



## ASSOCIATION BETWEEN PROTEINURIA AND ACTIVE HELICOBACTER PYLORI INFECTION IN NON-DIABETIC PATIENTS

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### ABSTRACT

**Background:** The incidence Helicobacter pylori infection and its possible relationship to different diseases are a focus of attention nowadays. Therefore, the aim of this study was to examine the association between proteinuria and active Helicobacter pylori infection in middle age non-diabetic patients.

**Material and Methods:** A Case-control study was conducted on 118 subjects and included 59 patients who suffered from H. pylori infection from October 2017 to April 2018. 59 patients were negative H. pylori infection included and served as a control group. Demographic and clinical data were collected.

**Results:** The infected H. Pylori group showed a significant higher ACR compared to the control group. In addition, infected H. Pylori group showed a significant lower hemoglobin and albumin compared to the control group.

**Conclusion:** Patients having H. Pylori infection show a significant elevation in the urinary albumin/creatinine ratio and a significant anemia suggesting a role of H. Pylori infection in the pathogenesis of proteinuria and anemia.

**Keywords:** Helicobacter pylori, Proteinuria.

### INTRODUCTION

**H.** Pylori bacteria is the main pathogenic organism that settles on the gastric mucosa of more than half the human population around the world, with more prominence in the developing countries.<sup>[1]</sup> H. Pylori had been found to be the main factor in acute and chronic gastritis, peptic ulcer diseases, and in most cases gastric malignancy. Beside to some extra gastro-intestinal diseases. Such as cardiac, pulmonary and hematological diseases.<sup>[2][3][4]</sup>

Helicobacter pylori had been considered to be one of the commonest bacterial infections in human being and its contribution to different diseases still at the core of attention.<sup>[5]</sup>

H. Pylori exclusively colonizes over the epithelium of the stomach, which suggests that it has a precise identification to gastric epithelial cell. H. Pylori produces adhesins in order to adhere to the epithelial cells, by which it binds to carbohydrates and lipids in the membrane of the epithelial cells.<sup>[8]</sup>

Helicobacter pylori colonies over the gastric mucosa can be a trigger for an immune response through bacterial or host dependent cytotoxic agents.<sup>[6]</sup>

By this way, a local inflammatory response can be triggered, although the inflammatory process is limited to the gastric mucosa, this inflammation may have a role in some extra-gastric disorders.<sup>[7]</sup> H. Pylori elaborates numerous enzymes that can lead to cellular damage either by direct or indirect pathways. Such as Urease, phospholipase and Catalase enzymes.<sup>[9]</sup>

H. Pylori is not an invasive bacterium, but it fires up severe and powerful immunological and inflammatory reactions in the form of adaptive and innate host immunologic reactions which are vital in the H. Pylori pathogenicity and related disease. Many inflammatory mediators were thought to be involved in the pathogenic way of extra digestive disorders caused by Helicobacter pylori infection which include; leukotriene C4, interleukin-1 (IL-1),

interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-6(IL-6), platelet-activating factor and tumor necrosis factor alpha- (TNF- $\alpha$ ).<sup>[10]</sup>

Proteinuria is a well-known indicator for renal disorders. The relationship between nephrotic range proteinuria (nephrotic syndrome) and hypoalbuminemia, edema, hyperlipidemia, susceptibility to infection, and hypercoagulability state also had been approved. For the last two decades, evidences had been accumulated and showed the presence of a direct inverse influence caused by proteinuria and renal diseases that provoke the progress from chronic kidney disease into end-stage renal disease.<sup>[11]</sup>

H. Pylori infection was hypothesized to motivate a strong inflammatory and immunological response. In addition, there were evidences that the inflammatory mediators and cytokines are produced at excessive amounts in this infection. In addition, the cross-reaction between the released factors and host immune system can cause gastric and the extra-digestive manifestations. In addition, some evidences referred to cytokines as being involved in the increased passage of plasma protein through the glomeruli.<sup>[12]</sup>

Therefore, the aim of this study is to determine the association between proteinuria and active Helicobacter pylori.

#### MATERIALS AND METHODS

This is a Case-control study that included 118 participating subjects from whom 59 patients were infected by H. pylori and 59 patients were negative for H. pylori. All of them were suffering from chronic and recurrent dyspeptic complains. All patients were selected from patients attending the Internal Medicine outpatient clinic of Zagazig University Hospitals in the period between October 2017 and April 2018.

After excluded patients with history of upper GIT bleeding or surgery, Diabetics, with evidence of any hepatic, renal, cardiac or respiratory diseases, pregnancy females. Malignancies, recent history of eradication therapy of Helicobacter pylori infection and PPI intake with two weeks before the study.

Patients were subjected to thorough history taking regarding age, sex, body mass index, arterial blood pressure. Full clinical examination was done.

Routine laboratory investigation were performed according to clinical pathology department of Zagazig university hospitals protocols and included CBC, kidney function tests, liver function tests, complete urine analysis and micro albuminuria, fasting blood glucose, HA1c, total cholesterol and Albumin to creatinine ratio (ACR). Stool samples were taken and examined for the presence of H.Pylori antigen.

Our study groups defined as:

- **Group (1):** included 59 non-infected H. pylori non-diabetic of both gender who served as a control group.
- **Group (2):** included 59 infected H. pylori non-diabetic patients of both gender who served as a case group.

#### Ethical

Written Informed consent was taken from the patient to participate in the study. Approval for performing the study was obtained from internal medicine Department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval

#### Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 24.0 for windows (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean  $\pm$  SD (Standard deviation) for parametric and median and range for non-parametric data. Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. Pearson's and Spearman's correlation coefficient were used for correlating normal and non-parametric variables. All statistical comparisons were two tailed with significance Level of P-value  $\leq$  0.05 indicates significant,  $p < 0.001$  indicates highly significant difference while,  $P > 0.05$  indicates Non-significant difference.

**RESULTS**

The demographic and clinical features of the patients are described (Table 1).

This table shows a highly significant difference between the two groups as regard albumin/creatinine ratio, serum albumin and hemoglobin.

**Table 1** Patients' characteristics between the groups.

	Control Group (N=59)	Case Group (N=59)	P
Age (years) Mean $\pm$ SD	31.09 $\pm$ 9.03	32.1 $\pm$ 9.31	.772
Female n (%)	27 (45.8%)	25 (42.4%)	.611
BMI (kg/m <sup>2</sup> ) Mean $\pm$ SD	22.27 $\pm$ 2.61	23.03 $\pm$ 2.42	.427
Systolic blood pressure Mean $\pm$ SD	114.09 $\pm$ 7.01	116.75 $\pm$ 10.79	.495
Diastolic blood pressure Mean $\pm$ SD	71.36 $\pm$ 8.39	71.5 $\pm$ 10.89	.983
Hemoglobin (g/dL) Mean $\pm$ SD	12.78 $\pm$ 0.75	10.51 $\pm$ 0.62	<b>&lt;0.001</b>
TLC (10 <sup>3</sup> / $\mu$ L) Mean $\pm$ SD	5.18 $\pm$ 1.14	5.98 $\pm$ 1.09	.066
Platelets (10 <sup>3</sup> / $\mu$ L) Mean $\pm$ SD	367.27 $\pm$ 62.62	355 $\pm$ 69.39	.630
Creatinine (mg/dL) Mean $\pm$ SD	0.75 $\pm$ 0.082	0.75 $\pm$ 0.084	.898
Albumin (mg/dL) Mean $\pm$ SD	3.82 $\pm$ 0.154	3.57 $\pm$ 0.39	<b>0.001</b>
ACR (mg/g) Mean $\pm$ SD	.205 $\pm$ .0184	.141 $\pm$ .017	<b>&lt;0.001</b>

**Table.2** Correlations between ACR and parameters in cases group

		ACR
Age	R	.340
	Sig. (2-tailed)	.143
BMI	R	-.012
	Sig. (2-tailed)	.961
Mean BP	R	.325
	Sig. (2-tailed)	.162
Hemoglobin	R	.304
	Sig. (2-tailed)	.193
RBS	R	.293
	Sig. (2-tailed)	.210
Albumin	R	-.841
	Sig. (2-tailed)	.001
S. creatinine	R	.331
	Sig. (2-tailed)	.154

This table shows a negative significant correlations between ACR and serum albumin in cases group.

## DISCUSSION

Our study aimed to investigate the presence of an association between proteinuria and active *Helicobacter pylori* infection in middle age non-diabetic patients.

In our study, *H. Pylori* infection had a high prevalence among our dyspeptic patients. Out of the 118 patients complaining from dyspepsia who had participated in our study; 59 patients (50%) were found to be +ve for *H. Pylori*.

The prevalence of *H. Pylori* infection differs from country to another, as regards to the socioeconomic standard and hygienic measures. A systematic review with meta-analysis done by Zamani et al.<sup>[13]</sup> analyzed 410 879 participants from 73 countries within six continents showed that the overall prevalence of *H. Pylori* infection was 44.3% worldwide. This rate ranged from 50.8% in developing countries compared with 34.7% in developed countries.

Another Systematic review with meta-analysis done by Hooi et al.<sup>[14]</sup> collecting data from 62 countries showed that Africa had the highest pooled prevalence of *H pylori* infection (79.1%), and according to this study the estimated prevalence in Egypt was about 40.9% of the general population. Based on the regional prevalence estimates, there were approximately 4.4 billion individuals with *H. Pylori* infection worldwide in 2015.

The prevalence of *H. Pylori* infection in Arabian countries differs from country to another. In Saudi Arabia, a study done by Saber et al.<sup>[15]</sup> showed that the *H. Pylori* infection was diagnosed in 72.8% of the studied patients.

Another study in the same country done by Abo-shadi et al.<sup>[16]</sup> showed that *H. Pylori* infection was detected in 64.7% of the gastric biopsy specimens from patients with upper gastrointestinal diseases.

On the other hand, another study done by Amer et al.<sup>[17]</sup> showed a very high prevalence of *H. Pylori* infection in an Egyptian group estimated to be 91% of the studied group.

Another study done by Ibrahim et al.<sup>[18]</sup> found that a male predominance of *H. Pylori* in both pediatric and adult populations and that

association was higher in adults than in children,

In our study, there was no significant difference between the two studied groups regarding; BMI, systolic and diastolic blood pressure, the serum level of TLC, Platelets, RBG and Creatinine.

In our study, the serum hemoglobin level was significantly lower in our group of patients infected by *H. Pylori* (mean =10.51 mg/dl) with a high statistical significance ( $p < 0.001$ ), in contrast to our control group who had a normal serum hemoglobin level (mean =12.78 mg/dl)

Multiple meta-analyses had provided a convincing evidences that an association exists between *H. Pylori* infection and iron deficiency anemia (IDA). A study done by Xu et al.<sup>[19]</sup> included 17,791 patients in Beijing found that *H. Pylori* infection had a higher association with anemia and a lower level of hemoglobin among the studied patients.

Another study regarding this issue done by Muhsen & Cohen<sup>[20]</sup> revealed an increased risk for iron deficiency anemia among *H. Pylori*-infected subjects.

On the other hand, many other studies found no relation between anemia and *H. Pylori* infection including the study done by John et al.<sup>[21]</sup> who did not found any association between IDA and *H. Pylori* infection in adult population.

Although, the mean serum level of albumin was significantly higher in our control group 3.82 mg/dl compared to our case group 3.57 mg/dl ( $p = 0.001$ ), the serum level of albumin was still within normal level. In addition, there was a negative significant correlation between urinary Albumin / Creatinine ratio (UACR) and serum albumin in our case group.

This result is consistent with another study done by Caliskan et al.<sup>[22]</sup> which was held to reveal the effect of *Helicobacter Pylori* eradication on proteinuria in patients with primary GN and revealed an elevation in the serum level of albumin after *H. Pylori* eradication. In this study the serum level of albumin was 34 g/l before eradication and became 40 g/l after eradication. ( $p = 0.001$ ) and it also had showed an improvement in the level

of proteinuria after H. Pylori eradication which was also consistent with our study.

In our study we found that our infected group with H. Pylori had a proteinuria slightly higher than normal level with a urinary Albumin / Creatinine ratio of 0.205 mg/g compared to the control group who had a UACR of 0.141 mg/g. ( $p < 0.001$ )

Our study showed a significant higher proteinuria in H. Pylori infected patients compared to non-infected individuals which was also consistent with some other studies.

Our results were consistent with the study of Aydogan et al. [23] who demonstrated that the treatment of H. pylori eradication significantly reduced the proteinuria within the normal limits. This refers to an impact of H. Pylori infection on the pathogenesis of proteinuria.

Also our study is consistent with another study conducted by Tanriverd [24] to examine the relationship between Helicobacter pylori infection and micro albuminuria in diabetic patients and found that Diabetic patients infected by Helicobacter pylori showed significantly higher micro albuminuria than non-infected patients.

Another case study related to this issue done by Sugimoto et al. [25] showed that there was a marked reduction of proteinuria after eradication of gastric Helicobacter pylori infection in a patient with membranous nephropathy.

In contrast to our study, there was a study conducted in china by Kong et al. [26] included 22,044 adults Chinese individuals and found that the prevalence of proteinuria and the overall CKD were not significantly different between these two studied groups (1.7 vs. 1.6%,  $P = 0.65$  and 3.0 vs. 2.7%,  $P = 0.2$ ). After adjusted for age, sex hypertension, diabetes, body mass index, uric acid, smoking drinking, total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol the odds of decreased eGFR and proteinuria were not significantly different between the H. Pylori positive and negative subjects.

In conclusion, Patients having H. Pylori infection show a significant elevation in the

urinary albumin/creatinine ratio and a significant anemia suggesting a role of H. Pylori infection in the pathogenesis of proteinuria and anemia.

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