between *H pylori*-Positive and -Negative Patients

Gastrointestinal Symptoms	<i>H pylori</i> -Positive (%)	<i>H pylori</i> -Negative (%)	<i>P</i>
Epigastric pain	35.3 (12/34)	32.1 (28/87)	NS
Halitosis	50 (17/34)	29.9 (26/87)	<.05
Bloating	17.6 (6/34)	19.5 (17/87)	NS
Postprandial fullness	44 (15/34)	33.3 (29/87)	NS
Nausea	5.9 (2/34)	12.6 (11/87)	NS
Vomiting	5.9 (2/34)	3.4 (3/87)	NS

NS indicates not significant.

RESULTS

No difference in the prevalence of *H pylori* infections between DM1 patients and controls was observed. In particular, 34 out of 121 DM1 patients and 43 out of 147 healthy controls proved to be *H pylori*-positive at ¹³C-UBT (28.1% vs 29.25%; odds ratio: 0.98; 95% confidence interval: 0.58–1.66; *P* = .954). Twenty-one (61.7%) of 34 positive patients and 24 (55.8%; *P* not significant) of 43 positive controls resulted infected with the more virulent Cag-A-positive strains. *H pylori*-positive children were older (16 ± 5.6 years) than negative participants (14.3 ± 5.5; *P* = .06). No difference in prevalence of infection was found between males and females both in patients and in controls. The prevalence of *H pylori* infection proved to be related to socioeconomic status (annual family income and overcrowding) as already described (Table 2 and Table 3). Twenty-six of (83%) 35 *H pylori*-positive patients and 61 (72%; *P* not significant) of 86 negative participants had associated dyspeptic symptoms. No difference in the prevalence of the gastrointestinal symptoms studied was observed between positive and negative patients (Table 4), with the exclusion of halitosis. In fact, among the investigated gastrointestinal symptoms, a higher incidence of halitosis was observed in patients with DM1 than in negative participants (*P* = .033). However after correction for age by means of logistic regression analysis prevalence of halitosis differ between group even if it was not significant (*P* = .08). Moreover, DM1 patients with halitosis did not show a different glycemic control when compared with patients without it. Interestingly, patients with halitosis and *H pylori* infection showed higher serum levels of HbA1c (8.6 ± 1.5 vs 7.9 ± 1; *P* < .05) and a longer history of disease (96.6 ± 54.2 vs 64.2 ± 49.1 month; *P* < .05) when compared with *H pylori*-negative patients with halitosis. An increased prevalence of severe symptoms, even if not statistically significant, was found for dyspepsia (*P* = .132), bloating (*P* = .154), nausea (*P* = .060), and vomiting (*P* = .158). No significant correlation was found between

TABLE 5. Metabolic Control in *H pylori*-Positive, *H pylori*-Negative, Cag-A-Positive, and -Negative DM1 Patients

	<i>H pylori</i> -Positive	<i>H pylori</i> -Negative	<i>P</i>	Cag-A-Positive	Cag-A-Negative	<i>P</i>
BMI (kg/m ²)	21.0 ± 3.3	20.8 ± 2.9	NS	22.6 ± 3.1	20.1 ± 3.1	NS
DI (mo)	89 ± 57	76 ± 54	NS	100 ± 55	82 ± 59	NS
HbA1c (%)	8.3 ± 1.1	8.2 ± 1.5	NS	8.3 ± 1.0	8.4 ± 1.2	NS
DIR (IU/kg/d)	0.76 ± 0.22	0.74 ± 0.30	NS	0.77 ± 0.21	0.75 ± 0.23	NS

DI indicates duration of illness; NS, not significant.

disease duration and both intensity or prevalence of gastrointestinal symptoms ($P > .05$). No correlation with *H pylori* infection was found for Raynaud's phenomenon, asthma, and other coexisting disease studied in the diabetic population. Patients with DM1 and *H pylori* infection showed no statistically significant difference when compared with uninfected patients for HbA1c serum levels, disease duration, DIR, and BMI as shown in Table 5.

Finally, Cag-A status did not affect either glycemic control or prevalence of gastrointestinal symptoms in both groups (Table 5 and Table 6).

DISCUSSION

H pylori infection is a worldwide infection that particularly affects participants with lower socioeconomic status, residence in less developed countries, and a clustered living environment.¹⁸ *H pylori* infection induces inflammation of the gastric mucosa with submucosal infiltration by neutrophils and monocytes. *H pylori* plays a proinflammatory role with the secretion of mediators promoting trafficking of neutrophils and other leukocytes in the gastric mucosa leading to mucosal damage and epithelial remodeling. The prevalence of *H pylori* gastric infection in patients with DM1 and its relation with glycemic control was studied by several researchers with discordant results. Some authors have found a high prevalence of the infection in such patients and an influence on metabolic control. These findings are generally explained by the impairment of cellular and humoral immunity in diabetics, by the reduction of both gastrointestinal motility and acid secretion and by the effect of a higher secretion of proinflammatory cytokines attributable to *H pylori* gastric infection itself. On the other hand, other studies have described the lack of any difference in prevalence between diabetic and control populations or even a lower rate of infection in diabetic patients. In these cases the results are explained by the higher number of antibiotics taken by diabetics (particularly by older participants) and a consequently more frequent occasional clearance of the infection. In an effort to

TABLE 6. Gastrointestinal Symptoms and Cag-A Status in DM1 Patients

	Cag-A-Positive (%)	Cag-A-Negative (%)	<i>P</i>
Epigastric pain	33.3 (7/21)	38.5 (5/13)	NS
Halitosis	47.6 (10/21)	53.1 (7/13)	NS
Bloating	19 (4/21)	15.4 (2/13)	NS
Postprandial fullness	42.8 (9/21)	46.2 (6/13)	NS
Nausea	0 (0/21)	15.4 (2/13)	NS
Vomiting	4.7 (1/21)	7.6 (1/13)	NS

NS indicates not significant.

clarify these discordances several studies were also performed on pediatric patients affected by DM1. In fact, the prevalence of *H pylori* infection is related to several confounding factors such as age and socioeconomic status, and children are less influenced by them. Unfortunately the results of these studies were discordant, too.¹⁹⁻²⁴ None of these studies took into account the prevalence and the effect on metabolic control of particular bacterial strains on diabetic patients. It has been shown that Cag-A-positive strains induce a higher production of proinflammatory cytokines than Cag-A-negative ones and they should induce a higher impairment of metabolic control in DM1 patients.

This study showed that participants with DM1 have a similar prevalence in *H pylori* infection when compared with control participants, matched for sex, age, and occupational social class. Patients with DM1 and *H pylori* infection showed no statistically significant difference when compared with uninfected patients as for HbA1c, disease duration, and DIR. As far as gastrointestinal symptoms are concerned, only halitosis proved to be slightly related to *H pylori* gastric infection. Our results are in contrast with previous reports of a higher prevalence of *H pylori* infection in young people with DM1. These discrepancies may be attributable to the methods used to detect the infection, different selection of control groups, sample sizes, lack of correction for age and socioeconomic status, or a different prevalence of Cag-A-positive cytotoxic strains. Two recent studies did not observe any difference in the prevalence of *H pylori* in diabetic patients and in control groups and were performed with a carefully described selection of control groups, with a large sample size and with adequate correction for age, sex, and socioeconomic status.^{10,23} Their findings are consistent with our results. We also investigated the prevalence of cytotoxic strains and no difference was observed in glycemic control between *H pylori*-negative, *H pylori*-positive Cag-A-negative and *H pylori*-positive Cag-A-positive patients. Although we observed a high incidence of gastrointestinal symptoms in DM1 patients only halitosis seems to be related to the infection. Moreover, the metabolic control of *H pylori*-positive DM1 patients with halitosis seems to be worse than in negative ones with halitosis. No one of the investigated gastrointestinal symptoms resulted related to Cag-A-positive *H pylori* infection.

CONCLUSION

Our study did not support any association between *H pylori* and DM1 in children and adolescents. Moreover, the presence of *H pylori* and cytotoxic

strains did not modify the incidence of gastrointestinal symptoms in the same participants.

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“Diamorphine, also known as heroin, was first synthesized for commercial use in 1897. The men who discovered it. . . had also, a couple of weeks earlier, invented aspirin; for some years, heroin could be bought over the counter and aspirin required a prescription.”

Lanchester J. High style. *New Yorker.* January 6, 2003

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