Original Article

Assessment of Association of Helicobacter Pylori Infection with Anaemia among Dyspeptic Patients in Tertiary Care Centre of Eastern India

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ABSTRACT

Introduction: H. pylori infection leads to anaemia by causing impairment in iron absorption due to chronic gastritis which causes gastric hypochlorhydria. It leads to impairment in reduction of the dietary iron from the ferric to ferrous form. Most dietary iron is in the ferric form and requires an acidic gastric pH and ascorbic acid to reduce it to the ferrous form for absorption. However, reports from different regions and countries are inconsistent regarding this association between anaemia and H. pylori infection, and the underlying mechanisms remain obscure.

Aims/ objective: To determine the association between H. pylori infection and anaemia in the Indian population.

***Materials* and Method:** A faecal sample of approximately 5 grams was collected from each dyspepsia patient and it was checked for the presence of H. pylori antigen. For laboratory data, 4 mL venous blood samples were collected in ethylene di-amine tetra-acetic acid (EDTA) tubes and analysed for haematological parameters using an automated haematology analyser. Anaemia was defined as a haemoglobin level ≤13.0 g/L for men and ≤12.0 g/L for women according to WHO gender-based criteria. Statistical significance between different groups was tested using chi-square test for categorical variables and independent t-test for continuous variables. A two-sided $P < 0.05$ was considered statistically significant.

Results: Out of 199 dyspeptic patients, 86 (43.22) tested positive for H. pylori antigen and 22 (11.06%) were anaemic. There were 13.95% dyspeptic patients with h. pylori infection as compared to 8.85% dyspeptic patients that tested negative for H. pylori antigen. Also, prevalence of moderate to severe anaemia was higher in H. pylori positive dyspeptic patients (4.65) as compared to H. pylori negative ones (1.77). But these differences were not statistically significant. Most of the patients were having normocytic anaemia followed by microcytic hypochromic anaemia.

Conclusion: We have found greater prevalence of anaemia in dyspeptic patients who had H. pylori infection. Routine screening and treatment of Helicobacter pylori and intestinal parasitic infections in adults with dyspepsia and large-scale community-based studies are recommended.

Keywords: Helicobacter Pylori, Anaemia, Dyspepsia, Haematological Parameter.

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INTRODUCTION

Anaemia is a universal public health problem affecting both developed and developing countries.[1] One study reported a global anaemia burden of 32.9% across all age groups combined.[2] Anaemia has serious health, social and economic consequences.[3] Infectious diseases affect the physical and work capacity of adults. [4, 5]

Identifying factors that may contribute to anaemia in different settings is critical to combating that burden and appropriately managing anaemic patients. Several studies have identified different factors associated with anaemia in adults.6-8 Recently, H. pylori infection has been associated with haematological conditions such as anaemia, iron and vitamin B12 deficiency. [9-11]

Helicobacter pylori (H. pylori) is a spiral-shaped pathogenic bacteria found in the human gastric mucosa, and its prevalence remains high in many parts of the world.[12] The prevalence of H. pylori infection was found to range from 8.7% to 85.5%, which generally increases with age and differs widely by geographic location, sex, race, ethnicity and socio-economic status.[13, 14] H. pylori infection has a major role in the pathogenesis of chronic gastritis, but the impact of its infection on haematological system diseases is not well explored.[15]

Colonization of the stomach by Helicobacter pylori generally lasts for decades and requires a continuous supply of nutrients essential for bacterial growth. [16] Rostami-Nejad et al. reported that H. pylori infection was associated with anaemia in which iron deficiency was detected and also in celiac disease patients. The

recommendation was strongly evidence based but it is weakly reflected in practice.[17] A range of evidence from epidemiological and clinical research indicate an association between anaemia and H. pylori infection.

H. pylori infection leads to anaemia by causing impairment in iron absorption due to chronic gastritis which causes gastric hypochlorhydria. It leads to impairment in reduction of the dietary iron from the ferric to ferrous form. [18, 19] Most dietary iron is in the ferric form and requires an acidic gastric pH and ascorbic acid to reduce it to the ferrous form for absorption. [20] Hence, H. pylori is therefore the main cause of chronic superficial gastritis, causing atrophy of the gastric glands and resulting in decreased gastric acid secretion. [21]

Helicobacter pylori absorb iron to compete with its host for growth. Increased hepcidin production as a result of Helicobacter pylori infection reduces the release of iron from macrophages and enterocyte. [4, 22] This is due to action of hepcidin as an acute-phase reactant in response to the inflammation induced in the gastric mucosa which results in anaemia of inflammation or chronic disease.[19] Other possible mechanisms include iron loss due to haemorrhagic gastritis and actively bleeding gastric ulcers. [23]

Helicobacter pylori infection is a common microbial infection worldwide, affecting 48.6% of the adult population worldwide.[24] It has been reported more frequently in dyspeptic patients and some studies have reported the prevalence of anaemia higher than 70 %.[25-27]

However, reports from different regions and countries are inconsistent regarding this association between anaemia and H. pylori infection, and the underlying mechanisms remain obscure. The studies to date have been incomplete and have significant shortcomings, as noted in meta-analyses including various studies on anaemia and Helicobacter pylori.[28] First, studies on H. pylori infection and anaemia were more focussed on women and children, especially pregnant women, than in the general population, and the sample size was relatively small. In most studies, the severity and type of anaemia were also not considered. Therefore, we conducted this study to investigate the association between H. pylori infection and anaemia in the Indian population.

MATERIALS AND METHODS

This was a cross-sectional study carried out in department of pathology in collaboration with department of general medicine in a tertiary care centre of eastern India. The anticipated risk to the patients as per the study plan was less than minimal, so the study was exempted from full review of institutional ethic committee. The study was conducted under the principle of Good Clinical Practice and declaration of Helsinki. The study duration was from August 2020 to July 2021.

Sampling Method: The sample size was calculated by using a single population proportion formula considering a 95% confidence interval (CI), a 5% margin of error and an anticipated 30 % prevalence of anaemia. After adding (10%) anticipated non-response rate the final sample size was found to be 199.

Inclusion Criteria: All consecutively identified adult dyspepsia patients of any gender and ≥18 years of age with dyspepsia symptoms were included in the study until the sample size was reached.

Exclusion Criteria: Patients treated for H. pylori infection within the past 3 months, gastric or small bowel surgery within the past 3 months, blood transfusion within the past 3 months, and anaemia treated prior to data collection, pregnant women and critically ill patients were excluded.

Participant information sheet was given and explained to all the study participants and written informed consent was taken from them.

A faecal sample of approximately 5 grams was collected from each dyspepsia patient and H.I. pylori antigen was analysed. For laboratory data, a laboratory technician collected 4-ml venous blood sample from each dyspepsia patient into an ethylene di-amine tetra-acetic acid (EDTA) tube for haematological parameter analysis and blood smear preparation. Haematological parameters were determined using an automated haematology analyser.

Outcome Measures: The key outcome (anaemia) was determined objectively with WHO haemoglobin cutoffs.[29] Anaemia was defined as a haemoglobin level ≤13.0 g/L for men and ≤12.0 g/L for women according to WHO gender-based criteria. Patients with anaemia were further categorized into two groups based on the severity of anaemia:

- Mild anaemia: haemoglobin greater than or equal to 11 g/dl and less than 11.9 g/dl for women and haemoglobin greater than or equal to 11 g/dl and less than 12.9 g/l for men
- Moderate to severe anaemia: haemoglobin < 11.0 g/l for men and women.

Patients with anaemia were also categorized into four groups based on the type of anaemia: [30]

- Normocytic anaemia: MCV greater than or equal to 80 pg and less than or equal to ≤ 100 pg
- Microcytic normochromic anaemia: MCV less than 80 fl and MCHC between 32 to 36 g/dl
- Macrocytic anaemia: MCV greater than 100 pg
- Microcytic hypochromic anaemia: MCV less than 100 fl and MCHC less than2 g/dl.

Statistical Analysis:

Data were organised into tabular form using Microsoft Excel 2010. Descriptive statistics were performed and continuous variables were expressed as the mean and standard deviation (SD). Categorical variables were

expressed as frequencies and proportions. Statistical significance of difference between various groups was evaluated using the chi-square test for categorical variables and independent t-test for continuous variables. A two-sided $P < 0.05$ was taken as measure of statistical significance.

OBSERVATIONS AND RESULTS

Out of 199 dyspeptic patients, 86 (43.22) tested positive for H. pylori antigen and 22 (11.06%) were anaemic.

Table 1: Comparison of Baseline demographic and clinical characteristic between H. Pylori Positive and negative patients

Variable	H. Pylori Positive (n=86)	H. Pylori Negative (n=113)	P-Value (Chi-Square)
Age, n (%)			
<30	18 (20.93)	28 (24.78)	0.62
31-45	31 (36.05)	40 (35.4)	
46-60	15 (17.44)	24 (21.24)	
>60	22 (25.58)	21 (18.58)	
Sex, n (%)			
Male	61 (70.93)	74 (65.49)	0.42
Female	25 (29.07)	39 (34.51)	
Food Habit, n (%)			
Vegetarian	31 (36.05)	46 (40.71)	0.50
Non-vegetarian	55 (63.95)	67 (59.29)	
Body Mass Index in kg/m^2 (Mean ± SD)	24.31 ± 3.46	23.97 ± 3.34	0.48 (Unpaired t-test)

There was no significant difference between two groups with respect to baseline demographic and clinical characteristics. Most of the patients with dyspepsia and H. pylori infection were males, non-vegetarian and were of age group 31-45.

Table 2: Comparison of Anaemia and its severity between H. Pylori Positive and negative patients

Parameters	H. Pylori Positive (n=86)	H. Pylori Negative (n=113)	P-Value (Chi-Square)
Normal haemoglobin level, n (%)	74 (86.05)	103 (91.15)	0.26
Any Anaemia, n (%)	12 (13.95)	10 (8.85)	
Mild Anaemia, n (%)	8 (9.30)	8 (7.08)	0.48
Moderate to severe anaemia, n (%)	4 (4.65)	2 (1.77)	

There were 13.95% dyspeptic patients with h. pylori infection as compared to 8.85% dyspeptic patients that tested negative for H. pylori antigen. Also, prevalence of moderate to severe anaemia was higher in H. pylori positive dyspeptic patients (4.65) as compared to H. pylori negative ones (1.77). But these differences were not statistically significant.

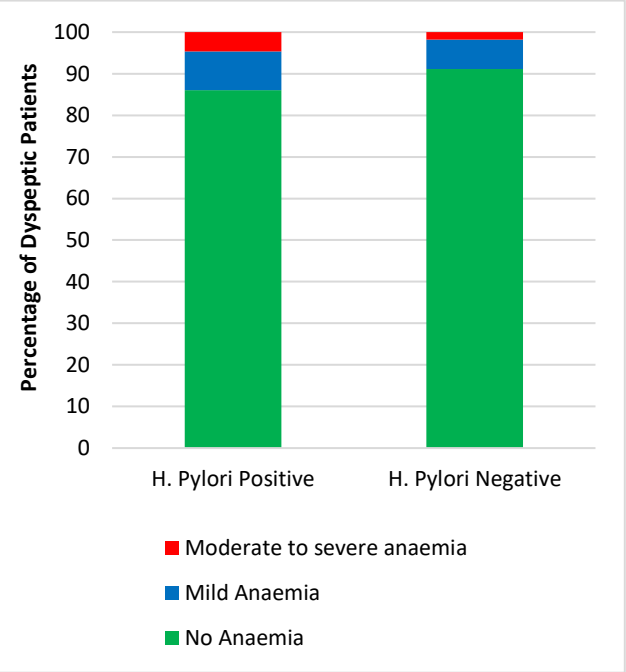

Table 3: Comparison of Anaemia and its severity between H. Pylori Positive and negative patients

Parameters	H. Pylori Positive (n=86)	H. Pylori Negative (n=113)	P-Value (Chi-Square)
No Anaemia, n (%)	74 (86.05)	103 (91.15)	0.60
Normocytic anaemia, n (%)	7 (8.14)	6 (5.31)	
Microcytic normochromic anaemia, n (%)	1 (1.16)	2 (1.77)	
Microcytic hypochromic anaemia, n (%)	3 (3.49)	2 (1.77)	
Macrocytic anaemia, n (%)	1 (1.16)	0 (0)	

Most of the patients were having normocytic anaemia followed by microcytic hypochromic anaemia. There was no statistical difference between H. pylori positive or negative dyspeptic patients with respect to type of anaemia.

Table 4: Comparison of Haematological Parameters between H. Pylori Positive and negative patients

Parameters	H. Pylori Positive (Mean ± SD)	H. Pylori Negative (Mean ± SD)	P-Value (Unpaired t-test)
Hb (g/dl)	12.67 ± 2.15	13.15 ± 1.68	0.0786
RBC/ µl	4.36 ± 1.05 x 10^6	4.59 ± 1.17 x 10^6	0.1528
PCV	40.71 ± 6.13	41.73 ± 4.28	0.1687
MCV (fl)	90.87 ± 6.61	91.34 ± 8.45	0.6706
MCH (pg)	32.13 ± 3.13	33.52 ± 4.72	**0.0191***
MCHC (g/dl)	31.22 ± 2.97	32.67 ± 4.07	**0.0058***
RDW	24.57 ± 1.54	26.87 ± 2.54	**<0.0001***

Hb: Haemoglobin, RBC: Red Blood Cell, PCV: Packed Cell Volume, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Corpuscular Haemoglobin Concentration, RDW: Red Cell Distribution Width

µl: micro liter, fl: femto litter (10−15L), pg: pico-gram (10−12g), * significant association

Although there was no statistical difference between H. pylori positive or negative dyspeptic patients with respect to mean haemoglobin and RBC count but MCH, MCHC and RDW were significantly lower in H. pylori positive dyspeptic patients ($p<0.05$).

DISCUSSION

This single cross-sectional study evaluated the relationship between H. pylori infection and anaemia in 299 adult patients with dyspepsia from tertiary care centre in the East India. Patients infected with H. pylori are more likely to be anaemic and may have low haemoglobin levels.

The prevalence of H. pylori infection and anaemia was found to be 43.22% and 11.5%, respectively, which were smaller than those reported by previous research done in Asian population.[31, 32] Another study reported that the prevalence of anaemia in elderly people living in urban areas was found to be 16.3% in men and 13.7% in women and this prevalence was found to be increasing significantly with age.[33] The prevalence of iron deficiency anaemia in study conducted in China in the year of 2008 was 0.37% and 0.17% in male and 0.20% in female.[34] As we did not collected any data on serum iron, serum ferritin and serum transferrin saturation, the prevalence of iron deficiency anaemia could not be calculated in our study. However, prevalence of iron deficiency anaemia may be represented by the prevalence of microcytic hypochromic study which was greater in this study than previous studies.

The relation between H. pylori infection and anaemia has been investigated in previous epidemiological surveys in various settings.[13, 32] Anaemia is also reported as a complication of H. pylori infection.[35] It was found in our study that dyspeptic patients with H. pylori infection had greater prevalence of anaemia. A meta-analysis reported a borderline significant and weak positive correlation between H. pylori infection and anaemia and a pooled odd ratio of 1.15 (95% CI: 1.00, 1.32).[28] Moreover, that meta-analysis also suggested that the magnitude of this correlation was greater when the analysis was limited to studies which were adjusted for confounders. The result of that meta-analysis was similar with our study.

There are several anaemia genetic mechanisms that could explain the relationship between Helicobacter pylori infection and anaemia. The most plausible pathology is gastrointestinal blood loss caused by H. pylori-induced gastritis or duodenitis.[36] Another may be sequestration of free iron by H. pylori bacteria affecting iron transport molecules, thereby inhibiting the absorption of free iron and also inhibiting cobalamin absorption from food. [37, 38] In addition, colonization of the stomach by H. pylori requires continuous replenishment of nutrients essential for bacterial growth and may utilize the host's own iron stores.[39] Severe anaemia was associated with H. pylori infection in a case report of a school age children, which suggest screening for H. pylori infection and subsequent proper treatment for severe anaemia due to iron deficiency.[40] However, a significant relationship between H. pylori infection and severity of anaemia was not found in our study. The reason may be characteristics of our study participants which may have a selection bias.

Our analysis also found statistically significant differences in RDW, MCH, and MCHC between H. pylori positive and H. pylori negative groups, but these differences are unlikely to be biologically significant and need further investigation. A health survey of 2,398 healthy subjects and a clinical research also found similar findings with respect to MCV, MCH, and MCHC.[41, 42] Moreover, a large survey on children with iron deficiency anaemia reported that H. pylori infection can be a causative agent in adverse haematological outcomes.[43] In this study, we also investigated the relationship between H. pylori infection and different types of anaemia. At the time of protocol writing, this was the first study which was going to explore relationship between H. pylori infection and type of anaemia. Patients with H. pylori infection had greater prevalence of normocytic anaemia, and similar relationship was also found in the female subjects. This result needs further clinical or molecular researches to investigate the mechanisms behind this relationship between H. pylori infection and different anaemia types.

We found a decreased haemoglobin level in the patients who had H. pylori infection. However, this relationship was not found in all patients which is consistent with findings previous research.[44] Another study found that haemoglobin levels were significantly different between

patient with no infection, recent infection, long-term infection and past infection. That study reported that a decreased haemoglobin level was associated with presence of gastric atrophy and higher age group rather than the existence of H. pylori infection itself.[41] A community-based survey in Arabic people found a significantly decreased haemoglobin level in children of age between 6 to 9 years who had H. pylori infection compared with their peers who were non-infected.[45]

Eradication of H. pylori may raise haemoglobin levels, according to a meta-analysis of randomised control studies.[46] In addition, it was noted that the amounts of haemoglobin, serum iron, and ferritin increased after the H. pylori infection was treated. Based on the aforementioned findings, we are of the opinion that there is a connection between H. pylori illness and haemoglobin level. Further study, particularly for masculine subjects, is still needed to determine the underlying cause of this.

Our results should prompt careful consideration of suitable H. pylori eradication interventions, even though this will take a lot of work, not only for the potential to improve anaemia status but also to offer protection against underlying diseases.

Our research has a number of drawbacks. First, because this is an observational research, we are unable to confirm the precise causality between H. pylori infection and anaemia. Second, there was selection bias because every participant came from dyspepsia patients. The third drawback is that serological testing for anti- H. Pylori IgG and IgM only detects exposure to these bacteria and not a current infection, which may have skewed the discovery of H. pylori infection. Additionally, we were unable to acquire the results of a laboratory test for iron status, so we are unable to provide specific information on the subjects who have iron deficiency anaemia. Finally, because of the characteristics of the unit from which the subjects were drawn, the ratio of male to female was high.

CONCLUSION

Anaemia is more common in individuals with dyspepsia who have H. pylori infection, according to our research. Anaemia was prevalent in this research, which suggests that it is a mild public health issue. The results of this research should be considered when creating intervention-based strategies for addressing the identified factors, particularly those related to the prevention and management of H. pylori and intestinal parasitic infection. Large-scale community-based studies should be conducted as well as routine H. pylori and intestinal parasite infection testing and treatment among people with dyspepsia.

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