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## GASTROENTEROLOGY & HEPATOLOGY | RESEARCH ARTICLE

# Decreased iron stores in patients with *Helicobacter pylori* infection is improved by eradication without corresponding changes in the intake of iron and vitamin C

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**Abstract:** *Background:* The relationship between *Helicobacter pylori* infection and iron metabolism has not been well studied in Japan. We examined the association of *H. pylori* infection and its eradication to iron metabolism. *Methods:* A total of 654 adults who completed a health survey in 2012 were enrolled. *H. pylori* stool antigen was tested and serum antibody titer and serum iron, ferritin and pepsinogen levels were estimated. Subjects reported on their daily intake of the diets to calculate daily intake of iron and vitamin C. Among the *H. pylori*-infected patients surveyed in 2012, 177 patients completed the same health survey in 2014. For these patients, the change of daily intake of iron and vitamin C and serum iron and ferritin levels were examined. *Results:* In 2012, 244 subjects (37.3%) were considered as infected with *H. pylori*. In male subjects aged 35–64 years, serum level of ferritin was 77.5 (SD 53.1) ng/mL in infected patients and 130.6 (114.3) ng/mL in non-infected subjects ( $p < 0.05$ ). In female subjects who received successful eradication therapy, serum level of ferritin increased from 47.9 (35.2) to 61.0 (35.4) ng/mL ( $p < 0.05$ ). The daily intake of iron and vitamin C was not significantly different between *H. pylori*-infected and non-infected subjects. Successful eradication did not change daily intake of iron and vitamin C. *Conclusions:* Lower serum levels of ferritin were observed in Japanese patients with *H. pylori* infection. Eradication of *H. pylori* increased the serum level of ferritin without corresponding changes in the intake of iron and vitamin C.

### ABOUT THE AUTHORS

This study is based on the results obtained in the Iwaki Health Promotion Project Health Survey, which has been taken place in an agricultural region of north Japan for more than 10 years. We have been published manuscripts from this survey about serum level of gastrin, gastric cancer risk screening, and accuracy of stool antigen test. We are now preparing manuscripts about “the influence of *Helicobacter pylori* infection and gastric mucosal atrophy on intestinal flora” and “long-term follow-up of serum level of pepsinogens”.

### PUBLIC INTEREST STATEMENT

*Helicobacter pylori* infection has been associated with iron deficiency anemia (IDA) in Western countries. In this study, we demonstrated that lower serum levels of ferritin were also observed in Japanese patients with *H. pylori* infection. Previous studies examined the association between *H. pylori* infection and IDA intake regardless the intake of nutrients such as iron and vitamin C. In this study, we assessed the intake of iron and vitamin C using a brief-type self-administered diet history questionnaires. As a result, eradication of *H. pylori* increased the serum level of ferritin without corresponding changes in the intake of iron and vitamin C.

**Subjects: Gastroenterology; Infectious Diseases; Clinical Nutrition**

**Keywords: *Helicobacter pylori*; eradication; vitamin C; iron store**

## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is the main cause of gastric or duodenal ulcers, gastric cancer, and atrophic gastritis (Asaka et al., 2010; Malfertheiner et al., 2017). *H. pylori* infection has also been associated with extra-gastric diseases (Malfertheiner et al., 2017). Among these, eradication of *H. pylori* has been suggested as effective for unexplained iron deficiency anemia (IDA) as well as idiopathic thrombocytopenic purpura. A previous meta-analysis had indicated that infection with *H. pylori* reduced iron stores while *H. pylori* eradication increased serum levels of ferritin in children (Muhsen & Cohen, 2008; Qu et al., 2010). A recent meta-analysis showed that *H. pylori* eradication, in addition to iron supplementation, might be beneficial in increasing ferritin and hemoglobin levels (Hudak, Jaraisy, haj, & Muhsen, 2017). At present, Western guidelines recommend *H. pylori* eradication for patients with IDA (Malfertheiner et al., 2017). However, in some countries and regions, *H. pylori* infection is not associated with IDA (Sandström, Rödger, Kaijser, & Börjesson, 2014). In Japan, the relationship between *H. pylori* infection and iron metabolism has not been fully investigated (Nakagawa et al., 2013; Sato et al., 2015). In the few studies that explored this relationship, the number of subjects was relatively small and the influence of menopause among female patients was not considered. Furthermore, in Japan, only one study examined the effect of *H. pylori* eradication on iron metabolism (Sato et al., 2015). Although there are many adult patients of refractory and/or unexplained IDA in Japan, *H. pylori* is not recommended for patients with IDA in the Japanese guidelines (Asaka et al., 2010).

Gastric acid and ascorbic acid (vitamin C) are important factors in the absorption of orally ingested iron (Betesh, Santa Ana, Cole, & Fordtran, 2015). Non-heme iron in ingested food is converted to ferrous iron by gastric acid, and absorbed in the upper jejunum (Betesh et al., 2015). In east Asian countries including Japan, most patients infected with *H. pylori* have severer atrophic gastritis, which causes reduction of gastric acid, comparing with Western infected patients. Therefore, there is a possibility that influence of *H. pylori* infection on the absorption of iron is greater in Japanese patients than Western patients. Vitamin C promotes iron absorption (Aditi & Graham, 2012). *H. pylori* infection both reduces the concentration of vitamin C in gastric fluid (Aditi & Graham, 2012), and causes gastric mucosal atrophy that results in a decrease in gastric acid concentration, which in turn will affect IDA (Betesh et al., 2015). Gastric acid secretion declines with the progression of gastric mucosal atrophy, which can be estimated by measuring the levels of serum pepsinogens (PG) (Iijima, Koike, Abe, & Shimosegawa, 2014). However, few reports have studied the relationship between the development of gastric mucosal atrophy and iron metabolism in patients with *H. pylori* infection. Moreover, few studies have examined whether or not supplementation with iron and vitamin C is affected by infection with *H. pylori* or its eradication.

In this study, we examined the association between *H. pylori* infection and iron metabolism, with consideration of the daily intake of iron and vitamin C, in a Japanese population taking a health survey to assess the possibility of *H. pylori* eradication for the improvement of iron metabolism in Japan.

## 2. Methods

### 2.1. Subjects

The subjects were 810 healthy adults (aged 21–87 years) who participated in the Iwaki Health Promotion Project Health Survey held between 26 May and 4 June 2012, in Hirosaki City located in north Japan. Subjects who had a previous history of *H. pylori* eradication therapy, successful or unsuccessful, within the prior 2 years of the study were excluded. Subjects who had undergone gastric surgery and/or receiving chemotherapy for malignant diseases were also excluded. Subjects

administering at least one of proton pump inhibitors (PPIs), iron preparation and antibiotics prior to participating in the health survey were also excluded.

Subjects reported on their daily intake of iron and vitamin C during the month prior to taking the survey, using a brief-type self-administered diet history questionnaires (BDHQ) (Kobayashi et al., 2011). The subjects also completed a survey about prior treatment and surgery, which included questions about PPI use, *H. pylori* eradication status, and gastric surgery history. Peripheral blood was collected to measure hemoglobin (Hb) and serum samples were transferred to the laboratory company on the day of collection and stored at  $-20^{\circ}\text{C}$  until assayed for two weeks. PG I and PG II levels were determined by radioimmunoassay. Serum anti-*H. pylori* IgG antibodies were measured using E-plate (Eiken Chemical Co., Ltd., Tokyo, Japan) (Kawai et al., 2002). An antibody titer of 10 U/mL or greater was considered seropositive for *H. pylori*, while a titer of less than 3 U/mL was considered seronegative. In the morning of their respective health check-ups, a stool sample was collected by each subject using a stool collection device. The stool samples were stored at  $-80^{\circ}\text{C}$  from the evening of the day of collection until assayed for a month. *H. pylori* stool antigen was measured using Testmate Pylori Antigen enzyme immunoassay (Wakamoto Pharmaceutical Co., Ltd., Kyowa Medex Co., Ltd., Tokyo, Japan) (Sato et al., 2012). Subjects with positive results from both serum antibody and stool antigen testing for *H. pylori* were considered to have *H. pylori* infection, and subjects with negative results from both tests were deemed not to have the infection. Subjects with inconsistent results between the two tests were excluded.

Among the subjects who were diagnosed to have *H. pylori* infection in the 2012 survey, 177 subjects participated in a version of the same health survey, which was conducted in 2014. Daily intake of iron and vitamin C and serum level of iron and ferritin in 2012 and 2014 were compared in 33 patients who received successful *H. pylori* eradication and also in 144 patients who did not receive eradication treatment.

This study was approved by Hirosaki University Medical Ethics Committee, and written informed consent was obtained from all participants.

## 2.2. Statistical analysis

SPSS Statistics for Windows, version 12.0 J (SPSS Inc., Chicago, IL, USA) was used for data input and analysis. The levels of serum iron, ferritin Hb were compared by analysis of covariance adjusted by daily iron intake and age. Comparison before and after eradication was performed using paired *t*-test. For the comparison of the level of ferritin, Wilcoxon signed-rank test was used. Pearson's correlation coefficient was made to assess the correlation between serum PG levels and serum levels of iron and ferritin. A *p*-value of  $<0.05$  was considered significant.

## 3. Results

### 3.1. Health survey in 2012

The characteristics of the enrolled 654 subjects are shown in Table 1. Positivity of serum IgG antibody and stool antigen test was 39.1 and 35.5% ( $\kappa = 0.82$ ), respectively. No gender-specific differences were found in the daily intake of iron and vitamin C between subjects with *H. pylori* infected and those who were not infected. Male subjects were classified into three groups by age: 16–34 years, 35–64, years, and 65 years or older. Female subjects were classified into two groups: premenopausal and postmenopausal female subjects. Levels of Hb and, serum iron and ferritin for each group are shown in Table 2. In male subjects aged 35–64 years, the mean serum level of ferritin was  $76.6 \pm 12.2$  ng/mL in infected patients and  $128.8 \pm 9.8$  ng/mL in non-infected subjects ( $p < 0.05$ ). In both premenopausal and postmenopausal females, no significant difference was observed in the serum levels of iron and ferritin between subjects with *H. pylori* infection and without infection.

**Table 1. The daily intake of iron and vitamin C in subjects according to *H. pylori*-infection status**

	Infected	Non-infected	<i>p</i>
<i>Male</i>			
Number of subjects	91	158	
Age (years)	53.8 (14.7)	55.6 (16.0)	0.360
Schooling duration			
9 / 12 / 13< (years)	14 / 61 / 16	33 / 90 / 34	0.312
Iron intake (mg/day)	7.9 (6.0–10.0)	8.0 (5.6–9.9)	0.964
Vitamin C intake (mg/day)	85.5 (52.7–121.1)	84.8 (58.5–119.2)	0.767
<i>Female</i>			
Premenopausal			
Number of subjects	47	73	
Age (years)	40.2 (8.1)	39.2 (8.8)	0.539
Schooling duration			
9 / 12 / 13< (years)	2 / 28 / 17	2 / 46 / 25	0.868
Iron intake (mg/day)	7.8 (5.9–11.8)	6.7 (5.0–9.1)	0.082
Vitamin C intake (mg/day)	93.9 (62.9–142.2)	86.3 (56.8–109.6)	0.104
Postmenopausal			
Number of subjects	106	179	
Age (years)	64.6 (9.0)	64.5 (8.5)	0.902
Schooling duration			
9 / 12 / 13< (years)	36 / 46 / 24	71 / 81 / 27	0.252
Iron intake (mg/day)	7.3 (5.4–9.3)	7.2 (5.5–8.9)	0.842
Vitamin C intake (mg/day)	83.3 (49.5–119.0)	82.9 (56.2–115.4)	0.895

Notes: Age are expressed as mean with SD in parentheses. Daily intake of iron and vitamin C are expressed as median (interquartile range).

### 3.2. Follow-up observation

There were 177 patients who were infected with *H. pylori* in the 2012 survey and participated in the same health survey in 2014. *H. pylori* was eradicated in eight male subjects and 25 female subjects. There were also 63 male subjects and 81 female subjects who did not receive eradication therapy after the survey of 2012. The daily intake of iron and vitamin C was unchanged among male and female subjects regardless eradication of *H. pylori* (Figure 1(A)). The change of Hb, serum level of iron and ferritin in female subjects are shown in Figure 1(B). In 25 female subjects, serum level of ferritin was  $47.9 \pm 35.2$  ng/mL in 2012 and significantly increased to  $61.0 \pm 35.4$  ng/mL in 2014 ( $p = 0.018$ ). However, in 81 female subjects who did not receive eradication, serum level of ferritin did not change significantly ( $69.4 \pm 55.0$  ng/mL in 2012 and  $63.0 \pm 57.6$  ng/mL in 2014). Hb and serum levels of iron were not significantly changed in both eradicated and non-eradicated subjects. On the other hand, in eight male subjects who received successful eradication, no significant change was observed. Hb was  $14.3 \pm 1.2$  g/dL in 2012 and  $14.1 \pm 1.9$  g/dL in 2014; serum level of iron was  $97.0 \pm 33.5$  µg/dL in 2012 and  $92.6 \pm 36.2$  µg/dL in 2014; and serum level of ferritin was  $207.7 \pm 172.5$  ng/mL in 2012 and  $222.1 \pm 305.1$  ng/mL in 2014.

### 3.3. Correlation of PG levels with iron and ferritin

In patients with *H. pylori* infection, the correlation between serum levels of PGs and of iron and ferritin were calculated. Lower PG I and PG I/II ratio are associated with severer atrophic gastritis while higher level of PG II is associated with severer gastric mucosal inflammation. However, no significant correlation was found between PG levels and iron or ferritin among men and both premenopausal and postmenopausal women (Table 3).

**Table 2. The serum levels of Hb, iron and ferritin in subjects infected and non-infected with *H. pylori***

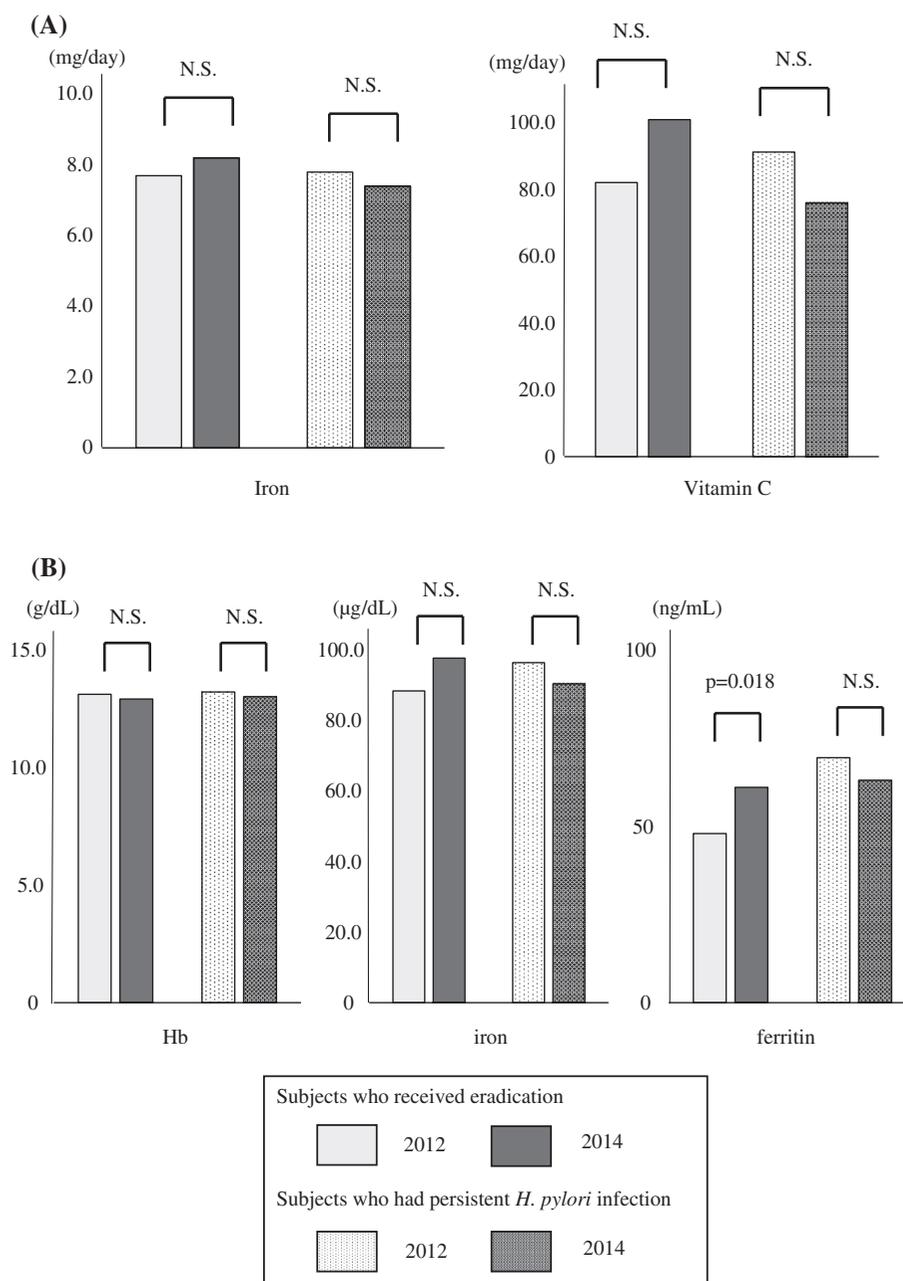
	<i>H. pylori</i> -infected	Non-infected	<i>p</i>
<i>Male</i>			
16–34 years old	<i>n</i> = 13	<i>n</i> = 23	
Hb (g/dL)	13.4 (1.0)	13.9 (1.4)	0.352
Serum iron (µg/dL)	113.4 (34.1)	103.1 (29.7)	0.347
Serum ferritin (ng/mL)	109.0 (99.0)	89.4 (94.7)	0.579
35–64 years old	<i>n</i> = 57	<i>n</i> = 89	
Hb (g/dl)	13.6 (1.5)	14.0 (1.4)	0.065
Serum iron (µg/dL)	107.8 (47.6)	105.6 (39.5)	0.763
Serum ferritin (ng/mL)	77.5 (53.1)	130.6 (114.3)	0.001
65 years or older	<i>n</i> = 21	<i>n</i> = 46	
Hb (g/dL)	13.7 (1.7)	13.7 (1.6)	0.987
Serum iron (µg/dL)	104.8 (41.3)	110.0 (44.0)	0.641
Serum ferritin (ng/mL)	113.5 (98.0)	112.7 (94.1)	0.973
<i>Female</i>			
Premenopausal	<i>n</i> = 47	<i>n</i> = 73	
Hb (g/dL)	13.8 (1.4)	13.8 (1.6)	0.913
Serum iron (µg/dL)	104.4 (33.1)	108.0 (44.3)	0.639
Serum ferritin (ng/mL)	110.0 (106.0)	141.4 (164.7)	0.263
Postmenopausal	<i>n</i> = 106	<i>n</i> = 179	
Hb (g/dL)	13.9 (1.4)	13.9 (1.6)	0.958
Serum iron (µg/dL)	98.0 (33.3)	107.3 (42.2)	0.054
Serum ferritin (ng/mL)	98.7 (78.3)	108.1 (94.9)	0.383

Note: Data are expressed as mean (SD).

**Table 3. Correlation between serum PGs and iron and ferritin in *H. pylori*-infected subjects**

	Iron		Ferritin	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
<i>Male (n = 91)</i>				
PG I	-0.192	0.068	0.072	0.496
PG II	-0.062	0.556	0.025	0.815
PG I/II	-0.080	0.451	0.016	0.879
<i>Female</i>				
Premenopausal ( <i>n</i> = 46)				
PG I	0.137	0.365	0.202	0.179
PG II	-0.141	0.351	0.255	0.087
PG I/II	0.288	0.052	-0.242	0.105
Postmenopausal ( <i>n</i> = 106)				
PG I	-0.092	0.350	-0.054	0.583
PG II	-0.027	0.783	-0.075	0.448
PG I/II	-0.028	0.773	0.071	0.471

**Figure 1. (A) Change of daily intake of iron and vitamin C and (B) change of Hb, serum level of iron and ferritin in female subjects between 2012 and 2014.**



#### 4. Discussion

To date, the relationship between *H. pylori* infection and iron metabolism has not been fully investigated in Asian populations, particularly for adults (Hudak et al., 2017). Only a few cross-sectional studies conducted in Japan and Taiwan have been reported in the literature (Nakagawa et al., 2013; Sato et al., 2015; Shih et al., 2013). This is the first study to demonstrate the effects of eradication of *H. pylori* infection on iron metabolism in Asian adults in consideration of the daily intake of iron and vitamin C.

Several studies in animal models have shown that *H. pylori* infection induced a decrease in serum level of ferritin, red blood cell count, and Hb (Burns et al., 2015; Sandström et al., 2014). In humans, a strong association between *H. pylori* infection and IDA has been shown in children (Sandström et al., 2014). In adults, many studies have implicated *H. pylori* infection with a decrease in iron levels

(Betesh et al., 2015; Hudak et al., 2017). In Japan, however, only a few studies have examined the relationship between *H. pylori* infection and iron metabolism in adults. A previous cross-sectional analysis in Japan showed lower serum ferritin levels in subjects with *H. pylori*-positive results of the urea breath test, particularly in patients aged greater than 50 years (Nakagawa et al., 2013). Another study showed decreased ferritin levels among patients with gastric hyperplastic polyp or nodular gastritis (Sato et al., 2015). In accordance with previous findings, levels of ferritin were lower in patients infected with *H. pylori* in this study. Although we grouped female subjects premenopausal and postmenopausal female subjects separately, serum levels of iron, ferritin and Hb were not lower in these patients with *H. pylori* infection. These results suggest that *H. pylori* infection might reduce iron stores in adults, but the development of IDA is not frequent.

Chronic gastritis induced by *H. pylori* infection has been suggested as one of the causes of IDA. *H. pylori* infection increases the serum level of hepcidin, resulting in the reduction of iron absorption (Azab & Esh, 2013). In a Japanese study, the serum level of iron was negatively correlated with the serum level of prohepcidin in patients with nodular gastritis (Sato et al., 2015). Additionally, *H. pylori* neutrophil-activating protein (HP-NAP) is known as an iron storage protein (Yokoyama & Fujii, 2014). Increases in the uptake of  $\text{Fe}^{3+}$  and  $\text{Fe}^{2+}$  by *H. pylori* might contribute to lower iron stores. Therefore, the severity of gastritis would be associated with iron storage in patients with *H. pylori* infection. The serum level of PG II is associated with the severity of gastritis and increased in patients with nodular gastritis (Kitamura et al., 2013, 2015). However, in this study, the serum level of PG II was not significantly correlated with the serum levels of iron and ferritin. Another possible cause of reduced iron stores is a reduction of gastric acid secretion. Gastric acid plays an important role in the absorption of iron. In Japanese adult patients with *H. pylori* infection, atrophic gastritis extends to corpus mucosa causing reduction of gastric acid secretion. When gastric mucosal atrophy becomes severe, the PG I and PG I/II ratios are decreased (Nakagawa et al., 2013). Thus, we assessed for a correlation between PG I and PG I/II ratios and the serum levels of iron and ferritin. However, no significant correlation was found. However, even in these patients, recovery of gastric acid is observed after successful eradication of *H. pylori* (Iijima et al., 2004). Furthermore, children infected with *H. pylori*, the development of IDA is associated with hypochlorhydria (Harris et al., 2013) and increased expression of interleukin-1 $\beta$ , which reduces acid secretion (Serrano, Villagrán, Toledo, Crabtree, & Harris, 2016). Although serum levels of PGs are not indicative of reduced iron store, eradication of *H. pylori* and following recovery of acid secretion would play a role in the increase of iron store.

In previous studies, the association of *H. pylori* infection and iron metabolism has been studied without consideration of the daily intake of iron and vitamin C. Although lower levels of serum ferritin were observed among subjects with *H. pylori* infection in this study, this did not correspond to a decrease in their daily intake of iron and vitamin C. A previous study showed that the daily intake of vitamin C was lower in patients with *H. pylori* infection (Henry, Carswell, Wirz, Fyffe, & McColl, 2015). However, the number of subjects was smaller than that in our study, and the subjects followed a Western diet. The amount of vegetables included in the Japanese diet is considerably higher than that in Western diet. This difference in diet might be associated with a normal or higher intake of vitamin C among subjects with *H. pylori* infection in our study. The plasma concentration of vitamin C was lower in patients with *H. pylori*-related gastric diseases (Henry et al., 2015). Even though the intake of vitamin C was not decreased, the level of plasma vitamin C might be reduced in patients with *H. pylori* infection, and could play a role in the reduction of iron stores.

We were able to investigate the association of *H. pylori* infection and its eradication to iron metabolism in consideration of related nutritional intake. The daily intake of iron and vitamin C was not different between patients with *H. pylori* infection and non-infected subjects. In female patients, the serum level of ferritin was significantly increased after eradication of *H. pylori*, without any changes in their daily intake of iron and vitamin C. These results indicate that an increase in iron stores by the eradication of *H. pylori* infection was not the results of an alteration in the daily intake of iron and vitamin C.

There are several limitations in this study. First, the subjects of this study did not undergo upper gastrointestinal endoscopy, because they were recruited as participants of a health survey. Therefore, we could not exclude gastrointestinal diseases, which can cause hemorrhage. For patients with peptic ulcers or hemorrhagic gastritis, eradication of *H. pylori* cures such diseases causing the increase iron stores. Second, patients with IDA are rarely included as participants in health surveys in Japan. Thus, we cannot determine from this study whether eradication of *H. pylori* infection is an effective treatment for Japanese patients with IDA. Third, follow-up study was observation but not interventional. Furthermore, most patients received eradication therapy 3 to 6 months after the survey in 2012 and the patients were followed 18–21 months after the successful eradication. Therefore, we cannot determine the adequate duration to follow iron stores after the eradication of *H. pylori*.

In conclusion, *H. pylori* infection is associated with decreased iron storage, and the benefits of its eradication include improvements in the iron stores of Japanese adults. The intake of iron and vitamin C is not be affected by infection with *H. pylori* or its eradication. Further study is required to elucidate whether eradication of *H. pylori* would be effective for adult Japanese patients with unexplained IDA as recommended by Western guidelines.

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#### Competing interests

The authors declare no competing interest.

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