HELICOBACTER PYLORI

Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with *Helicobacter pylori* gastritis and associated iron deficiency anaemia

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Background: Seroepidemiological and clinical studies suggest that *Helicobacter pylori* may cause iron deficiency anaemia (IDA) in the absence of peptic lesions by undefined mechanisms, which still remain to be fully elucidated. Gastric acidity and ascorbic acid (AA) promote iron absorption. AA is lowered in the presence of *H pylori* infection. *H pylori* can cause atrophic body gastritis with achlorhydria, decreased iron absorption, and consequent IDA. Whether alterations in intragastric acidity and AA concentrations play a role in IDA developing in patients with *H pylori* gastritis remains to be determined.

Aim: To evaluate gastric juice pH and gastric juice and plasma AA in patients with *H pylori* infection and unexplained IDA, compared with controls with IDA and a healthy stomach or with controls with *H pylori* infection and no IDA.

Results: Patients with IDA and *H pylori* gastritis were characterised by concomitant increased intragastric pH (median value 7) and decreased intragastric AA (median value 4.4 µg/ml) compared with controls with a healthy stomach (median pH 2; median intragastric AA 17.5 µg/ml) and with *H pylori* positive controls without IDA (median pH 2.1; median intragastric AA 7.06 µg/ml). Intragastric AA was inversely related to pH ($r=-0.40$, $p=0.0059$) and corporal degree of gastritis ($r=-0.53$, $p=0.0039$). Plasma AA concentrations were lower in all infected groups than in healthy controls.

Conclusions: Patients with unexplained IDA and *H pylori* gastritis present concomitant changes in intragastric pH and AA that may justify impaired alimentary iron absorption and consequent IDA.

Recently, several seroepidemiological studies have suggested an association between iron deficiency anaemia (IDA) and *Helicobacter pylori* infection,^{1–4} and improvement in IDA after *H pylori* eradication has been demonstrated in case series and in clinical trials in both children and adults with otherwise unexplained IDA.^{5–8} It has also been reported that up to 18% of patients with refractory IDA and no gastrointestinal symptoms have *H pylori* gastritis as the only associated cause of their anaemia.⁹

The possible mechanisms by which *H pylori* is involved in the development of IDA, in the absence of bleeding lesions, still remains to be elucidated, and given the high prevalence of the infection it is still unclear why only some patients with *H pylori* develop IDA.^{10–11} The possibility that some *H pylori* strains have a specific ability to interfere with iron metabolism seems unlikely as neither virulence factors such as Cag-A⁺ nor mutations in the bacterial genes involved in iron uptake have been demonstrated to be associated with IDA.¹²

We have recently shown that extension of gastritis to the corporal mucosa is observed in a higher percentage of patients with *H pylori* infection and IDA compared with non-anaemic infected controls, and that this corporal involvement results in an increase in intragastric pH.¹³ *H pylori* infection is also involved in the development of atrophic body gastritis¹⁴ that can in turn cause decreased gastric acid secretion and IDA.^{15–16}

Some 80% of dietary iron in Western countries is in the non-haemic ferric form, and it needs an acidic intragastric pH to be reduced to ferrous and be absorbed.¹⁷ This reaction is promoted by ascorbic acid (AA) which is therefore considered the most potent enhancer of iron absorption.^{18–19} AA is actively secreted from plasma to the gastric juice^{20–21} and is reversibly depleted in the gastric juice of patients with *H pylori* gastritis.^{22–24} However, the possibility that alterations in gastric acidity and in the concentration of AA in the gastric juice

might link *H pylori* infection with the development of IDA has not yet been investigated.

Therefore, the hypothesis tested in the present study was whether pH values as well as gastric juice and plasma AA concentrations in patients with IDA associated with *H pylori* infection differ from those of *H pylori* negative IDA patients and from those *H pylori* positive patients without IDA.

PATIENTS AND METHODS

Study design/patients

Between January 2000 and April 2001, patients with IDA referred to our gastroenterology department from the haematology department were studied for evaluation of their anaemia, as previously reported.^{3–9} IDA was defined as a haemoglobin concentration <14 g/dl for males and <12 g/dl for females, in the presence of ferritin <30 µg/l and mean corpuscular volume <80 fl. As reported elsewhere,^{5–13} patients presenting manifest causes of blood loss, such as active gastrointestinal haemorrhage, epistaxis, menometorrhagia or heavy menstrual loss, or any other non-gastrointestinal disease likely to cause IDA were not referred to us from the haematology department. All patients underwent colonoscopy to exclude bleeding sites. A positive colonoscopy or refusal to undergo the examination were exclusion criteria for the present study. All patients completed a detailed questionnaire regarding diet and habits, as previously published.^{5–9} Also excluded from the study protocol were patients with previous gastric surgery, and those who previously received anti-*H2 pylori* treatment or antisecretory drugs. Alcoholism, drug

Abbreviations: IDA, iron deficiency anaemia; AA, ascorbic acid; JAA, gastric juice ascorbic acid; PAA, plasma ascorbic acid.

Table 1 Characteristics of patients and controls in the three groups

	Iron deficiency anaemia	<i>H. pylori</i> infection
Group A patients	Positive	Positive
Group B controls	Positive	Negative
Group C controls	Negative	Positive

addiction, anorexia, and vegetarian or iron poor diet were also considered as causes for exclusion. Withdrawal from oral iron therapy, vitamin C supplementation, or any other over the counter medications containing iron or AA for at least four weeks before the examinations was a criterion for eligibility.

According to these strict criteria, we initially enrolled 52 eligible IDA patients. These patients underwent gastroscopy with multiple biopsies, as described below. We excluded from the present study however four patients in whom duodenal histology revealed coeliac disease, one with gastric cancer and four with peptic ulcer, as these findings were likely to be the cause of their IDA. The remaining 43 patients with unexplained IDA were subsequently assigned to the following groups according to their gastric histology.

Group A: IDA positive/*H. pylori* positive patients

This group comprised 30 patients (24 females and six males; median age 47 years, range 19–66) with a diagnosis of *H. pylori* associated gastritis and no other likely causes of IDA, as described elsewhere.^{5 9 13}

Group B: IDA positive/*H. pylori* negative controls

Thirteen (12 females and one male; median age 37 years; range 18–60) patients presenting with a normal gastric histology, with no other likely causes of IDA, were included as the first control group.

Group C: IDA negative/*H. pylori* positive controls

During the same time, we selected among outpatients undergoing gastroscopy in our department for evaluation of dyspepsia, those negative for macroscopic lesions (ulcer, cancer) but positive at histology for *H. pylori* gastritis. Exclusion criteria for this group included: IDA, peptic ulcer (present or past), malignancies, moderate to severe oesophagitis (endoscopic diagnosis), histological diagnosis of coeliac disease, previous gastric surgery, previous anti-*H. pylori* treatment, and previous or current use of antisecretory drugs, iron, or AA acid preparations.¹³

Eleven patients (nine females and two males; median age 48 years, range 19–67) with *H. pylori* positive chronic superficial gastritis were included in this second control group.

The main characteristics of the three groups are shown in table 1.

A subgroup of patients in group A was re-evaluated six months after appropriate eradication therapy. All patients and controls gave written informed consent; the local ethics committee approved the study protocol.

Methods

Gastroscopy

All patients and controls underwent gastroscopy at 9:00 am after an overnight fast. All individuals were sedated before the procedure using intravenous midazolam (2.5–10 mg). Endoscopists were unaware of the presence/absence of IDA. Three biopsy samples from the antrum (smaller and greater curve, anterior or posterior walls) and three from the midbody along the greater curve were taken using a standard biopsy forceps,

as reported elsewhere.^{14 25} Two duodenal biopsies (II portion) were also taken to exclude coeliac disease.

Histological procedures

All gastric biopsies were immediately fixed in Bouin's solution for 4–8 hours at room temperature, rinsed in 0.1 M phosphate buffered saline solution, pH 7.4, and embedded in wax. Serial 5 µm thick sections of gastric mucosa, perpendicular to the mucosal surface, were stained with haematoxylin-eosin for conventional histopathological examination. *H. pylori* infection was evaluated with Giemsa staining. Assessment of the degree of gastritis was performed according to the updated Sydney system.²⁶ The following scores were assigned to each graded variable: 0=absence, 1=mild, 2=moderate, and 3=severe degree. Atrophy of the fundic mucosa was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands.²⁵ The diagnosis of fundic atrophy was confirmed by fasting hypergastrinaemia and reduced pepsinogen I levels. Atrophy of the antral mucosa was defined as focal or complete replacement of antral glands by intestinal metaplastic epithelium.

Gastric juice pH determination and storage

At gastroscopy, immediately after passing the endoscope into the stomach, a sterile Teflon catheter was passed through the biopsy channel, and starting from the midbody along the greater curve approximately 5 ml of gastric juice were aspirated and collected in a sterile tube containing EDTA. Gastric juice pH values were immediately measured with a glass electrode pH meter (HI9321; Hanna Instruments, Padova, Italy), as described elsewhere.¹³ Two aliquots (0.5 ml) of gastric juice were then stored at –80°C, each with 25 µg of hypoxanthine (reference standard for high performance liquid chromatography) and 1.5 ml of 2% metaphosphoric acid.

Plasma collection and storage

Immediately prior to the time of gastroscopy, 10 ml of plasma were obtained from each patient and collected in a sterile tube with EDTA. Two aliquots of 0.5 ml were treated and stored as reported above for gastric juice.

Ascorbic acid determination

AA was measured in plasma and gastric juice samples, treated as described above, by a Shimadzu liquid chromatograph on an analytical Supelcosil LC-18-DB column (24 cm×4.6 mm, 5 µm, Supelco) plus guard column, by using in line both a photodiode array detector set at 265 nm and an ESA CoulArray (oxidation potential +500 mV). All determinations were carried out within seven days of collection. Samples were centrifuged for 10 minutes and 20 µl of the supernatant injected into the high performance liquid chromatography system. AA was quantitated by comparison of areas with those of authentic standards, including the reference standard (hypoxanthine), as described elsewhere.²⁷ The mobile phase consisted of 0.02 M NaH₂PO₄, 0.06% (w/v) metaphosphoric acid, and 0.4% (v/v) CH₃CN (pH 3.0); flow 0.8 ml/min. The limit of calculation for the assay used to allow statistical analyses and ratio calculation when the compound was not detectable was 0.1 µg/ml. Normal values for plasma AA in 50 healthy individuals (31 females and 19 males, median age 32 years, range 18–55) in our laboratory were 7.5–30 µg/ml.

Statistics

Continuous data are expressed as median (range) and were evaluated by appropriate statistical tests (*t* test or Mann Whitney U test). Proportions were compared by means of Fisher's exact test. Correlations were evaluated using the Spearman rank correlation test. A value of *p*<0.05 was considered statistically significant.

Figure 1 (A) Intragastric pH values in patients with *Helicobacter pylori* infection and iron deficiency anaemia (group A), controls without *H. pylori* infection and with iron deficiency anaemia (group B), and controls with *H. pylori* infection and no iron deficiency anaemia (group C). Data expressed as box (95% confidence intervals) and whiskers (range). Bars indicate median values. The broken line indicates the pH limit of 3, which is critical for iron stability. *** $p < 0.0001$ compared with groups B and C. (B) Gastric juice ascorbic acid (JAA) concentrations in the three groups. ** $p < 0.005$ versus groups B and C.

RESULTS

Extension and degree of gastritis

Thirteen (43 %) of 30 patients with *H. pylori* infection and IDA (group A) had atrophic gastritis in the fundic mucosa, nine (69%) also had atrophic changes in the antrum, while the remaining four patients had an antral chronic superficial gastritis. All but one of the other 17 patients (94%) had a chronic superficial gastritis of the antral and corporal mucosa (pangastritis). In contrast, none of the *H. pylori* positive controls (group C) had atrophic changes in the antral or fundic mucosa, and only five (5/11, 45%) had gastritis extended to the corporal mucosa, the others presenting with an antrum restricted gastritis ($p = 0.0069$). The median (range) values of the sum of all Sydney score variables for the antral and body mucosa were, respectively: 3 (0–5) and 7 (2–12) in group A, and 3 (1–6) and 1 (0–4) in group C. While there were no differences between groups regarding antral scores, the gastric body score was significantly higher in group A compared with group C ($p < 0.0001$).

Intragastric pH

Median intragastric pH values were 7 (1.9–8.2) in group A, 2 (1.2–7) in group B, and 2.1 (1.3–5) in group C (fig 1A). Group A was found to be significantly different compared with groups B and C ($p < 0.0001$) whereas no difference was found between the two control groups ($p = 0.8$).

Gastric juice ascorbic acid (JAA)

As shown in fig 1B, gastric juice ascorbic acid (JAA) concentration was significantly lower in group A (median 4.4 µg/ml, range 0.1–23.4) compared with group B (median 17.5

Figure 2 Gastric juice/plasma ascorbic acid (JAA/PAA) ratio in patients with *Helicobacter pylori* infection and iron deficiency anaemia (group A), controls without *H. pylori* infection and with iron deficiency anaemia (group B), and controls with *H. pylori* infection and no iron deficiency anaemia (group C). Filled circles indicate ratio values < 1 ; open circles indicate values ≥ 1 . The limit of 1 is also indicated by the broken line. Ratio values > 2 are highlighted and indicated by an arrow; * $p < 0.05$ versus groups B and C.

µg/ml, range 0.34–44.8; $p = 0.0033$) and group C (median 7.06 µg/ml, range 4.2–28; $p = 0.029$). The difference between the two control groups was not significant ($p = 0.09$).

Plasma ascorbic acid (PAA)

Median plasma ascorbic acid (PAA) concentrations were: 11 µg/ml (range 5.9–21.4), 19 µg/ml (range 5.3–49), and 8.28 µg/ml (range 2.69–21.4) in groups A, B, and C, respectively. Patients with IDA and *H. pylori* (group A) had significantly lower PAA concentrations compared with group B ($p = 0.002$). Group C controls also had lower, yet not significantly different ($p = 0.09$), concentrations compared with healthy controls. Smoking status did not significantly affect PAA concentrations. In fact, the median PAA concentration was 14.5 µg/ml (range 5.5–32.4) in smokers and 10.5 µg/ml (range 5.7–75) in non-smokers ($p = 0.9$).

Gastric juice/plasma AA ratio

The distribution of the juice/plasma AA ratio values of the three groups is shown in fig 2. The median juice/plasma AA ratio was 0.38 (0.001–1.09) in group A, being significantly lower compared with group B (median 0.6, range 0.06–3.25; $p = 0.026$) and group C (median 0.6, range 0.17–4.6; $p = 0.029$). Median ratio values did not differ between the two control groups. Moreover, only one of 30 patients in group A (3.3%) had a ratio > 1 (fig 2) compared with six of 13 patients in group B (46%; $p = 0.0017$) and four of 11 in group C (36%; $p = 0.0138$).

Relationship between severity and degree of gastritis, intragastric pH, and gastric juice AA

Gastric juice AA concentration was negatively correlated (Spearman $r = -0.40$, 95% confidence interval -0.62 to -0.11 ; $p = 0.0059$) with intragastric pH. In patients with gastritis (groups A and C) there was a significant negative correlation between the sum of the Sydney score variables in the corporal mucosa and JAA (Spearman $r = -0.53$; $p = 0.0039$). In contrast, a correlation was not found between the sum of Sydney score variables in the antrum and JAA concentrations ($p = 0.44$).

Table 2 Effect of *Helicobacter pylori* eradication in subgroups of patients with iron deficiency anaemia with or without gastric body atrophy

	Before therapy	6 months after therapy
No gastric body atrophy (n=5)		
pH	4 (1.93–7)	2 (1.2–3.6)
JAA (µg/ml)	9.02 (1.29–16.6)	14.48 (4–31.9)
PAA (µg/ml)	18.1 (14.8–20.7)	9 (7.4–32.2)
JAA/PAA	0.45 (0.07–0.85)	1.17 (0.29–1.99)
Gastric body atrophy (n=6)		
pH	7 (6.5–8.2)	6 (3–8.6)
JAA (µg/ml)	3.6 (0.1–11.1)	0.78 (0.1–8.6)
PAA (µg/ml)	7 (6.5–8.2)	6 (3–8.6)
JAA/PAA	0.01 (0.01–0.64)	0.01 (0.007–0.7)

Data are expressed as median (range). No statistically significant differences were observed in the two groups after therapy. JAA, gastric juice ascorbic acid; PAA, plasma ascorbic acid.

Among group A patients, 13 with atrophic changes in the fundic mucosa differed significantly from those without in terms of intragastric pH (median 7 v 4.8; $p=0.0317$), JAA concentrations (median 0.38 µg/ml v 5.6; $p=0.028$), and JAA/PAA ratio (median 0.043 v 0.49; $p=0.004$). The 17 patients in group A with no atrophic changes in the fundic mucosa differed significantly from the *H pylori* positive controls in terms of intragastric pH (median 4.8 v 2.1; $p=0.0028$) but not in terms of JAA concentrations (median 5.6 µg/ml v 7.06; $p=0.18$). No relationship was observed between age of the patient and gastric juice ($p=0.79$) or plasma ($p=0.69$) AA levels.

Effect of eradication in IDA patients

Seven of 11 (63%) treated group A patients were successfully cured six months after therapy. The effect of therapy on pH and JAA values was related to the presence of fundic atrophy. In fact, irrespective of the outcome of therapy, a further decrease in JAA concentrations (median from 3.6 to 0.78 µg/ml) was observed in six patients who had fundic atrophy whereas treatment had no effect on intragastric pH or JAA/PAA ratio. In contrast, in the subgroup of five patients with *H pylori* infection and IDA without fundic atrophy, therapy led to a decrease in pH values and to an increase in JAA levels (median from 9.02 to 14.48 µg/ml) and in the JAA/PAA ratio, as detailed in table 2. However, statistical evaluation of these data did not appear to be meaningful on account of the small sample size.

DISCUSSION

The main finding of our study was that patients with *H pylori* gastritis, associated with otherwise unexplained IDA, presented with a concomitant increase in intragastric pH and a decrease in gastric juice AA.

Patients with IDA associated with *H pylori* gastritis showed an increase in intragastric pH, presenting with a median value of pH >3, a value known to be critical in the process of iron absorption.²⁸ Moreover, patients with *H pylori* gastritis and IDA had significant lowering of JAA concentrations compared with both healthy and *H pylori* positive controls. These findings suggest that these two physiological mechanisms, which are necessary for alimentary iron to be absorbed in the duodenal mucosa, are impaired in patients with *H pylori* gastritis and IDA.

It is well known that *H pylori* infection when affecting the gastric body, irrespective of the presence of fundic atrophy, induces gastric acid hyposecretion.²⁹ It has also been clearly demonstrated that *H pylori* gastritis induces lowering of intragastric AA concentrations and that *H pylori* eradication can reverse this negative effect.^{22–24 30 31} However, all of these previous studies focused on features different from ours, and

indeed the possibility that such alterations in intragastric pH and AA might interfere with the process of iron absorption has not been considered until now.

Intragastric acidity is a key factor in the process of iron absorption^{17–19 28} but AA is also essential for alimentary iron absorption. It is worthwhile stressing that this has given rise to the intriguing hypothesis that iron, like vitamin B12, has a gastric intrinsic factor (that is, AA) that aids absorption.¹⁹ In fact, AA not only converts ferric iron to the ferrous form, which maintains solubility at the alkaline pH of the duodenum, but also forms chelates with ferric chloride which is also stable at a pH >3.²⁸

The possibility that an increased intragastric pH impairs alimentary iron absorption and determines IDA has been considered in the course of antisecretory therapy,³² and the investigation of Zollinger-Ellison syndrome patients treated with proton pump inhibitors for long periods failed to reveal any significant changes in iron homeostasis.³³ However, it is worthwhile noting that the model of hypochlorhydria induced by antisecretory drugs is different from that due to fundic gastritis. In fact, intragastric pH was still <3 for more than one third of the day during a 24 hour monitoring period in patients treated with antisecretory drugs at standard doses.³⁴ It has also been demonstrated that pharmacologically induced hypochlorhydria results in depletion of gastric juice vitamin C concentration in *H pylori* positive, but not *H pylori* negative, subjects.³⁵

Previous studies have suggested that otherwise unexplained IDA can be caused by hypo/achlorhydria due to atrophic body gastritis.^{36 37} However, the possibility that similar mechanisms lead to IDA in some *H pylori* infected subjects without atrophic gastritis is far less commonly considered.

In the present study, we linked for the first time alterations in gastric acidity and AA in *H pylori* gastritis with the presence of IDA, demonstrating that patients with unexplained IDA associated with *H pylori* gastritis are characterised by a concomitant increase in intragastric pH and a lowering of intragastric concentrations of AA. These alterations are consequent to the peculiar pattern of gastritis observed in these patients. In fact, a significant percentage (43%) of our *H pylori* positive IDA patients presented atrophic changes in the gastric body, and the remaining had a chronic superficial gastritis extended to the fundic mucosa, in contrast with *H pylori* positive controls.

Moreover, in our study, we observed an inverse correlation between intragastric pH and JAA levels (fig 2) and, while we failed to find any correlation between JAA and the degree of gastritis in the antral mucosa, as reported by others,³⁰ JAA concentrations were lower in patients with more severe damage in the gastric body. This finding is in agreement with those of others^{23 24} and suggests that increased intragastric pH may be more important than the polymorphonuclear leucocyte oxidative burst caused by the inflammatory activity of *H pylori* gastritis³⁰ in determining JAA depletion. However, depletion of JAA in patients with *H pylori* gastritis may also be due to its consumption by scavenging reactive oxygen species produced by mucosal inflammation and by preventing the formation of N-nitroso compounds.³⁸

Another interesting result obtained in the present study was the finding of lower plasma AA concentrations in all groups of patients with gastritis compared with controls with a healthy stomach. This observation is in agreement with a recent study carried out on a large number of individuals with/without *H pylori* infection that suggested impaired systemic bioavailability of AA in patients with *H pylori*, independent of diet.³⁹ Alternatively, the lower plasma AA concentrations in patients with gastritis may be the consequence of increased active secretion of AA from plasma to the gastric juice in the attempt to restore the physiological ratio between the two compartments.

If *H pylori* gastritis affects gastric acid secretion and AA stability, eradication should lead both to reversal of these alterations and to recovery from IDA. Unfortunately, in the present study, evaluations were not repeated in all patients after treatment to establish the effect of possible recovery of acid secretion and AA on IDA. However, we evaluated the effect of *H pylori* cure on intragastric pH and JAA concentrations in a subgroup of patients with IDA and *H pylori* gastritis. The effect of the cure in these patients was related to the presence of atrophic body gastritis before therapy. In fact, after treatment, the subgroup of patients with chronic superficial *H pylori* gastritis showed a decrease in intragastric pH and increase in JAA as well as in the juice/plasma ratio. In contrast, as antimicrobial therapy had no effect on gastric atrophy, as reported elsewhere,⁴⁰ we observed no changes in intragastric pH or JAA after treatment in the subgroup of patients with atrophic body gastritis. We also observed that while the subgroup of patients with atrophic body gastritis had significantly lower levels of JAA compared with *H pylori* positive controls, this difference was not significant for the subgroup of patients with chronic superficial gastritis. This unexpected result may have two possible explanations: firstly, it is possible that in patients with a chronic superficial gastritis the observed alteration of intragastric acidity plays a major role in affecting iron availability, even in the presence of JAA concentrations similar to those of *H pylori* positive controls; and secondly, it is possible that the difference between chronic superficial gastritis patients and controls in terms of JAA concentrations is small and therefore a larger number of patients are needed for it to be detectable.

It is also possible to speculate that looking at the association between IDA and gastritis from another viewpoint, gastric damage could be a consequence of IDA, as occurs in mouth and tongue epithelium and as suggested in the very early literature,⁴¹ and not therefore the cause of the anaemia. However, we consider this unlikely as the association reported by others¹⁻⁴ and us¹³ is not between IDA and non-specific gastritis, eventually caused by nutritional deficiency, but between IDA and *H pylori* infection and the related gastritis, as also suggested by reversal of IDA after *H pylori* cure.³⁻⁶

A possible limitation of the present study is the poor repeatability of the gastric juice pH measurements performed during gastroscopy. However, while a formal evaluation both of basal and pentagastrin stimulated gastric acid secretion may have been more correct to assess the amount of gastric acid secreted, the gastric pH may per se indicate whether the gastric juice affects the stability of ferric iron, as suggested by in vitro studies.²⁸

In conclusion, our findings indicate that patients with IDA associated with *H pylori* gastritis present with alterations in the intragastric milieu, such as increased pH and decreased AA. The concomitant occurrence of these two alterations may plausibly account for impaired iron absorption and consequent IDA in these patients.

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