Rayner, Christopher Keith; Talley, Nicholas Joseph; Horowitz, Michael
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Stomach Bugs and Diabetes: An Astounding Observation or Just Confounding?

The discovery that a Gram-negative spiral bacillus was responsible for most peptic ulcer disease (1) created a paradigm shift that culminated in Marshall and Warren being awarded the Nobel Prize in Physiology or Medicine for 2005. *Helicobacter pylori* induces inflammation that may be limited to the gastric antrum, or can involve the corpus with subsequent mucosal atrophy, and is characterized, particularly in those strains that are positive for cytotoxin-associated gene A, by induction of cytokines including interleukins (IL-) 1, 6, and 8, and tumor necrosis factor-α (2). *H. pylori* is an established risk factor for gastric adenocarcinoma and lymphoma arising from mucosa-associated lymphoid tissue (MALT).

H. pylori appears to be acquired mainly in childhood by the fecal-oral or gastro-oral route. In developing countries, 80% or more of the population are infected by 20 years of age, while in the developed world the prevalence of infection increases with age. In each subsequent cohort, improving socioeconomic conditions lead to lower rates of infection in childhood (3). In Australia, for example, seroprevalence was recently estimated at ~30% for those ≥70 years of age, but only 5% for those <40 years of age (4).

Over the last 15–20 years, an increased prevalence of diverse diseases, including coronary artery (5) and cerebrovascular (6) disease, Alzheimer disease, migraine, Raynaud phenomenon, and chronic urticaria (7), has been reported in those with evidence of *H. pylori* infection. Plausible explanations to account for these associations include infection-induced systemic inflammation with increased "oxidative stress" and molecular mimicry (for example, between *H. pylori* and endothelial antigens) (7). However, many studies have potentially been biased, particularly when control groups were recruited opportunistically, and it is not always clear that appropriate adjustment has been made for confounders like age and socioeconomic status. For example, in relation to coronary artery disease, when a socioeconomically homogeneous sample such as from the Physicians' Health Study was examined, no increased risk of future myocardial infarction was evident among those seropositive for *H. pylori* (8). Currently, none of these putative associations is widely accepted as causally linked (9).

In this month's issue of *Diabetes Care*, Jeon et al. (10) report their analysis of a Latino cohort from the Sacramento, California, area. They followed 782 people aged ≥60 years twice yearly for a decade; participants were not known to have diabetes at entry and had serum assayed for antibodies to *H. pylori*, herpes simplex virus 1 (HSV-1), varicella zoster virus, cytomegalovirus (CMV), and *Toxoplasma gondii*, as well as inflammatory markers (IL-6 and C-reactive protein [CRP]), lipids, glucose, and insulin. During follow-up, 144 individuals developed diabetes (presumably type 2), with the rate being more than double in those who were seropositive for *H. pylori* at entry compared with the seronegative, even after adjusting for age, sex, education, and covariates such as smoking, BMI, blood pressure, and lipids. In contrast, antibodies to the other infectious agents were not associated with an increased risk of developing diabetes, nor was *H. pylori* seropositivity associated with higher concentrations of IL-6 or CRP. As expected, the presence of insulin resistance (evaluated by homeostasis model assessment [HOMA-IR]) predicated subsequent diabetes; however, HOMA-IR was not related to *H. pylori* status.

Simon at al. (11) were the first to report an association between *H. pylori* infection and type 2 diabetes, and positive reports have subsequently come from groups in the Netherlands (12), Italy (13), Turkey (14), and Africa (15). These all have significant methodological limitations, including small sample sizes, case-control designs, recruitment from clinical populations, and potential for sociodemographic confounding. Moreover, other studies have been unable to substantiate the association (16,17), while the largest study (1,000 individuals from ethnically diverse U.S. communities) (18) found that an apparent higher prevalence of diabetes in those seropositive for *H. pylori*, CMV, hepatitis A, and HSV became nonsignificant after adjustment for demographic covariates.

The strength of the study of Jeon et al. is its prospective nature. However, the rate of seropositivity to *H. pylori* was extraordinarily high (over 90%), so there were few seronegative individuals; no information is provided regarding the sensitivity and specificity of the assay. Furthermore, serology cannot distinguish current from previous infection, and the proportion of subjects previously given eradication therapy is unknown. Residual confounding (for example, by socioeconomic factors) cannot be excluded, and the mechanism by which *H. pylori* infection could predispose to diabetes remains unclear, particularly as there were no increases in the markers of systemic inflammation that were examined. Several reports have linked *H. pylori* infection to insulin resistance (19,20), but the HOMA-IR did not differ with *H. pylori* status in the current study, and an association between *H. pylori* seropositivity and insulin resistance is not supported by analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) (21). Jeon et al. suggest that changes in gastric emptying could adversely affect glycemia, but delayed gastric emptying is a potential advantage, rather than a disadvantage, in relation to glycemic control in type 2 diabetic patients not treated with insulin (22); moreover, *H. pylori* has been shown not to affect the rate of gastric emptying in patients with diabetes (23). *H. pylori*-induced gastritis can potentially affect the secretion of "gastric" hormones including leptin and ghrelin (24), which might feasibly predispose to diabetes. Whether *H. pylori* could induce a defect in insulin secretion remains speculative. Type 2 diabetes would seem highly unlikely to predispose to *H. pylori* infection given the age at which the latter is usually acquired.

It would be premature to advocate an aggressive test-and-treat strategy for

H. pylori in those at risk for developing type 2 diabetes on the basis of the current evidence. Demonstrating that such an intervention would reduce the subsequent incidence of diabetes would require a very large, long-term prospective study given that any effect is likely to be relatively small. Universal attempts to eradicate *H. pylori* carry concomitant risks of drug-related morbidity and antibiotic resistance, although it is likely that infection rates will continue to decline in developing countries as socioeconomic status improves. Currently accepted indications to test for *H. pylori* include active, or previous, peptic ulcer disease, gastric MALT lymphoma, early gastric cancer, and "uninvestigated" dyspepsia (9); the latter applies to younger patients without "alarm features" for malignancy. Diabetes is itself associated with an increased prevalence of gastrointestinal symptoms, including dyspepsia (25), but the presence of symptoms in diabetes has not consistently been shown to relate to *H. pylori* status (17). Meta-analyses indicate a small, but statistically significant, benefit in eradicating *H. pylori* in nonulcer dyspepsia in the general population (9), but there is insufficient evidence as to whether this applies to patients with diabetes.

CHRISTOPHER K. RAYNER, MBBS, PHD[1,2]
NICHOLAS J. TALLEY, MD, PHD[3]
MICHAEL HOROWITZ, MBBS, PHD[1,2]

From the [1]University of Adelaide Discipline of Medicine, Royal Adelaide Hospital, Adelaide, Australia; the [2]Centre of Clinical Research Excellence in Nutritional Physiology, Interventions and Outcomes, University of Adelaide, Adelaide, Australia; and the [3]Faculty of Health, University of Newcastle, Callaghan, Australia.
Corresponding author: Christopher K. Rayner, chris.rayner@adelaide.edu.au.

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