Helicobacter pylori infection and iron deficiency anemia: accumulating evidence in support of a real association

Iron deficiency is estimated to be the most common nutritional deficiency in both developed and underdeveloped nations, the most common cause of anemia, and one of the most common organic disorders in clinical practice. Gastroenterologists are frequently asked to perform endoscopic evaluation of patients with iron deficiency to determine if mucosal lesions causing chronic blood loss are present, including neoplasms, ulcers, and angiodysplasias. Depending on the clinical population and setting, stool testing for ova and parasites to rule out hookworm and serology or duodenal biopsies to rule out celiac sprue may also be appropriate. Despite a thorough clinical and endoscopic evaluation, large case series have shown that more than one-third of patients do not have a lesion to account for their iron deficiency, raising the question as to whether there are as yet unrecognized causes of iron deficiency. Could Helicobacter pylori infection account for some of these unexplained cases of iron deficiency? Accumulating evidence suggests that this is the case, i.e., that H. pylori gastritis, without peptic ulcer, can be associated with low iron stores and anemia.

The evidence to support a causal association between H. pylori gastritis and decreased iron stores comes from case reports, epidemiologic studies and small clinical trials. The initial case report describing a possible causal association between H. pylori gastritis and iron deficiency anemia (IDA) was published by Dufour et al, in which a seven-year-old boy with refractory unexplained IDA had resolution of anemia following treatment of H. pylori-related pangastritis. This case report was followed by several other similar case reports that describe IDA with no apparent cause other than H. pylori-associated gastritis, with normalization of hemoglobin and iron indices after successful H. pylori treatment (without need for continuing iron supplementation).

Most published case reports have described a thorough evaluation for other causes of IDA including upper endoscopy with gastric and small bowel biopsies, Meckel’s scanning as appropriate, stool studies for infectious pathogens, and colonoscopy as appropriate. The largest prospective case series to date showed impressive results following H. pylori treatment for 30 H. pylori-infected adults with unexplained IDA who were unresponsive to oral iron therapy. In this series, patients using non-steroidal anti-inflammatory drugs, who had fecal occult blood positivity, or an obvious cause of blood loss (including heavy menses) were excluded, a dietary history was taken to rule out nutritional deficiency, and double-contrast barium enema or colonoscopy, small bowel studies, or Meckel’s scans were performed if indicated, and EGD scope was performed in all cases along with duodenal biopsies to rule out celiac disease. Patients positive for H. pylori on urease test and/or histology were treated for H. pylori and then observed without iron replacement. During a follow-up period of 12-24 months, all patients cured of H. pylori infection had resolution of anemia and iron deficiency without further iron supplementation, whereas the three patients unsuccessfully treated for H. pylori infection had no change or a slight decrease in iron parameters at 6 months’ follow up.

The results from the study by Valiyaveettil et al in this issue of the Journal provides evidence in the form of a randomized controlled trial that supports a role for treatment of H. pylori infection for patients with H. pylori gastritis and unexplained IDA. In the only other randomized controlled trial in the literature, Choe et al showed a benefit for H. pylori treatment for patients with unexplained IDA who have H. pylori-gastritis. Choe et al randomized 22 H. pylori-positive subjects to one of three treatment groups: oral iron plus triple therapy for H. pylori, placebo plus triple therapy, or iron plus placebo. They found that patients who underwent H. pylori treatment, with or without iron, had a significantly greater rise in hemoglobin level at 8 weeks after therapy compared with those who received only iron supplementation. The current study by Valiyaveettil et al is in agreement with these findings. IDA patients with H. pylori infection who received anti-H. pylori treatment had a significantly greater increase in hemoglobin level one month following anti-H. pylori treatment compared to IDA patients with H. pylori infection who did not receive anti-H. pylori treatment (3.6 g/dL vs. 1.1 g/dL, p=0.025). Although these randomized controlled trials are very small, and larger randomized trials are needed, the findings are consistent with published uncontrolled case series, epidemiologic studies and physiologic studies that support an effect of H. pylori on iron metabolism that, in some cases, is clinically relevant and warrants anti-Helicobacter treatment.
Epidemiologic studies have shown that persons seropositive for *H. pylori* infection have a significantly lower serum ferritin level.\(^{23-27}\) In a population-based study (n=2794) from Denmark, *H. pylori*-seropositive persons were at 40% increased risk of having reduced serum ferritin level (<30 \(\mu \text{g/L}\)) compared to seronegative individuals (after adjustment for age, gender, menopausal status, socioeconomic status, blood donation, and alcohol consumption).\(^{24}\) Analysis of a cross-sectional national health survey from Germany (n=1806) revealed that persons with *H. pylori* infection had 17% decrease (95% CI 9.8-23.6) in serum ferritin concentration, after adjustment for age and sex.\(^{23}\) A study of Alaskan natives (n=2080) also showed an increased risk of low serum ferritin for persons seropositive for *H. pylori* infection (relative risk 1.13, p=0.013).

Positive findings were also reported in a study of Korean children aged 6-12 (n=753), in whom *H. pylori* seropositivity was associated with lower mean serum ferritin level (24 ng/mL vs. 39 ng/mL, p<0.001), and a significantly increased prevalence of iron deficiency (serum ferritin <15 ng/mL).\(^{27}\) Another study of Korean adolescents (n=937) confirmed a significant association between *H. pylori* seropositivity and anemia, hypoferritinemia and iron deficiency.\(^{28}\) An epidemiologic study of Australian women showed significantly lower ferritin levels in women with *H. pylori* infection compared to non-infected controls despite similar dietary iron intake.\(^{26}\)

While the above studies support an association between *H. pylori* infection and indices of iron stores, a few (usually smaller) epidemiologic studies have not found significant association between *H. pylori* infection and iron indices. In a study of 1060 adults from New Zealand, there was no significant differences in serum ferritin level according to *H. pylori* status,\(^{28}\) and a study of 693 Korean children found no significant difference in the prevalence of *H. pylori* infection for children with and without IDA.\(^{30}\)

How could *H. pylori* gastritis cause IDA? Several mechanisms have been hypothesized to explain the possible effect of *H. pylori* infection on iron stores. It appears that chronic gastrointestinal blood loss is not the likely culprit, since most published cases and case series found no bleeding lesions after investigation and the subjects had negative fecal occult blood testing.\(^{5,6,7,9,10,13,14}\) A more likely mechanism is decreased iron absorption from hypo- or achlorhydria resulting from chronic gastritis. Gastric hydrochloric acid facilitates iron absorption by reducing non-heme iron from the ferric to ferrous form.\(^{31}\) Persons with *H. pylori* infection and IDA appear more likely to have corpus gastritis as compared to *H. pylori*-infected patients without anemia.\(^{7,32,33,34}\) Corpus gastritis results in decreased gastric acid secretion and increase in intragastric pH that may impair iron absorption.\(^{33}\) Acid secretion returns to the normal range after eradication of *H. pylori*.\(^{35,36}\)

Another important effect of *H. pylori* gastritis that may cause reduced iron absorption is a decrease in gastric juice ascorbic acid concentration. Ascorbic acid facilitates iron absorption by reducing iron to the ferrous form.\(^{37}\) Ascorbic acid is secreted into gastric juice, and it has been shown that gastric juice ascorbic acid levels are significantly lower in *H. pylori*-infected vs. uninfected persons,\(^{33,38}\) and that ascorbic acid level increases after cure of *H. pylori* infection.\(^{39,40}\) Finally, another mechanism hypothesized to explain decreased iron absorption associated with *H. pylori* infection is increased hepcidin production from hepatocytes in response to IL-6 production associated with *H. pylori* gastritis.\(^{41}\) These physiological effects may be clinically relevant; *H. pylori* infected persons have been shown to have decreased oral iron absorption as compared to uninfected persons, with improvement of oral iron absorption 2 months after *H. pylori* cure.\(^{34}\)

Another hypothesized mechanism to explain an association between *H. pylori* infection and iron deficiency is uptake of iron by the *H. pylori* organism. Like many bacteria, *H. pylori* require iron as a growth factor, and it possesses a 19-kDa iron-binding protein resembling ferritin (Pfr), that may play a role in storage of excessive iron by the bacteria.\(^{42}\) Ferrokinetic studies in *H. pylori*-associated IDA have suggested diversion of iron to an extramedullary site, possibly (but not shown to be) *H. pylori* gastritis.\(^{6}\) Acquisition and storage of iron in *H. pylori* are controlled by the ferric uptake regulator gene product (Fur), which regulates transcription of iron uptake genes and Pfr iron storage.\(^{43}\) A fur mutant has been described that causes increased *H. pylori* whole cell iron content,\(^{43}\) but whether strain variations in iron-regulatory genes are associated with the clinical phenotype of iron deficiency remains unstudied.

Another possible mechanism by which *H. pylori* could result in decreased availability of iron is sequestration of iron in lactoferrin in the gastric mucosa. *H. pylori* takes up iron from human lactoferrin through a receptor-mediated method,\(^{44,45}\) and lactoferrin secretion in the gastric mucosa appears to be influenced by the *H. pylori* organism.\(^{46,47}\) Lactoferrin
may play a role in IDA, since gastric mucosa lactoferrin levels have been shown to be significantly higher in H. pylori-positive IDA persons compared to persons who are non-anemic H. pylori-negative, non-anemic H. pylori-positive, and H. pylori-negative with IDA.46

In summary, a growing body of evidence supports a clinically significant influence of H. pylori infection on body iron stores. The report by Valiyaveettil et al provides further data that patients with unexplained IDA benefit from testing and treatment for H. pylori infection. Epidemiologic studies also support an association between H. pylori infection and low iron stores, and several reports have shown resolution of refractory cases of anemia after H. pylori treatment. Given the relative ease and simplicity of H. pylori treatment and the encouraging results in literature, H. pylori testing and treatment for persons with unexplained IDA appears to be clinically indicated.

David J Kearney
University of Washington School of Medicine, VA Puget Sound Health Care System, Seattle, WA, USA

References