

**Helicobacter pylori** infection as a cause of iron deficiency anaemia of unknown origin

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**Abstract**

**AIM:** To assess the aetiological role of *Helicobacter pylori* (**H. pylori**) infection in adult patients with iron refractory or iron-dependent anaemia of previously unknown origin.

**METHODS:** Consecutive patients with chronic iron deficient anaemia (IDA) with **H. pylori** infection and a negative standard work-up were prospectively evaluated. All of them had either iron refractoriness or iron dependency. Response to **H. pylori** eradication was assessed at 6 and 12 mo from follow-up. **H. pylori** infection was considered to be the cause of the anaemia when a complete anaemia resolution without iron supplements was observed after eradication.

**RESULTS:** **H. pylori** was eradicated in 88 of the 89 patients. In the non-eradiated patient the four eradicating regimens failed. There were violations of protocol in 4 patients, for whom it was not possible to ascertain the cause of the anaemia. Thus, 84 **H. pylori** eradicated patients (10 men; 74 women) were available to assess the effect of eradication on IDA. **H. pylori** infection was considered to be the aetiology of IDA in 32 patients (38.1%; 95%CI: 28.4%-48.8%). This was more frequent in men/postmenopausal women than in premenopausal women (75% vs 23.3%; \( P < 0.0001 \)) with an OR of 9.8 (95%CI: 3.3-29.6). In these patients, anaemia resolution occurred in the first follow-up visit at 6 mo, and no anaemia or iron deficiency relapse was observed after a mean follow-up of 21 ± 2 mo.

**CONCLUSION:** Gastric **H. pylori** infection is a frequent cause of iron-refractory or iron-dependent anaemia of previously unknown origin in adult patients.

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**Key words:** Helicobacter pylori; Iron-deficiency anaemia; Iron refractoriness; Gluten-sensitive enteropathy; Menopause

**Core tip:** Data on the effect of *Helicobacter pylori* (**H. pylori**) eradication on adult patients with iron-refractory or iron-dependent anaemia of previously unknown origin are scarce, and thus the frequency of **H. pylori** infection as the cause of anaemia in that setting is unknown. Resolution of iron-deficient anaemia (IDA)
was observed in 32 out of the 84 H. pylori eradicated patients (38.1%). In all of them there was no relapse after a mean follow-up of 21 ± 2 mo. Thus, H. pylori infection was considered the aetiology of IDA in these cases. H. pylori infection as the aetiology of IDA was greater in men plus postmenopausal women than in premenopausal women (75.0% vs 23.3%, P < 0.0001).

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INTRODUCTION

Iron-deficiency anaemia (IDA) occurs in 2%-5% of adult men and postmenopausal women in the developed world, with blood loss from the gastrointestinal tract being the most common cause[1-4]. In addition, IDA also occurs in 5%-12% of otherwise healthy premenopausal women[5]. IDA is a common cause of referral to gastroenterologists (4%-13% of referrals)[6], and for 5%-10% of patients with IDA without gastrointestinal bleeding the cause of the condition remains obscure in spite of extensive examination[7].

Helicobacter pylori (H. pylori) colonisation in gastric mucosa may impair iron uptake and increase iron loss, potentially leading to IDA. The speculative mechanisms by which H. pylori may produce IDA have recently been reviewed[8-10]. Four meta-analyses to assess the effect of H. pylori eradication combined with ferrous supplementation on the treatment of IDA have been published[11-14]. The conclusions suggest that H. pylori eradication therapy improves iron absorption, since H. pylori eradication combined with iron administration was more effective than iron administration alone for the treatment of IDA. However, there was no follow-up of patients after oral iron therapy was completed, and relapse of IDA after H. pylori eradication was not evaluated; thus, it was not established whether H. pylori infection was the cause of IDA. Most of the intervention trials have been performed in geographical areas where both IDA and H. pylori infection are highly prevalent, and where the aetiology of IDA may be multifactorial (malnutrition, vitamin deficiencies, chronic parasitic infections, malaria). In western countries there are only some uncontrolled intervention studies showing recovery from anaemia after H. pylori eradication[15,16]. In light of the above-mentioned studies, H. pylori infection has been considered as a risk factor for IDA. The British Society of Gastroenterology recommends eradication of H. pylori infection in patients with IDA and normal colonoscopy and oesophagogastroduodenoscopy (Grade of recommendation, C)[17], and the Maastricht guidelines suggest to eradicate H. pylori in patients with IDA (Grade of recommendation, A)[18,19]. However, data on the effect of H. pylori eradication on adult patients with iron-refractory or iron-dependent IDA of previously unknown origin are scarce, and thus the frequency of H. pylori infection as the cause of IDA in that setting is unknown. Therefore, the aim of the present study was to assess the aetiologic role of H. pylori infection in such patients, in a geographical background where concomitant causes of IDA are unusual.

MATERIALS AND METHODS

Patients

Consecutive patients with unexplained chronic IDA or isolated iron deficiency (ID) referred to the Gastroenterology Department from January 2007 to December 2010 were prospectively evaluated.

Patients were included if they were older than 18 years of age with all the following: (1) chronic IDA defined as haemoglobin < 10.5 g/dL in women and < 11.5 g/dL in men, and serum ferritin < 13 μg/L or ID defined as only serum ferritin < 13 μg/L; (2) gastric H. pylori infection; (3) iron refractoriness or iron dependency (see below for definition); (4) negative faecal immunochemical tests for occult blood (at least three negative samples); (5) negative coeliac serology [both serum immunoglobulin A (IgA)-antiendomysial Antibodies and IgA-human anti-tissue transglutaminase antibodies], although patients diagnosed with coeliac disease in whom IDA persisted in spite of being on a strict gluten-free diet with negative coeliac serology and no villous atrophy were included; (6) normal gastroscopy and full colonoscopy; (7) normal physical examination, blood analysis (including routine biochemical tests, C reactive protein, folate and vitamin B12 levels), and urinalysis; and (8) normal gynaecological examination.

Patients with the following conditions were excluded from the study: (1) frequent (three times a week or more) use of non-steroidal anti-inflammatory drugs or salicylates during the previous 6 mo; (2) use of dicumarinics; (3) other conditions which cause anaemia or interfere with erythropoiesis including malignancy, haematological diseases, connective tissue disease, chronic diseases such as chronic renal failure, chronic liver disease, severe cardiac and respiratory disease, and previous gastrointestinal surgery; (4) pregnancy or lactation; (5) history of alcoholism or drug addiction; (6) heavy menstrual flow (cycles > 5 d, associated with passage of clots after the three first days) and/or metrorrhagia; (7) obvious blood loss (melena, haematochezia, haematuria, recurrent epistaxis); (8) adherence to vegetarian or iron-deficient diet; and (9) expected lack of cooperation.

Capsule endoscopy was not routinely performed since one inclusion criterion was that repeated faecal immunochemical tests for occult blood were negative. In individual cases (12 patients), it was performed by the decision of the physician at charge, yielding in all cases normal results.
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All patients had received iron supplements and all of them fulfilled the criteria of either iron refractoriness or iron dependency. Iron refractoriness was defined as an inappropriate increase in haemoglobin levels (< 2 g/dL) after completion of a 5000 mg dosing cycle of ingested elemental iron over one month or longer[16]. Iron dependency was defined as the patient’s requiring daily oral iron supplementation (ferrous sulphate, 100-200 mg daily of elemental iron) to maintain adequate haemoglobin levels.

Study design
The following tests were prospectively performed in all included patients: (1) two endoscopic biopsies from both gastric body and antrum, and four biopsies from distal duodenum; (2) histological examination of antral biopsies and/or 13C-urea breath test to assess H. pylori infection; and (3) human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 haplotypes of predisposition to coeliac disease.

In all patients H. pylori was eradicated using a standard 7-d triple regimen with omeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid. Two-week quadruple regimens were used as a rescue therapy for patients failing the first-line eradication therapy, and in some cases a levofloxacin-based third-line rescue therapy was used. H. pylori eradication was evaluated by histological examination of antral biopsies and/or 13C-urea breath test. Analytical response to H. pylori eradication was assessed at 6 and 12 mo of follow-up. In cases with associated lymphocytic duodenitis (LD), histological follow-up was also performed at 6 and 12 mo.

Final diagnosis
H. pylori infection was considered to be the cause of IDA or ID when eradication achieved a complete response (i.e., IDA or ID recovery, with normal serum ferritin levels), without iron supplements, was observed at 12 mo of follow-up. A diagnosis of gluten-sensitive enteropathy was performed in patients with LD and positive coeliac genetics (HLA-DQ2 and/or HLA-DQ8) without response after achieving H. pylori eradication, when there was a sustained (at 12 mo follow-up) complete clinical and histological response on a strict gluten-free diet[19]. The cause of either IDA or ID was considered to be unknown in patients without response to both H. pylori eradication and gluten-free diet (when indicated).

Histological studies
Four endoscopic biopsies from the 2nd-3rd portions of the duodenum and two biopsies from both body and antrum were obtained in the index endoscopy. H. pylori infection was investigated in gastric antral mucosal samples by standard histopathological assessment[20]. Duodenal samples were processed with haematoxylin/eosin staining and CD3 immunophenotyping, and these were blindly evaluated by an expert gastrointestinal pathologist (Salas A). LD was defined as 25 or more intraepithelial lymphocytes per 100 epithelial nuclei and normal villous architecture, as suggested in recent literature[21]; the cut-off value was validated in our laboratory[19]. This cut-off value was also selected to define LD due to gluten-sensitive enteropathy, which corresponds to the Marsh 1 type lesion of the coeliac disease spectrum[21].

Helicobacter pylori status
Patients were classified as having H. pylori infection when either histology or 13C-urea breath test was positive. 13C-urea breath test was performed on those patients with negative histology who either were taking proton-pump inhibitors or had antral intestinal metaplasia at the index endoscopy, as previously described[20]. In the case of proton-pump inhibitors, the breath test was performed 4 wk after discontinuation.

Ethics
The protocol was approved by the Ethics Committee of the Hospital Universitari Mutua Terrassa, and all participants provided informed consent.

Statistical analysis
Results are expressed as mean ± SE and as percentages plus their 95%CI. Chi-square statistics were used to assess significant associations between qualitative variables. The OR and 95%CI of the significant associations were computed.

RESULTS
One hundred thirty-six consecutive adult patients fulfilled the inclusion criteria during the study period. Twenty-two were excluded due to presence of exclusion criteria, 7 patients had previously unrecognised non-steroidal anti-inflammatory drug intake, and 15 had other causes of anaemia (1 infection by intestinal parasites, 2 recurrent rectal bleeding attributed to haemorrhoids, 1 chronic renal failure, 2 small bowel Crohn's disease, 1 gastrinoma, and 8 pernicious anaemia). Twenty-five additional patients (18.4%) were lost in follow-up before achieving a definite diagnosis of their anaemia. Thus, 89 patients were finally included in the study (10 men; 79 women; mean age: men, 54.0 ± 15.8 years; premenopausal women, 44.0 ± 8.6 years; postmenopausal women, 59.0 ± 9.8 years). There were no significant differences in demographic data or frequency of menopause, H. pylori-related chronic gastritis, associated enteropathy (ID) or coeliac genetics between included patients and those lost in follow-up (Table 1).

H. pylori was eradicated in 88 of the 89 patients. In the non-eradicated patient the four eradication regimens failed. There were violations of protocol in 4 patients, for whom it was not possible to ascertain the cause of the anaemia. Thus, 84 H. pylori-eradicated patients were available to assess the effect of eradication on IDA.

Resolution of IDA or ID was observed in 32 out of the 84 H. pylori-eradicated patients (38.1%; 95%CI: 28.4-48.8). In all of them, IDA or ID recovery was observed at the 6-month follow-up visit after H. pylori-erad-
The final diagnosis of IDA in the remaining 48 patients, who were mainly premenopausal women, was unknown. Despite H. pylori eradication there was a need to maintain iron supplementation during follow-up, with persistent iron-dependent IDA. A relation with menstrual blood loss was observed in 30 of the premenopausal women since anemia recovered after either entering menopause or starting hormonal contraceptive therapy. As previously mentioned, none of them had heavy menstrual blood loss at inclusion, and for all of them the gynaecologic examination had been normal.

**DISCUSSION**

Results of the present study suggest that H. pylori infection is a frequent cause of IDA in adult patients with iron refractoriness or iron dependency in whom the standard diagnostic work-up is negative. In 38% of such patients H. pylori eradication was associated with both IDA resolution without the need for more iron supplementation and an absence of IDA relapse after nearly two years mean follow-up. These observations argue in favour of causality of H. pylori infection. In addition, the efficacy of H. pylori eradication to recover from IDA in such patients was compared between men and postmenopausal women. There was IDA recovery in 75% and 23% of them, respectively, with highly significant differences. In fact, the OR of H. pylori infection as the cause of IDA was almost 10 times higher in the first group than the second.

We have to take into account that the H. pylori re-infection rate after cure in our geographical area is low; around 1% patient-year; this implies that the present results might not be extrapolated to other regions with higher re-infection rates.

Results of the present study on premenopausal women are in disagreement with previous results of Annibale et al[19], since they showed recovery from anaemia at 12 mo of follow-up after H. pylori eradication in 92% of patients, mainly premenopausal women. The discrepancies revolve around the definition of response. In our study, response to H. pylori eradication was defined as anaemia recovery with normalisation of serum ferritin levels. In Annibale’s study, however, ferritin levels returned to normal in only 17% of the patients despite recovery from anaemia, which is a figure similar to that of the 23% obtained in our study. Taking into account the meta-analysis data mentioned in the introduction[11-14], and the results of the present study in men and postmenopausal women, H. pylori infection may also be a contributing factor to IDA in premenopausal women, and H. pylori eradication is indicated to improve iron absorption. In this sense, it would be of interest to assess whether iron requirements change after H. pylori eradication in these patients. Regrettably, iron requirements were not sufficiently well recorded in the present study to allow for this evaluation.

Other factors may contribute to IDA in otherwise healthy premenopausal women such as menstrual loss, increased iron demands on pregnancy and breast feeding, and dietary deficiency[20]. Hormonal contraceptive therapy may reduce menstrual blood loss by approximately 50%, even in women with average or slightly above-average blood loss[20]. In the present study, this type of therapy was effective for IDA recovery in those premenopausal women in whom increased iron requirements persisted after H. pylori eradication.

H. pylori infection may be a cause of LD, which may disappear after eradication of the infection[15,24]. However, whether H. pylori-infected patients with LD are more prone to developing IDA is unknown. The present study shows that the frequency of H. pylori infection as the final diagnosis of IDA is similar for patients with and without associated enteropathy. Therefore, these data argue against a pathophysiological role for this mild enteropathy in the development of IDA in H. pylori-infected patients.

In 4.5% of the included patients the final diagnosis was gluten-sensitive enteropathy. These results agree with

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**Table 1** Comparison of demographic, clinical, and biological data between included patients and those lost in follow-up

| Age (yr), mean ± SE | Loss of follow-up patients (n = 89) | Included patients (n = 25) |
|--------------------|-------------------------------------|---------------------------|
| Sex (M/F)          | 46.0 ± 11.8                         | 41.0 ± 14.2               |
| Postmenopausal women | 10/79                              | 4/21                       |
| Chronic antral gastritis | 17.90%                             | 16.00%                    |
| Chronic body gastritis | 81.80%                             | 78.30%                    |
| Associated enteropathy | 83.00%                             | 78.30%                    |
| HLA-DQ2 and/or DQ8+ | 59.50%                              | 60.00%                    |
| HLA-DQ2 and/or DQ8+ | 48.30%                              | 40.00%                    |

There were no significant differences in any parameter. HLA: Human leucocyte antigen; M/F: Male/female.
a previous study by our group showing that a subgroup of patients with IDA of previously unknown origin and positive coeliac genetics presented a gluten-sensitive mild enteropathy with negative coeliac serology.\(^\text{[23]}\)

In conclusion, the results of the present study show that \(H.\ pylori\) infection is a frequent cause of IDA in men and postmenopausal women with either iron refractoriness or iron dependency, in whom other causes of IDA have been previously ruled out. \(H.\ pylori\) eradication therapy produces long-term resolution of IDA in such patients. Also, \(H.\ pylori\) infection may be a contributing factor to IDA in otherwise healthy premenopausal women without heavy menstrual blood loss, and it is the aetiology of IDA in almost 25% of them.

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**COMMENTS**

**Background**

Iron deficiency anaemia (IDA) is a common cause of referral to gastroenterologists (4%-13% of referrals), and for 5%-10% of patients with IDA without gastrointestinal bleeding the cause of the condition remains obscure in spite of extensive examination. Previous data suggest that \(H.\ pylori\) eradication therapy improves iron absorption, since \(H.\ pylori\) eradication combined with iron administration was more effective than iron administration alone for the treatment of IDA. The Maastricht guidelines suggest to eradicate \(H.\ pylori\) for the treatment of IDA. The Maastricht guidelines suggest to eradicate \(H.\ pylori\) in all patients with IDA.

**Research frontiers**

\(H.\ pylori\) eradication may improve iron absorption, but how often is gastric \(H.\ pylori\) infection the cause of IDA? Data on the effect of \(H.\ pylori\) eradication on adult patients with iron-refractory or iron-dependent anaemia of previously unknown origin are scarce, and thus, the frequency of \(H.\ pylori\) infection as the cause of IDA in that setting is unknown.

**Innovations and breakthroughs**

This study is performed in a large prospective series of consecutive patients using very strict inclusion criteria, with a long follow-up after \(H.\ pylori\) cure. Resolution of anaemia was defined as both haemoglobin and iron stores normalization, which was long-term maintained without requiring iron supplements. Frequency of IDA resolution was compared between men/post-menopausal women and pre-menopausal women.

**Applications**

Gastric \(H.\ pylori\) infection may be a frequent cause of iron-refractory or iron-dependent anaemia of previously unknown origin in adult patients, mainly in men and post-menopausal women. In these patients, \(H.\ pylori\) infection eradication produced the cure of IDA. In addition, \(H.\ pylori\) infection may be a contributing factor to IDA in otherwise healthy premenopausal women without heavy menstrual blood loss, being the aetiology of IDA in almost 25% of them.

**Peer review**

The authors in this article have focused on the possible role of \(H.\ pylori\) infection in causation of IDA. They have stated that 38% of the patients may have the anaemia due to the infection by \(H.\ pylori\).

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