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High reinfection rate of *Helicobacter pylori* in young type 1 diabetic patients: a three-year follow-up study

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Abstract. – BACKGROUND: Several studies have demonstrated that *Helicobacter pylori* (*H. pylori*) eradication does not affect metabolic control in diabetic patients. The prevalence of *H. pylori* infection and reinfection rate in adult diabetic patients seems to be higher than in controls.

AIM OF OUR STUDY: To evaluate the reinfection rate of *H. pylori* three years after a standard eradicating treatment and the late effect of eradication upon metabolic control in young diabetic patients.

METHODS: We enrolled 75 diabetic patients and 99 controls, from previous our studies in which we had evaluated *H. pylori* infection. In all subjects we re-evaluated the presence of *H. pylori* by means of ^{13}C-Urea Breath Test, metabolic control and the prevalence of gastrointestinal symptoms. The effect of age, sex and socio-economic factors on *H. pylori* reinfection were also evaluated.

RESULTS: The prevalence of *H. pylori* infection was higher in diabetic patients (17/69, 24%) than in dyspeptic controls of similar age, gender and socio-economical status after three years of follow-up. The reinfection rate was higher in diabetic patients than in controls. Multivariate analysis confirmed that age and socio-economical status were independently associated with *H. pylori* reinfection.

CONCLUSIONS: Young patients with diabetes present a higher risk of *H. pylori* gastric reinfection than controls. In addition, age and mean annual income are associated with reinfection.

Key Words:
Helicobacter pylori, Type 1 diabetes mellitus, Children, Adolescents.

Introduction

Helicobacter pylori (*H. pylori*) gastric infection is one of the most prevalent bacterial diseases worldwide[1]. It has been related to the development of gastritis, gastric and duodenal peptic ulcer, low grade MALT-lymphomas and several extra-intestinal diseases[2,3]. Moreover, *H. pylori* is considered one of the main risk factor for gastric adenocarcinoma[4]. Several studies have been performed to investigate a putative role of this infection in the metabolic control and in the pathogenesis of gastrointestinal symptoms in patients with type 1 diabetes mellitus (DM1)[5-18]. Only few studies have demonstrated a beneficial effect of eradication both on symptoms and on glycemic control of such patients[5-10], so that the overall effect of *H. pylori* infection on diabetes is widely considered to be poor until now. However, follow-up studies are mostly short (with a global duration of about one year) and long-term effects are not yet evaluated. Moreover, high reinfection rate has been showed in adult patients with DM1, whilst data on reinfection rate in young DM1 patients are still lacking.

DM1 is associated with an increased risk of developing chronic illnesses such as ischemic heart disease[19], cerebrovascular stroke[20], atherosclerosis or malignancies[21] and it is hugely debated whether we should eradicate *H. pylori* (a risk factor for both cancer and ischaemic heart disease) in DM1 patients. The effect of eradication upon the reduction of gastric malignancies should induce to test and treat diabetic patients, but on the contrary the low eradication rate and the supposed high reinfection rate could reduce the beneficial effect of the eradication itself. Aim of our study was to evaluate the reinfection rate of *H. pylori* in a population of young DM1 patients and the late effect of *H. pylori* eradication on the metabolic control after a follow-up of three years.

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Patients and Methods

We enrolled 75 out of 121 consecutive patients (66 males and 55 females, mean age 14.8 ± 5.4 years, range 6-21) affected by DM1, initially enrolled in the Pediatric Diabetology Centre of the Catholic University of the Sacred Heart, Rome, Italy for a previous study[12]. Forty-six patients were lost at the follow-up. Six out of 75 refused to take part in the study and were excluded. In the remaining 69 patients (41 males, 28 females, mean age: 16.8 years, range: 9-21) we re-evaluated the presence of *H. pylori* by means of ^{13}C-Urea Breath Test and studied metabolic control with a blood test revealing levels of glycosylated hemoglobin A (HbA1c) combined with the calculation of daily insulin requirement (DIR, expressed in IU/kg/day). The ^{13}C-Urea Breath Test was performed with the following technique: two breath samples were collected in test tubes in duplicate before and 30 minutes after administration of urea (75 mg) labeled with ^{13}C in 200 mL of orange juice. The amount of $^{13}CO_2$ in test tubes was measured by gas isotope ratio mass spectrometry (BreathMat, Finnigan, Bremen, Germany) and the delta over the baseline was calculated. An excess delta of 3.5 was considered indicative of *H. pylori* infection. Gastrointestinal symptoms (epigastric pain, bloating, halitosis, nausea, post-prandial fullness) and socio-economical status (global annual family income) were also evaluated by means of a simple form of answers. Written informed consent was obtained from each subject or from related parents and all the procedures followed in the study were in accordance with the ethical standards of the Committee on Human Experimentations of our University and with the Helsinki Declaration. No enrolled subject had received antibiotics, proton pump inhibitors, H_2 receptor blockers, sucralfate or bismuth-containing compounds, non steroid anti-inflammatory drugs (NSAIDs), antacids in the two months prior the Urea Breath Test. Demographic data, socio-economical status and gastrointestinal symptoms were reassumed in the Table I.

In the previous our study 54 out of 69 patients were negative and 15 positive for *H. pylori* infection at the enrolment. Ninety-nine of 147 healthy subjects matched for sex, age and social class were recruited as controls from the control group of the previous study (55 males and 44 females; mean age: 16.3±3.8 years, range 9-24 years). Among 99 control subjects 77 were negative and 22 were positive for *H. pylori* infection at the enrolment. All positive patients were successfully eradicated by means of a standard triple therapy (according to Maastricht 2 Consensus Conference guidelines). Eradication of *H. pylori* was confirmed by means of ^{13}C-Urea Breath Test performed at least six weeks after antibiotic therapy. In addition, we analyzed the role of age and delta over baseline (DOB) values of Urea Breath Test at the enrolment on infection and reinfection rate of DM1 patients.

Table I. Demographic data, socio-economic status and gastrointestinal symptoms in DM1 patients and healthy controls

	Patients	Controls
Age (years)	19.8 ± 4.3	19.8 ±4.3
Females (%)	40.6 (28/69)	44.4 (44/99)
Males (%)	59.4 (41/69)	55.6 (55/99)
BMI (kg/m^2)	23.4 ± 4	25.1 ± 3
Annual family income (€)	%	%
< 15000	43.4 (30/69)	41.5 (41/99)
15000-30000	36.2 (25/69)	34.4 (34/99)
30000-45000	11.6 (8/69)	15.1(15/99)
> 45000	8.8 (6/69)	10 (9/99)
Gastrointestinal symptoms	%	%
Epigastric pain	43.5 (39/69)	48.1 (48/99)
Halitosis	50.7 (35/69)	41.1 (41/99)
Bloating	33.3 (23/69)	35.1 (35/99)
Post-prandial fullness	5,7 (4/69)	6.1 (6/99)
Nausea	2.8 (2/69)	4.1 (4/99)

BMI: body mass index.

Statistical Analysis

Data were evaluated using the software STATA 6.0 TM (Stata Corporation, University of Texas, TX, USA). The comparison between data of categorical type was performed with χ^2 test for proportions or, if necessary, with Fisher exact test. The comparison between continuous variables was performed with Mann-Whitney U test. Multivariate logistic regression analysis was used to assess whether an independent association exists between all the potential predictor variables examined and reinfection rate. A value of $p < 0.05$ was considered significant. Age was a continuous variable, sex and income were binary variables (cut-off value in the salary: > 30,000 € to be high and < 30,000 € to be low).

Results

The prevalence of *H. pylori* infection in young type 1 diabetic patients after three years from the initial enrolment was higher (17/69; 24%) than in the controls (7/99; 7%; $p < 0.005$; OR: 1.96 [1.67-11.04]). The reinfection rate was higher in DM1 patients than in controls [33.3% (5/15) vs 4.5% (1/22); $p < 0.05$]. After three years of follow-up, no difference in the prevalence of *H. pylori* infection was found between patients negative at the enrolment and patients initially positive and then eradicated [22.2% (12/54) vs 33.3% (5/15); p = ns]. No statistical difference was found in the prevalence of *H. pylori* infection comparing control subjects initially negative (6/77; 7.8%) with controls eradicated before the follow-up period (1/22; 4,5%; p = ns). No statistical difference in HbA1c was found between positive and negative type 1 diabetic patients at three years (8.8% ± 0.8 vs 8.4 ± 0.7, respectively). In 54 diabetic patients always negative for *H. pylori* HbA1c was similar at the enrolment and after three years of follow-up (8.04% ± 1 vs 8.4% ± 0.7; p = ns; Table III). Also in the 17 patients reinfected by *H. pylori*, HbA1c did not show any significant difference at enrolment and after follow-up (7.7% ± 1.8 vs 8.8% ± 0.8, p = ns). DIR was similar between *H. pylori*-positive and negative patients after the follow-up (0,82% ± 0.4 vs 0.75% ± 1.6, respectively). Considering patients remained negative, no difference was found in DIR at the enrolment and after three years (0.81% ± 1.6 vs 0.75% ± 1.6, respectively). Negative patients at the enrolment and positive ones after a follow-up of three years presented a slightly but not significant increased DIR at the follow-up evaluation than at the enrolment (0.82% ± 0.4 vs 0.63% ± 1.6).

Among positive patients no difference for the socio-economical status was found between patients with a previous *H. pylori* infection (eradicated patients) and patients found infected for the first time (Table II). Moreover, according with previously published data, a family annual income less than 30,000 € was related to the infection, considering diabetic patients and all enrolled subjects (Table III). The prevalence of a low annual income in reinfected subjects was significantly higher than in high annual income group (79% vs 21%; $p < 0.0001$; Table IV). After correcting for all confounding factors (age, sex, annual family income), both age ($p = 0.01$) and annual family income ($p = 0.03$), resulted independently associated with *H. pylori* reinfection in young DM1 patients. No differences in DOB values (%) in the previous study and age were found between patients positive and negative for *H. pylori* infection (1.1 ± 0.7 vs 1.1 ± 10; p= ns and 17.8 ± 6.2 years vs 17.1 ± 5.3 years, p = ns).

Discussion

It has been largely hypothesized that *H. pylori* gastric infection could play an important role in

Table II. Prevalence of *H. pylori* reinfection (%) in the different socio-economical groups of diabetic patients.

Annual family income (€)	DM1 reinfected patients (%)	DM1 first time patients (5)	p
< 15,000	17.6 (3/17)	29.4 (5/17)	ns
15,000-30,000	11.8 (2/17)	17.7 (3/17)	ns
30,000-45,000	0 (0/17)	17.7 (3/17)	–
> 45,000	0 (0/17)	5.8 (1/17)	–
All	29.4 (5/17)	70.6 (12/17)	–

DM1: Type 1 diabetes mellitus.

Table III. Prevalence of *H. pylori* infection in all enrolled patients according to the different socio-economical groups.

Income	< 30,000	> 30,000	*p*
DM1 patients	18.8 (13/69)	5.8 (4/69)	0.017
Controls	6.1(6/99)	1.0 (1/99)	0.059
Patients and controls	11.3 (19/168)	2.9 (5/168)	0.002

DM1: Type 1 diabetes mellitus.

the metabolic control of patients with DM1. However, studies actually available in the medical literature that found such a correlation are uncorrected for confounding factors, such as socio-economical status. Most studies were concordant to exclude any correlation between DM1 and *H. pylori* infection at least in short-term follow-up studies. Our study confirms that, even with a long-term follow-up *H. pylori* eradication does not modify significantly metabolic control in young DM1 subjects. However, patients affected by diabetes are at higher risk than the general population to develop infectious diseases and, indeed, a high rate (33.3%) of *H. pylori* reinfection emerges from our evaluation after a follow-up of three years. These results are concordant with a recent study performed on adult diabetic patients (48±9 years) in which reinfections were found in 27% of subjects (11/40) after five years of follow-up[22]. In the same study reinfected diabetics patients showed a poorer metabolic control and a higher prevalence of diabetic complications when compared with uninfected patients. However, this difference might be due to the social status, that is well-known to be associated both with reinfection and poor metabolic control.

In our study, after a follow-up of three years, the prevalence of *H. pylori* infection in a population of young diabetic patients results significantly higher than in controls. The infection rate is similar between negative at the enrolment and positive/eradicated young DM1 patients: the prevalence of *H. pylori* infection does not differ at the enrolment and after three years. In addition, *H. pylori* reinfection in diabetic patients appears to be related with age and socio-economical status, both in DM1 patients and controls after the correction for confounding factors. This finding may be related to the higher susceptibility of patients affected by DM1 to developing infection than not diabetic patients. Moreover, it is possible that at least a percentage of positive results of Urea Breath Test after the follow-up are due to a recrudescence of the *H. pylori* gastric infection, rather than a real new infection. Further studies, with evaluation of bacterial fingerprints, could explain this issue. Finally, metabolic control in diabetic patients, evaluated by means of DIR and HbA1c, was not associated with *H. pylori* infection.

In conclusion, we can state that at the end of a three-year follow-up higher rates of *H. pylori* reinfection (or recrudescence) were observed in young DM1 patients than in controls. Socio-economical status and age seem to be the most important risk factors independently associated with *H. pylori* reinfection (or recrudescence). Screening for *H. pylori* infection seems to be not useful in the clinical management of young pa-

Table IV. Annual family income in *H. pylori* reinfected patients.

Annual family income (€)	DM1 patients (%)	Controls (%)	Total
< 15,000	47.1 (8/17)	42.8 (3/7)	45.8 (11/24)
15,000-30,000	29.4 (5/17)	42.8 (3/7)	33.33 (8/24)
30,000-45,000	17.7 (3/17)	14.4 (1/7)	16.67 (4/24)
> 45,000	5.8 (1/17)	0 (0/7)	4.2 (1/24)
Patients and controls	**Income < 30,000**	**Income > 30,000**	***p***
	79 (19/24)	21 (5/24)	< 0.0001

DM1: Type 1 diabetes mellitus.

tients with DM1. It should be a choice of the individual physician to test and eventually treat the individual diabetic patient for *H. pylori* gastric infection, considering that its eradication could be less easy and even followed by a higher risk of reinfection (or recrudescence) than in not-diabetic young people.

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