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The effect of *Helicobacter pylori* infection on iron stores and iron deficiency in urban Alaska Native adults

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Abstract

Background—*Helicobacter pylori* (*H. pylori*) infection has been correlated with low serum ferritin and iron deficiency. As a secondary analysis of a study of *H. pylori* reinfection, we investigated the association of *H. pylori* infection and the effect of its eradication on serum ferritin and iron deficiency.

Methods—Alaska Native adults undergoing esophagogastroduodenoscopy had sera collected and a ¹³C urea breath test (UBT) performed. Those *H. pylori* positive were treated with an antibiotic regimen; those who tested negative 2 months after treatment were evaluated at 4, 6, 12, and 24 months by UBT and serum ferritin with an immunoradiometric assay. We excluded persons from further analysis if they were prescribed iron by their provider.

Results—We measured serum ferritin for 241 persons; 121/241 were *H. pylori* positive. The geometric mean ferritin (GMF) for persons with and without *H. pylori* infection were 37 µg/L and 50 µg/L, respectively (p=0.04). At enrollment, 19/121 *H. pylori*-positive persons had iron deficiency compared with 8/120 *H. pylori* negative (p=0.02). Among 66 persons tested at 24 months, the GMF was higher at 24 months (49.6 µg/L) versus enrollment (36.5 µg/L; p=0.02). Six of 11 persons with iron deficiency at enrollment no longer had iron deficiency and had a higher GMF (p=0.02) 24 months after treatment.

Conclusions—*H. pylori* infection was correlated with lower serum ferritin and iron deficiency. After *H. pylori* eradication, serum ferritin increased and approximately half of persons resolved their iron deficiency. Testing for *H. pylori* infection and subsequent treatment of those positive could be considered in persons with unexplained iron deficiency.

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Introduction

Iron is the most common micronutrient deficiency in the world and iron deficiency affects up to 50% of the world's population (1, 2). Many of the adverse consequences of iron deficiency are associated with its most severe form, iron deficiency anemia, however iron deficiency without anemia has been linked to an increased risk in pregnant women of preterm delivery and low birth weight babies and to negative impacts on cognitive development in children (3–5). *Helicobacter pylori* (*H. pylori*) infection impairs iron uptake (6) and a number of studies have found an association between *H. pylori* infection and low serum ferritin levels or iron deficiency (7–10). Additional studies have provided evidence that eradication of *H. pylori* can increase serum ferritin levels and resolve iron deficiency, however some studies have shown little or no change in these outcomes after eradication (11–14). Both *H. pylori* infection and iron deficiency are common in Alaska (7, 15–17). Here we investigate whether *H. pylori* infection and *cagA*-positive *H. pylori* infection are associated with lower serum ferritin levels and iron deficiency in Alaska Native adults living in Anchorage, Alaska. In addition, we report on a subset of these persons who were found to have *H. pylori* infection and were subsequently treated and followed to investigate if eradication results in an increase in serum ferritin levels and a resolution of iron deficiency.

Methods

Enrollment and Twenty Four Month Follow-Up

This study is a secondary analysis of an investigation of *H. pylori* reinfection in Alaska Native adults living in an urban environment. The study design and characteristics of this cohort of Alaska Native adults have been previously described (18). Briefly, from September 1998 through December 2000, we enrolled adults scheduled for esophagogastroduodenoscopy (EGD) evaluation at the Alaska Native Medical Center in Anchorage, Alaska. We established the diagnosis of *H. pylori* infection by EGD evaluation and ¹³C urea breath test (UBT; Meretek Diagnostics Inc., Nashville, TN; Lafayette, CO). Patients found to be *H. pylori* negative by UBT were discontinued from the study and patients found to be *H. pylori* positive by UBT and at least one of CLO, histology, or culture were treated with an antibiotic regimen at the discretion of the patient's medical provider. Patients who tested negative by UBT two months after treatment were eligible for enrollment in a 24 month follow-up study. Persons in follow-up were tested by UBT for *H. pylori* recurrence four, six, 12, and 24 months after treatment. During this time we considered a person negative for active *H. pylori* infection if they continued to have a negative UBT. If a participant tested positive by UBT during follow-up we considered them to be reinfected and they were discontinued from the study. We analyzed data from persons who remained *H. pylori* negative by UBT throughout the study period.

We did not prescribe iron supplementation to any participant because serum ferritin testing and diagnosis of iron deficiency were done on stored sera after study completion. We reviewed participant's medical charts to see if their provider had prescribed them iron at any point during their time in the study. If a person was prescribed iron, we removed them from analysis starting at the time point of the initial prescription. We did not collect information

about non-prescription iron supplementation and cannot rule out that some participants may have been taking iron therapy on their own.

The study was approved by both the Centers for Disease Control and Prevention and Alaska Area Institutional Review Boards as well as the Southcentral Foundation Board of Directors. All participants signed informed consent to participate.

Serologic Measurement of Serum Ferritin

Each time a UBT test was performed (zero, two, four, six, 12, and 24 months post treatment), we also collected a serum sample, stored it at -30°C , and later tested it for serum ferritin by a commercial immunoradiometric assay (Quantimune Ferritin IRMA; Bio-Rad, Hercules CA). This assay uses ^{125}I -labeled antibody to ferritin as the tracer and ferritin antibodies immobilized on polyacrylamide beads as the solid phase. All specimens were analyzed blindly with regard to patient identification, infection status, and time since treatment. We defined iron deficiency as a serum ferritin level $< 12 \mu\text{g/L}$.

H. pylori culture and *cagA* genotyping

During EGD, providers collected gastric biopsies from the antrum and fundus of the stomach. Biopsies were cultured as previously described (19). For DNA extraction, *H. pylori* cells from each plate were collected together by sweeping a 1 uL inoculating loop across the media. The *H. pylori* cells were placed in 100 uL of phosphate buffered saline and vortexed to create a uniform turbidity. DNA was extracted with the MagNA Pure Compact using the MagNA Pure Compact nucleic acid isolation kit I and DNA culture cells v3.1 protocol (Roche Applied Science, Indianapolis, IN). This protocol uses proteinase K and a chaotropic salt-containing lysis buffer to lyse the cells and magnetic glass particles to collect the nucleic acids. *H. pylori* DNA was subjected to PCR analysis for presence of the *cagA* gene and the *cagA* empty site (indicating absence of the *cag* PAI) using previously described primers (20, 21).

Statistical analysis

Ferritin levels ($\mu\text{g/L}$) were log-transformed prior to analysis; geometric mean ferritin levels are reported. Mean ferritin levels were compared using a t-test (independent and paired, as appropriate) and the proportion with iron deficiency was compared with a likelihood ratio chi-square test. A generalized linear model with normal response was used to adjust for age class and gender when comparing ferritin levels between persons negative and positive for a *H. pylori* infection at the initial study visit. A paired t-test was used to account for the dependence across observations induced by measuring ferritin in the same individuals at two different time points. All p-values are two-sided and exact when sample size necessitated. All statistical tests were run in SAS version 9.2 (Cary, NC) and StatXact9 (Cytel Corporation, Cambridge, MA).

Results

Ferritin levels at enrollment

There were 317 persons recruited into the original study (18) and we measured a serum ferritin level from 254 (80%) of those persons; the remaining 63 persons did not have sufficient serum available for testing. After excluding 13 persons that had an iron supplement prescription documented in their medical record at the time of enrollment, 241 persons, both positive and negative for an *H. pylori* infection, remained and were included in the analysis (Table 1). At enrollment, the geometric mean serum ferritin level (GMF) for females was lower than males ($p < 0.01$). The GMF in females increased with increasing age class ($p < 0.01$), but not for males ($p = 0.41$). *H. pylori* infection was detected by UBT in 121/241 (50%) persons. Females infected with *H. pylori* had a lower GMF than uninfected females ($p = 0.003$), but this was not true for males ($p = 0.70$). Females in the two age classes corresponding with likely premenopausal status (<45, 45–<55) had a lower GMF if they were infected with *H. pylori* compared with those not infected ($p = 0.03$, for both). This was not true for females in the postmenopausal age class (>55; $p = 0.47$). After adjusting for age class and sex, persons infected with *H. pylori* had a lower GMF than persons not infected (37 $\mu\text{g/L}$ vs. 50 $\mu\text{g/L}$; $p = 0.04$). The GMF was not different in persons infected with *cagA*-positive versus *cagA*-negative strains of *H. pylori* (35 $\mu\text{g/L}$ vs. 60 $\mu\text{g/L}$; $p = 0.14$).

Iron deficiency was detected in 27/241 (11%) persons (Table 1). Females were not more likely than males to have iron deficiency ($p = 0.14$), and there was no difference in iron deficiency by age class for females or males ($p = 0.37$ and $p = 0.59$, respectively). Females infected with *H. pylori* were more likely to have iron deficiency than uninfected females ($p = 0.008$), but not for males ($p = 1.00$). After adjusting for age class and sex, persons with a *H. pylori* infection were more likely to have iron deficiency than persons without infection ($p = 0.03$). The prevalence of iron deficiency was not different in persons infected with *cagA*-positive versus *cagA*-negative strains of *H. pylori*.

Ferritin levels 2 months after *H. pylori* antimicrobial therapy

Of 116 persons that were not prescribed iron supplementation and who had a serum ferritin level measured before and 2 months after *H. pylori* treatment, 80/116 (70%) had cleared their infection as determined by a negative UBT. As compared with before treatment, 2 months after treatment neither the GMF nor the percentage of persons with iron deficiency changed in those with their *H. pylori* infection eradicated ($p = 0.63$ and $p = 1.00$, respectively) or those without successful eradication ($p = 0.59$ and $p = 0.18$, respectively; Table 2).

Ferritin levels among persons followed for 24 months after *H. pylori* eradication

Eighty-seven persons had their *H. pylori* infection eradicated, were followed for 24 months or until *H. pylori* reinfection, and had at least one serum tested for ferritin level after the first 2 months. Among the persons with a ferritin level measured at enrollment and 12 and 24 months post-treatment, the GMF had not changed significantly between enrollment and 12 months (36.5 $\mu\text{g/L}$ vs. 43.7 $\mu\text{g/L}$, respectively; $p = 0.26$, $n = 63$) but was higher at 24 months (49.6 $\mu\text{g/L}$; $p = 0.02$; Table 3, $n = 66$). Of 15 persons with iron deficiency at enrollment, 11 had a serum ferritin level measured again at 24 months and 55% of them (95% CI: 23%–

83%) no longer had iron deficiency. Of these same 15 persons, the GMF had not changed significantly between enrollment and 12 months (4.8 µg/L vs. 9.4 µg/L, respectively; $p=0.20$), but was higher at 24 months (10.8 µg/L; $p=0.02$).

Discussion

Recent meta-analyses concluded that *H. pylori* infection is associated with iron deficiency and iron deficiency anemia and treatment for the infection could be effective in improving anemia and iron stores (8, 22–25). Data from this study of Alaska Native adults living in urban Alaska also showed that infection with *H. pylori* is associated with lower iron stores and iron deficiency. Additionally, eradication of the *H. pylori* infection without known iron supplementation was associated with an increase in serum ferritin levels and a 50% decrease in the number of persons with iron deficiency.

Our results are consistent with previous data from four large studies evaluating the effect of *H. pylori* infection on iron metabolism (7, 9,10, 26). In two studies involving over 7,000 and over 1,800 participants, there were 13.9% and 17%, respectively, lower serum ferritin levels in persons infected with *H. pylori* than in those uninfected (9, 10). A third study of almost 3,000 persons showed that both men and postmenopausal women infected with *H. pylori* had lower mean serum ferritin levels than uninfected persons (26). Finally, a survey of over 2,000 sera from Alaska Native persons found an association with *H. pylori* seropositivity and low serum ferritin levels (7). Similar to our data, three of these studies also included data showing an increase in the prevalence of iron deficiency among *H. pylori*-infected persons (7, 9, 26).

There have been four meta-analyses published in the past two years that have investigated whether *H. pylori* eradication is effective in improving iron deficiency and/or iron deficiency anemia; all of them concluded that *H. pylori* eradication improved ferritin levels and could be effective in improving anemia or iron deficiency (22–25). The studies included in these meta-analyses differ from our study in two important ways. First, these meta-analyses involved only patients with iron deficiency or iron deficiency anemia. As our study involved a secondary analysis of an investigation of *H. pylori* reinfection, participants included anyone with a documented *H. pylori* infection. Second, all of the studies in these meta-analyses were required to include iron supplementation as well as anti-*H. pylori* treatment; in our study, participants were excluded when their medical record indicated an iron supplement was prescribed. These two differences make it more difficult for our study to demonstrate a positive relationship between *H. pylori* eradication and improved iron stores when compared with these meta-analyses. However, in spite of the study design differences, after eradication of *H. pylori*, we also documented a statistically significant increase in serum ferritin levels and improvement of iron deficiency.

We know of six additional published studies that measure the effect of *H. pylori* eradication on serum ferritin levels without iron supplementation (11, 14,27–30).. In four of these six studies, authors documented an increase in serum ferritin within six months post-*H. pylori* eradication (11, 14,27, 29). Although we also saw increases in serum ferritin, it was not until two years after eradication. In one study conducted in Alaska Native children 7–11 years old

it took >14 months to see changes in iron metabolism after eradication of *H. pylori* even with iron supplementation, a finding that would be consistent with our result in adults (31). Although the actual mechanism is not known, one way *H. pylori* might negatively affect iron metabolism is from changes in iron absorption due to chronic gastritis (6, 32–34). Some studies in adults have shown that it can take many months, possibly years, to resolve gastritis after *H. pylori* eradication (35, 36). In Alaska, infection with *H. pylori* occurs in childhood and is thought to last a lifetime unless treated (7, 37–39) and two studies conducted in Alaskan adults showed a predominance of chronic gastritis caused by *H. pylori*.(15, 17) It is possible that *H. pylori* infection beginning in childhood may cause gastrointestinal changes, particularly atrophic gastritis, that take many months to heal after eradication of infection. This might contribute to the slow recovery of serum ferritin levels and delay the resolution of iron deficiency.

Because we also cultured and genotyped the *H. pylori* organisms collected as part of our original study, we were able to investigate how infection with *cagA*-positive strains of *H. pylori* affect iron stores and iron deficiency. Previous studies have shown that infection with a *cagA*-positive strain of *H. pylori* increases risk of gastric atrophy compared with a *cagA*-negative strain (40–42). Therefore, we would speculate that infection with a *cagA*-positive strain of *H. pylori* could lead to even lower serum ferritin levels and increased iron deficiency than infection with a *cagA*-negative strain. However, in this study we did not see that relationship. The prevalence of iron deficiency at enrollment was similar in persons having a *cagA*-positive or *cagA*-negative *H. pylori* infection, However, although it did not reach statistical significance, GMF was lower in persons having a *cagA*-positive infection than in those with a *cagA*-negative infection. Two additional studies in children have demonstrated an association between *CagA*-positive strains and lower levels of serum ferritin, (43, 44) however, just as in our study, neither found a statistically significant association. Additional work on this topic is warranted.

The main limitation of this study is, except for provider-prescribed iron, not collecting information on factors that could influence ferritin levels such as non-prescription iron supplementation, diet history, blood donation, use of hormonal contraception medications, or acute phase reactants. However, because testing for serum ferritin was done after study completion, we also did not inform study participants of their iron status so did not bias their iron intake in that way. To our knowledge, none of these factors potentially influencing ferritin levels affect infection with *H. pylori*. Thus, we have no reason to believe any of these would be more prominent in our *H. pylori*-infected versus non-infected persons or in the successfully treated persons we followed for 24 months. However, we cannot rule out that possibility and this does not rule out the possibility of confounders, such as diet, affecting the relationship between *H. pylori* infection and ferritin levels. We also do not have a complete understanding of the study participant's iron status or reason for iron deficiency because, except for measuring serum ferritin levels, we did not perform any other iron test such as iron-binding capacity, hemoglobin level, mean cell volume, or fecal occult blood. Finally, as we cannot ethically give antibiotics to persons without *H. pylori* infection and *H. pylori* eradication can lead to the loss of other microbes (45), we cannot know for

sure that the change in ferritin levels was completely an *H. pylori*-specific event and did not involve additional organisms.

In conclusion, the findings from this study suggest that among persons with unexplained iron deficiency, testing for *H. pylori* infection could be important. Subsequent treatment for those positive for the bacteria could be considered, as successful treatment and remaining infection free for many months may play a role in the resolution of iron deficiency.

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Table 1

Serum ferritin levels and iron deficiency at study enrollment in Alaska Native adults with and without a *Helicobacter pylori* infection; Anchorage, Alaska; September, 1998 – December, 2000.

	Geometric mean ferritin	Iron deficiency ^a
Study cohort (n=241)	42 µg/L	27 (11%)
Female (n=158)	36 µg/L	21 (13%)
<45 years (n=70)	27 µg/L	10 (14%)
45 –<55 years (n=47)	35 µg/L	8 (17%)
55 years (n=41)	60 µg/L	3 (7%)
Male (n=83)	61 µg/L	6 (7%)
<45 years (n=37)	51 µg/L	3 (8%)
45 –<55 years (n=22)	79 µg/L	2 (9%)
55 years (n=24)	63 µg/L	1 (4%)
<i>H. pylori</i> negative ^b (n=120)	50 µg/L ^c	8 (7%) ^d
<i>H. pylori</i> positive ^b (n=121)	37 µg/L ^c	19 (16%) ^d
<i>cagA</i> positive ^e (n=95)	35 µg/L ^f	15 (16%)
<i>cagA</i> negative (n=10)	60 µg/L ^f	1 (10%)

^a serum ferritin level of <12.0 µg/L

^b urea breath test

^c p = 0.04 *H. pylori* negative vs. *H. pylori* positive

^d p = 0.02 *H. pylori* negative vs. *H. pylori* positive

^e includes persons with both *cagA* positive and *cagA* negative colonies

^f p = 0.14 *cagA* positive vs. *cagA* negative

Table 2

Ferritin levels and iron deficiency in Alaska Native persons before and after eradication of *Helicobacter pylori* compared with those who failed treatment; Anchorage, Alaska; September, 1998 – December, 2000.

Characteristic	Persons successfully treated (n=80)	Persons who failed treatment (n=36)	P-value ^a
Geometric mean ferritin			
Pre-treatment	35.7 µg/L	35.1 µg/L	0.94
Post-treatment ^b	34.5 µg/L	37.1 µg/L	0.77
P-value ^c	0.63	0.59	
Iron Deficiency ^d			
Pre-treatment	14 (18%)	5 (14%)	0.63
Post-treatment ^b	14 (18%)	8 (22%)	0.55
P-value ^c	1.00	0.18	

^a persons successfully treated versus persons who failed treatment

^b two months after completion of antimicrobial therapy

^c pre- versus post-treatment

^d serum ferritin level of <12.0 µg/L

Table 3

Ferritin levels and iron deficiency in Alaska Native persons successfully treated for a *Helicobacter pylori* infection and followed for 24 months; Anchorage, Alaska; September, 1998 – December, 2002.

Visit	All participants		Participants with iron deficiency at enrollment	
	Geometric mean ferritin ^a	Iron deficiency ^b	Geometric mean ferritin	Iron deficiency
Enrollment	36.5 µg/L (n=87)	17% (15/87)	4.8µg/L (n=15)	100% (15/15)
2 month	34.3 µg/L (n=83)	17% (14/83)	6.8 µg/L (n=14)	71% (10/14)
4 month	43.2 µg/L (n=69)	13% (9/69)	7.5 µg/L (n=10)	60% (6/10)
6 month	34.0 µg/L (n=62)	21% (13/62)	7.9 µg/L (n=10)	73% (8/11)
12 month	43.7 µg/L (n=63)	17% (11/63)	9.4 µg/L (n=11)	45 % (5/11)
24 month	49.6 µg/L (n=66)	15% (10/66)	10.8 µg/L (n=11)	55% (6/11)

^aThe number of observations vary because 1) each participant did not have a serum ferritin measured at every time point and 2) participants were removed from further analysis at the time point they had an iron supplement prescription documented in their medical record.

^b serum ferritin level of <12.0 µg/L