Helicobacter pylori Infection and Insulin Requirement Among Children With Type 1 Diabetes Mellitus

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ABSTRACT. *Objective. Helicobacter pylori* **induces gastric inflammation and the production of cytokines in infected individuals. Theoretically, this increased production of cytokines could be deleterious for the control of the glycemia of patients with diabetes. This study aimed to describe the insulin requirement among patients with type 1 diabetes and *H pylori* infection compared with uninfected counterparts.**

Methods. **Cross-sectional design. Demographic information (age, gender, race, annual family income, and number of individuals per room in the household) and clinical information (age at diagnosis of diabetes, duration of illness, weight, height, compliance with clinical appointments, daily insulin units per kilogram of body weight [IU/kg/d], and glycosylated hemoglobin A level) was obtained from children and adolescents with diagnosis of type 1 diabetes mellitus who were seen at Children's Hospital in New Orleans. A total of 2 mL of blood was also collected and sera were tested for *H pylori*-specific immunoglobulin G antibodies using an enzyme immunoassay. The daily insulin requirement among infected and uninfected children was compared, and the effect of other variables was evaluated with multiple linear regression.**

Results. **Of the 71 subjects who were evaluated (median age: 11 years), 11 (15.5%) were found to be infected. *H pylori* infection was more frequent among subjects who were older, who had a lower family income, and who were black. Infected children were found to require more insulin (1.2 vs 0.9 IU/Kg/d) and their glycosylated hemoglobin A level was higher (14.9 vs 11.8) than the level found in uninfected subjects. Multiple linear regression analysis identified *H pylori* infection duration of illness, race (black), body mass index, and gender (female), to be associated independently with increased daily insulin requirement (IU/kg/d).**

Conclusion. **In our study population, children with type 1 diabetes and *H pylori* infection had an increased daily insulin requirement compared with the requirement of their uninfected peers. The reason for this association requires additional investigation. *Pediatrics* 1999; 103(6). URL: http://www.pediatrics.org/cgi/content/full/103/6/e83; *Helicobacter pylori, diabetes, children, cytokines, insulin.***

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ABBREVIATIONS. IU/kg/d, insulin units per kg of body weight per day; HbA_{1c}, glycosylated hemoglobin A.

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia that affects ≥15 million individuals in the United States.[1] The basic pathophysiology of the disease is insulin deficiency attributable to different degrees of either decreased insulin secretion (as seen in type 1 diabetes) or resistance to insulin action (as seen in type 2 diabetes).[2] During acute infections, patients with diabetes mellitus can experience a rise in their glycemia and can require additional doses of insulin for appropriate control of their glucose metabolism; in its most severe form, this manifests as diabetic ketoacidosis, a life-threatening condition primarily seen among type 1 diabetics.[3] The mechanisms are not clear, but the altered glucose metabolism during infections is thought to be mediated by the secretion of counterregulatory hormones attributable to stress as well as to the production of cytokines.[4] Cytokines by themselves can stimulate the secretion of insulin counterregulatory hormones and can also affect directly carbohydrate metabolism.[4] In addition, in vitro data support a role for cytokines in the pathogenesis of type 1 diabetes mellitus and its complications, as reviewed elsewhere.[5]

Helicobacter pylori was cultivated first from human gastric mucosa in 1983[6] and since has emerged as one of the most common chronic bacterial infections in the world, affecting about 40% and 80% of the general population in developed and developing countries, respectively.[7] Infection with this bacterium induces gastric inflammation in most subjects and has been associated with an increased production of cytokines such as tumor necrosis factor-α, interferon-γ, and interleukin-1, -6, and -8.[8] Also, gastric parietal cell autoantibodies have been identified more frequently in diabetic patients with concomitant *H pylori* infection compared with uninfected patients.[9]

Theoretically, this inflammation and increased production of cytokines could be deleterious for the control of the glycemia of patients with diabetes. Therefore, the present study aimed to describe the prevalence of and the factors associated with *H pylori* infection among children with diabetes mellitus and to evaluate its effect on their insulin requirement.

METHODS

This study had a cross-sectional design with evaluation of a convenience sample of children seen consecutively at our center. Children and adolescents with diagnosis of type 1 diabetes mellitus[2] who were seen at the Diabetes Clinic of Children's Hospital in New Orleans, Louisiana were invited to participate. The study was approved by the Institutional Review Board of Louisiana State University and Children's Hospital. Consent was obtained from the parents of participating children, and assent was obtained from subjects >7 years old.

At our center, type 1 diabetic patients are managed routinely with meal and exercise planning, and their daily insulin dose (IU/kg/d) is adjusted according to their glycosylated hemoglobin A (HbA_{1c}) level to achieve if possible a value <10%. Measurement of HbA_{1c} is made with a capillary electrophoresis system, previously described,[10] with a normal reference range of 5.7% to 8.1% (J. Hempe, personal communication). Home blood and urine glucose monitoring is also advised routinely to the patients, but compliance is variable.

From the subjects who agreed to participate in the study, demographic information (age, gender, race, annual family income, and number of individuals per room in the household) and clinical information (gastrointestinal symptoms, age at diagnosis of diabetes, duration of illness, weight, height, compliance with clinical appointments, IU/kg/d requirement, and HbA_{1c} level) were obtained. Also, 2 mL of blood was collected, and sera were separated for the determination of *H pylori*-specific immunoglobulin G antibodies using an enzyme immunoassay (HM-CAP; Enteric Products Inc, Stony Brook, NY). Using control sera, specimens were tested in duplicate according to the manufacturer's specifications,[11] which categorize results as negative, indeterminate, or positive if absorbance values (for sera diluted 1:100 at 450 nm) are <1.8, 1.8 to 2.2, or >2.2 units, respectively. Consistent results (both positive and negative) were classified accordingly; discordant or indeterminate results were repeated and if they remained indeterminate, the patients were excluded from additional analyses. Patients with a positive serologic result were tested additionally with the urea breath test (Meretek UBT; Meretek Diagnostics, Inc, Houston, TX).[12]

Statistical analyses were performed with the Epi Info, Version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA) and Statistical Package for the Social Services (SPSS), Version 6.1 (SPSS, Inc, Chicago, IL) software. For comparison of infected and uninfected subjects the nonparametric Mann-Whitney rank-sum test was used for continuous variables and the χ^2 or Fisher's exact test with Yate's correction for proportions. The effect of multiple variables was evaluated with multiple linear regression analysis (Method: enter, probability F_{in} = .05, probability F_{out} = .10). For this part of the analysis, categorical data (eg, gender, race, and *H pylori* infection) were converted into dummy variables (0 = absent and 1 = present), and only variables with a probable association ($P < .10$) with either *H pylori* or IU/kg/d were included in the model. The possibility of multicollinearity was evaluated by calculating the variance inflation factors.[13] Because the dependent variable IU/kg/d is predictably erratic at the beginning of diabetes illness to evaluate its association with *H pylori* infection that part of the analysis was circumscribed to children with illness durations of ≥1 year (this eliminated 8 [11%] of the subjects).

RESULTS

Of the 73 children who were enrolled between October 1996 and April 1998, 2 were excluded because of indeterminate serologic test results. Of the 71 patients who were able to be evaluated, 11 (15.5%) tested positive for the presence of *H pylori*-specific immunoglobulin G antibodies and all were confirmed with the urea breath test. The study group had a median age of 11 (range: 2–18) years; 36 (51%) of the subjects were males; 36 were white, 31 black, 2 Asian, and 1 Hispanic; and their median income was $28 000 with 65% of households reporting an income ≤$40 000 (the median income for the US).

Gastrointestinal symptoms (abdominal pain, bloating, or nausea) were referred by 31 (44%) patients and were described as sporadic and mild, not interfering with their daily activities or requiring medical attention. No patient referred a personal history of peptic ulcer disease or gastrointestinal bleeding, but 3 patients referred having a relative who had been diagnosed with peptic ulcer disease. As shown in Table 1, *H pylori*-infected subjects tended to be older, were more frequently black, and reported a lower income than uninfected subjects. Gender distribution and crowding (measured as number of persons per room in the household) did not differ significantly between the two groups. Regarding their diabetes illness, infected subjects had been diagnosed with diabetes for a longer time and were less compliant with their clinical appointments; in addition, they were found to have a significantly higher IU/kg/d requirement and their HbA_{1c} was higher than that found in uninfected subjects.

Because the primary outcome variable was IU/kg/d, we looked additionally into the variables affecting IU/kg/d (Table 2). Only patients with duration of diabetes illness ≥1 year are included in Table 2. Univariate analyses using simple linear regression showed that IU/kg/d increased significantly with higher HbA_{1c} level, as well as with increasing age, female gender, longer duration of diabetes illness, increased body mass, and (as previously stated) *H pylori* infection. Next, all these variables (in addition to race, income, and compliance that affected significantly the rate of *H pylori* infection) were included in a multivariate regression analysis that identified an independent effect of duration of diabetes illness,

TABLE 1. Sociodemographic and Diabetes Illness Characteristics According to *H pylori* Infection Status

Characteristic	*H pylori*-Positive	*H pylori*-Negative	*P* Value
Number	11	60	
Age (y)*	13 (7–17)	11 (12–18)	.16
Gender (female)†	6 (56)	29 (48)	.96
Race (black)†	11 (100)	20 (33)	<.0001
Income (×1000)*	14.5 (10–22)	30 (10–150)	.01
Crowding (no. persons/room)*	1.4 (1.0–3.0)	1.3 (.3–6.5)	.59
Age first diagnosed (y)*	5.4 (1.9–12.5)	6.7 (.3–14)	.97
Duration of diabetes (y)*	5.0 (.2–14.1)	3.4 (.5–13)	.08
Compliance (with visits)*	.7 (.2–1.0)	.9 (.4–1.0)	.003
Body mass index (kg/m^2)*	19.7 (14.5–24.9)	20.1 (13.4–33.0)	.90
IU/kg/d*	1.2 (.7–1.5)	.9 (.2–1.5)	.02
HbA_{1c} (%)*	14.9 (8.1–23.6)	11.8 (5.8–20.1)	.006

* Median (range); Mann-Whitney rank-sum test.
† Number with characteristic (percentage); χ^2 test.

TABLE 2. Variables Affecting Daily Insulin Requirement (IU/kg/d) of Children With Type 1 Diabetes and Duration of Illness ≥1 Year

Variable	Total Group ($N = 63$)						Blacks ($N = 28$)					
	Univariate			Multivariate			Univariate			Multivariate		
	β	SE	P Value	β	SE	P Value	β	SE	P Value	β	SE	P Value
H pylori infection	+.261	.102	.013	+.275	.125	.035	+.361	.120	.006	+.268	.119	.035
HbA_{1c} (%)	+.021	.012	.086	+.016	.012	.213	+.027	.017	.125	+.015	.014	.293
Age (y)	+.040	.008	<.0001	−.005	.012	.648	+.046	.015	.004	+.007	.017	.661
Duration of diabetes (y)	+.059	.013	<.0001	+.041	.015	.009	+.066	.019	.002	+.044	.018	.020
Compliance rate	−.078	.189	.681	+.004	.201	.984	−.243	.303	.430	+.108	.241	.658
Body mass index (Kg/m^2)	+.036	.008	.0001	+.036	.011	.002	+.032	.014	.027	+.030	.014	.040
Income (×1000)	−.001	.001	.503	−.001	.001	.336	−.002	.004	.612			
Gender (female)	+.141	.077	.071	+.132	.066	.054	+.155	.130	.246			
Race (black)	−.022	.079	.781	−.346	.092	.0006						

β, regression coefficient; SE, standard error of β.

black race, body mass, female gender, and *H pylori* infection on the daily insulin requirement of our patients. The variance inflation factor values were <4 for all variables; therefore, no modification to the model was necessary for multicollinearity.[13]

Finally, analyses were repeated comparing infected black subjects to uninfected black subjects only (Table 2). Because of smaller sample size some variables such as gender, and HbA_{1c} lost their significant effect on IU/kg/d. By univariate analyses, there was an association between IU/kg/d and age, duration of diabetes, body mass, and *H pylori* infection. On multivariate analysis, duration of diabetes illness, body mass and *H pylori* infection remained independent predictors of IU/kg/d requirement.

DISCUSSION

The subjects enrolled in this study seem to be representative of the patients seen at our Diabetes Clinic in terms of age, gender, race distribution, and HbA_{1c} levels. The corresponding values for our overall type 1 diabetic population ($n = 187$) are age: 12.6 ± 4.2 years; gender: 52% female; race: 50% white, 45% black, and 5% other; HbA_{1c}: 12.8% ± 3.2% for blacks and 11.0% ± 2.3% for whites (S. Chalew, personal communication). Also, their reported income is in accordance with the median for the state of Louisiana, and the sociodemographic factors that we found associated with *H pylori* infection (ie, increasing age, poor socioeconomic class, and race [black]) are well recognized.[7,14]

H pylori infection was determined using a serologic test with a reported sensitivity and specificity of 98% and 94%, respectively.[15] Because the validity of commercially available serologic kits in children has been questioned by some researchers,[16] we confirmed the positive results with the urea breath test which, in children, has shown a sensitivity and specificity of 100% and 98%, respectively, compared with histology.[17] The prevalence of *H pylori* infection found in our study (17.2% among children 6–18 years of age) is similar to previously reported values for nondiabetic US children of comparable age (24.1%).[14] Some authors have suggested an increased prevalence of *H pylori* infection among diabetic patients;[18] however, the validity of those findings has been severely criticized[19] and our results do not support such a notion. Attention should be drawn to the infection rate among the different race groups. All our infected patients were black. The infection rate we found among 6- to 18-year-old blacks was 37.9%, similar to the 40.1% previously described in a population-based study in the US.[14] The same study also reported an infection rate of 17.0% among white children; yet, none of our white patients were found to be infected, although some of them presented the sociodemographic risk factors mentioned above. We have no explanation for this discrepancy at this point, and we are conducting additional seroprevalence studies to clarify this issue.

The primary findings of our study are the increased IU/kg/d requirement and the increased level of HbA_{1c} among the infected subjects. These two factors are not independent because an elevated HbA_{1c} level would lead to an increase in the dose of insulin. However, the association between IU/kg/d and *H pylori* infection remained significant even after controlling for the HbA_{1c} level (as well as many other possible confounding variables) suggesting that infected children required higher doses of insulin than uninfected children did to achieve comparable levels of HbA_{1c}. In addition, because all our infected patients were black and diabetes mellitus is known to behave differently in that racial group compared with others, we repeated the analyses including only black patients (infected vs uninfected subjects) and found again that *H pylori* infection was associated independently with increased IU/kg/d requirement. The regression coefficients obtained by either set of analyses did not vary markedly, again implying an independent effect. The regression coefficients were consistent with an increase of ~.33 ± .12 IU/kg/d in the insulin requirement among infected children. The clinical relevance of this increased insulin requirement is not directly evident from our cohort, but specially coupled with the elevated HbA_{1c} levels (~3% higher among infected subjects), it would suggest a less optimal control of the glycemia that in turn has been associated with the development and progression of long-term complications of diabetes.[20] In that particular study, patients on conventional insulin therapy had a HbA_{1c} level on average 2% higher than those on intensive insulin therapy and developed significantly more retinopathy, nephropathy, and neuropathy.

Although the analyses of our data document the

presence of an association between *H pylori* infection and increased IU/kg/d, interpretation of our results should be cautious. First, similar studies need to be repeated in other populations to ensure that the findings are related to the presence of the infection itself and are not a peculiarity of the *H pylori*-infected subjects in our community (eg, due to particular dietary or living habits). Second, the observational nature of the study does not allow an evaluation of causality or, for that matter, its direction. In other words, does the presence of the infection affect negatively the control of diabetes, or does the poor control of diabetes favor acquisition of the infection? Or, do unidentified variables lead to both infection and poor control of diabetes? Although all these scenarios are possible, we explained above the biologic plausibility that the presence of *H pylori* infection could induce chronic inflammation and production of cytokines, leading to impaired secretion of insulin, increased anti-insulin activity, and altered carbohydrate metabolism, all these effects translating into decreased glycemia control.[4,5]

We must acknowledge difficulty in evaluating two of the study variables: income and compliance. Income was measured by self-report and only 73% of families provided the information; therefore, we do not know if any bias could have been introduced. Compliance with the treatment regimen is an important factor for the glycemia control of diabetic patients. Unfortunately, we could not measure compliance with insulin dose administration directly and we used compliance with clinical appointments instead. This surrogate marker did seem to correlate as expected with the other variables (data not shown); however, because it is not a direct measure, we have no way to quantify how much, if any, bias may have been introduced.

CONCLUSION

In summary, our data document an association between the presence of *H pylori* infection and an increased IU/kg/d requirement among our patients with type 1 diabetes mellitus. The nature of this association requires additional investigation. Intervention studies would be most appropriate to elucidate causality; however, these may be difficult to implement. Deliberate infection would probably not be ethical, whereas eradication of the infection may result in improved insulin requirement but only if the insulin-secreting cells are not yet depleted. Early intervention studies or studies in other forms of diabetes (eg, type 2) may prove more informative.

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