Frequency and Impact of *Helicobacter Pylori* Infection on Glycemic Control and Insulin Requirements among Children with Type 1 Diabetes Mellitus

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Abstract

Background: Children with type 1 diabetes mellitus (T1DM) are at risk of many infections, including Helicobacter pylori (H. pylori).

Objectives: To evaluate the frequency of H. pylori infection and its effect on glycemic control and insulin needs in children with T1DM.

Patients and methods: A case-control study including 40 children with T1DM and 40 non-diabetic control children. Clinical and demographic data and the presence of gastrointestinal symptoms were assessed in both groups. Data about the duration of diabetes, insulin doses, and glycemic control were collected in children with T1DM. The H. pylori antigen in stool, complete blood count, and glycated hemoglobin (HbA1c) levels were assessed in all the study participants.

Results: In children, T1DM was associated with a higher prevalence of H. pylori in stool samples compared to those without diabetes (32.5% vs. 10%, $p = 0.01$). Among children with T1DM, those with H. pylori in their stool had more gastrointestinal symptoms than those without ($p < 0.001$). However, H. pylori status did not affect daily insulin dose, basal insulin dose, or HbA1c levels in children with T1DM ($p = 0.97$, 0.49, and 0.38, respectively).

Conclusion: Although H. pylori infection was more frequent among children with T1DM, it had no significant impact on the insulin requirement or the glycemic control. However, the frequencies of gastrointestinal symptoms were increased among T1DM children with positive H. pylori stool antigen.

Keywords: Type 1 diabetes; H. Pylori infection; Children; Infection.

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Introduction

Type 1 diabetes mellitus (T1DM) represents a significant chronic disease affecting the pediatric population, notably children and adolescents **(Esmaeili et al., 2020).** Children with T1DM are more vulnerable to infections due to factors like immune system dysfunction, altered stomach function, and frequent hospital stays **(Bazmamoun et al., 2016).**

Helicobacter pylori (H. pylori), a bacterium residing in the stomach and duodenum **(Fashner and Gitu, 2015),** is less common in children in developed countries but highly prevalent in developing nations, often infecting over 80% of the population before puberty **(Salih, 2009).**

Risk factors for H. pylori infection include low socioeconomic status, limited education, overcrowding, and lack of access to clean water **(Nouraie et al., 2009).** While known to cause chronic gastritis, H. pylori has also been implicated in autoimmune gastritis and various extra-gastrointestinal autoimmune disorders, including some affecting the liver, systemic lupus erythematosus, vasculitis, thrombocytopenic purpura, thyroiditis, and diabetes mellitus **(Smyk et al., 2014).**

The relationship between T1DM and H. pylori remains debated. Some research suggests that higher H. pylori prevalence in T1DM patients is linked to factors such as diabetes duration, age, sex, BMI, blood pressure, fasting glucose, and HbA1c levels **(Fayed et al., 2014).** While data on the prevalence and effects of H. pylori infection in T1DM children are scant, a previous study suggested the role of H. pylori on hyperglycemia in T1DM children. While the exact mechanisms are not known, it has been hypothesized that cytokines are released by H. pylori, which in turn stimulates secretion of counter-regulatory hormones, thereby influencing carbohydrate metabolism **(Zekry and Abd Elwahid, 2013).**

This study investigates the frequency and impact of H. pylori infection on glycemic control and insulin needs in Egyptian children with T1DM.

Patients and methods

From June 2020 to May 2021, a case-control study was carried out at Sohag University Hospital. Cases were children aged 2-12 years with a T1DM diagnosis of at least one year, attending the hospital's pediatric diabetes clinic. Controls were age- and sex-matched children without diabetes, presenting at the hospital's general pediatric clinic for minor acute illnesses. Children with known congenital or acquired gastrointestinal disorders were excluded. Parental written informed consent was obtained, and ethical approval was granted by the Sohag Faculty of Medicine research ethics committee (Soh-Med20-05-07)

All participants underwent a comprehensive medical history review and physical examination, with particular attention to age, sex, and body mass index (BMI). Gastrointestinal symptoms, including abdominal pain, vomiting, constipation, diarrhea, and abdominal distension, were assessed. For the T1DM group, data collected included diabetes duration, bolus and basal insulin types, and insulin dosages. The Socioeconomic state was analyzed using the Egyptian Health Research Socioeconomic Status Scale **(El-Gilany et al., 2012)**. The scale covers seven domains comprising 84 points in total: Education and Intellectual Level, Employment and Occupation, Family Property and Means of Life, Family Life Linkage, Housing Hygiene, Economy, and Health Care. By score quartiles, socioeconomic level was graded as very low, low, middle or high.

This study focused on children with T1DM managing their condition with multiple daily injections (MDI) of insulin, a common and effective treatment approach. These children utilized carbohydrate counting, a key component of modern diabetes management, to tailor their insulin doses to the specific carbohydrate content of their meals and snacks **(Annan et al., 2022).** This personalized approach helps to minimize blood glucose excursions after eating. The rapid-acting insulin analogs used for mealtime boluses included insulin lispro (Humalog), insulin aspart (Novorapid), and insulin glulisine (Apidra). These analogs are designed to mimic the body's natural insulin response to food intake, providing better control of postprandial glucose levels compared to older, regular insulin. For basal insulin, providing a steady, background level of insulin throughout the day, participants used either insulin degludec 100 Units/mL (Tresiba) or insulin glargine 100 Units/mL (Lantus). Both are long-acting insulin analogs, but degludec offers an ultra-long duration of action, often allowing for more stable glucose levels. These basal insulins were administered once daily between 8 and 10 PM, aiming to cover insulin needs between meals and overnight.

Precise bolus insulin dosing was achieved through the application of two essential calculations: the insulin-to-carbohydrate ratio (ICR) and the insulin sensitivity factor (ISF) **(Tascini et al., 2018).** The ICR, a practical tool for meal planning **(Hegab, 2022),** indicates how many grams of carbohydrate are covered by one unit of insulin. For example, an ICR of 1:10 means that one unit of insulin will cover 10 grams of carbohydrate. This ratio allows individuals to calculate the appropriate insulin dose based on the carbohydrate content of their meal. The ISF, also known as the correction factor **(Hegab, 2019)**, quantifies the amount by which blood glucose levels are lowered by one unit of insulin. This is expressed either in mg/dL or mmol/L. For instance, an ISF of 50 mg/dL means that one unit of insulin will lower blood glucose by 50 mg/dL. ISF enables individuals to adjust their insulin doses to correct for high blood glucose levels or to prevent hypoglycemia. Together, the ICR and ISF empower individuals with T1DM to fine-tune their insulin regimens for optimal glycemic control, minimizing both hyperglycemia and hypoglycemia.

A Bio-Rad D-10 (AGAPPE Diagnostics Switzerland GmbH, Switzerland**)** analyzer high - performance liquid chromatography (HPLC) was used to determine the HbA1c levels.Complete blood counts (CBC) were performed through the Abacus 380 hematology analyzer (DIATRON Abacus 380, Hungary).

H pylori antigen detection in stool samples was conducted using the ichroma system (Boditech Med Inc., Korea), is a qualitative test based on high sensitivity fluorescence immunoassay (FIA). Specificity: 91%- 97% and Sensitivity: 95%- 97%.

Based on previous research, the estimated H. pylori infection prevalence was 80% in children with diabetes and 50% in non-diabetic children (**El-Eshmawy et al.,2011)**, A sample size calculation, assuming 80% statistical power and a 5% significance level, determined that 40 participants per group were required.

Statistical analysis

IBM SPSS Statistics (v22.0) was used for all statistical analyses. Continuous data are reported as mean ± SD (normally distributed) or median (IQR) (non-normally distributed), with normality determined by the Kolmogorov-Smirnov test. Frequencies and percentages describe categorical variables. Group differences were assessed

using independent t-tests (normal continuous data), Mann-Whitney U tests (non-normal continuous data), and Chi-square tests (categorical data). Significance was defined as $p < 0.05$.

Results

The study enrolled 80 participants, comprising 40 children with T1DM and 40 age- and sex-matched controls. A statistically significant difference was observed in socioeconomic status, with a higher proportion of controls belonging to very low and low socioeconomic classes compared to the T1DM group (**Table.1**).

Table 1. Clinical and demographic characteristics of study participants

Variables	Patients with T1DM (n = 40)	Patients without T1DM (n = 40)	P-value
Age (years), median (IQR)	11.0 (6.1 – 12.0)	10.5 (6.3 – 12.0)	0.96**
Body mass index (Kg/m^2), median (IQR)	16.35 (15.27 – 18.30)	16.50 (15.25 – 17.45)	0.73**
Gender, n (%) • **Female** • **Male**	 24 (60%) 16 (40%)	 24 (60%) 16 (40%)	1.00***
Socioeconomic status, n (%) • **Very low and low classes** • **Middle and high classes**	 20 (50.0%) 20 (50.0%)	 33 (82.5%) 7 (17.5%)	**0.01***

Bold: P significant; IQR: interquartile range; T1DM: type 1 diabetes mellitus; **Mann-Whitney U tests; ***Chi-square tests.

Gastrointestinal symptom frequencies among participants are illustrated in (**Fig.1**). Children with T1DM experienced significantly more frequent abdominal pain ($p = 0.01$), vomiting ($p = 0.04$), diarrhea ($p = 0.02$), and abdominal distension ($p = 0.03$). Constipation frequency, however, did not differ significantly between the two groups ($p = 0.18$).

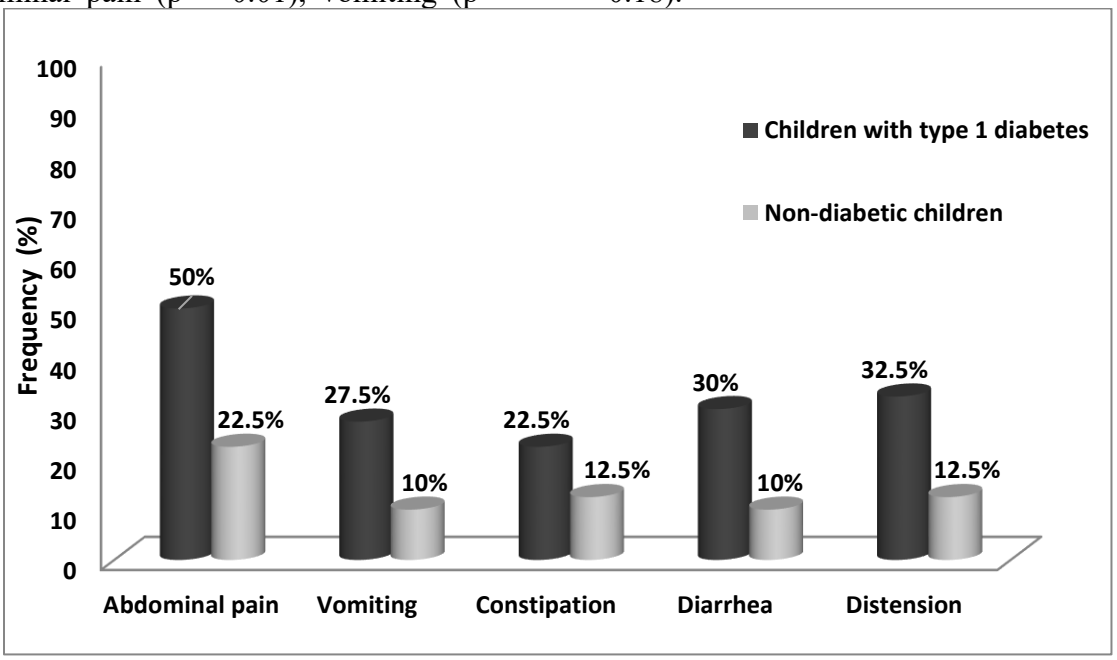

Fig.1. The frequencies of gastrointestinal symptoms among the study participants with and without T1DM

Participants with T1DM exhibited significantly elevated HbA1c levels ($p < 0.001$). Hemoglobin concentration and platelet counts did not differ significantly between groups. However, white blood cell counts were significantly higher in the T1DM group ($p = 0.018$) (**Table.2**).

Table 2.Laboratory characteristics of the study participants

Variables	Patients with T1DM (n = 40)	Patients without T1DM (n = 40)	P value
Hemoglobin A1c (%), median (IQR)	9.1 (7.9 – 10.2)	4.9 (4.7 – 5.1)	**< 0.001****
White blood cells (10^3/µl), median (IQR)	9.2 (7.75 – 11.43)	7.9(5.97 – 9.57)	**0.018****
Hemoglobin concentration (g/dL), Mean ± SD	12.19 ± 1.10	11.91 ± 0.86	0.21***
Platelet count (10^3/µl), median (IQR)	330.5 (300.2 – 371)	323 (292.5 – 386)	0.65 **

Bold: P significant; IQR: interquartile range, SD: standard deviation; T1DM: type 1 diabetes mellitus; **Mann-Whitney U tests; *** independent t-tests.

H pylori antigen in stool was significantly more frequent among children with T1DM (32.5% vs. 10%, $p = 0.01$) (**Table.3**).

Table 3. Frequency of H. pylori antigen in stool among participants

H. pylori antigen in stool	Patients with T1DM (n = 40)	Patients without T1DM (n = 40)	P value
• **Positive** • **Negative**	13 (32.5%) 27 (67.5%)	4 (10.0%) 36 (90.0%)	**0.01***

Bold: P significant; T1DM: type 1 diabetes mellitus; *Chi-square tests.

(**Table .4**) shows the clinical and demographic characteristics among children with T1DM with positive and negative H. pylori antigen. There were no statistically significant differences between diabetic children with positive and negative H. pylori antigen in stool as regards age, sex, BMI, socioeconomic classes, or duration of diabetes. The frequencies of gastrointestinal symptoms were significantly higher among T1DM children with positive H. pylori stool antigen compared to those with negative antigen.

Table 4.Clinical and demographic characteristics in relation to H. pylori stool antigen

Variables	T1DM children with positive H. pylori antigen (n = 13)	T1DM children with negative H. pylori antigen (n = 27)	P-value
Age (years), median (IQR)	12.0 (9.5 – 13.5)	10.0 (6.0 – 12.0)	0.08**
Gender, n (%) • **Female** • **Male**	 9 (69.2%) 4 (30.8%)	 15 (55.6%) 12 (44.4%)	0.41***
Body mass index (Kg/m^2), median (IQR)	17.2 (16.1 – 18.8)	15.8 (15.1 – 17.3)	0.10**
Duration of diabetes (years), median (IQR)	3.0 (1.7 – 5.0)	3.0 (2.0 – 6.5)	0.81**
Socioeconomic status, n (%) • **Very low and low**	 8 (61.5%)	 12 (44.4%)	0.31***

classes • **Middle and high classes**	5 (38.5%)	15 (55.6%)	
Gastrointestinal symptoms, n (%) • **Abdominal pain** • **Vomiting** • **Constipation** • **Diarrhea** • **Abdominal distension**	 12 (92.3 %) 11 (84.6%) 9 (69.2%) 10 (76.9%) 12 (92.3%)	 8 (29.6%) 0 (0%) 0 (0%) 2 (7.4%) 1 (3.7%)	 **<0.001***** **<0.001***** **<0.001***** **<0.001***** **<0.001*****

Bold: P significant; IQR: interquartile range; T1DM: type 1 diabetes mellitus; **Mann-Whitney U tests; ***Chi-square tests.

(**Table.5**) shows the insulin types, doses and Hb A1c levels among children with T1DM with positive and negative H. pylori antigen. There were no significant differences between both groups as regards the type of basal or bolus insulins, the total daily insulin dose, the basal dose, ICR, ISF, and the Hb A1c levels.

Table 5. Insulin types, doses, and glycated hemoglobin levels in relation to H. pylori antigen in stool

Variables	T1DM children with positive H. pylori antigen (n = 13)	T1DM children with negative H. pylori antigen (n = 27)	P-value
Type of bolus insulin, n (%) • **Insulin glulisine** • **Insulin lispro** • **Insulin aspart**	 3 (23.1%) 4 (30.7%) 6 (46.2%)	 7 (25.9%) 9 (33.3%) 11 (40.7%)	0.95*
Type of basal insulin, n (%) • **Insulin glargine 100U/ml** • **Insulin degludec 100U/ml**	2 (15.38%) 11 (84.62%)	6 (22.22%) 21 (77.78%)	0.61*
• **Total daily insulin dose (u/kg /day), mean ± SD**	0.91 ± 0.11	0.92 ± 0.09	0.97***
• **Total basal insulin dose (u/kg/day), mean ± SD**	0.42 ± 0.07	0.44 ± 0.06	0.49***
Insulin/carbohydrate ratio (grams/ unit of insulin), median (IQR)	10.0 (7.5 – 13.5)	12.0 (10.0 – 15.0)	0.22**
Insulin sensitivity factor (mg/dL per unit of insulin) median (IQR)	50 (40 – 70)	75 (50 – 80)	0.17**
Hemoglobin A1c (%), mean ± SD	9.41 ± 1.22	8.97 ± 1.56	0.38***

IQR: interquartile range; SD: standard deviation; T1DM: type 1 diabetes mellitus; *Chi-square tests; **Mann-Whitney U tests; ***independent t-tests.

Discussion

H. pylori is a common human bacterial infection associated with a variety of gastric disorders **(Van Blankenstein et al., 2013)**. Previous research has found a greater incidence of H. pylori infection in

diabetics than in controls, as well as a strong link between H. pylori infection and both insulin resistance and diabetic complications **(Kayar et al., 2015)**.

The current investigation found a statistically significant increase in the prevalence of positive H. pylori stool antigen in pediatric patients with T1DM compared to non-diabetic controls. This observation is consistent with prior research documenting elevated H. pylori infection rates in children with T1DM. **Bazmamoun et al. (2016)**, in a study of 80 diabetic and 80 non-diabetic children, reported a higher H. pylori infection frequency in the T1DM group (60%) compared to the control group (40%). Similarly, **Zafar et al. (2016)**, investigating 69 individuals (30 non-diabetic and 39 diabetic), found a greater prevalence of positive H. pylori Ag in the diabetic patients. Additionally, **Zekry and Abd Elwahid (2013),** in an Egyptian study, observed significantly higher H. pylori Ag levels in T1DM patients compared to a healthy control group.

El-Eshmawy et al. (2011), in a study of 162 patients with T1D and 80 controls, also reported a statistically significant increase in H. pylori seropositivity in the diabetic group. The observed increase in H. pylori colonization among diabetic patients may be related to impaired gastric motility and elevated blood glucose levels associated with poorly controlled diabetes.

Conversely, several studies have not demonstrated a significantly higher prevalence of H. pylori infection in children with T1DM. **Candelli et al. (2003) and Keramat et al. (2013)** discovered no significant difference in H. pylori infection rates among diabetic and non-diabetic children. Furthermore, **Osman et al. (2016),** found a greater frequency of positive H. pylori antigen in non-diabetic children than in those with T1DM (65.5% vs. 62.2%), albeit this difference was not statistically significant ($p = 0.21$).

The current study demonstrated that gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea, and abdominal distension were significantly more frequent in H. pylori-positive children compared to H. pylori-negative children. Among children with T1DM, those with positive H. pylori stool antigen had significantly higher frequencies of gastrointestinal symptoms (abdominal pain, vomiting, diarrhea, constipation, and abdominal distension) compared to those with negative H. pylori stool antigen. These findings were in line with **Gulcelik et al. (2005).**

While **Bazmamoun et al. (2016)** reported no significant difference in gastrointestinal symptoms between H. pylori-positive and H. pylori-negative diabetic children, this study found no association between H. pylori stool antigen status and diabetes duration in T1DM children. This finding is consistent with some prior research **(Candelli et al., 2003; Demir et al., 2008)**, which also failed to demonstrate a link between diabetes duration and H. pylori infection. Conversely, other studies, including **El-Eshmawy et al. (2011)** and **Bazmamoun et al. (2016)**, have reported a significant association between these two variables.

This study observed no statistically significant differences in total or basal daily insulin doses between children with type 1 diabetes mellitus (T1DM) stratified by H. pylori stool antigen status. This observation aligns with several prior studies **(Candelli et al., 2003; Demir et al., 2008; Fayed et al., 2014; Bazmamoun et al., 2016)** that have reported no significant association between H. pylori infection and daily insulin requirements in diabetic patients.

While **El-Eshmawy et al. (2011)** and **Dai et al. (2015)** reported increased

insulin requirements in diabetic patients with H. pylori infection compared to those without, **Devrajani et al. (2010)** observed the opposite, with lower insulin requirements in H. pylori-positive diabetic patients. These discrepancies may be attributable to variations in factors influencing glycemic control across studies, such as insulin and dietary regimens and patient compliance, rather than solely the presence or absence of H. pylori infection.

This study observed no statistically significant differences in either the ICR or ISF between pediatric participants with T1DM categorized by H. pylori stool antigen status. This represents, to the authors' knowledge, the first investigation of the association between H. pylori infection and these critical insulin dosing parameters in the pediatric T1DM population.

This study found no statistically significant difference in HbA1c levels between pediatric participants with T1DM stratified by H. pylori stool antigen status. This null finding is concordant with the results reported by **Candelli et al. (2003)** and **Bazmamoun et al. (2016).** Conversely, several other investigations **(El-Eshmawy et al., 2011; Fayed et al., 2014)** have observed statistically significant elevations in HbA1c among T1DM children with concurrent H. pylori infection.

Limitations of the present study include small sample size and single center study. Consequently, larger-scale, more comprehensive investigations are warranted to validate these findings and to further elucidate the complex interplay between H. pylori infection and various T1DM management parameters in the pediatric population.

Conclusion

H. pylori infection is significantly more prevalent in the pediatric T1DM population compared to non-diabetic children. Among children with T1DM, those with positive H. pylori stool antigen exhibited a significantly higher frequency of gastrointestinal symptoms. However, H. pylori infection status did not demonstrate a statistically significant impact on either insulin requirements or glycemic control in this pediatric T1DM cohort.

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