Helicobacter pylori and its hematological effect

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Background

Helicobacter pylori causes several gastric, intestinal, and extraintestinal manifestations. It also causes persistent infection and can cause serious various hematological effects.

Aims

To investigate the hematological effect of H. pylori infection.

Patients and methods

This is a cohort study that included 50 adult (age range: 18–75 years) patients infected with H. pylori and 50 adult patients who presented with symptoms suggestive of gastritis. All patients underwent upper endoscopy, and biopsies were taken. Moreover, the patients underwent complete blood count, iron studies, hepatitis C virus antibodies, vitamin B_{12} level, and bone marrow aspirate.

Result

The results showed that hemoglobin level, serum iron level, vitamin B_{12} levels, and platelets count were much lower in patients infected with H. pylori than the control group.

Conclusion

H. pylori causes iron-deficiency anemia, vitamin B_{12} deficiency, and thrombocytopenia, and treatment of H. pylori causes much improvement in these parameters.

Keywords:

Helicobacter pylori, iron-deficiency anemia, iron deficiency, thrombocytopenia, vitamin B_{12}

Introduction

Helicobacter pylori is one of the most common infection in humans. It causes several gastric, intestinal, and extragastric manifestations. H. pylori causes chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma [1]. It also causes more than 50 extragastric manifestations, including cardiac, dermal, endocrinal, gynecological, obstetrical, pneumatology, neurological, ophthalmological, and hematological ones [2].

Our study is only concerned with hematological manifestations, including iron-deficiency anemia, vitamin B12 deficiency, and immune thrombocytopenia.

Iron-deficiency anemia

Iron deficiency is a serious medical problem whether associated with anemia or not. It occurs mostly in a chronic process with a slow onset, in which the iron imbalance may take several years to establish and manifest clinically [3].

The mechanism by which H. pylori causes iron-deficiency anemia is not well understood. Studies show that serum hepcidin is elevated in patients infected with H. pylori, and these levels are normalized after eradication of the infection, allowing the iron to be absorbed by the enterocytes and released from macrophages of the reticuloendothelial system, where they are confined [4].

Other explanation of iron imbalance in patients infected with H. pylori is chronic blood loss which occurs owing to chronic gastritis, which may be so severe up to causing erosive gastritis, especially in patients with active bleeding peptic ulcers and in patients who chronically ingest NSAID including aspirin [5].

Furthermore, highly virulent strains such as H. pylori with the cytotoxin-associated gene A (CagA) related to gastric tumor and the vacuolating cytotoxin A (VacA) related to gastric ulceration, act through molecular mimicry mechanisms to produce or magnify iron deficiency in patients compared with patients infected with other less virulent strains [6].

Other explanation may be the interaction between VacA and Cag-pathogenicity island (PAI), as there are two types of *H. pylori* strains, type I or type II, that depend on the presence or not of both the Cag-PAI and the VacA, respectively.

H. pylori strains that have PAI are found to be more virulent than those that do not. A new study revealed that CagA inhibits VacA-induced apoptosis by preventing pinocytotic uptake of VacA, resulting in a decrease in vacuole formation within the host cell [7], so *H. pylori* uses CagA and VacA to take iron from mucosal epithelial cells. Moreover, CagA increases transferrin uptake from the basolateral surface, giving it to the apical surface to be released into the lumen, whereas VacA increases transferrin-receptor uptake from the surface and transfers it to the sites of bacterial attachment, causing decrease in serum iron level [8].

Treatment of *H. pylori* infection in cases of unexplained iron-deficiency anemia leads to improvement of ferrokinetic parameters [6,9].

Vitamin B12 deficiency
Vitamin B_{12}, also called cobalamin, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system via the synthesis of myelin, and the formation of red blood cells. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid, and amino acid metabolism [10].

Vitamin B_{12} deficiency is very common, and there are serious health problems owing to inability of the body cells to synthesize it, and it needs to be externally supplemented. Its incidence varies from 20 to 60% in developing countries and up to 20% in developed countries [11].

Mechanisms by which *H. pylori* causes vitamin B_{12} deficiency are not fully clarified.

Persistent infections by *H. pylori* cause chronic gastritis that may proceed to atrophic gastritis and achlorhydria, leading to intrinsic factor deficiency. The lack of intrinsic factor reduces the absorption and transport of vitamin B_{12} from the diet. This leads to vitamin B_{12} deficiency over long periods and depletion of its reservoir over many years [12].

Thrombocytopenia
It is an autoimmune disease characterized by isolated thrombocytopenia (peripheral blood platelet counts $<100\times10^9$/l) in the absence of other causes or disorders. Immune thrombocytopenia (ITP) is a diagnosis of exclusion, and it is necessary to exclude causal diseases such as systemic lupus erythematous and HIV or acquired immunodeficiency syndrome before diagnosis [13].

H. pylori infection leads to production of autoantibodies by B-lymphocytes, which leads to overactivation of innate and acquired immunity to the number of the circulating platelets count by decreasing the levels of the inhibitory receptor FcγRIIB in monocytes, leading to increased monocyte function with nonspecific phagocytosis and autoreactivity with B and T lymphocytes [14].

Amino acid sequences of virulence factors (VacA and CagA) and urease B are present in *H. pylori* infection and are the major antigens associated with autoimmune response against platelets. The homology of these antigens with platelet surface glycoproteins including glycoprotein IIIa and other platelet antigens associated with antibodies anti-CagA shows the importance of *H. pylori* infection in ITP [15].

Patients and methods
Our study was done on 50 patients and 50 controls, who were recruited from Outpatient Clinics and Inpatients of Gastroenterology Unit of Internal Medicine Department of Assiut University Hospitals. All patient had signed a written consent of their agreement to perform upper endoscopy and biopsy were taken and lab tests were performed and their agreement to involve their results in the research for publication.

Inclusion criteria
All of them complained of symptoms suggestive of gastritis whether acute (within 2 weeks) or chronic (3 or more months) and were diagnosed at endoscopy to have *H. pylori* infection by biopsy.

Patients aged more than 18 years old of both sexes (44 of them were males and 56 of them were females) were included.

Exclusion criteria
Patients with malignant diseases or gastric malignancy, other causes of thrombocytopenia such as systemic lupus erythematous and HIV and/or acquired immunodeficiency syndrome, other causes of anemias with or without blood loss, and hepatitis C virus (HCV) infection were excluded.

Data collection

Sample size

A total of 100 patients were presented with symptoms suggesting of gastritis, and they were grouped as follows: group A included 50 patients with positive *H. pylori* biopsy result and group B included 50 patients with negative *H. pylori* biopsy result.

The two groups were subjected to assessment of age, sex, associate diseases, and family history of the same illness or others. Detailed history about gastric symptoms and duration of the disease was taken. Full clinical examination was done. Laboratory investigations included complete blood count with reticulocyte count, upper endoscopy, diagnostic biopsy, serum iron, total iron binding capacity and serum ferritin, vitamin B_{12}, folic acid level if indicated, and bone marrow aspirate if indicated.

Statistical analysis

Statistical analysis and tabulation were done using statistical package for the social science (SPSS for Windows). The following statistical tests were used:

(1) Descriptive statistics: frequencies, percentages, means, and SDs.
(2) Tests of significance: χ^2 test.
(3) Statistically significant differences were considered when *P* value was less than or equal to 0.05%.

Result

A total of 100 patients were enrolled in the study, with 44 males and 56 females. Overall, 42 patients were between 18 and 29 years, 22 patients were 30 and 49 years, 35 patients were between 50 and 70 years, and one patient was 75 years old.
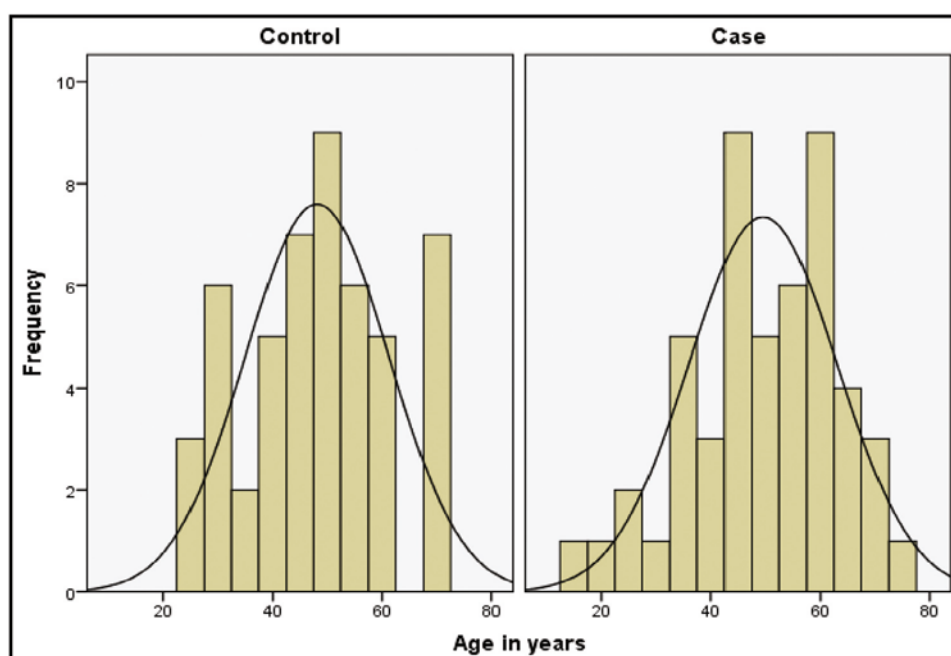
Our study showed no difference in incidence regarding age. In control, mean±SD was 48.12±13.1 years, and cases, it was 49.50±13.6 years, as shown in Fig. 1.

Regarding sex, our study showed no sex predilection for *H. pylori* infection. The prevalence of male in control was 40% compared with 48% in cases, and female prevalence in control was 60% to 52% in cases, as shown in Fig. 2.

There was no statistically significant relation between smoking (cigarettes) and presence of *H. pylori* infection, as 32% of the patients were cigarette smokers with *H. pylori* infection versus 42% nonsmokers, as shown in Fig. 3.

Our study showed no ulcer detection in control (*H. pylori* negative), whereas in cases (*H. pylori* positive), there was 62% detection of ulcer and 38% detection of gastric inflammation. So, iron-deficiency anemia may be secondary to chronic blood loss in patients with *H. pylori* infection and may be owing to *H. pylori* itself (as ulcers were nonactive at the time of the research, as it was under treatment), as shown in Figs 1 and 4.

Figure 1

Mean age differences between cases and controls.

Figure 2
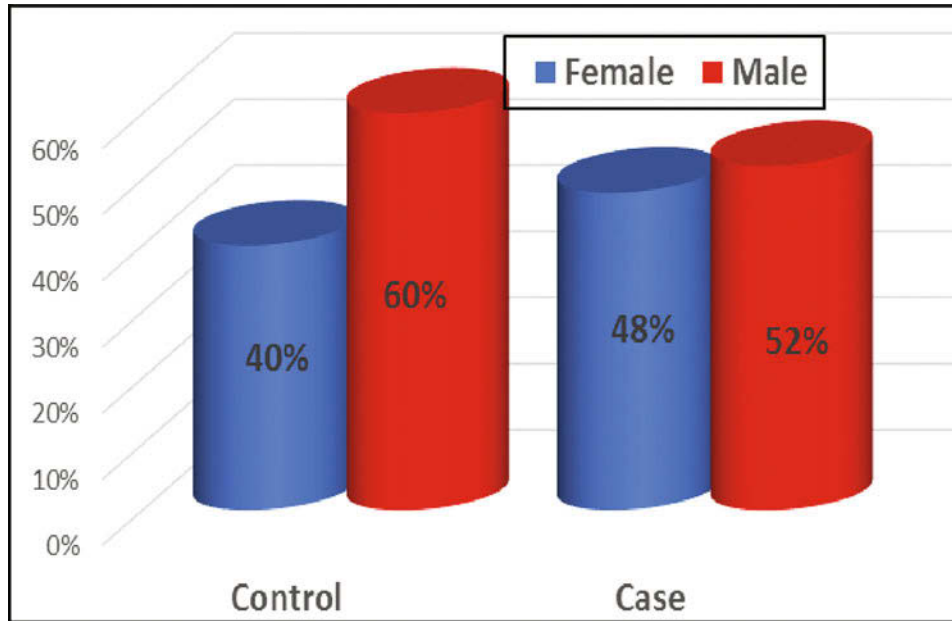
Sex distribution among cases versus controls.

Our study showed there was no difference in white blood cell (WBC) (cells×10^3/μl) in control, with mean ±SD of 5.61±0.3, and in cases, with 6.86±0.4. The current study showed slight decrease in hemoglobin (Hb) (g/dl) level in cases versus control, as in control mean±SD was 12.89±1.2 and in cases was 10.35±1.6. In control, mean±SD mean corpuscular volume (MCV) was 84.43±3.3 and in cases was 82.98±10.6. There is no difference between mean corpuscular hemoglobin (MCH) between control (mean±SD: 29.24±1.1) and cases (28.09±4.2).

In our study, there was a statistically significant correlation between cases and control in the number of platelet count (plt×10^3/μl), as there was an increase in control (mean±SD: 335.90±14.2) versus cases (236.76±17.1), as shown in Figs 2 and 5.

In the current study, there was a statistically significant correlation between *H. pylori* infection and various parameters of iron loss, as such serum iron (μg/dl), vitamin B_{12} (μg/dl), folic acid (ng/ml), and total iron binding capacity (TIBC).

Regarding comparative analysis, our study showed there was a significant decrease in serum iron level and a significant increase in TIBC. In cases, serum iron (mean±SD) was 35.10±9.2 and TIBC was 523.48 ±48.7, as shown in Figs 3 and 6.

Our study showed there was a significant decrease in vitamin B_{12} level (mcg/dl) and folic acid (ng/ml) in

cases (mean±SD 135.31±7.3 and 135.31±7.3, respectively), as shown in Figs 4 and 7.

Regarding bone marrow aspirate, our study showed there was a significant difference between control and cases. There were 80% of cases with abnormal finding in bone marrow aspirate in the form of decrease number of platelets versus 20% normal findings, as shown in Figs 5 and 8.

HCV infection was excluded from thrombocytopenic patient.

10 patients were diagnosed to have HCV positive antibodies , none of them had thrombocytopenia in CBC.

As shown in Table 1, there was no statistical correlation between combined conditions as diabetes mellitus (DM) (*P*=0.685), hypertension (*P*=0.673), and family history (*P*=0.041) and increased incidence of *H. pylori* in cases versus controls, and regarding comorbidity and family history, our study showed there was no difference in incidence of having DM in control 40% and in cases 44%.

Regarding hypertension, our study showed there was no difference in the incidence of having hypertension between controls (32%) and cases (36%).
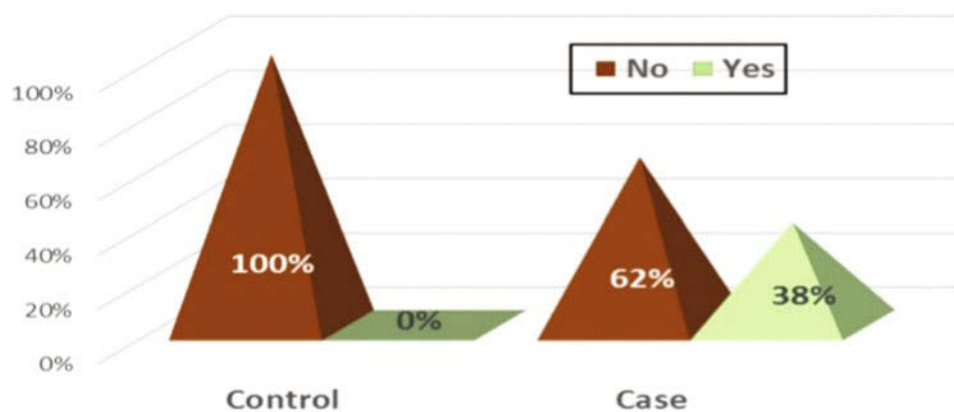
Regarding family history of *H. pylori* infection, our study showed there was a significant increase in

Figure 3
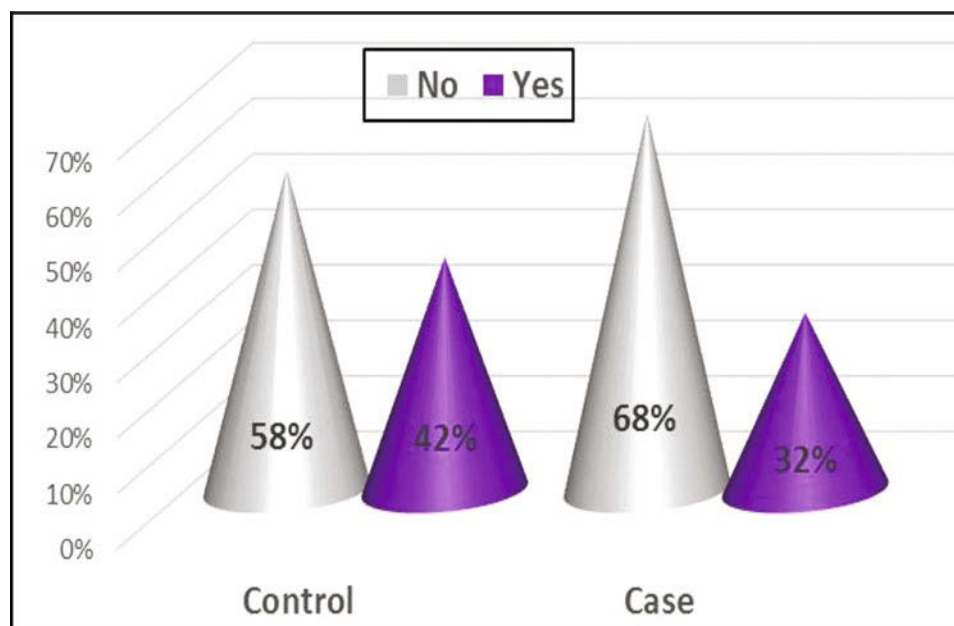
Smoking distribution among cases versus controls.

Figure 4

Gastric ulcer prevalence among cases versus controls.

incidence in cases (42%) versus in controls (28%), as shown in Table 1.

Our study showed there were significant factors influencing *Helicobacter* infection, as shown in Table 2:

(1) There was no significance difference in relation to age or sex to *H. pylori* infection between control and cases, as regarding age, the unadjusted odds ratio was 1.01 and *P* value was 0.603, and regarding sex, the unadjusted odds ratio was 0.72 and *P* value was 0.421.

(2) Regarding WBC, there was a 23 times increasing incidence of *H. pylori* infection with each 1000 cell/dl increase in number of WBC, as the unadjusted odds ratio was 1.23 and *P* value was 0.020.

(3) As regard Hb, there was a 74 times decreasing incidence of *H. pylori* infection with each increase in Hb level by 1 mg, as the unadjusted odds ratio was 0.26 and *P* value was 0.001.

(4) Regarding platelet count, there was a two times decreasing incidence of *H. pylori* infection with an increase of platelets number by 1000, as the unadjusted odds ratio was 0.98 and *P* value was 0.001.

(5) Regarding family history, there was 86 times increased risk of *H. pylori* infection with a positive family history, as the unadjusted odds ratio was 0.98 and *P* value was 0.001.

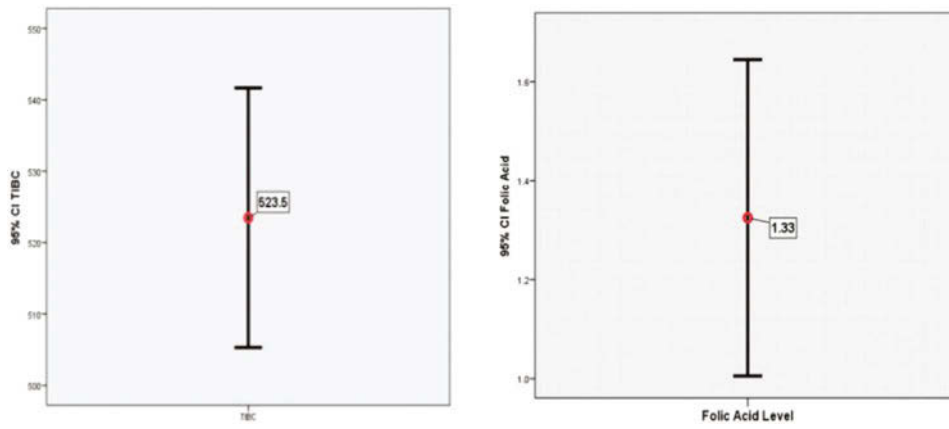There were significant factors influencing *Helicobacter* infection in this study in multivariate logistic regression analysis, as shown in Tables 3 and 4:

Figure 5
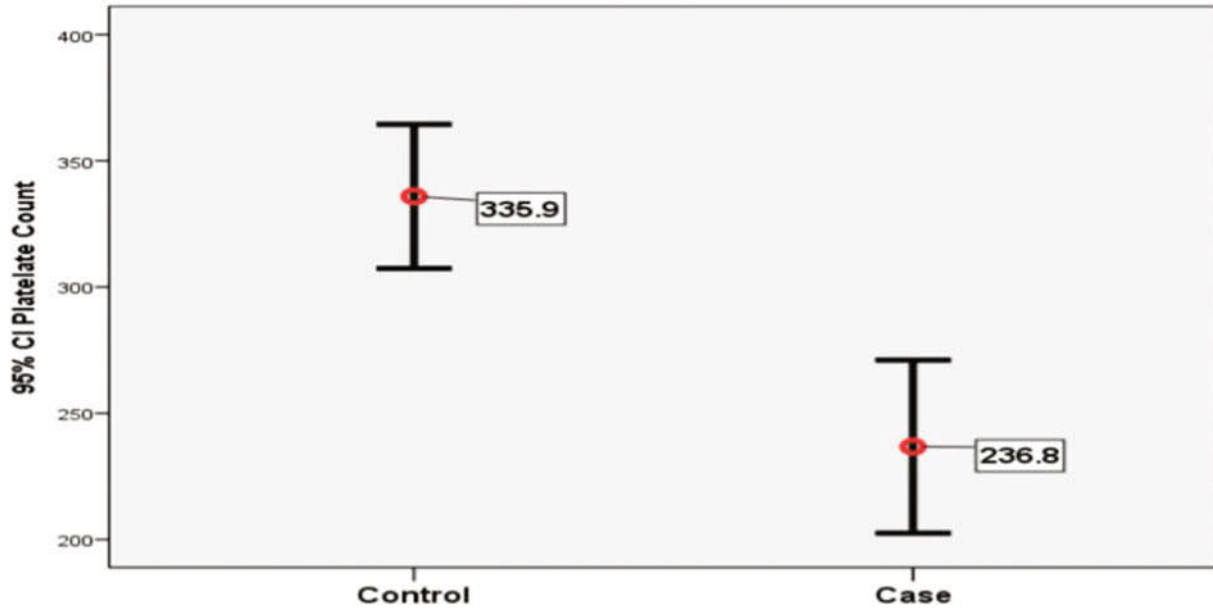
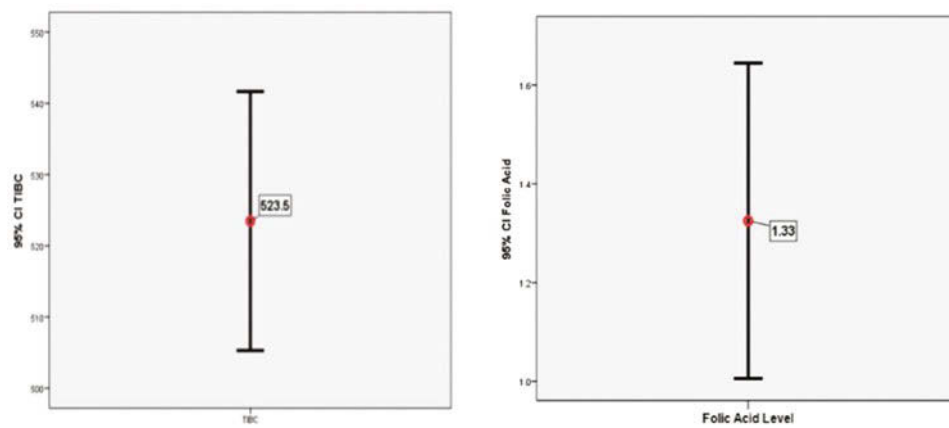
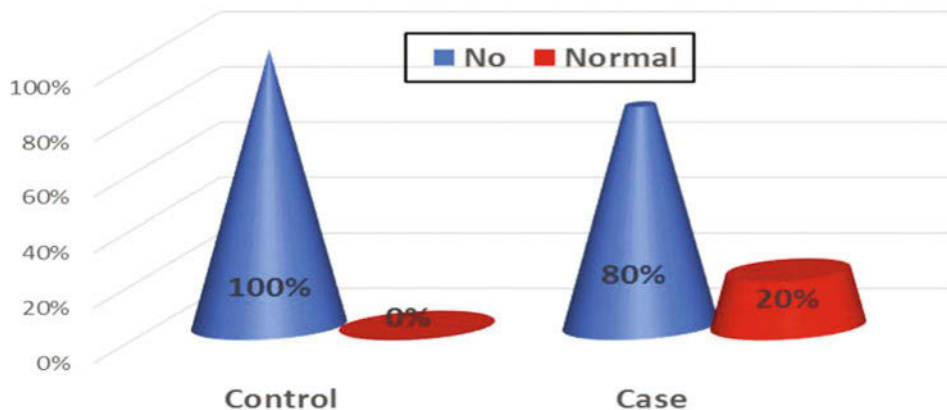Mean platelet count differences between cases and control.

Figure 6

Mean total iron and TIBC level differences between cases and controls.

Figure 7

Mean vitamin B$_{12}$ and folic acid level differences between cases and controls.

Figure 8

Distribution of the study cohort according to the performance of bone marrow aspirate.

Table 1 Sociodemographic and clinical data differences between cases and controls

	Control (N=50) [n (%)]	Case (N=50) [n (%)]	P value
Age (years)	48.12±13.1	49.50±13.6	0.607*
Sex			
Male	20 (40)	24 (48)	0.420**
Female	30 (60)	26 (52)	
Smoking			
No	29 (58)	34 (68)	0.300**
Yes	21 (42)	16 (32)	
Gastric ulcer			
No	50 (100)	31 (62)	<0.001**
Yes	0 (0)	19 (38)	

*t test was used to compare the mean difference between groups. **χ^2 test was used to compare the percentages between groups.

Table 2 Comparison between cases and controls regarding comorbidity and family history

	Control (N=50) [n (%)]	Case (N=50) [n (%)]	P value*
DM			
No	30 (60)	28 (56)	0.685
Yes	20 (40)	22 (44)	
Hypertension			
No	34 (68)	32 (64)	0.673
Yes	16 (32)	18 (36)	
Family history			
Negative	36 (72)	29 (58)	0.041
Positive	14 (28)	21 (42)	

DM, diabetes mellitus. *χ^2 test was used to compare the percentages between groups.

Table 3 Significant factors influencing helicobacter infection: univariate logistic regression analysis

Factors	Unadjusted odds ratio	95% CI	P value
Age (years)	1.01	0.98–1.04	0.603
Sex (male)	0.72	0.33–1.60	0.421
WBCs(cells×10^3/μl)	1.23	1.03–1.46	0.020
Hemoglobin (g/dl)	0.26	0.15–0.43	<0.001
Platelet ×10^3 (cells/μl)	0.98	0.97–0.99	<0.001
Positive family history	1.86	1.02–4.29	0.014

CI, confidence interval; WBC, white blood cell.

Table 4 Significant factors influencing helicobacter infection: a multivariate logistic regression analysis

Factors	Adjusted odds ratio	95% CI	LRT (P value)
Age (years)	1.01	0.96–1.06	0.726
Sex (male)	11.20	2.16–28.02	0.004
WBCs (cells×10^3/μl)	1.16	0.86–1.58	0.325
Hemoglobin (g/dl)	0.15	0.07–0.33	<0.001
Platelet ×10^3 (cells/μl)	0.99	0.98–0.99	0.050
Positive family history	2.06	1.02–6.44	0.012

CI, confidence interval; LRT, likelihood ratio test; WBC, white blood cell.

(1) Regarding sex, there was an 11 times increased risk of getting *H. pylori* infection in males more than females, as adjusted odds ratio was 11.20 and *P* value was 0.004.
(2) Regarding Hb level, there was an 85 times decreased incidence of getting infection by *H. pylori*, with each increase of Hb level by 1 g/dl as adjusted odds ratio was 0.15 and *P* value was less than 0.001.
(3) Regarding family history, there was a 98 times increasing risk of getting infected with *H. pylori* in patients with positive family history, as adjusted odds ratio was 2.06 and *P* value was 0.012.

Discussion

Our study showed no significant correlation between age and occurrence of hematological problems with *H. pylori* infection, which differs from Schwarz *et al.* [16]

and Bruce and Maaroos [17] who found that *H. pylori* infection is usually acquired during childhood (2–6), which was more prevalent in male (29.4%) than females (14.9%) and more with older age, as described by Xu *et al.* [18]. This differs from a study done by de Martel C and Parsonnet [19] which showed that *H. pylori* infection in children occurred with the same rates in males and females.

Our study showed that there was no statistically significant relation between cigarette smoking and presence of *H. pylori* infection. There were 32% cigarette smokers with *H. pylori* infection versus 42% nonsmokers with *H. pylori* infection.

Our study showed there was no difference in WBC, as in control group (mean±SD) was 5.61±0.3 and in cases was 6.86±0.4. This nondifference could be owing to the presence of inflammation in the study control group as well as most control population of our study, who were complaining of inflammation at time of diagnosis, which may narrow the difference in WBCs count between control and cases. This differed from Linz *et al.* [20] and Kodaman *et al.* [21] who described that infected cases had significantly elevated WBC counts compared with noninfected ones, which showed elevated total WBC counts, neutrophil counts, and monocyte counts. This could explain the exaggerated systemic inammatory response in cases with *H. pylori* infection. This is in disagreement with Gupta *et al.* [22] who found that *H. pylori* infection causes autoimmune neutropenia, Papadaki *et al.* [23,24].

The current study showed slight decrease in Hb level in cases versus control. In control, mean±SD was 12.89 ±1.2, and in cases was 10.35±1.6. There was a statistically significant correlation between *H. pylori* infection and various parameters of iron loss such as serum iron and TIBC (iron-deficiency anemia). This is in concordance with Xu *et al.* [18], Gheibi *et al.* [25], DeLoughery [26], Mubarak *et al.* [27], Queiroz *et al.* [28], Xia *et al.* [29], and Senkovich *et al.* [30], who found that the prevalence of iron-deficiency anemia in the *H. pylori* + group was significantly higher than in the *H. pylori* – group.

The pathogenic mechanisms by which *H. pylori* might contribute to anemia in asymptomatic people are not well understood and may be owing to several explanations such as owing to a chronic idiopathic iron deficiency represented by autoimmune atrophic gastritis, which had been shown to be responsible for refractory iron-deficiency anemia in more than 20% of patients with no evidence of gastrointestinal blood loss.

Such a disease was considered a possible outcome of a long-lasting *H. pylori* infection. Infected patients, in fact, had circulating antibodies to the H^+,K^+-ATPase of the gastric parietal cells. Hershko and Ronson [31] and others such as Queiroz *et al.* [28] and Rad *et al.* [32] referred this to owing to blood loss from asymptomatic gastric erosions, impaired absorption of iron owing to increased gastric pH, reduced vitamin B_{12} levels owing to atrophic gastritis, and parietal cell loss.

Other mechanisms such as chronic gastrointestinal blood loss were a well-known cause of iron deficiency anemia, and there was gastric ulceration without gastrointestinal blood loss in a high proportion of the *H. pylori*-infected patients. In addition, we detected increased gastric pH and parietal cell loss in *H. pylori*-infected animals. Therefore, both blood loss from gastric ulceration and *H. pylori*-induced hypochlorhydia (with the resulting impaired iron absorption) probably contributed to the development of anemia [26,33].

Another possibility was that the *H. pylori* bacterial sequestration of free iron affects iron transporter molecules, thereby inhibiting free iron absorption and causing food cobalamin malabsorption. In addition, *H. pylori* gastric colonization required continuous supplementation of nutrients essential for bacterial growth and could use the host's own iron stores. Severe anemia was related to *H. pylori* infection in one case report on school-age children, which recommends screening for *H. pylori* infection and appropriate treatment for severe iron-deficiency anemia [34,27].

Our study showed there was a significant decrease in vitamin B_{12} level in cases infected with *H. pylori*. This is in agreement with Vannella *et al.* [35], Andrès *et al.* [36], Saito *et al.* [37], and Kaptan *et al.* [38]. This might be owing to the presence of antibodies against intrinsic factor and parietal cells and H^+/K^+ ATPase autoantibodies, which were closely linked to classical autoimmune gastritis and were also significant indicators for mucosa atrophy in chronic *H. pylori* gastritis. *H. pylori* infection could cause malabsorption of different micronutrients among which included the vitamin B_{12}.

Likewise, *H. pylori* eradication in vitamin B_{12} deficiency patients was followed by increasing of serum levels of vitamin B_{12} and decreased serum levels of homocysteine. Moreover, it was known that there was an association of *H. pylori* with stomach cancer, and it was already widely recognized by the

scientific community that pernicious anemia was closely related to the development of stomach cancer [39]. This association was recently verified by Vannella *et al.* [35] after a systematic review and meta-analysis showed that the relative risk to develop gastric cancer in patients with pernicious anemia was elevated at 6.8.

The current study showed there was a significant relationship between *H. pylori* infection and thrombocytopenia, which is in agreement with the study published by Department of Biological Engineering, Massachusetts Institute of Technology (2014), and a systematic review by Sato *et al.* [40] of 25 studies (1555 adult patients), all of which included at least 15 patients, which found that platelet counts in patients with ITP tended to increase after *H. pylori* eradication. The possible role of *H. pylori* infection in the development of ITP was a subject of extensive investigation. Systematic reviews of past literature showed an overall platelet response in more than 50% of the patients successfully treated for the infection and increased response rates in countries with a high prevalence of *H. pylori* infection in background populations, that is, in patients with less severe degrees of thrombocytopenia and in those with shorter disease duration [41,14]. As far as the putative mechanisms that may account for such an association were concerned, an Italian group suggested that infection by *H. pylori* strains expressing CagA could play a role in chronic ITP cases, which evoked host systemic immune response that produced autoantibodies that cross-reacted with the host platelet [42,43].

Although a definitive mechanism by which *H. pylori* may induce thrombocytopenia remained elusive, proposed pathways include molecular mimicry of CagA by host autoantibodies against platelet surface glycoproteins, as well as perturbations in the phagocytic activity of monocytes. Traditional treatments of ITP had been largely empirical, involving the use of immunosuppressive agents and immunoglobulin therapy. However, based on the findings of clinical reports emerging over the past 20 years, health organizations around the world increasingly suggested the detection and eradication of *H. pylori* as a treatment for ITP. Elucidating the exact molecular mechanisms of platelet activation in *H. pylori*-positive ITP patients, while considering biogeographical differences in response rates, could offer insight into how best to use clinical *H. pylori* eradication to treat ITP [44].In a multicenter randomized controlled trial performed in Thailand's children with ITP showed that eradication of *H. pylori* led to an increase in platelet counts in patients with ITP [45]. However, some studies had reported that there was no significant improvement of platelet counts after eradication of *H. pylori* infection in patients with ITP [46,47].

However, another study showed that there was a positive relationship between *H. pylori* infection and thrombocytosis as infected gerbils had significantly higher platelet count than uninfected ones [48]. These findings indicated that *H. pylori* colonization of the infected stomach leads to not only a gastric mucosal inflammatory response but also a systemic one.

Our study showed there was no relationship between hypertension and *H. pylori* infection. This was in disagreement with a study by Xu *et al.* [18], which showed that patients with hypertension demonstrated to have higher prevalence of *H. pylori* infection.

Our study showed there was no significant relationship between *H. pylori* and having DM. This was in agreement with Ciortescu *et al.* [49] and Krause *et al.* [50] who did not find any correlation between *H. pylori* infection and glycemic status in both type 1 and 2 DM. On the contrary, Gunji *et al.* [51] performed a study examining the association between *H. pylori* infection and insulin resistance, and results showed that *H. pylori* infection significantly and independently contributed to promoting insulin resistance.

Another study by Wang *et al.* [52] conducted on type 2 DM patients showed that *H. pylori* infection had a significant effect on the daily blood glucose level and blood glucose fluctuation in those patients. Eshraghian *et al.* [53] performed a study and showed that *H. pylori* infection was associated with higher fasting serum insulin levels.

Our study showed that there was a statistically significant relationship between *H. pylori* infection and positive family history. This was in agreement with Eyermann *et al.* [54] who showed that having an infected parent especially an infected mother increased the risk of *H. pylori* infection apart from interfamilial spread.

Conclusion and recommendations
In conclusion, the recognition of hematologic diseases associated with *H. pylori* infection and their inclusion as indications for study and eradication in the international consensus and management guides on *H. pylori* infection, represent a deep change in the management paradigm of these diseases and a great

breakthrough for humanity. Many benefits can be brought by eradiation of the infection, especially those related to gastric cancer, peptic acid disease, and many hematological disorders.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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