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

Rodolfo E. Begue, MD; Ayesha Mirza, MD; Terry Compton, RN; Ricardo Gomez, MD; and Alfonso Vargas, MD

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 A1c 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 A1c 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.

ABBREVIATIONS. IU/kg/d, insulin units per kg of body weight per day; HbA1c, glycosylated hemoglobin A1c.
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 mellitus1 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 10 diabetic patients were managed routinely with meal and exercise planning, and their daily insulin dose (IU/kg/d) is adjusted according to their glycosylated hemoglobin (HbA1c) level to achieve as close as possible a value <10%. Measurement of HbA1c is made with a capillary electrophoresis system, previously described,20 with a normal reference range of 5.7% to 8.1% (H. Hempel, 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 HbA1c level) were obtained. Also, 2 mL of blood was collected, and sera were separated from the subjects. The study group was determined with the urea breath test. The study group comprised 71 patients who were able to be evaluated, 11 (15.5%) tested positive for the presence of Helicobacter 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 interferring with their daily activities or requiring medical attention. No patient referred a personal history of peptic ulcer disease or gastrointestinal bleeding, but 5 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 HbA1c 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 age (P < .05), race (P < .05), female gender (P < .05), and duration of diabetes (P < .05). The rate of *H pylori* infection significantly increased 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th><em>H pylori</em>-Positive</th>
<th><em>H pylori</em>-Negative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age (y)*</td>
<td>13 (7–17)</td>
<td>11 (12–18)</td>
<td>.16</td>
</tr>
<tr>
<td>Gender (female)†</td>
<td>6 (56)</td>
<td>29 (48)</td>
<td>.96</td>
</tr>
<tr>
<td>Race (black)†</td>
<td>11 (100)</td>
<td>20 (33)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Income (&lt;$40 000)*</td>
<td>14.5 (10–22)</td>
<td>30 (10–150)</td>
<td>.01</td>
</tr>
<tr>
<td>Crowding (no. pers./room)*</td>
<td>1.4 (1.0–2.0)</td>
<td>1.3 (3.3–6.5)</td>
<td>.59</td>
</tr>
<tr>
<td>Age first diagnosed (y)*</td>
<td>5.4 (1.9–12.5)</td>
<td>6.7 (3.1–14)</td>
<td>.97</td>
</tr>
<tr>
<td>Duration of diabetes (y)*</td>
<td>5.0 (2.14–1.4)</td>
<td>3.4 (5.1–15)</td>
<td>.08</td>
</tr>
<tr>
<td>Compliance (with visits)*</td>
<td>.7 (2.1–1.0)</td>
<td>.9 (4.1–10)</td>
<td>.003</td>
</tr>
<tr>
<td>Body mass index (kg/m2)*</td>
<td>19.7 (14.5–24.9)</td>
<td>20.1 (13.4–33.0)</td>
<td>.90</td>
</tr>
<tr>
<td>IU/kg/d†</td>
<td>1.2 (7–1.5)</td>
<td>9.2 (1.5)</td>
<td>.02</td>
</tr>
<tr>
<td>HbA1c (%)†</td>
<td>14.9 (8.1–23.6)</td>
<td>11.8 (5.8–20.1)</td>
<td>.006</td>
</tr>
</tbody>
</table>

* Median (range); Mann-Whitney rank-sum test.
† Number with characteristic (percentage); χ² test.
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.

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 HbA1c 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 HbA1c 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; HbA1c: 12.6 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Group (N = 63)</th>
<th>Blacks (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td><em>H pylori</em> infection</td>
<td>+.261</td>
<td>.102</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>+.021</td>
<td>.012</td>
</tr>
<tr>
<td>Age (y)</td>
<td>+.040</td>
<td>.008</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>+.059</td>
<td>.013</td>
</tr>
<tr>
<td>Compliance rate</td>
<td>-.078</td>
<td>.189</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>+.036</td>
<td>.008</td>
</tr>
<tr>
<td>Income (&gt;10000)</td>
<td>-.001</td>
<td>.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>+.141</td>
<td>.077</td>
</tr>
<tr>
<td>Race (black)</td>
<td>-.022</td>
<td>.079</td>
</tr>
</tbody>
</table>

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

The clinical relevance of this increased insulin requirement is not directly evident from our cohort, but specially coupled with the elevated HbA1c level (−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. In that particular study, patients on conventional insulin therapy had a HbA1c 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.45

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.

**ACKNOWLEDGMENTS**

We thank Ms Jane Denning and Abbott Laboratories, Dallas, Texas, for their donation of the urea breath test kits.

**REFERENCES**

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