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Relationship between Helicobacter Pylori infection and iron deficiency anemia in hemodialysis patients

Dr. Mohamed Mahmoud Nuseir[1], Dr. Ayman AbdelAzize Abdel Rhman[2], Dr. El-Sayed farag El-sayed[3*]

[1] Professor of Internal Medicine, Faculty of Medicine, Al-Azhar University, Assuit, Egypt

[2] Assistant Professor of Internal Medicine, Faculty of Medicine, Al-Azhar University, Assiut, Egypt

[3] Resident of Internal Medicine Department Faculty of Medicine –Al-Azhar University, Assiut, Egypt

Abstract

Background: Many studies in the general population have shown a link between Helicobacter pylori infection and iron-deficiency, often resulting in iron-deficient anemia. Despite the high prevalence of iron deficiency in hemodialysis patients, no studies have been performed in this population.

Objective: To evaluate the role of Helicobacter pylori infection in the appearance of anemia and the iron requirements in our hemodialysis population.

Material and methods: After excluding patients with severe pathology and short life expectancy and those with blood losses secondary to other causes, 90 patients were included. Iron requirements and anemia were determined by serum iron, ferritin, and hematocrit values; and by transfusion, erythropoietin and iron requirements. The diagnosis of Helicobacter pylori status was established by fecal antigen of Helicobacter.

Results: Prevalence of Helicobacter pylori infection was 55.6%. No significant differences Between patients infected or not by Helicobacter pylori were found in any of the variables analyzed, serum iron in H. pylori positive group was lower than in H. pylori negative group (86 ± 17.5 vs. 87 ± 18.2 ug/dl) but it was not statistically significant (p=0.960) Biochemical studies revealed that mean TIBC in H. pylori positive group was higher than in H. pylori negative group (321.1 ± 95.0 vs. 295.1±101.0 ug/dl) but it was. not statistically significant (p=0.232), Regarding Transferrin saturation, it was lower in H. pylori positive group than in H. pylori negative group (26.79 % ± 18.42 % vs. 29.83% ± 18. 01 %) but it was not statistically significant (p=0.596) that mean serum ferritin in H. pylori positive group was lower than in H. pylori negative group (284.8 ± 60,5 vs. 301.4 ± 50.1 ng/dl) but it was not statistically significant (p=0.069).

Conclusion: H. pylori was found in 55.56% of studied patient, no relation between dyspeptic symptom and H. pylori infection was found, H. pylori infection does not have any influence on anemia severity or iron deficiency in these patients.

Keywords: helicobacter pylori, anemia, hemodialysis

Introduction

Helicobacter pylori is a Gram-negative bacterium that colonizes the human gastric mucosa of approximately 50% of the human population and induces a chronic inflammatory process. The infection can remain active in gastric mucosa for decades and may progress into peptic ulcers, delayed healing of ulcer, mucosa associated lymphoid tissue (MALT) lymphoma and gastric cancer. (GC). Accordingly, H. pylori was classified as a type I carcinogen by the WHO. The H. pylori pathogenic mechanisms are complex, but one of the best recognized virulence factors involved in carcinogenesis is the CagA protein and the presence of the type four secretion system (T4SS) encoded in the cag pathogenicity island (cagPAI) [1]. The molecular syringe encoded by the cag PAI is used to inject the Cag A oncoprotein into the gastric epithelial cells inducing a pro-inflammatory and antiapoptotic response, affecting cell-to-cell communication by disrupting the tight junctions, and altering cell motility with cytoskeletal rearrangements [2]. Several other genes might be associated with disease development and analysis at whole genome level is necessary to better understand the mechanisms involved in cancer pathogenesis. Currently, the National center for biotechnology reports over 500 H. pylori genome sequences obtained from strains of different geographical regions around the world, although most of these sequences are not fully assembled [3]. H. pylori infection results in decreased host ability to transport iron for further use by the body [4]. The pathogen is competing with the host for iron, by decreasing the amount of iron available for use by the host. H. pylori infection increases the amount of iron in AGS cells, perturbing intracellular iron homeostasis [5]. Another mechanism by which H. pylori infection may contribute to iron deficiency is through alteration of gastric pH. H. pylori infection may progress to atrophic gastritis with loss of parietal cells, which results in hypochlorhydria or achlorhydria, potentially causing or exacerbating IDA [6]. This occurs because the absorption of dietary iron is dependent upon an acidic gastric environment for reduction of ferric iron to the ferrous form this is the only form of iron that can be transported across the luminal membrane of enterocytes. Gastrin levels, at both the serum and local level, also affect absorption of iron in the stomach [7]. There is a growing body

of literature that supports the important role that the gut-brain axis plays in central nervous system function [8]. The diagnosis of iron-deficiency anemia in CKD is difficult. The most common biomarkers used to gauge the sufficiency of iron storage are ferritin concentration and transferrin saturation. Both ferritin concentration and transferrin saturation decline in iron-deficiency anemia. The thresholds of ferritin and transferrin at which iron stores are deficient are not known. Although opinions exist on what these thresholds should be, the scientific evidence to back these thresholds is soft. Ferritin, for example, is a positive acute-phase reactant. In other words, its concentrations increase in the setting of inflammation. Transferrin, conversely, is a negative acute-phase reactant; its concentrations decrease in patients with inflammation. Accordingly, in an iron-deficient patient, the ferritin concentration may be high and transferrin saturation may be low even in the setting of inflammation [9].

Patients and methods

This is a cross sectional study included 90 adult patients with end-stage renal disease (ESRD) on maintenance hemodialysis randomly selected from dialysis unit in Al-Azhar university. All patients were subjected to Signing of informed written consent for approval to participate in this study, Full history & clinical examination including information on age, sex, upper gastrointestinal symptoms (epigastric pain, epigastric burning, postprandial fullness, early satiety, bloating and belching), co-morbidities (DM and HTN), Blood transfusion frequency and medication (antibiotics, NSAIDs, iron supplementation, erythropoietin stimulating agents, proton pump inhibitors). Laboratory tests including H. Pylori antigen in stool was detected by using enzyme linked immunoassay [10]. Complete blood count, patient considered anemic if Hb Less than 10 g/dl. Iron study (serum ferritin, serum iron, total iron binding capacity, Transferrin saturation), IDA was diagnosed if TSAT less than 30%, S. Albumin, C-reactive protein (normal titer is below 6). Venous blood samples were collected during the mid-week HD session and before heparin administration. Blood samples were collected from the patients by vacuum venipuncture, using a dry 5-mL tube. The serum was separated, centrifuged, aliquoted and stored at -20°C.Stool samples were collected from patients in boxes given to them to attain stool at home, H. pylori stool antigen was detected by using International Immuno-Diagnostics MICRO WELL ELISA© [11]. All patient are ESRD on regular hemodialysis for at least 6 months before study, Older than 18 years at time of the study, Stoppage antacids, proton pump inhibitors, antibiotics and iron therapy for 1 month before enrollment in the study. Exclude patient which Refusal to participate in this study, Clinical evidence of acute cardiovascular events (acute coronary syndrome, acute heart failure or acute arrhythmias.), Patients with severe associated pathologies (e.g. malignancy, advanced liver disease). Patients on immunosuppressive drugs, Patients with obvious clinical causes of blood losses (e.g. hematemesis, epistaxis, operation or trauma),

Chronic active infection (e.g. TB, infected shunt), Patients known to be smokers or chronic non-steroidal anti-inflammatory drugs users and Patients with active collagen disease.

Results

This study included 90 adult patients with ESRD on hemodialysis the mean age of patients was 47 ± 15, Males number was 62 (69%) and females was 28 (31%). 50 % of patients had GIT symptoms in the form of epigastric pain, vomiting, dyspepsia and reflux symptoms 38 % of patients had DM, and 58 % had HTN. According to the Results of H. pylori stool, antigen, Patients were divided into two groups:

*Group 1: Positive H. pylori stool antigen.

* Group 2: Negative H. pylori stool antigen.

It was found that H. pylori stool antigen was positive in 50 patients (55.6%), while 40 patients were negative H. pylori (44.4%). Positive H. pylori group (35 men and 15 women with mean age 48.3±14.5 yr.) and negative H. pylori group (27 men and 13 women with mean age 45.4 ±15.8 yr.). No significant statistical differences were found between mean ages and sex (p=0.105, p=0.999) respectively, as shown table

Table 1: Comparison between the positive and negative Helicobacter pylori cases according to age.

Age (years)	Positive H. pylori	Negative H. pylori
Mean	48.33	45.40
+SD	14.53	15.80
t.test	1.675	
p. value	0.105	

Table 2: Comparison between the positive and negative Helicobacter pylori cases according to sex.

Sex			+ve H. pylori	-ve H. pylori	Total
Male		**N**	**35**	**27**	**62**
		%	70%	67.5 **%**	68.88 %
Female		N	15	**13**	28
		%	30%	32.5 %	31.12%
		N	50	40	90
Total		%	100.0%	100.0%	100.0%
Chi-	X^2	1.00			
Square	P-value	0.999			

Anemia and iron status

The results of biochemical studies revealed that mean serum iron in H. pylori positive group was lower than in H. pylori negative group (86 ± 17.5 vs. 87 ± 18.2 ug/dl) but it was not statistically significant (p=0.960) as shown in table (3).

Table 3: Comparison between the positive and negative Helicobacter pylori cases according to serum iron level.

S. iron ug/dl	Positive H. pylori	Negative H. pylori
Mean	86	88
±SD	17.52	18.27
t. test	0.403	
p. value	0.960	

Biochemical studies revealed that mean TIBC in H. pylori positive group was higher than in H. pylori negative group (321.1 ± 95.0 vs. 295.1±101.0 ug/dl) but it was not statistically significant (p=0.232) as shown in table (4).

Table 4: Comparison between the positive and negative Helicobacter pylori cases according to serum TIBC level.

TIBC ug/dl	Positive H. pylori	Negative 11. pylori
Mean	321.1	295.1
±SD	95.09	30.08
t. test	1.077	
p. value	0.232	

Regarding Transferrin saturation, it was lower in H. pylori positive group than in H. pylori negative group (26.79 % ± 18.42 % vs. 29.83% ± 18. 01 %) but it was not statistically significant (p=0.596) as shown in table (5).

Table 5: Comparison between the positive and negative Helicobacter pylori cases according to Transferrin saturation,

T. sat. %	Positive H. pylori	Negative H. pylori
Mean	28.79 %	29.83 %
±SD	18.42%	18.01%
t. test	0.740	
p. value	0.596	

Serum ferritin in H. pylori positive group was lower than in H. pylori negative group (284.8 ± 60,5 vs. 301.4 ± 50.1 ng/dl) but it was not statistically significant (p=0.069) as shown in table (6).

Table 6: Comparison between the positive and negative Helicobacter pylori cases according to serum ferritin level.

ferritin ng/mi	Positive H. pyion	Negative H. pylori
Mean	284.8	301.4
±SD	60.5	50.1
t. test	1.523	
p. value	0.069	

Hemoglobin concentration was lower in H. pylori positive group than in H. pylori negative group (8.96±1.8 vs.9.76±1.4 g/dl) respectively with (p = 0.325) which was not statistically significant.

Table 7: Comparison between the positive and negative Helicobacter pylori cases according to hemoglobin level.

HB g/dl	Positive H.pylori	Negative H.pylori
Mean	9.06	9.76
±SD	1.87	1.42
t. test	1.273	
p. value	0.325	

Nutritional and Inflammatory status

Albumin as a marker of nutritional status, was lower in H. pylori positive group than in H. pylori negative group (3.26 ±1.3 vs. 3.46 ± 1.4 g/dl) respectively with (p=0.325) which was not statistically significant, as shown in table (8).

Table 8: Comparison between the positive and negative H. pylori cases according to albumin level.

Albumin g/dl	Positive H.pylori	Negative H.pylori
Mean	3.26	3.46
[±SD	1.37	1.42
t. test	1.273	
p. value	0.325	

C reactive protein (C-RP) as a marker of inflammatory status, was higher in H. pylori positive group than in H. pylori negative group (13 ± 8 vs. 11 ± 7 mg/dl) respectively with (p =0.215) which was not statistically significant, as shown in table 9.

Table 9: Comparison between the positive and negative Helicobacter pylori cases according to C-RP level.

CRP mg/dl	Positive H.pylori	Negative H. pylori
Mean	13	11
±SD	8	7
t. test	1.273	
p. value	0.325	

Discussion

Helicobacter pylori is a Gram-negative, flagellated bacteria which was first isolated in 1983 by Warren and Marshall. It is widely prevalent with approximately 50% of the Western world and over 80% of those living in developing countries infected with the bacterium **(11).** Initial infection typically occurs during childhood after oral ingestion and the bacterium persists for the life of the host unless treated [12]. Person to person transmission via contact with infected secretions is the most likely means of transmission [13]. Clinically, H. pylori have been associated with a number of diseases including peptic ulcer disease, gastric cancer, and MALT lymphoma. But, despite the high prevalence of infection, H. pylori produce symptoms in only a minority of patients [14]. Routine screening is not recommended, but any individual with confirmed gastric or duodenal ulcers, or MALT lymphoma, should be tested [15]. The urea breath test, serologic tests for anti- H. pylori antibodies, and the stool antigen test are all reliable, noninvasive diagnostic methods [16]. Effective treatments are readily available and consist of antibiotics and either a proton pump inhibitor or an H2 receptor antagonist for 7–14 days. The stool antigen test should be used to confirm eradication 8 weeks after therapy [16].

Anemia is a common complication in patients with chronic kidney disease (CKD), developing gradually and increasing in severity as kidney disease progresses [17]. The prevalence of anemia (hemoglobin #12 g/dl) is high (47.7%) in patients with non-dialysis CKD and increases as CKD progresses, being present in approximately 42% of patients with stage 3 CKD, increasing to approximately 76%in stage 5 CKD [17]. Erythropoietin (EPO) deficiency remains the major cause of anemia in CKD patients due to the decrease in renal EPO production [18]. Nephrologists have been focusing on iron Deficiency in hemodialysis patients and intravenous iron is routinely administered during the dialysis sessions. Iron loss in dialysis patients has been related to several factors such as blood loss from dialyzer and tubing, regular blood tests, impaired dietary iron absorption and gastrointestinal losses [18]. Iron deficiency, whether caused by a nutritional deficiency or through chronic blood loss due to endo parasitism or neoplasia, is a serious public health problem worldwide [19]. Infectious diseases such as H. pylori have gained recognition as important contributors to the development of ID/IDA, and there is interest in elucidating the mechanism of pathogenesis. H. pylori is able to disturb host cell polarity to use the apical cell surface as a replicative niche, and disrupts host

intracellular iron-trafficking in vitro. This is a novel mechanism of iron acquisition by H. pylori, and represents a means by which H. pylori infection results in decreased host ability to transport iron for further use by the body [4].

Helicobacter pylori is specially adapted to survive in the gastric lumen requiring metabolizing urea into ammonia. ESRD patients present urea levels within the gastric lumen considerably, higher than those for the associated with a higher predisposition to H.pylori infection [20].

However, significant differences in H.pylori infection prevalence have not been observed between HD patients and general population, H.pylori infection rates being 30-70% depending on the diagnostic technique used and the population studied [21]. Some works even report an infection rate somewhat lower among dialysis patients [22].

In this study, H.pylori infection prevalence is 55.6 %similar to that observed in other studies on HD patients [21, 23] and lower than the one expected in tire general population, as prevalence of H. pylori infection in Egypt in general population was variable, in one report was 68.9% [24].

In dialysis patients the presence of dyspeptic symptoms is common presenting as nausea, vomiting, heartburn, as well as the existence of gastro duodenal pathology (gastritis and duodenitis) [25].

In this study, dyspeptic symptoms were assessed without observing statistically significant differences between H.pylori infected and non-infected groups, thus not being able to ascribe dyspeptic symptoms in our patients due to the presence of H. pylori infection.

Where as in the general population H.pylori infection may be associated with the presence of dyspeptic symptoms, the results from studies were controversial in HD patients, Whereas Ala-Kaila *et al.*, showed a greater prevalence of dyspeptic symptoms [26]. In H.pylori infected dialysis patients, other authors have not find any relationship [27].

The origin of dyspepsia in HD patients is multifactorial, with the participation of factors related with uremia, stress, concomitant medication, and associated pathologies [25].

In this study, no significant differences was found between H.pylori infected and non-infected patients for hemoglobin levels, neither for S.iron, T1BC, ferritin nor TSAT.

Trimarchi *et al*. carried out a study on 29 HD patients; they did not observe any significant difference between H.pylori infected and non-infected groups for hemoglobin or hematocrit levels, neither for iron levels [28].

Lopez *et al*. studied 79 HD patients, found that 34 from 79 patients were H.pylori positive and 45 from 79 patients were H.pylori negative, they observed no difference. Correlation between H. pylori infected and non- infected groups [25].

On the opposite side, Fahbian *et al*. earned out endoscopic studies on 51 patients on HD, assessing the presence and degree of anemia in them- Tkey-nsteerved. That H.pylori infection was independently related with hemoglobin decrease [29].

Also, Nasri conducted a study on 39 patients on HD to assess the relation between anemia and H.pylori infection, and found that H.pylori aggravates anemia and causes IDA [30].

Some works have observed an association between the presence of H.pylori infection and nutritional and inflammatory status of HD patients. H.pylori infected patients showed lower albumin value and higher C reactive protein values, parameters that significantly improve after clearance of this germ [31].

In this study, we did not observe significant differences between the groups in albumin levels or inflammatory parameters analyzed (C reactive protein).

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