Association Between *Helicobacter pylori* Colonization and Glycated Hemoglobin Levels: Is This Another Reason to Eradicate *H. pylori* in Adulthood?

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(See the article by Chen and Blaser, on pages 1195–202.)

*Helicobacter pylori* infection is acquired in early childhood and becomes a chronic infection if left untreated [1]. The majority of infected people remain asymptomatic, and only a small portion develop illness, usually in adulthood [2]. *Helicobacter pylori* infection causes gastric and duodenal ulcers. It also increases the risk of gastric cancer [2, 3]; the bacterium was classified by the International Agency for Research on Cancer as a group 1 (definite) carcinogen in gastric carcinoma [4]. *Helicobacter pylori* also increases the likelihood of gastric lymphoma [5]. Moreover, positive associations between *H. pylori* infection and extragastric manifestations, such as iron deficiency anemia [6] and idiopathic thrombocytopenic purpura, also have been reported [7].

Many of the above-mentioned diseases and conditions are associated with the primary *H. pylori* virulence factors, cytotoxin-associated gene A (cagA) and vacuolating-associated gene A (vacA). Chronic *H. pylori* infection causes a continuous activation of the immune system, with a skewed T-helper 1 response [8, 9]. This response has been proposed as a possible mechanism responsible for some potential beneficial effects of *H. pylori* infection, such as protection against diarrheal diseases [10] and asthma [11].

Type 2 diabetes is an emerging pandemic, with estimates of 3.8 million deaths attributed to the disease in adults globally [12]. Lifestyle (eg, diet, obesity, physical activity), genetic, and socioeconomic factors are among the risk factors for the disease [13, 14]. There are conflicting reports concerning the association between *H. pylori* infection and the various clinical manifestations of the metabolic or insulin-resistance syndrome [15]. The roles of *H. pylori* infection in cardiovascular disease and its risk factors [16–18] and in type 2 diabetes are not clear. Although no association was found between *H. pylori* immunoglobulin G seropositivity and diabetes mellitus [19], a significantly higher prevalence of *H. pylori* gastritis was reported in patients with type 2 diabetes, compared with age-matched healthy controls (80% vs 56%; *P* = .03) [20]. A recent systematic review summarized the epidemiological evidence concerning the association between *H. pylori* infection and quantitative indexes of insulin resistance and indicated that such an association may exist. The authors of the review concluded, however, that further studies are needed to determine whether this is a causal association [15]. Studying biomarkers of diabetes mellitus, such as glycated hemoglobin levels (HbA1c) and insulin resistance, can contribute substantially to an understanding of the etiologic role of *H. pylori* infection in diabetes mellitus.

In this issue of the *Journal*, Chen and Blaser report findings of a seroepidemiological study in which they examined the association between seroprevalence of *H. pylori* infection and the mean levels of HbA1c in 2 large national surveys: the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2000. They report that *H. pylori* seropositivity, and especially *H. pylori* cagA positivity, was associated with higher mean HbA1c levels, an association that persisted after excluding individuals with a history of diabetes mellitus and controlling for potential confounders. The association was evident mainly in adults aged >18 years. Chen and Blaser also show a synergistic effect of *H. pylori* and body mass index (BMI) on increased levels of HbA1c in that higher levels were found in *H. pylori*-infected subjects with
BMI ≥25 but not in those with lower BMI. It is worth emphasizing that these findings were consistent in both independent surveys. The authors found a progressive increase in HbA1c levels when they compared *H. pylori*–negative, *H. pylori*–positive cagA-negative, and *H. pylori*–positive cagA-positive subjects. *H. pylori* cagA positivity was linked to HbA1c levels in participants with a lower BMI as well as those with a higher BMI. A significant interaction was also found between higher BMI and *H. pylori* cagA positivity on HbA1c. The association between *H. pylori* infection and diabetes mellitus, which was based on self-report of a physician diagnosis or insulin use, was inconsistent. In their analyses, the authors thoroughly adjusted for potential confounders by stratification as well as by multivariable linear and logistic regression models.

Many of the prior studies that addressed the association between *H. pylori* infection and diabetes mellitus or insulin resistance were conducted in selected and small samples. In the current study, Chen and Blaser utilized two independent large national samples of the general population. In addition, the use of a reliable biomarker of diabetes as a dependent variable confers originality to the article because prior studies on the association between *H. pylori* and HbA1c have been limited [21]. It also helped circumvent the methodological challenges faced by researchers who examined the association between *H. pylori* infection and diabetes mellitus using the definition of diabetes mellitus based on the accuracy of self-reporting, which might be affected by information and recall biases. The present findings on the positive association between *H. pylori* colonization and increased levels of HbA1c derive from a cross-sectional study. However, in view of the large amount of published data on *H. pylori* epidemiology, it can be assumed that *H. pylori* colonization that is acquired early in life precedes the high HbA1c levels characteristic of type 2 diabetes. Nevertheless, further studies, especially randomized controlled trials, are needed to examine the impact of anti- *H. pylori* therapy on HbA1c levels and the development and control of type 2 diabetes. Replication of Chen and Blaser’s study in other populations is also needed because the host genotype and exposure to different environmental factors may affect the strength of the association between *H. pylori* infection and HbA1c levels.

One potential biological mechanism that might explain the link between *H. pylori* infection and HbA1c levels is related to the role of *H. pylori* in the host metabolic homeostasis by affecting the production of ghrelin and leptin [22–24]. These 2 hormones are involved in the regulation of appetite and energy expenditure. Ghrelin decreases energy expenditure and promotes weight gain [25], whereas leptin, which is expressed mainly by adipocytes, reduces food intake and increases energy expenditure [26]. *Helicobacter pylori* infection was associated with lower levels of circulating ghrelin [27] through decreases in the ghrelin-producing cells in the gastric mucosa and increases in gastric leptin levels [22–24].

Chen and Blaser report that cagA positivity enhanced the association between *H. pylori* infection and HbA1c levels. Most *H. pylori* strains carry the cag-pathogenicity island. A type IV secretory apparatus in these strains allows translocation of the protein cagA into the host cell [9]. CagA induces proinflammatory and proliferative epithelial cell signaling [8] and is the determinant of the chronic gastric inflammation associated with *H. pylori* infection. CagA could be an important contributor to the inflammatory disorders involved in the metabolic syndrome and may, at least in part, also explain the link between *H. pylori* infection and HbA1c levels.

If confirmed, the findings reported by Chen and Blaser on the link between *H. pylori* infection and HbA1c could have important clinical and public health implications. *Helicobacter pylori*–infected adults with higher BMI, even if asymptomatic, may need anti-*H. pylori* therapy to control or prevent diabetes mellitus. With the continuous trend in the decline in *H. pylori* infection rates in developed countries, the relative importance of *H. pylori* in the etiology of diabetes mellitus will probably decrease. Nevertheless, there will be still many years in which older individuals, especially those with a higher BMI and glucose intolerance, will benefit from this new information.

**Note**

Potential conflicts of interest. All authors: No reported conflicts.

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**References**


