Effect of Helicobacter Pylori Infection on Nutrition, Metabolism, Cognition, and Serum Vitamin B12 in the Elderly

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Abstract:

Background: *Helicobacter pylori* infection is one of the most common infections in humans. The rate of *H. pylori* infection and its complications is increasing with age worldwide. Many articles have published on the fascinating topic of extra-gastroduodenal manifestations of *H. pylori* infection, most of which are commonly seen in the elderly population.

Aim: To investigate the effect of *H. pylori* infection on nutrition, metabolism, cognition, and serum vitamin B12 in the elderly.

Subjects and Methods: This study was conducted on 30 elderly patients with *H. pylori* infection diagnosed by stool antigen test and 30 healthy control subjects matched for age, sex and socioeconomic status. Full history, complete physical examination, anthropometric measurements, laboratory parameters (routine laboratory investigation, metabolic parameters, serum iron level, serum vitamin B12 level), and HOMA-IR score. Moreover, all participants completed the mini mental state examination (MMSE) and mini nutritional assessment (MNA) questionnaires.

Results: the results showed that patients with *H. pylori* infection had significantly lower hemoglobin levels, lower serum iron levels, lower vitamin B12 levels, higher insulin levels, and higher prevalence of insulin resistance (defined as a HOMA-IR score ≥2.5). There were no significant differences between the groups regarding the mean MMSE score, the mean MNA score, or the prevalence of metabolic syndrome according to the definition of the National Cholesterol Education Program Adult Treatment Panel III.

Conclusion: *H. pylori* seems to be associated with iron deficiency anemia, vitamin 12 deficiency and insulin resistance in the elderly.

Keywords: *H. pylori*, iron, vitamin B12, metabolic syndrome, cognition

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Introduction

H. pylori infection is one of the most common infections in humans, affecting more than half of the population. Many articles have been published on the fascinating topic of extra-gastroduodenal manifestations of *H. pylori*

infection[1].

H. pylori infection can cause deficiencies in vitamins and essential minerals [2]. Several studies have revealed an association between *H. pylori* infection and iron- deficiency anemia. Moreover, elderly people are particularly at risk of vitamin B12 deficiency. Studies have demonstrated a link between chronic *H. pylori* infection and malabsorption of vitamin B12 [3], and an increased prevalence of Mets. [4].

Subjects

This analytical case control study was conducted on 60 subjects above the age of 65 years and divided into two groups; 30 elderly patients with *H. pylori* infection diagnosed by stool antigen test and 30 healthy control subjects matched for age, sex and socioeconomic status.

Exclusion criteria included; severe renal or liver impairment, chronic debilitating disease (severe renal impairment, advanced liver disease, advanced heart failure, chronic severe bronchial asthma, cerebrovascular stroke), thyroid diseases, history of eradication treatment for *H. pylori*, malignant diseases, and history of previous gastrointestinal surgery. Informed consent was obtained from all patients who participated in the study.

Methods

This study was conducted between May 2018 and June 2019. All patients were subjected to full history taking (with special stress on complaints of epigastric pain, heartburn, dyspepsia, vomiting, hematemesis, melena and loss of weight, history of *H.pylori* infection and with treatment, drug history, disease historyand surgical history) and complete physical examination.

Anthropometric measurements of all participants were taken and included:

- Body weight, height and Body Mass Index (BMI) were calculated as weight in kg / (height in m^2.
- Mid-arm circumference (midpoint of the upper arm, halfway between the tip of the acromion process and the tip of the olecranon process).

- Calf circumference (Measured at the calf's greatest girth with the subject standing).
- Waist circumference (Mid-way between the lowest rib and the iliac crest with the subject standing).

Peripheral blood samples were collected from all subjects in the morning after overnight fasting, and serum iron, fasting blood glucose (FBG), insulin, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), Albumin (Alb), blood urea nitrogen (BUN), creatinine (Creat), CBC, and vitamin B12 were measured in serum samples.

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III). **Subjects were classified as having MetS if they had any three of the following five risk factors [5]:**

1. Waist circumference > 102 cm for men and > 88 cm for women.
2. Triglycerides concentration ≥ 150mg/dL (or drug treatment).
3. High density lipoprotein cholesterol (HDL-C) <40mg/dL in men and <50mg/dL in women (or drug treatment).
4. Blood pressure ≥ 130/ 85 mm Hg (or drug treatment).
5. Fasting glucose ≥ 100mg/dL (or drug treatment).

The homeostasis Model Assessment 2 (HOMA2) calculator was used to estimate steady state beta cell function (%B) and insulin resistance (%S) (HOMA-IR) according to the updated computer based HOMA2 mode in subjects with normal or impaired glucose tolerance. Insulin resistance was defined as a HOMA-IR score ≥2.5[6].

All participants completed the mini nutritional assessment (MNA) questionnaire for Nutritional assessment. The MNA is the most popular and most frequently used nutritional screening and assessment tool for the elderly. It is correlated with clinical assessment and comprehensive nutritional assessment, including biochemical tests, anthropometric measurements, and dietary assessment [7].

All participants completed the mini mental state examination (MMSE) questionnaire for cognition assessment. The MMSE is effective as a screening

instrument that can be used to systematically and thoroughly assess cognitive impairment in older adults. The maximum score was found to be 30. A score of 24 is the most widely used cutoff for dementia [8].

Statistical Analysis

Data were collected, coded, revised and entered into the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non- parametric distribution**. Chi-square test** was used in the comparison between two groups with qualitative data and **Fisher's exact test** was used instead of the Chi-square test when the expected count in any cell was less than 5. An **independent t-test** was used for the comparison between two groups with quantitative data and parametric distribution and the **Mann-Whitney test** was used for the comparison between two groups with quantitative data and non-parametric distribution. **Spearman correlation coefficients** were used to assess the significant relationship between two the quantitative parameters in the same group. All results were interpreted at a 5% level of significance where the difference between the study groups was considered significant if $P \leq 0.05$.

Ethical approval

The protocol was approved by the ethical committee in the faculty of medicine, Alexandria University.

Results:

Demographic data of the studied patients revealed that there was no significant statistical difference between the studied groups in terms of age (p=0.744) or gender (p=0.791). There were no significant statistical differences between the *H. pylori* +ve and –ve groups with regard to any of the studied anthropometric measurements including weight (Wt) (p=0.535), height (Ht) (p=0.322), body mass index (BMI) (p=0.510), mid-arm circumference (MAC) (p=0.525), calf circumference (p=0.592) waist circumference (WC) (p=0.351) (table1).

Table (1): The demographic characteristics and anthropometric measurements of study groups

	H.pylori +ve (No.=30) Mean ±SD	H.pylori –ve (No.=30) Mean ±SD	P value
Age	69.20±3.54	68.93±3.62	0.774
Gender			
Female (No) Male (No)	11(36.70%) 19(63.30%)	12(40.00%) 18(60.00%)	0.791
Wt. (Kg)	79.47±10.80	77.60±12.33	0.535
Ht. (m)	1.66±0.08	7.43±31.65	0.322
BMI (Kg/m^2)	28.79±4.10	28.07±4.32	0.510
MAC (Cm)	28.43±3.46	29±3.40	0.525
Calf circum (Cm)	36.40±5.11	35.77±3.91	0.592
WC (Cm)	101.77±12.95	98.40±14.75	0.351

Regarding the clinical characteristics of the study participants; *H. pylori* +ve subjects had significantly lower serum hemoglobin levels than H.pylori –ve subjects (p=0.001) but there were no statistically significant differences regarding platelets (p=0.093), WBC (p=0.236), serum albumin (0.245), cholesterol (p=0.149), LDL (p=0.129), HDL (p=0.242), TG (p=0.148), creatinine.(p=0.650), BUN (p=0.701), and CRP (P=0112) between the two groups. Serum iron levels were significantly lower in the *H. pylori* +ve group (p=0.001) while there was no statistically significant difference between the two groups regarding FBS (P=0.192). Insulin levels were statistically significant higher in the *H. pylori* +ve Group (p=0.017) but there was no statistical significant difference between the two studied groups regarding HOMA-IR (p=0.079) or MNA (p=0,573) (table 2).

Table (2): clinical characteristics of the study population.

	H. pylori +ve (No.=30) Mean ± SD	H. pylori –ve (No.=30) Mean ± SD	P value
Hb (g/dl)	11.68±2.08	13.39±1.12	<0.001
Plt (×10³/mm³)	221.20±107.07	185.63±39.69	0.093
WBC (×10³/mm³)	6.77±2.48	6.13±1.53	0.236
Alb (g/dl)	4.48±0.36	4.59±0.35	0.245
TC (mg/dl)	203.10±49.05	186.40±38.84	0.149
LDL (mg/dl)	133.27±47.24	117.00±33.48	0.129
HDL (mg/dl)	46.23±12.32	49.83±11.24	0.242
TG (mg/dl)	116.07±53.06	98.67±37.60	0.148
Creat (mg/dl)	0.93±0.26	0.90±0.22	0.650
BUN (mg/dl)	16.62±3.55	16.29±3.13	0.701
CRP (mg/dl)	7.39±10.04	4.26±3.46	0.112
Iron (µg/dl)	67.07±18.11	122.37±27.17	<0.001
FBG (mg/dl)	85.40±25.90	77.60±19.38	0.192
Insulin (µu/ml)	7.60±4.93	4.93±3.36	<0.017
HOMA-IR	1.69±1.79	1.01±1.03	0.079
MNA	26.40±1.93	26.70±2.16	0.573
MMSE	27.20 ± 2.75	28.50 ± 2.43	0.057

*: Statistically significant at $p \leq 0.05$

In this study B12 level was <200pg/ml in 50% of H. pylori +ve cases and >200 pg/ml in the other 50% of the same cases but all H pylori –ve cases had B12>200pg/ml. B12 level was statistically significant lower in H pylori +ve group (p=0.001) (table 3).

Table (3): Comparison between H. pylori +ve &-ve cases as regards Vitamin B12 level

	H pylori +ve (No.=30) No(%)	H pylori –ve (No.=30) No(%)	Chi square test Independent test X^2/t*(p value)
B12 (pg/ml)			
<200	15 (50.0%)	0(0.0%)	20.000(0.001*)
>200	15 (50.0%)	30 (100.0%)	
B12			
Mean± SD	207.82±139.54	510.27±127.00	-8.780(0.001*)
Range	50-629	243-701	

*: Statistically significant at $p \leq 0.05$

Regarding IR 80% of H. pylori +ve cases were insulin sensitive and 20% were insulin resistant but H pylori –ve cases only 3.30% had insulin -resistant, so H. pylori +ve cases had statistically significant IR than H pylori –ve cases (p=0.044). 30.0% of

H. pylori +ve cases had MetS while 26.70% of H pylori –ve had MetS with no statistical significant difference between the two groups (p=0.774). About 83.3% of H. pylori +ve cases had MMSE ≥24 and only 16.7% had MMSE<24 but in H pylori –ve cases only 3.3% were found to have MMSE<24 with no statistically significant difference between the two groups regarding MMSE (0.085) (table 4).

Table (4): Comparison between H. pylori +ve &-ve cases as regards IN and Mets

	H pylori +ve (No.=30) No (%)	H pylori –ve (No.=30) No (%)	Chi square test X^2(p)
IR			
Isulin sensetive	24(80.0%)	29(96.7%)	4.043(0.044*)
Insulin resistant	6(20.0%)	1(3.3%)	
Mets			
Normal	21(70.0%)	22(73.3%)	0.082(0.774)
Metabolic syndrome	9(30.0%)	8(26.7%)	
<24	5(16.7%)	1(3.3%)	X^2/t*(p)
≥24	25(83.3%)	29(96.7%)	2.963(0.085)
MMSE Score			
Mean±SD	27.20±2.75	28.50±2.43	-1.941(0.057)
Range	23-30	21-30	

IR: Insulin resistance
Mets: metabolic syndrome
MMSE: Minimental Status Examination score

Discussion:

H. pylori infection is one of the most common infections in humans, affecting more than half of the population. Recently, many articles have published on the fascinating topic of extra-gastroduodenal manifestations of *H. pylori* infection, including hematological, metabolic, cardiovascular, neurodegenerative and allergic disorders.

The present study was conducted on 60 subjects above the age of 65 years divided into two groups; 30 elderly patients with *H. pylori* infection diagnosed by stool antigen test and 30 healthy control subjects matched for age, sex and socioeconomic status.

The results revealed that no statistically significant differences were determined between the *H. pylori* +ve and –ve groups regarding gender or age. This balance in the baseline characteristics offered the basis to compare the study groups as it helped

decreasing bias.

The nutritional status of the patients, was assessed through anthropometric measurements, MNA score, along with laboratory indices (such as serum albumin, TC, TG, BUN, Vit B12, serum iron and Hb level). Various nutritional indices had been used in the assessment of nutritional status in previous researches that studied the impact of *H. pylori* infection on nutritional status of old patients, but MNA score had not been used.

The nutritional status, evaluated by the assessment of: BMI, mid arm muscle area, serum albumin, vitamin B12, folate, iron, ferritin, transferrin, and Hb, was not affected by the existence of anti-*H. pylori* IgG in a study that was carried out by D Mustafa [9]. In addition, no correlations were detected between *H. pylori* infection and nutritional indices (including BMI, mid arm muscle area, triceps skin fold, serum prealbumin& albumin, FBG, BUN, Hb, iron, and transferrin) in a study that carried out on 96 patients in a geriatric institute [10]. From the previous two studies, the results of this study comply with some findings (as anthropometric measurements, serum albumin, FBG, BUN, TC and TG) and was in contrast to other parameters in the same study (as serum iron, Hb level and serum vitamin B12).

The present study revealed that no statistically significant differences were found between the *H. pylori* +ve and –ve groups regarding any of the studied anthropometric measurements including Wt, Ht, BMI, mid-arm circumference, calf circumference and WC. These findings came in line with those of the cross-sectional study that was done by Upala et al [11] on 1,300 elderlies, average age of 69.23 ± 7.31, revealed that *H. pylori* infection wasn't related to BMI. However, Yang et al [12] revealed that *H. pylori* infection ensured by gastric biopsy histopathology was associated with obesity assessed by BMI in elderly Chinese individuals.

Anemia is one of the complications of *H. pylori* infection. There are various mechanisms explaining the relationship between *H. pylori* infection and anemia. The most accepted one is gastrointestinal blood loss as a result of *H. pylori*-induced gastritis or duodenitis. In addition to the iron sequestration *by H. pylori* and *H. pylori* induced food cobalamin malabsorption [13].

The results of this study showed that elderly patients with *H. pylori* +ve infection had significantly lower haemoglobin (Hb) levels compared with controls. These results were in agreement with what study done by Muhsen K [14] in a cross-sectional study that was performed on 646 asymptomatic elderly males (mean age= 79.4± 8.9, range= 65-100 years) and found that the prevalence of anemia (Hb cutoff value of 120 g/L) in the *H. pylori* +ve group, was significantly elevated in comparison with that in -ve group (5.3% vs. 2.2%, P= 0.033). In contrast to results of this study no significant difference in Hb level according to *H. pylori* status was reported in a recent study which enrolled 50 patients with positive *H. pylori* biopsy result and 50 healthy controls as it found a slight non-significant decrease in Hb level in *H. pylori* (+ve) cases versus controls in a study performed by Boyanova L [15].These contradictory results can be explained by the fact that Hb level could be within normal ranges with very low or absent iron stores as Hb level is kept within normal range till the body iron stores are depleted.

As for serum iron level, these results showed that elderly patients with *H. pylori* infection had significantly lower iron level compared with controls. The causal relation between the *H. pylori* infection and iron deficient anemia (IDA) can be explained by several mechanisms. First, the uptake of iron by the bacteria is induced during the bacterial growth [16]. Second, it has been proved that Cag A protein participates in iron acquisition from interstitial holotransferrin. In addition to blood loss as a result of chronic erosive gastritis and reduced iron absorption caused by chronic active gastritis and hypochlorhydra [17].

These findings comply with a study performed by Mwafy et al [18] who investigated 150 *H. pylori* +ve patients (confirmed by positive stool antigen test) and 150 matched controls for several hematologic parameters, and they reported significantly reduced level of iron in patients with *H. pylori* in comparison with uninfected subjects (71.6 ± 24.8 vs 80.1 ± 20.7 µg/dL). Similar results found that *H. pylori* infected patients (diagnosed by rapid urease test) had a significantly decreased mean serum ferritin level in comparison with non-infected cases (P<0.001). A study which was conducted by John S on 168 subjects had also

documented a significant decreased value of mean MCV and MCH in *H. pylori* +ve patients (P<0.001) [19].

Nevertheless, Goddard AF and et al who performed their study on 523 subjects, did not find an association between unexplained ID or IDA and *H. pylori* infection (diagnosed by rapid urease test or histology) in older adult without peptic ulcer disease or significant upper gastrointestinal source of blood loss. In summary, the association of *H. pylori* and IDA was proved in several studies. Current international as well as national guidelines recommend treatment of the infection in patients suffering unexplained IDA [20]. The current study proved that elderly patients with *H. pylori* infection had significantly lower mean vitamin B12 level and significantly higher prevalence of vitamin B12 deficiency compared with controls.

Chronic *H. pylori* infection with intestinal microbial proliferation is an important factor that participates in food-cobalamin malabsorption in old patients. And this could be explained by several mechanisms; 1) *H. pylori* is potentially related with chronic active gastritis of the gastric antrum causing impaired gastric acid and pepsin secretion resulting in malabsorption of vitamin B12. 2) *H. pylori* also contribute in the development of gastric ulcers which hinder the absorption of consumed vitamin B12. 3) The hypochlorhydria accompanied by atrophic gastritis might result in inability to split B_{12} from food binders and its subsequent transport to salivary R-binder in the stomach, thereby causing B_{12} malabsorption [21].

In agreement with these results, a case-control study that was carried out by El Demerdash [22] on 120 subjects demonstrated that the mean serum vitamin B12 level in the *H. pylori* +ve group was significantly lower than that in the -ve group (278±110 versus 590±128, respectively P= 0.0002). Also, a case-control study that involved 300 subjects found that *H. pylori* infected subjects had significantly lower mean serum vitamin B12 compared to controls (262.5 ± 100.0 vs. 378.2 ± 160.6 pg/mL, respectively, p <0.001). And vitamin B_{12} elevated significantly and was restored to near normal level following therapy.

The current study revealed a higher mean insulin level and a higher prevalence of insulin resistance (IR) in the *H. pylori* +ve group compared to *H. pylori* -ve group. Meanwhile, no statistically significant differences were found between both groups regarding the prevalence of metabolic syndrome (MetS) according to the definition of NCEP/ATP III.

The mechanism that links *H. pylori* infection and IR isn't clear; however, a chronic inflammatory response and the accompanying cytokine release after *H. pylori* infection might be account for IR pathogenesis.

The results of the current study came in agreement with a study that conducted by Chen NW [23] as it demonstrated that *H. pylori* seropositivity was obviously elevated in cases with insulin resistance (HOMA-IR ≥ 2.5) in comparison with cases without IR (HOMA-IR <2.5) (39.4 vs 28.7%, p=0.027). Similar results were also reported in a community-based cohort study performed by Allam [24] who found that subjects with the *H. pylori* antibody had higher rates of insulin resistance (HOMA-IR >2.5) when compared with individuals without the *H. pylori* antibody.

On the contrary to the current study results, Naja et al [25] concluded that the prevalence of *H. pylori* infection was not significantly different between insulin sensitive (HOMA-IR score <2.5) and insulin resistant (HOMA-IR score ≥2.5) participants (56.1 and 47.2%, p >0.05), they also reported that there were no significant difference between *H. pylori* seropositive participants and *H. pylori* seronegative participants according to mean fasting serum insulin level (21.07 ± 9.29 and 24.45 ± 19.38 μU/mL, P >0.05).

In agreement to the results of this study, a cross-sectional study that was conducted on 211 subjects showed that the prevalence of MetS (based on the International Diabetes Federation criteria) among *H. pylori* +ve and *H. pylori* -ve patients was 76.6% versus. 69.8% (p=0.27), according to NCEP-ATPIII criteria it was 90.4% vs. 87.2% (p=0.5), and the differences was not significant [26]. In addition, Kim et al. [27] showed that *H. pylori* seropositivity was not associated with the presence of metabolic syndrome among 37,263 subjects (according to the NCEP ATP III criteria).

However, the relation between *H. pylori* infection and MetS has been proved by many investigations with contradictory results to these study. A study that was performed on 191 Chinese elderly (mean age of 73.19± 11.03 years) demonstrated that participants with *H. pylori* infection had a higher rate of MetS than those without *H. pylori* infection (53.75% vs 37.84%, P<0.001) [28]. In this study the diagnosis of *H. pylori* infection was confirmed by histopathological examination and the rapid urease test, and MetS was diagnosed using the China Adult Dyslipidemia Prevention Guide on MetS. [29]. In addition, a Community-Based Study which was carried out on 2113 individuals, the mean age was 56.4±13.0 years, found that participants with MetS (based on the ATP III criteria) had a higher rate of *H pylori* infection (diagnosed by ^{13}C-UBT) than those without MetS (60.1% vs 50.8%, P<0.001) [30]. This difference between results might be explained by the difference in the age of included subjects, and the various screening approaches for *H. pylori* infection among different studies.

Finally, the present study revealed that no statistically significant difference was found between the *H. pylori* +ve and –ve groups as regards the mean MMSE score nor in the percentage of cases with abnormal low MMSE score (<24).

Similar to results of this study, no significant differences were found between *H. pylori* +ve and -ve patients regarding to cognitive functions which were assessed by Neri MC [9] using the Short Portable Mental Status Questionnaire

(SPMSQ). In addition, a cross- sectional study conducted on 1514 person with an average age of 69.3±7.4 years reported that no significant relation was determined between the level of *H. pylori* antibody and MMSE score (r = 0.039, P = 0.129).

On the other hand, in a study carried out in France with a sample of 53 patients suffering AD, Roubaud-Baudron et al. reported that *H. pylori* infection was related to reduced MMSE score (P= 0.024) [31].

Conclusion:

In conclusion: *H. pylori* seems to be associated with iron deficiency anemia, vitamin 12 deficiency and insulin resistance in the elderly. Further clinical studies are needed to verify the associations and to disclose the underlying mechanisms, taking into account the bacterial virulence factors and the host genetic polymorphisms.

Conflict of interest:

Authors declare that there is no conflict of interest.

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