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The Relevance of *Helicobacter pylori* Infection to Iron Deficiency Anemia in Duhok City

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Abstract

Background *Helicobacter pylori* (*H. pylori*) infection had been criticized for many deleterious effects and had been amalgamated to iron deficiency by many authors, frequently based on correlative rather than direct relationship studies and often opposed by others.

Objective To evaluate the role of *H. pylori* infection in the etiology of iron deficiency anemia and to study the impact of the bacterial eradication on the response to iron therapy.

Methods The current study represents an interventional prospective study and involved 52 non-pregnant females with iron deficiency anemia. All patients were tested for the presence of active *H. pylori* infection by stool antigen test and they followed after one month of iron therapy. Patients with positive *H. pylori* infection followed for another month after eradication of *H. pylori* and iron therapy.

Results Fifteen patients (28.85%) were positive for *H. pylori*. Hematological and biochemical data were not different among both groups (*H. pylori* positive and negative) at presentation despite significant better response among *H. pylori* negative individuals. Continuation of iron therapy after eradication of *H. pylori* infection improve the response to therapy significantly.

Conclusion Eradication of *H. pylori* enhances the response to iron therapy significantly.

Keywords Iron deficiency anemia, *H. pylori*, iron therapy, eradication

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List of abbreviations: *H. pylori* = *Helicobacter pylori*, Hb = Hemoglobin, IDA = Iron deficiency anemia

Introduction

Anemia is one of the common disorders that disturbs a quarter of the population worldwide, and the higher prevalence is found among preschool-age children and the menstruating females [1-3]. As the hemoglobin (Hb) is the most abundant iron-containing protein in humans, and anemia is a characteristic trait of iron deficiency, thus, iron deficiency anemia (IDA) is considered to be the most common nutrient deficiency and the most common cause of anemia globally [4]. Iron deficiency anemia by many researchers has been related to a longer stay in hospital and reduced life expectancy [5]. IDA is a consequence of depletion of the iron stores because of either diminished iron uptake or increased iron loss/use. Body iron homeostasis is mainly through controlling iron entrance to the body rather than controlling its excretion as the body has limited excretion capacity and the gastrointestinal tract is a common site of blood loss and their diseases may cause malabsorption of iron [6].

Some studies showed that *Helicobacter pylori* (*H. pylori*) infection is linked to the increased probability of diminished iron storage, and *H.*

pylori eradication therapy may be beneficial in increasing ferritin levels. Several reported data supported the efficacy of *H. pylori* treatment in moderately to severely anemic patients compared to those with mild anemia. Nonetheless, it should be noted that some studies show negative correlations between *H. pylori* infection and IDA. It is now recommended that *H. pylori* infection must be tested and treated in patients with unexplained IDA [7].

A conflicting data exist about the relation of *H. pylori* infection to the etiology of IDA and the response of patients to therapy; thus, this study had been initiated to evaluate the role of *H. pylori* in IDA particularly in our locality in Iraq.

Methods

The current study represents a quasi-experimental interventional prospective study and performed at Azadi Teaching Hospital at Dohuk City, Iraq. Sample collection was done in a period of six months, from September 1st, 2019 to February 29th, 2020. The study was approved by the Ethical Committee at the Directorate of Health/ Duhok. A total of 52 patients (females), diagnosed as IDA by clinical and laboratory screening were enrolled in this study. All patients were from Duhok Governorate. Any female with age lower than 18 years, gastrointestinal bleeding, pregnancy, lactation, heavy vaginal bleeding, or chronic or significant diseases including chronic inflammatory diseases like rheumatoid arthritis or systemic lupus erythematosus were excluded from the current study.

At first, the process was explained to the patients and informed consent taken from all enrolled individuals. Then 3 ml of peripheral venous blood was taken by a clean and appropriate venipuncture technique from each patient. One milliliter in a sterilized tube containing EDTA, mixed well and subjected for complete blood count using Swelab Hematology Analyzer (Ds Biomed, Sweden) and the remaining 2 milliliters of blood in a gel tube with clot activator for the biochemical test including serum iron, unbound iron-binding capacity, transferrin saturation and serum ferritin using Cobas 6000 (Roche-Germany). All selected patients were tested also for the presence of active *H. pylori* infection by stool antigen using the One-Step *H. pylori* Antigen Test Kit (Plasmatec laboratory products, UK); infected patients were received oral iron therapy then re-assessed after one month and then received eradication therapy with oral iron therapy and re-assessed after another month, while patients with negative *H. pylori* infection received only oral iron therapy and assessed after one month. After data collection, data were analyzed using statistical package for social sciences (SPSS), version 24.0 (2016). Student t-test was used for comparison of continuous variables, and chi-square or Fisher exact tests were used for comparison of categorical variables. Two-sample paired t-test was used to assess the response and the P-value were considered to be significant if it's less than 0.05.

Results

Demographic data of all individuals are shown in (Table 1) and it reveals a total of 52 females with IDA had been enrolled in the current study with age ranging from 18-45 years (median 30±7.58 years). From these, 15 (28.85%) patients had *H. pylori* antigen in the stool and the remaining 37 (71.15%) were negative for *H. pylori* antigen.

Their hematological data reveals that the majority had mild 24/52 (46.15%), to moderate 21/52 (40.39%) anemia and only 7/52 (13.46%) had severe anemia. Regarding the severity of anemia among both groups; a majority of patients with *H. pylori*-positive had moderate 6/15 (40%) to severe anemia 4/15 (26.67%) in comparison to *H. pylori*-negative females who had mild 19/37 (51.35%) to moderate 15/37 (40.54%) anemia. No significant difference was seen among both groups (P= 0.09). There were no statistically significant differences in the Hb, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), iron, total iron binding capacity (TIBC), transferrin saturation (Ts), and ferritin levels between patients with or without *H. pylori* infections with P-value consistently more than 0.05 for the above-examined parameters.

Table 1. Characteristic of patients with *H. Pylori* positive and negative

Parameters	*H. pylori* positive (N = 15) Mean ± SD	*H. pylori* Negative (N = 37) Mean ± SD	P value
Age (Years)	32.20 ± 7.514	28.81 ± 7.486	0.152
≤20 (Years) (No.)	1	7	
21-30 (Years) (No.)	6	15	
31-40 (Years) (No.)	6	12	
>40 (Years) (No.)	2	3	
Hb (g/dl)	9.15 ± 1.19	9.78 ± 1.158	0.095
10-11.9 (g/dl) (No.)	5	19	
8.0-9.9 (g/dl) (No.)	6	15	
<8.0 (g/dl) (No.)	4	3	
PCV (%)	29.00 ± 3.41	30.92 ± 2.881	0.070
MCV (fl)	67.03 ± 4.28	68.59 ± 4.597	0.247
MCH (pg)	21.15 ± 2.03	21.65 ± 2.226	0.562
IRON (µg/dl)	31.37 ± 1.79	28.30 ± 6.916	0.521
TIBC (µg/dl)	405.07 ± 62.05	447.51 ± 50.390	0.539
Transferrin saturation (%)	6.95 ± 2.38	6.30 ± 1.777	0.320
Ferritin (ng/ml)	6.00 ± 2.21	7.14 ± 3.002	0.118

After one-month oral iron therapy in *H. pylori*-negative patients and using a two-sample paired t-test, results showed a statistically significant difference in the all examined parameters including Hb, PCV, MCV, MCH, Iron, TIBC, Ts and ferritin (Table 2).

Table 2. Hematological and biochemical parameters difference after Oral iron therapy among H. pylori negative (N = 37)

Parameters	Before Treatment	After treatment	Mean difference	P value
Hb (g/dl)	9.78±1.16	11.97±1.02	2.20	< 0.001
PCV (%)	30.93±2.82	36.38±3.08	5.47	< 0.001
MCV (fl)	68.65 ± 4.60	78.53±4.79	9.88	< 0.001
MCH (pg)	21.69 ± 2.18	25.82 ± 1.99	4.13	< 0.001
IRON (µg/dl)	31.55 ± 1.59	32.85 ± 1.38	1.30	<0.001
TIBC (µg/dl)	419.22 ±51.38	298.78±59.34	120.43	< 0.001
Transferrin saturation (%)	6.31 ± 1.74	18.61 ± 9.70	12.30	< 0.001
Ferritin (ng/ml)	7.16 ± 2.91	17.24 ± 5.88	10.08	< 0.001

The result among *H. pylori*-positive showed lesser changes in all examined parameter, though the statistically significant difference in the all examined parameters including Hb, PCV, MCV, MCH, Iron, TIBC, Ts and ferritin (Table 3) and with the eradication of *H. pylori* further significant increment seen per the second months but still lower than *H. pylori*-negative patients (per month), however, after considering the response of the two months of therapy, the result showed highly significant changes with normalization of all parameter including the S. ferritin.

Table 3. Hematological and biochemical parameters difference among H. pylori positive (N = 15) after first month; second month (after *H. pylori* eradication) and both months together following oral iron therapy

Parameters	Before Treatment	After treatment First month			After second month treatment and *H. Pylori* eradication			Two months taken together	
			Mean difference	P value		Mean difference	P value	Mean difference	P value
Hb (g/dl)	9.15 ± 1.19	10.88 ± 1.05	1.73	< 0.001	12.53 ± 0.72	1.65	< 0.001	3.38	< 0.001
PCV (%)	29.00 ± 3.41	33.79 ±3.5.79	4.79	< 0.001	37.49 ± 2.24	3.69	< 0.001	8.49	< 0.001
MCV (fl)	67.03 ± 4.28	73.49 ± 2.87	6.45	< 0.001	81.14 ± 2.95	7.65	< 0.001	14.11	< 0.001
MCH (pg)	21.15 ± 2.03	23.66 ± 1.05	2.51	< 0.001	27.1 ± 1.26	3.44	< 0.001	5.95	< 0.001
IRON (µg/dl)	31.37 ± 1.79	32.19 ± 1.25	0.83	0.037	75.07 ± 22.63	28.13	<0.001	44.67	0.002
TIBC (µg/dl)	405.07 ± 62.05	367.67 ± 56.83	67.8	< 0.001	339.0 ± 51.37	28.67	0.107	96.47	< 0.001
Transferrin saturation (%)	6.95 ± 2.38	13.08 ± 6.05	6.14	< 0.001	21.91 ± 7.28	8.83	< 0.001	14.97	< 0.001
Ferritin (ng/ml)	6.00 ± 2.21	12.25 ± 3.61	6.26	< 0.001	21.76 ± 5.67	9.51	< 0.001	15.76	< 0.001

Tables 4 shows the average increment in the Hb, PCV, MCV, MCH, S. Iron and S. ferritin and decrement in the TIBC in both *H. pylori*-negative and *H. pylori*-positive (the first month before *H. pylori* eradication; the second month of iron therapy following eradication of *H. pylori* and two months together) patients and they reveal significant higher response among *H. pylori*-negative patients to iron therapy in the first month in MCV, MCH, S. Iron and S. ferritin; significant higher response in the second month in Hb, PCV, and TIBC; and significantly better response among H. pylori-positive patients in the Hb, PCV, MCV, MCH, S. ferritin if 2 months taken together.

Table 4. Mean changes in the hematological and biochemical parameters among *H. pylori* negative following iron therapy and *H. pylori* positive (first moth of iron therapy alone); (second month of iron therapy + *H. pylori* eradication) and (combined first- and second-months including *H. pylori* eradication)

Parameters	*H. pylori* Negative (N = 37) Mean ± SD	*H. pylori* positive (N = 15) Mean ± SD					
	First month only	First month only	P value (1)	Second month only	P value (2)	Both months together + *H. pylori* eradication	P value (1+2)
Hb (g/dl)	2.20 ± 0.78	1.73 ± 1.24	0.105	1.65 ± 0.69	0.022	3.38 ± 1.32	<0.001
PCV (%)	5.457 ± 2.78	4.793 ± 3.87	0.482	3.69 ± 2.19	0.032	8.49 ± 3.00	0.001
MCV (fl)	9.88 ± 4.14	6.45 ± 5.00	0.013	7.65 ± 3.11	0.066	14.11 ± 4.62	0.002
MCH (pg)	4.12 ± 1.42	2.51 ± 1.81	0.001	3.44 ± 1.35	0.115	5.95 ± 2.43	0.001
IRON (µg/dl)	37.41 ± 25.86	16.53 ± 16.63	0.005	28.13 ± 20.11	0.219	44.67 ± 17.98	0.326
TIBC (µg/dl)	-79.97 ± 46.20	-67.8 ± 43.02	0.385	-28.67 ± 64.43	0.002	-96.47 ± 77.34	0.346
Transferrin saturation (%)	12.30 ± 9.59	6.14 ± 5.05	0.02	8.83 ± 5.48	0.195	14.97 ± 5.88	0.322
Ferritin (ng/ml)	10.08 ± 4.84	6.26 ± 4.04	0.009	9.51 ± 4.68	0.697	15.76 ± 6.03	<0.001

Discussion

The prevalence of *H. pylori* shows large geographical variations reaching up to 50% of the population in some developing countries, while the prevalence of *H. pylori* in industrialized countries generally remains under 40% and is considerably lower in children and adolescents than in adults and elderly people [8].

The current study revealed no significant difference between *H. pylori*-positive and negative patients in Hb, PCV, MCV, MCH, S. iron, Ts, TIBC and ferritin; similar results were shown in studies from Turkey and from Iran in which they suggest no correlation between *H. pylori* infection and IDA without assessing treatment response [9,10]. Another study from Egypt has shown almost same results but they found significant results after treatment among *H. pylori*-infected patients [11] and their data augment the current results of a significant better response to iron replacement therapy among *H. pylori*-negative individuals, however a study from Alaska found a significant association between low serum ferritin levels and the prevalence of *H. pylori* infection, also a German study found significantly lower levels of hemoglobin in pregnant women suffering from *H. pylori* infection [12,13]. Moreover, an American study found that those who were seropositive for *H. pylori* infection had significantly lower serum ferritin levels compared with seronegative individuals [14]. This variability in studies could be due to differences in the geographical and ethnic distribution of patients, age, sample size, sampling procedures, methods of detecting anemia, and methods of detecting H. pylori infection.

Following one month of therapy with iron, the changes in MCV, MCH, S. iron, Ts, and ferritin were significant, while they were non-significant in Hb, PCV, and TIBC and these changes were concordances with data from Egypt, China and from Israel [11, 15-17].

After *H. pylori* eradication and continuous therapy with oral iron in *H. pylori*-positive group patients, results showed a statistically significant difference in the Hb, PCV, MCV, MCH, iron, TIBC, Ts and ferritin and with the consideration of the results of the last month after eradication of *H. pylori*, the significant difference still can be observed with the continuation of the iron therapy in all examined parameters (HB, PCV, MCV, MCH, iron and ferritin) except TIBC, this is considered the most reliable evidence for a cause-effect relationship between *H. pylori* infection and IDA. This result corroborated many other studies that showed that the eradication of *H. pylori* shows significant improvement in iron stores with or without hematological response such as from Israel [17,18], Egypt [11], China [15,16], and from India [19], which support our results. However, some other studies show a negative relation between *H. pylori* eradication and IDA from the USA [20] and Bangladesh [21].

Different mechanisms had been claimed to explain the impaired response to iron therapy among *H. pylori*-positive individuals including mucosal lining penetration by the bacteria to establish infection [8], chronic gastritis with impaired absorption, peptic ulcer with continuous iron loss [22].

In conclusion, hematological and biochemical parameters were not different among both *H. pylori*-positive and -negative patients. Patients without *H. pylori* infection show significantly better response to iron therapy than patients with *H. pylori* infection and eradication of *H. pylori* improve the response to iron therapy significantly.

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Author contribution

Dr. Eissa: Analysis of data and manuscript preparation. Dr. Mirza: data collection.

Conflict of interest

The authors declare that they have no competing interests in this work.

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