Helicobacter Pylori Infection in Children with Type 1 Diabetes Mellitus

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Abstract

Objective: To evaluate *H. pylori* infection and virulent strain in diabetic children.

Patients: In this study 53 type 1 diabetics and 53 of normal volunteers were included.

Methods: All studied children were subjected to assessment of glycosylated hemoglobin (HbA1), Anti *H. pylori* antibodies (IgA, IgG, IgM), Anti-cytotoxin associated gene A antibodies (Anti Cag A IgG).

Results: Anti *H. pylori* antibodies IgA, IgG, total antibodies and anti Cag A IgG were significantly higher in diabetics. Diabetic patients with positive anti Cag A IgG had a lower age of onset of diabetes, higher age of patients, body mass index (BMI) and HbA1.

Conclusion: High prevalence of infection with the virulent strain of *H. pylori* among diabetic children with older age, large BMI, high HbA1 and younger age of onset of disease. The screening for the virulent strain in diabetic patients with poor metabolic control is mandatory. Control of diabetes is essential to present the infection with *H. pylori*.

Introduction

The relationship between diabetes mellitus (DM) and Helicobacter pylori (*H. pylori*) infection is controversial. According to some studies there is a high prevalence of *H. pylori* infection in patients with either type 1 [1] or type 2 DM [2].

An impaired immune response in diabetes that alters both humoral and cellular immunity, and the high prevalence of upper gastrointestinal symptoms, have led to speculation that *H. pylori* may be linked to diabetes [3]. This could be related to a reduced gastric motility and peristaltic activity, various chemical changes in gastric mucosa following non-enzymatic glycosylation processes [4] and an impaired non-specific immunity observed in diabetic patients [5].

We are aiming to evaluate *H. pylori* infection and virulent strain in diabetic children. Also to detect its relation to (gastrointestinal tract) G.I.T symptoms and glycemic control.

Patients and Methods

It is a cross sectional study, performed after obtaining approval by the ethical committee of the national Research Centre. Written informed consent was obtained from all patients and their parents after full discussion about the aim of the study.

The study included 53 patients with type 1 DM among those attending to the endocrine clinic National Research Center. The control group consisted of 53 age and sex matched healthy normal volunteers.

Exclusion criteria

- Children with other types of diabetes.

- Diabetic children with other chronic disease.

- Children on or used medical treatment for eradication of *H. pylori* within the last two months.

Methods

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All studied children were subjected to complete history taking with special emphasis on GIT symptoms.

Anthropometric measurements

Anthropometric measurements in the form of weight, height were taken for each participant. The weight and height of the participants were measured up to 0.01 kg and 0.1 cm using a Seca Scale Standing Balance and a Harpenden Stadiometer (Holtain, Ltd, Crymmych, Wales, U.K.). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

Table 1: Comparison between Demographic data of diabetic patients and controls.

Variables	Patients	Controls	P-value
Sex:			
Males N (%)	24 (45.3)	28 (52.8)	0.4
Females N (%)	29 (54.7)	25 (47.2)	
Age (yrs)			
Mean ± SD	12.2 ± 3.0	12.5 ± 3.5	0.8
BMI (kg/m²)			
Mean ± SD	21.86 ± 5.06	18.15 ± 2.77	0.0001
HbA1 (%)			
Mean ± SD	9.6 ± 1.6	5.4 ± 0.7	0.0001

Chi Square test [N (%)]; Mann Whitney U test for independent variables : Mean ± SD; BMI: body mass index.

Laboratory investigation

Glycosylated hemoglobin (HbA1) was done every 3 months and the mean value was calculated per year. It was measured using high pressure liquid chromatography (Nichols Institute, Van Nuys, California).

Anti *H. pylori* antibodies (IgA): Using quantitative enzyme immuranssay kit. The test kit was suppliedcalbitech, catalog No, HPO14A, USA [6].

Anti *H. Pylori* antibodies (IgM) using quantitative enzyme immunoassay kit. The test kit was supplied by calbiotech catalog No. Hp015M, USA [7]. ELISA sensitivity and specificity were 90%, and the predictive value of negative result is high.

Anti *H. Pylori* antibodies (IgG) using enzyme immunoassay for quantitative and qualitative determination of anti H. pylori IgG in human serum or plasma. The test kit was supplied by Diakey catalog No, DE101 USA [8].

Anti-cytotoxin associated gene A antibodies (Anti Cag A IgG): It's an ELISA for the quantitative determination of anti Cag A IgG antibodies in human serum or plasma for in vitro diagnostic use only. The kit was supplied by ELISA, catalog No 4138, USA [9].

Statistical Analysis

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) program version 15.0 (Chicago, Illinois, USA). Mann Whitney U test for independent variables was done as

data was not symmetrically distributed. Chi- Square test was used for qualitative data.

Results

The study included 53 type 1 diabetic patients (24 males and 29 females), their mean age was 12.2 ± 3.0, mean duration of diabetes was 4.5 ± 3.3, mean insulin dose/kg was 1.4 ± 0.5, mean BMI was 21.86 ± 5.06 and mean HbA1 was 9.6 ± 1.6. Comparison between sex, age, BMI, HbA1 of diabetics and controls was shown in Table 1.

Table 2: Comparison between H. pylori antibody (IgA, IgG and IgM) and Anti Cag A IgG of patients and controls.

Variables	Diabetics		Controls		P-value
	No.	%	No.	%	
Anti H. Pylori IgA:					
Positive	6	11.3	0	0	**0.012**
Negative	47	88.7	53	100	
Anti H. Pylori IgM:					
Positive	2	3.7	1	1.8	0.558
Negative	51	92.4	52	98.2	
Anti H. Pylori IgG:					
Positive	38	71.7	24	45.28	**0.006**
Negative	15	28.3	29	54.72	
Total antibodies :					
Positive	40	75.5	13	24.5	**0.001**
Negative	25	47.2	28	52.8	
Anti Cag A IgG:					
Positive	30	56.6	0	0	**0.0001**
Negative	23	43.4	53	100	

Chi Square test; Positive total antibodies: either IgA or IgM or IgG is positive; Negative total antibodies: all antibodies (IgA, IgM and IgG) are negative.

Anti *H. Pylori* (IgA, IgG and total antibodies) and Anti Cag A IgG were significantly higher in diabetics than controls (Table 2).

Table 3: Comparison between demographic data, HbA1 and clinical data regarding total antibodies in diabetics

Variables	Negative total antibodies	Positive total antibodies	P-value
Sex:			
Males N (%)	5 (38.5)	19 (47.5)	0.3
Females N (%)	8 (61.5)	21 (52.5)	
Age (yrs)			
Median	12.0	13.0	
Mean ± SD	11.8 ± 3.2	12.5 ± 3.5	0.4
Range	5 -16	4-17	
Duration of disease (yrs)			
Median	6.0	3	
Mean ± SD	5.6 ± 3.3	4.2 ± 3.2	0.1
Range	2 -12	1 -11	
Age of onset of disease (yrs)			
Median	6.0	8.0	
Mean ± SD	6.2 ± 3.7	8.4 ± 4.2	0.08
Range	1 -12	1 -15.5	
Insulin dose (U/kg)			
Median	1.4	1.4	
Mean ± SD	1.4 ± 0.3	1.5 ± 0.6	0.8
Range	0.8 – 2.2	0.6 – 3.4	
BMI (kg / m²)			
Median	21.6	21.6	
Mean ± SD	22.1 ± 5.3	21.8 ± 5.0	0.7
Range	12 – 30	13 – 34	
HbA1 (%)			
Median	8.0	7.5	
Mean ± SD	7.9 ± 1.3	7.4 ± 1.6	0.1
Range	4.5 – 10.1	3.0 – 10.6	
Clinical data:			
Epigastric pain:			
Negative N (%)	1 (6.7)	7 (18.4)	0.3
Positive N (%)	14 (93.3)	31 (81.6)	
Recurrent abdominal pain:			
Negative N (%)	6 (40)	22 (57.9)	0.2
Positive N (%)	9 (60)	16 (42.1)	
Nausea & vomiting:			
Negative N (%)	5 (33.3)	18 (47.4)	0.3
Positive N (%)	10 (66.7)	20 (52.6)	
Abdominal distension:			
Negative N (%)	10 (66.7)	16 (42.1)	0.1
Positive N (%)	5 (33.3)	22 (57.9)	

Mann Whitney U test (median/mean ± SD) range; Chi Square test [N (%)]; BMI: body mass index; HbA1: Glycosylated hemoglobin; Positive total antibodies: either IgA or IgM or IgG is positive; Negative total antibodies: all antibodies (IgA, IgM and IgG) are negative.

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Comparison between demographic data, HbA1 and clinical data regarding total antibodies and anti Cag A IgG antibody in diabetics is shown in Tables 3 and 4.

Table 4: Comparison between demographic data, HbA1 and clinical data regarding Anti Cag A IgG.

Variables	Negative anti Cag A IgG antibodies	Positive anti Cag A IgG antibodies	P-value
Sex:			
Males N (%)	7 (30.4)	17 (56.7)	0.07
Females N (%)	16 (69.6)	13 (43.3)	
Age (yrs)			
Median	12.0	13.0	0.04
Mean ± SD	11.2 ± 3.8	12.9 ± 1.9	
Range	3.5 – 16.0	8.0 – 17.0	
Duration of disease (yrs)			
Median	3.0	4.0	0.4
Mean ± SD	3.8 ± 2.4	5.2 ± 3.7	
Range	2.0 – 10.0	1.0 – 12.0	
Age of onset of disease (yrs)			
Median	9.0	7.0	0.03
Mean ± SD	4.6 ± 3.2	6.4 ± 2.8	
Range	1.0 – 15.5	1.0 – 15.0	
Insulin dose (U/kg)			
Median	1.4	1.4	0.8
Mean ± SD	1.4 ± 0.2	1.5 ± 0.7	
Range	0.8 – 1.8	0.6 – 3.4	
BMI (kg / m2)			0.007
Median	19.5	23.3	
Mean ± SD	19.7 ± 3.7	23.5 ± 5.4	
Range	12.0 – 28.0	13.0 – 34.0	
HbA1 (%)			
Median	7.4	8.0	0.03
Mean ± SD	7.1 ± 1.5	8.1 ± 1.4	
Range	3.0 – 10.2	5.0 – 10.6	
Clinical data:			
Epigastric pain:			
Negative N (%)	5 (21.7)	3 (10)	0.2
Positive N (%)	18 (78.3)	27 (90)	
Recurrent abdominal pain:			
Negative N (%)	11 (47.8)	17 (56.7)	0.4
Positive N (%)	12 (52.2)	13 (43.3)	
Nausea & vomiting:			
Negative N (%)	9 (39.1)	14 (46.7)	0.4
Positive N (%)	14 (60.9)	16 (53.3)	
Abdominal distension:			
Negative N (%)	13 (56.5)	13 (43.3)	0.3
Positive N (%)	10 (43.5)	17 (56.7)	

Mann Whitney U test (median/ mean ± SD/range); Chi Square test [N (%)]; BMI: body mass index; HbA1: Glycosylated hemoglobin; Positive total antibodies: either IgA or IgM or IgG is positive; Negative total antibodies: all antibodies (IgA, IgM and IgG) are negative.

Discussion

The role of gender as a risk factor for *H. pylori* infection is still debated. The present study showed that there was no significant difference in the prevalence of infection between boys and girls regarding total antibodies or infection with virulent strain of *H. pylori* (anti Cag A Ig G positive) in the diabetics. This result comes in agreement with Mahmoud *et al.* [10], who revealed that no gender difference in *H. pylori* infection was found. On the other hand, another study confirmed the male predominance of *H. pylori* infection [11], while the study of Kanbay *et al.* [12] stated that *H. pylori* infected females were predominant as compared to males.

Our study confirmed the previously described increased prevalence of *H. pylori* infection with age (13-16), as it was detected by increased total antibodies (either IgA or IgM or IgG is positive) in diabetic group, but this increase was not statistically significant. This age is related to increase in the seroprevalence of *H. pylori* infection may be due to progressive acquisition of infection by the increase of age [17], and changes in the environmental factors [18]. Our study revealed that body mass index (BMI) was a statistically significant higher in diabetics and is related to the presence of insulin resistance [19].

The present study revealed that the prevalence of *H. pylori* infection regarding total anti-*H. pylori* antibodies was significantly higher in the diabetic group (75.5%). These coincide with the result of Mohammed and Abdel-Kareem [20], who reported that the prevalence was 74%. On the other hand, it was higher than that reported by Salardi *et al.* [21] and Arslan *et al.* [1] (48.5 % and 55.6 % respectively). It is related to the higher prevalence of *H. pylori* infection in the developing than developed countries.

The relation between type 1 DM and *H. pylori* infection is still controversial. According to some studies, there is a high prevalence of *H. pylori* infection in patients with either type1 DM [1], or type 2 DM [2], which is correlated with the duration of DM, age of diabetic patients [21], the presence of dyspeptic symptoms [2], gender, BMI, blood pressure, fasting blood sugar and HbA1 [22]. This could be related to a reduced gastric motility and peristaltic activity [23], various chemical changes in the gastric mucosa following non-enzymatic glycosylation processes of mucus and increased sialic acid production which acts as a receptor for *H. pylori* on the cell surface by promoting adhesion of *H. pylori* to gastric mucosa cells [24]. However, there is limited data regarding the influence of *H. pylori* infection on the clinical course of diabetes, with controversial results [25].

In the current study, the prevalence of infection with the virulent strain of *H. pylori* (anti Cag A IgG) in the diabetic group was (56.6%). This result was higher than that detected by Fayed *et al.* [16] who reported that the prevalence of infection by virulent strain of *H. pylori* was (35%) in a group of children with GIT complaints and not diabetic.

The present study revealed that there was no significant difference in GIT symptoms regarding total anti *H. pylori* antibodies and anti Cag A IgG in diabetics. On the other hand, Leo *et al.* [26], reported that epigastric pain was predominant in *H. pylori* infected children. Fayed *et al.* [16] found that the most commonly recorded GI symptoms were anorexia and diarrhea (50% each), recurrent abdominal pain (RAP) (41.7%) and recurrent vomiting (16.7%) but those patients were non diabetic. Fayed *et al.* [27], found that the most commonly recorded (gastrointestinal) GI symptoms, in association with *H. pylori* infection were anorexia and diarrhea (40% each), RAP (41.79%), heart burn (33.3%), dyspepsia (25%), vomiting (16.7%) and abdominal distension (8.3%). This contradiction regarding the relation between *H. pylori*

infection and GIT symptoms in different studies may be due to the different studied samples and the infection with different pathogenic strains of *H. pylori.* Supporting this hypothesis is the increased frequency of RAP among children infected by toxin producing strains (virulent strains) when compared to children infected by non virulent strains [16]. The other factors that influence the variability of symptoms arising are the genetic constitution, the age of the host, the duration of illness and the environmental factors [28].

As regard infection by the virulent strain of *H. pylori*, our study reported that the prevalence of infection by the virulent strain in the diabetic group was 56.6%, while no one was infected by the virulent strain of *H. pylori* in the control group and this can explain the absence of GIT symptoms in the control group, although (24.5%) of them were infected by non-virulent strain of *H. pylori* (positive total antibodies).

In the current study, we found that diabetic patients infected with the virulent strain of *H. pylori* (Anti Cag A IgG) were older than those who are anti Cag A negative. This result comes in agreement with Fayed *et al.* [16]. This might be due to more exposure of the population to the organism with increasing the age.

Our study revealed that the duration of diabetes is longer in diabetic group as regard anti Cag A IgG, but it was not statistically significant (P>0.05). This result comes in agreement with Mohammed and Abdel-Kareem [20], Gasbarrini *et al.,* [29]; Saladi et al., [21] and Arslan [1], who found that the duration of diabetes was the only factor affecting *H. pylori* status in these patients. However, other investigators did not find any association between *H. pylori* infection and the duration of diabetes mellitus [4, 30].

The present study revealed that infection with *H. pylori* regarding total antibodies was not associated with poor glycemic control in the diabetic group (i.e., no significant change in the level of HbA1) (P>0.05). This result comes in agreement with Ojetti *et al.* [31]. In contrast, Dore *et al.* [32], reported that infection with *H. pylori* was associated with poor glycemic control of diabetics.

On the other hand, we found that diabetics with virulent strain of *H. pylori* (Anti-Cag A IgG) had a significant higher level of HbA1. This result was in agreement with Rodolfo et al. [33]. One possible explanation of that finding was that metabolic derangements that occur in diabetes may impair a number of host defenses in both humoral and cellular immunity (neutrophil dysfunction, chemotaxis failure and decreased lymphocyte activity) It has been speculated that alterations in the glucose metabolism may promote *H. pylori* colonization [23]. BMI was significantly higher in our diabetics with positive Anti Cag A IgG. This can be explained that, uncontrolled diabetic patients usually had increase in insulin resistance and it lead to increase in BMI of diabetics.

On the present study, total daily insulin dosage/kg had no significant relation to infection with *H. pylori* (total antibodies) or the virulent strain of *H. pylori.* On the contrary, Begue *et al.* [34], reported that children with type 1 diabetes and *H. pylori* infection had an increased daily insulin requirement compared with the requirement of their uninfected peers.

We conclude that, diabetic children are more vulnerable to infection by *H. pylori* virulent strain as it was detected by anti Cag A IgG. Also, the infection by virulent strain is associated with older age of patients, larger BMI, Higher HbA1 and lower age of onset of diabetes. We recommend screening for the virulent strain in patients with poor metabolic control of diabetes. Further large scale studies that address the role of *H. pylori* infection in the pathogenesis of diabetes mellitus are needed, as well as searching for a hopeful vaccine to prevent the so widely prevalent organism and to avoid the dangerous complications.

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