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RESEARCH ARTICLE

Helicobacter pylori infection and type 1 diabetes mellitus in children

Mohammad Reza Esmaeili Dooki[1] · Morteza Alijanpour Aghamaleki[1,2] · Negar Noushiravani[3] · Seyed Reza Hosseini[4] · Leila Moslemi[1,5] · Mahmoud Hajiahmadi[1] · Mohammad Pournasrollah[6]

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Abstract

Objectives This study aimed to investigate the association between Helicobacter pylori infection with diabetes mellitus type one and the effect of infected Helicobacter pylori on glycemic control.

Methods This case control study was conducted on children with and without type 1 diabetes mellitus (T1DM). Demographic data and gastrointestinal symptoms in both groups and glycemic control status and duration of diabetes were recorded in patients with T1DM. Stool test was done on all children to detect Helicobacter pylori antigen.

Results Sixty three children with T1DM with a mean of 10.88 ± 2.84 years and 105 control children with an average age 10.17 ± 2.55 years ($P = 0/09$) were involved in this study. The frequency of Helicobacter pylori infection in patients with T1DM was 17/63 (27%) and 25/105 (23.8%) in control group, ($P = 0/64$). The frequency of bloating, epigastric pain and nausea was not significantly different between the two groups. The frequency of epigastric pain in children with diabetes with helicobacter infection was significantly higher than non-infected children with diabetes (29.4% vs. 2.2%) ($P = 0.004$).The mean duration of diabetes ($P = 0.53$), age diagnosis of diabetes ($P = 0.09$), fasting blood glucose ($P = 0.18$), glycosylated hemoglobin ($P = 0.08$) and the daily insulin dose ($P = 0.18$) in patients with T1DM with and without helicobacter pylori infection had not significantly different.

Conclusions There was no significant association between Helicobacter pylori infection and diabetes in children 5–15 years old, and glycemic control status was not difference in patients with T1DM with and without Helicobacter pylori infection.

Keywords Child · Diabetes mellitus type 1 · Helicobacter pylori · Infection

Introduction

Type-1 Diabetes Mellitus (T1DM) is a complex disease resulting from the interplay of genetic, epigenetic and environmental factors [1]. T1DM is the most common metabolic disorder in children and adolescents. The results of a large epidemiological study showed that the incidence of T1DM has increased by 2–5% worldwide [2]. T1DM can affect other organs too, such as the digestive system, as it starts from an early age [3]. children with Diabetes Mellitus can develop various infections due to different factors, including immune disorders, gastric motility disorders, increased number of hospital visits and gastrointestinal complaints; it therefore appears that Helicobacter pylori (*H. pylori*) infection causes some gastrointestinal symptoms [4].

H. pylori, which inhabits various areas of the stomach and duodenum, is a Gram-negative helix-shaped bacterium. *H. pylori* infection leading to chronic gastritis is asymptomatic in the majority of carriers, but is considered a major risk factor

✉ Morteza Alijanpour Aghamaleki
m.alijanpour@yahoo.com

1 Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR, Iran

2 Non-Communicable Pediatric Diseases Research Center, Amirkola Children's Hospital, No 19, Amirkola, Babol, Mazandaran Province 47317-41151 IR, Iran

3 Student Research Committee, Health Research Institute, Babol University of Medical Sciences, Babol, IR, Iran

4 Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR, Iran

5 Health Reproductive Research Center, Sari Branch, Islamic Azad University, Sari, IR, Iran

6 The Clinical Research Development Unit of Amirkola Children's Hospital, Babol University of Medical Sciences, Babol, IR, Iran

for the development of gastric and duodenal ulcers and gastric malignancies [5].

The prevalence of *H. pylori* infection is associated with age. The overall prevalence of *H. pylori* infection is less than 10% in children from developed countries. *H. pylori* infection is more common in the developing world, and more than 80% of the population are infected before puberty [6]. A study in Sudan showed that 51% of children were seropositive for *H. pylori* infection [7]. The risk of acquiring *H. pylori* infection is associated with socioeconomic status, family education, overcrowding and lack of running water [8]. The effects of *H. pylori* in children include peptic ulceration, gastrointestinal malignancies, gastritis, malnutrition, anemia and digestive disorders leading to growth and physical retardation [9]. The link between T1DM and *H. pylori* still remains controversial. Some studies have suggested that the high prevalence of this infection in patients with T1DM [10–14] is related to the duration of diabetes, dyspepsia, age, sex, BMI, blood pressure, fasting plasma glucose (FPG) and Hemoglobin A1c (HbA_1c) level [10, 11]. *H. pylori* infection can lead to hyperglycemia in children with Diabetes Mellitus, and its mechanisms are unknown but are thought to include the secretion of counterregulatory hormones due to stress in addition to the production of cytokines. Cytokines can stimulate the secretion of counterregulatory hormones, and thus directly affect carbohydrate metabolism [15, 16]. In contrast, other studies have reported that *H. pylori* infection is not associated with T1DM and there is no difference in the prevalence of *H. pylori* infection between children with Diabetes and children without Diabetes Mellitus [17–19]. Therefore, the relationship between diabetes and *H. pylori* still remains a controversial issue.

Due to the conflicting results about the relationship between *H. pylori* and diabetes in children, this study was conducted to compare the frequency of *H. pylori* infection in children with Diabetes and children without Diabetes Mellitus in Amirkola Children's Hospital of Babol (North of Iran) and to compare the glycemic control status between the children with Diabetes, with and without *H. pylori* infection.

Materials and methods

This study was conducted on patients with T1DM (at least 6 months after the onset of diabetes), referred to the Endocrine Clinic of Amirkola Children's Hospital of Babol in 2014–2015. All patients received basal-bolus protocol of insulins' Glargine and Asparte. They were compared to a group of children without Diabetes Mellitus selected from Babol schools through cluster sampling. The two groups were matched for age and gender.

The inclusion criteria consisted of consenting to participate in the study and the age 5–15 years; the exclusion criteria consisted of the use of antibiotics over the last month.

Sample size

Based on previous studies, the frequency of *H. pylori* infection is 79% in children with diabetes and %51.2 in those without diabetes. With a 90% statistical power at a 5% significance level, the sample size was calculated as 67 per group [20]. To enable a better comparison, the group of children without Diabetes Mellitus was considered double.

This study was approved by the Ethics Committee of Babol University of Medical Sciences under the code 1393.9. All the children or their parents signed consent forms, which included a comprehensive description of the study protocol and objectives.

Examination and laboratory protocol

All the children were examined by one physician and they and/ or their parents responded to questions regarding their demographic data and gastrointestinal symptoms in the past 2 weeks, such as nausea, bloating and abdominal pain. As for the patients with diabetes, data were obtained from the medical records and included the duration of diabetes (the time from disease diagnosis until entering the study), mean insulin doses (required average daily dose of insulin per week), last HbA_1c and FPG level. If the recorded HbA_1c and FPG belonged to more than 3 months ago, these factors were re-measured.

For measurement of HbA_1c level, enzymatic method by Hitachi auto analyzer (manufactured by Diazine, USA) was used.

In the children without Diabetes Mellitus, a glucometer (GLUCOCARD 01_mini, ARKRAY Inc., Healthcare Pvt. Ltd., made in Japan) was used to measure the venous blood glucose in order to rule out their Diabetes Mellitus, and those with abnormal glucose levels were excluded. According to Bazmamoun et al. [14], the criteria for diabetes were FPG > 126 (mg/dl) and plasma glucose>200 mg/dl 2 h after meals. The children with T1DM were divided into two subgroups; the first subgroup included "the patients with diabetes" with H.pylori vs. "the patients with diabetes" without H.pyolri; the second subgroup included "the patients with diabetes" with positive H.pylori who had epigastric pain vs. those without epigastric pain. A comparison was made between the two subgroups in terms of glycemic status and the average HbA_1c, daily insulin dosage and FPG.

The stool test was carried out in both groups to detect *H. pylori* antigens. A swab was dipped in 250 mg of fresh stool up to 5 mm and slowly rotated to the sides. The stool-containing swab was placed in a buffer vial and shaken for a

minute after closing its lid. The test cassette was then removed from its pouch and placed on the table. In the next step, one to two drops of the buffer were mixed with the stool and poured into the cassette, and after 10 min of waiting, the test result was read.

The test was considered negative with the appearance of a purple line and positive with the appearance of two purple lines.

The antigen was measured by the monoclonal antibody method using *H. pylori* stool kit (manufactured by Generic Assays, Germany).Internal procedural controls were included in the test. A colored band appearing in the control region (C) was considered an internal positive procedural control. It confirmed sufficient volume and correct procedural technique. Sensitivity and specificity for *H. pylori* antigen test were 98.5% and 98.1%, respectively. Positive predictive value was 97.7% and negative predictive value was 98.6%. All the tests were performed at the same laboratory (Amirkola Children's Hospital). The height and weight of the children were measured with a stadiometer and Seca scale (Seca, Germany) and their BMI was also calculated.

Statistical analysis

The data collected were analyzed SPSS-17 (Chicago, IL, USA). Descriptive statistics were used to describe the subjects' characteristics, and the Chi-square test or Fisher's exact test were used to independently determine the relationship between the variables. The mean ± SE plus the t-test were used for the normally distributed data. *P* values less than 0.05 were considered statistically significant.

Results

This study was conducted on 63 children with and 105 without Diabetes Mellitus (Table 1). Overall, 42 (25%) children were infected by *H. pylori*. The prevalence of *H. pylori* infection was 17 (27%) in the children with Diabetes Mellitus and 25 (23.8%) in the control group. There were no significant differences between the two groups ($P = 0.64$). The prevalence of *H. pylori* infection was not different between the two age groups of 5–10 and 10–15 years (21.4% vs. 28.6%, $P = 0.28$).

Table 1 A comparison of demographic data between the children with diabetes and children without diabetes mellitus

Groups Variable	Children with diabetes	Children without diabetes	*P* value
Sex: N(%) Male	34(54)	47(44.8)	0.24
Female	29(46)	58(55.2)	
Ethnicity: N(%) (Tabari)	63 (100)	105 (100)	–
Age: yr (Mean ± SD)	10.88 ± 2.84	10.17 ± 2.55	0.09
BMI[a]: Kg/m^2 (Mean ± SD)	18.89 ± 3.65	18.43 ± 3.22	0.39

[a] *BMI* Body mass index

Clinical data including epigastric pain, flatulence and nausea were observed in ten (9.5% vs. 3.8%, $P = 0.17$), three (0 vs. 1.8%, $P = 0.29$) and one (0 vs. 1%, $P = 1$) of the children in both groups, respectively.

The children with T1DM were divided into two groups based on *H. pylori* infection: positive: 27% ($n = 17$) and negative: 73% ($n = 46$). Moreover, 23.5% of the 5–10 age group and 76.5% of the10–15 age group were infected by *H. pylori* ($P = 0.04$). Age at the time of diabetes diagnosis was 8.84 ± 2.03 years in the *H. pylori* positive group and 7.45 ± 2.9 years in the *H. pylori* negative group ($P = 0.07$); and the average duration of diabetes was 2.74 ± 1.62 years in the *H. pylori* positive group and 3.16 ± 2.57 years in the *H. pylori* negative group ($P = 0.09$). The average HbA_1c measured was 8.08 ± 1.51 (%) in the *H. pylori* positive group and 9.08 ± 1.87 (%) in the *H. pylori* negative group ($P = 0.08$): the average daily insulin dosage was 28.2 ± 24.06 units in the *H. pylori* positive group and 21.58 ± 13.94 units in the *H. pylori* negative group ($P = 0.18$); the average FPG was 168.17 ± 72.28 mg/dl (9/33 ± 4 mmol/l) in the *H. pylori* positive group and 198.7 ± 81.61 (11 ± 4.5 mmol/l) in the *H. pylori* negative group (P = 0.18). The frequency of epigastric pain was 9.5% (6) in the children with and 3.8% (4) in the children without diabetes ($P = 0.17$).

The frequency of epigastric pain was 29.4% (5) in "the patients with diabetes" with and 2.2% [1] in those without H.pylori infection ($P = 0.004$).

Discussion

In the present study, we report no evidence of a relationship between *H. pylori* infection and T1DM in children, and *H. pylori* infection has no effect on glycemic control in children with diabetes, as in agreement with the results of some other studies [13, 14, 19, 20]. Unlike the present study, many studies have suggested that the prevalence of *H. pylori* infection is higher in children with diabetes, compared to children without diabetes [16, 17]; it is therefore still a controversy whether *H. pylori* infection is potentially linked to DM in aspects such as glycemic control, gastrointestinal symptoms, prevalence of infection, eradication rate and reinfection rate [20]. The possible reasons for the disparity observed in the prevalence of infection include differences in study populations in terms of age and sample size. Age should be considered as a factor affecting *H. pylori* infection, as the exposure to *H. pylori* organisms increases with age [8, 14], and it is imperative to compare similar age groups when studying the

prevalence of *H. pylori* infection. In addition, *H. pylori* infection has been diagnosed in different studies using different methods, such as the Urea Breath Test (UBT), the measurement of anti H.pylori IgA, IgG and IgM or *H. pylori* antigen in the stool and anti Cag A IgG; these different methods justify the disparate findings on this subject. The Present study evaluated fecal *H. pylori* antigens, which may be more relevant than the measurement of *H. pylori* antibody in the serum for active gastrointestinal infection in select patients with diabetes; also the serologic method cannot differentiate between recent and past infections.

Based on the results of some studies, many factors can influence the prevalence of *H. pylori* infection among children with Diabetes, such as age, age at the onset of diabetes, duration of diabetes, BMI, FPG and HbA_1c1 [10, 16]. In one study, Feyad et al. Found that children with diabetes and positive *H. pylori* infection comorbidity are older, have had an earlier onset of diabetes, have a larger BMI and a higher HbA_1c compared to the negative infected group [10].

Zekry et al. also found that children with diabetes with *H. pylori* infection have lived with diabetes foe a longer duration of time and have higher insulin dose and HbA_1 c; they observed a linear relationship between anti-H pylori IgG titers and HbA_1 c [16]. According to some previous studies, screening for *H. pylori* infection should be performed in patients with poor metabolic control [1]. One of the possible mechanisms of the association between diabetes and *H. pylori* is that many chemical changes occur following non-enzymatic glycosylation in the stomach that increase sialic acid production, which acts as a receptor for *H. pylori* in the cell surface to attach to the stomach cells [21]. moreover, given the impaired immune response in diabetes, which changes the hormonal and cellular immunity, and also the high prevalence of upper gastrointestinal symptoms in this disease, *H. pylori* may be correlated with diabetes. The findings of the noted study [21], however, are in contrast with the present findings. The present and other researchers [22–24] have found that children with diabetes with and without *H. pylori* infection do not differ in terms of glycemic control.

In this study, the incidence of epigastric pain was significantly higher in the children with diabetes and *H. pylori* infection comorbidity compared to the children without *H. pylori* infection. No evidence could be obtained on the effects of *H. pylori* infection in children with diabetes from the north of Iran. This study has examined the relationship between *H. pylori* infection and T1DM for the first time in this region, and its findings can help design other studies that may strive to overcome the limitations of the present study. One of these limitations was the cross-sectional design of the project; an analytical study can better clarify the exact relationship between *H. pylori* infection and T1DM and its effects on glycemic control. On the other hand, available diagnostic tests for detection of H.pylori don't have 100% accuracy for final diagnosis. So, two or more tests should be performed [25], which is recommended for further studies. Another limitation of the present study was that we didn't deal to gastrointestinal co-morbidities such as coeliac disease, which is recommended for future studies. Also, some variables such as weight loss, socioeconomic status and household size remained undetected, and considering these variables in future studies can help provide a better interpretation of the subject.

To conclude, this study showed that the frequency of *H. pylori* infection was not significantly different between the children with diabetes and the control group. Glycemic control was also not different between the children with diabetes and without *H. pylori* infection.Nonetheless, this finding may be influenced by other confounders such as insulin dose, nutrition status and socioeconomic status.

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Compliance with ethical standards

Conflict of interest The Authors have No conflicts of interest to declare.

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