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Helicobacter Pylori Cytotoxin-Associated Gene A -Seropositivity in Type 2 Diabetic Patients; Relation to Moderately Increased Albuminuria and Inflammatory Markers

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Abstract

Background and Aim: *The pathogenesis of moderately increased albuminuria (Malb) in type 2 diabetic patients is still unclear. Infection with Helicobacter pylori (H. pylori), especially with strains carrying the cytotoxin-associated gene A (CagA), might play a role. In this study, we investigated the possible association between H. pylori CagA-seropositivity in type 2 diabetic patients and Malb as well as increased inflammatory markers.*

Subjects and Methods: *Ninety type 2 diabetic patients with Malb were included in the study. These patients were divided into two groups as H. pylori seropositive (35 patients) or seronegative (55 patients). In the 2 groups, level of urine albumin creatinine ratio (UACR), inflammatory markers (CRP, ESR), glycemic control indices (fasting blood glucose, HbA1c) and other parameters were compared.*

Results: *There was a significant progressive increase in UACR mean values and thus in Malb comparing H. pylori CagA seropositive and seronegative group (p = <0.001). Malb has significant positive correlation with anti-CagA IgG titer (r=0.497, p<0.001). CagA seropositive patients had significantly higher inflammatory markers (CRP, ESR), p value <0.001. They also showed a significantly poor glycemic control (p = <0.001) and higher lipid profile than the seronegative group.*

Conclusions: *H. pylori CagA antibodies per se may play a role in the pathogenesis of Malb and increased inflammatory response in type 2 diabetic patients. Thus it may play an important role in the development or progression of diabetic nephropathy.*

Keywords: *Cag A seropositive, Helicobacter pylori, moderately increased albuminuria, type 2 diabetes mellitus*

Introduction

Diabetes is an important metabolic disorder worldwide and is characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.[1] Type 2 diabetes mellitus is a leading cause of morbidity including several microvascular complications, such as kidney disease and retinopathy, which are frequent and contribute to the total disease burden. Abnormal levels of urinary albumin occur in 30–40% of patients with type 2 diabetes. Moderately increased albuminuria (Malb, previously termed microalbuminuria)[2], an early marker of diabetic nephropathy, is also a risk factor for a more generalized vascular damage targeting the cardiovascular system and the brain.[3, 4] Malb also identifies patients who need more rigorous cardiovascular risk management, especially more intensive blood pressure control, and strict attention to glycemic control and lipid levels.[5]

Albuminuria in type 2 diabetes mellitus may be secondary to factors unrelated to diabetes mellitus such as hypertension, congestive heart failure, or infection.[6]

Helicobacter pylori (*H. pylori*), a gram negative microaerophilic spiral bacterium, is one of the most common chronic infections worldwide, particularly notable in developing countries, and affecting approximately 50% of the world population.[7] In addition to the gastrointestinal symptoms related to *H. pylori*, some extragastric diseases such as cardiovascular diseases, lung diseases, hematologic diseases, eye and skin diseases, hepatobiliary diseases, and neurological disorders have been also linked to *H. pylori* infection.[8] It has been reported that that *H. pylori* infection may be also responsible for some endocrine disorders including diabetes mellitus.[9]

Although the relationship between *H. pylori* infection and DM and the complications secondary to diabetes is not clear, it has been shown that there is a significant relationship between microvascular complications (nephropathy, neuropathy, and retinopathy) and *H. pylori*.[10, 11] Due to the fact that diabetic patients have a low level of immunity, they are usually at risk of acquiring infections including *H. pylori* infection. Some researchers have investigated the role of *H. pylori* in occurrence of Malb in diabetic patients.[12, 13, 14, 15]

The cytotoxin-associated gene A (CagA) cassette is a very important virulence factor of H. pylori. CagA encodes genes that are of type IV secretion system. It is able to induce a prominent inflammatory response. [16]

Infection with *H. pylori*, especially with strains carrying CagA, might have a role in the development of Malb, since anti-CagA antibodies elicited by infection may cross-react with endothelial antigens[17], increasing the vascular damage associated with diabetes itself and consequent albumin leakage. CagA is also able to induce an increase in inflammatory cytokines such as interleukin-1, -6, and -8; tumor necrosis factor alpha (TNF-α); and vascular permeability growth factor (VPGF).[16] In fact, these inflammatory cytokines increase the vascular permeability of the glomerular membrane, thus leading to the loss of albumin.[12, 14, 18] Chronic *H. pylori* infection also

causes decrease in the level of vitamin B12 and folic acid, which leads atrophic gastritis and results in increased levels of homocysteine in blood and consequently increases vascular endothelial damage.[19]

Aim and objectives

The aim of this study was to evaluate the possible pathogenic role of anti CagA-positive H. pylori antibodies in type 2 diabetic patients with moderately increased albuminuria. We also evaluated the possible association of CagA positivity and increased inflammatory markers as a risk factor for the progression of diabetic nephropathy.

Subjects and Methods

This cross-sectional prospective study was conducted at Alexandria Police Hospital between January and December 2014. During the study period, a total of 90 dyspeptic type 2 diabetic male patients with moderately increased albuminuria were included in the study. The study subjects were divided into two groups according to seropositivity of *H. pylori* CagA IgG as Group 1: CagA positive (+) and Group 2: CagA negative (-).

The study was approved by the ethics committee of Alexandria University Hospitals. An informed written consent was taken from each patient for participation in the study

Inclusion criteria were the following parameters: age of onset >40 years, absence of proteinuria with the dipstick test, serum creatinine <1.5 mg/dl, serum triglyceride level <400 mg/dl, negative urine culture, and the absence of any exclusion criteria.

Exclusion criteria were as follows: (i) subjects previously diagnosed to have H. pylori infection or those who had undergone or were currently undergoing H. pylori eradication, (ii) subjects receiving proton-pump inhibitors or H2 receptor blockers in the last three months, (iii) subjects with evidence of connective tissue, neoplastic ,hematological disorders or inflammatory diseases, (iv) Subjects with end stages renal diseases ,severe liver disease, severe cardiac decompensation, and severe uncontrolled hypertension, (v) Subjects with urinary tract infection or any other infectious diseases (vi) smokers.

Subjects were diagnosed as suffering from type 2 diabetes mellitus (DM) according to the report of the Expert Committee for the Diagnosis and Classification of Diabetes Mellitus.[20] The presence of DM was defined as a fasting serum glucose level greater than or equal to 126 mg/dl.

Dyspeptic symptoms were regarded as present complaints of epigastric pain, bloating, nausea, vomiting and early satiety, gastrointestinal bleeding, and weight loss.

Malb was estimated using Cobas C311 automated analyzer (Roche diagnostics, Germany). Malb was defined as two positive urine samples with UACR of 30-300 in the past 3 months.[2, 21]

Demographic and Clinical assessment

All study subjects were subjected to history taking including age, duration of diabetes and complete physical examination including anthropometric

measurements. Height and body weight were measured using a digital scale, and body mass index (BMI) was calculated as follows: BMI = body weight (kg)/height squared (m^2). A body mass index <25 kg/m2 was considered to be normal. Systolic and diastolic blood pressures were measured in a sitting position after a 5-min rest. Patients were categorized as hypertensive patients if the systolic blood pressure was >140 mm Hg and / or diastolic blood pressure was >90 mm Hg.

Laboratory investigations

Blood samples were collected from all subjects after at least a 12 h of fasting and used to determine blood glucose (mg/dl), total cholesterol (mg/dl), triglyceride (mg/dl), high-density lipoprotein-cholesterol (HDL-C, mg/dl), low-density lipoprotein-cholesterol (LDL-C, mg/dl), serum creatinine (mg/dl) using Olympus AU640 analyzer using reagent kits supplied by the manufacturer of the analyzer. C-reactive protein (CRP, mg/dl) was measured by a nephelometeric test. Erythrocyte sedimentation rate (ESR, mm/hour) was performed manually. Glycosylated hemoglobin (HbA1c, %) was measured using an automated high performance liquid chromatography (Bio-Rad Laboratories, USA). HbA1c level of 4%-6% was considered normal.

H. pylori testing

1. Detection of stool *H. pylori* antigen

A stool sample was collected from each participant and stored at 4°C till processing. H pylori antigen was detected using an immunochromatographic rapid test (onsite rapid test, Biotech, USA) according to the manufacturer's instructions.

2. Determination of serum *H. pylori* anti-CagA IgG antibodies

A blood sample was obtained from each subject and the sera were separated and stored at - 20°C until analysis. Serum IgG antibodies to *H. pylori* CagA were measured by enyme-linked immunosorbent assay (EUROIMMUN Medizinische Labordiagnostika AG) according to the manufacturer's instructions. The cut-off values were set according to the manufacturer's recommendations. According to manufacturer guideline the results were obtained as relative units (RU)/ml and the value of 20 RU/ml was used to discriminate the negative from positive samples.[15]

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. Correlations between two quantitative variables were assessed using Pearson coefficient. For abnormally distributed data, comparison between two independent populations were done using Mann Whitney test, Correlations between two quantitative variables were assessed using

Spearman coefficient. P-values of less than 0.05 were considered significant.

Results

Out of the 90 type 2 diabetic patients, 35 (**38.9%**) patients were seropositive and 55 (61.1%) were seronegative for H. pylori CagA. The 35 CagA seropositive included 24 (68.5%) *H. pylori* antigen positive and 11 (31.5%) H. pylori negative patients, while the 55 CagA seronegative patients included 30 (54.5%) H. pylori positive and 25 (45.5%) H. pylori negative. A total of 54/90 (**60%**) patients had active H. pylori infection, of them 24/54 (44.4%) were also CagA seropositive. Therefore, 24/90 (**26.6%**) patients were *H. pylori* positive/CagA seropositive and 11/90 (12.2%) were *H. pylori* negative/CagA seropositive.

Although the mean age of CagA seropositive patients was higher than seronegative patients, this was not statistically significant. (p = 0.335). On the other hand systolic and diastolic blood pressure were significantly higher in seropositive group (p=0.028 and 0.045 respectively). The body mass index mean was lower (24.74 ± 1.82) in CagA positive than in CagA negative group (29.89 ± 1.55). (Table 1)

CagA seropositive patients had significantly higher inflammatory markers (CRP, ESR), p value <0.001. Evaluation of the lipid profile showed that total cholesterol, triglycerides, and LDL-C were significantly higher in CagA seropositive group (p values; 0.005, <0.001, 0.026 respectively) while HDL-C was significantly lower (p value= 0.001). The fasting blood sugar levels as well as the HbA1c were higher in CagA positive group (p <0.001 each). These results showed that the association between poor glycemic control in type 2 diabetic patients and positive CagA antibodies was statistically significant. (Table 1)

The results revealed no significant association between CagA seropositivity and serum creatinine, liver profile (ALT) and total leucocytic count (p=>0.05) (Table 1)

When comparing the same clinical and laboratory parameters between *H. pylori* positive (n=24) and negative (n=11) patients in the seropositive group, it was found that the mean age of *H. pylori*/CagA positive patients was significantly higher than the *H. pylori* negative/CagA positive patients (p=0.028). Also, the *H. pylori* positive/CagA positive patients showed a significant high inflammatory markers (CRP, ESR, p <0.001) and more poor glycemic control (higher HbA1c levels, p=0.02). Although fasting blood sugar level was higher in *H. pylori* positive/CagA positive than in *H. pylori* negative/CagA positive patients, this was not statistically significant (p=0.683). (Table2)

The mean values of UACR were much higher in CagA seropositive groups than in seronegative group and this difference was statistically significant (p <0.001). (Table 1). The mean UACR values were also higher in CagA positive than in CagA negative patients in *H. pylori* positive group (p <0.001) as well as in *H. pylori* negative stool antigen group (p=0.001). (Table 3)

Figure (1) shows that there is progressive increase in UACR mean values and thus in Malb comparing *H. pylori* negative/CagA negative (98.2 ± 44.23), *H. pylori* positive/CagA negative

(116.53 ± 38.51), *H pylori* negative/CagA positive (160.55 ± 38.31), and *H pylori* positive/ CagA positive (200.83 ± 48.95) groups in the overall study population. This difference was statistically significant (p <0.001). (Table 3)

Because CagA *H. pylori* seropositivity was found to be significantly associated with Malb in diabetic subjects, we evaluated the relation between the severity of UACR and *H. pylori* seropositivity. The titer of *H. pylori* CagA igG was found to increase gradually with UACR levels, suggesting that *H. pylori* seropositivity is positively associated with Malb in diabetic subjects. Thus, according to table (4) and Figure (2) it was found that Malb has significant positive correlation with anti-CagA IgG titer (r=0.497, p<0.001). However, the correlation between Malb and other variables was statistically insignificant (p> 0.05).

Table (1): Comparison between the CagA (+) and CagA (-) groups according to different clinical and laboratory parameters.

Parameter	CagA (+ve) (n = 35)	CagA (-ve) (n = 55)	p value
Demographic & Clinical			
Age (years)	47.49 ± 4.45	48.42 ± 4.45	0.335
Duration of DM (years)	5.03 ± 3.15	4.18 ± 2.63	0.193
BMI	24.74 ± 1.82	29.89 ± 1.55	**<0.001**
Systolic blood pressure (mmHg)	132.86 ± 6.67	128.91 ± 10.12	**0.028**
Diastolic blood pressure (mmHg)	84.11 ± 5.88	81.18 ± 7.13	**0.045**
Laboratory			
Fasting blood Sugar (mg/dl)	282.23 ± 67.58	194.38 ± 77.89	**<0.001**
HbA1c (%)	9.01 ± 0.90	7.01 ± 1.23	**<0.001**
WBCs (10^3/mm^3)	6.43 ± 1.87	7.89 ± 9.44	0.369
Creatinine (mg/dl)	0.94 ± 0.26	1.02 ± 0.17	0.068
ALT (mg/dl)	39.31 ± 19.63	35.07 ± 17.34	0.286
Total Cholesterol (mg/dl)	247.77 ± 60.33	215.15 ± 46.57	**0.005**
TG (mg/dl)	283.86 ± 89.71	195.47 ± 101.41	**<0.001**
LDL-C (mg/dl)	154.43 ± 47.01	125.85 ± 37.71	**0.026**
HDL-C (mg/dl)	47.60 ± 11.19	56.33 ± 11.33	**0.001**
Inflammatory markers			
CRP (mg/dl)	15.94 ± 10.17	5.05 ± 2.59	**<0.001**
ESR (mm/hour)	36.29 ± 16.56	18.02 ± 12.16	**<0.001**
Moderately increased albuminuria			
UACR	188.17 ± 49.12	108.20 ± 41.84	**<0.001**

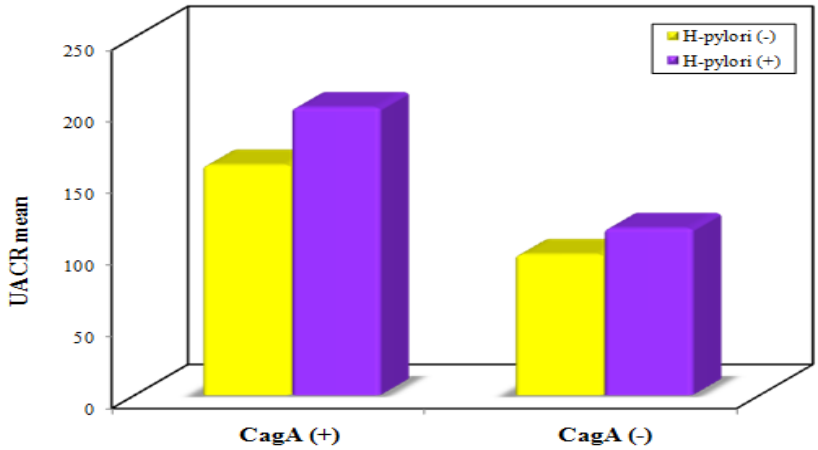

Figure (1): Comparison between different groups according to UACR.

Table (2): Comparison between the *H. pylori* positive and negative patients in the CagA seropositive group.

Parameter	H. pylori (+ve) (n =24)	H. pylori (-ve) (n = 11)	p value
Demographic & Clinical			
Age (years)	48.42 ± 4.81	45.45 ± 2.73	**0.028**
Duration of DM (years)	5.21 ± 3.39	4.64 ± 2.66	0.773
BMI	25.0 ± 2.06	24.19 ± 1.01	0.231
Systolic blood pressure (mmHg)	132.50 ± 7.37	133.64 ± 5.05	0.647
Diastolic blood pressure (mmHg)	83.37 ± 5.66	85.73 ± 6.31	0.278
Laboratory			
Fasting blood Sugar (mg/dl)	284.92 ± 79.31	276.36 ± 31.72	0.683
HbA1c (%)	9.24 ± 0.93	8.49 ± 0.58	**0.020**
WBCs (10^3/mm^3)	6.46 ± 2.0	6.36 ± 1.63	0.892
Creatinine (mg/dl)	0.92 ± 0.29	0.98 ± 0.16	0.473
ALT (mg/dl)	38.0 ± 19.89	42.18 ±19.69	0.566
Total Cholesterol (mg/dl)	242.54 ± 58.67	259.18 ± 65.17	0.457
TG (mg/dl)	305.75 ± 97.38	236.09 ± 43.50	0.067
LDL-C (mg/dl)	146.0 ± 40.63	172.82 ± 56.34	0.294
HDL-C (mg/dl)	47.17 ± 12.85	48.55 ± 6.67	0.741
Inflammatory markers			
CRP (mg/dl)	19.67 ± 10.05	7.82 ± 3.63	**<0.001**
ESR (mm/hour)	42.88 ± 15.88	21.91 ± 4.50	**<0.001**
Moderately increased albuminuria			
UACR	200.83 ± 48.95	160.55 ± 38.31	**0.022**

Table (3): Comparison between different groups according to UACR.

UACR	CagA (+) (n = 35)		CagA (-) (n = 55)		F	p value
	H-pylori (-) (n = 11)	H-pylori (+) (n = 24)	H-pylori (-) (n = 25)	H-pylori (+) (n = 30)		
Min. – Max.	100.0 – 241.0	108.0 – 270.0	33.0 – 210.0	47.0 – 189.0	27.566	**<0.001**
Mean ± SD.	160.55 ± 38.31	200.83 ± 48.95	98.20 ± 44.23	116.53 ± 38.51		
Median	163.0	203.50	90.0	118.0		
	p_1 = **0.001**, p_2 = **<0.001**					

F: F test (ANOVA), Significance between groups was done using Post Hoc Test.

p_1: p value for comparing between cag-A positive and CagA negative in H-pylori negative group.

p_2: p value for comparing between cag-A positive and CagA negative in H-pylori positive group.

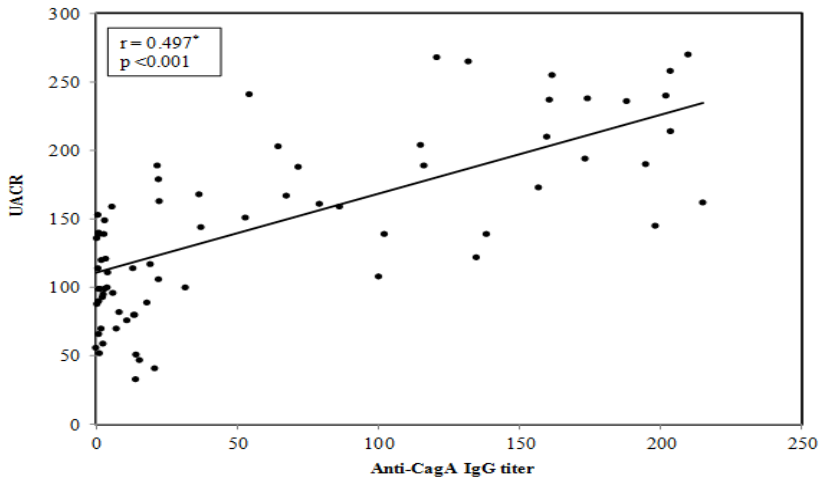

Figure (2): Correlation between Malb and titer of anti-CagA IgG antibodies.

Table (4): Correlation between Malb and different studied parameters.

Risk factor	Malb	
	r	p value
Age (years)	0.120	0.492
Duration of DM (years)	0.110	0.529
BMI	-0.144	0.408
Systolic Blood pressure (mmHg)	0.019	0.913
Diastolic Blood pressure (mmHg)	-0.123	0.482
FBS (mg/dl)	0.137	0.431
HbA1C (%)	0.124	0.478
WBCs (mm3)	0.034	0.847
Creatinine (mg/dl)	-0.066	0.706
ALT (mg/dl)	0.181	0.299
CRP (mg/dl)	0.245	0.157
ESR (mm/hr)	0.272	0.114
LDL. C (mg/dl)	-0.176	0.312
HDL (mg/dl)	0.091	0.603
TG (mg/dl)	0.083	0.635
Total cholesterol (mg/dl)	-0.165	0.345
Titer of CagA	0.497*	**<0.001**

r: Pearson coefficient

Discussion

Diabetic nephropathy is one of the most important diabetic complications. It is responsible for 30% of cases of kidney failure. The disease is diagnosed by proteinuria, high blood pressure, and kidney failure. Malb occurs at very early onset of the disease and can predict future kidney failure.[22]

The relationship between DM and *H. pylori* infection is controversial. It is not clear whether

diabetics have more susceptibility to this infection or *H. pylori* infection increases the susceptibility to diabetes. *H. pylori* infection is thought to be a risk factor for diabetes as it is associated with increased insulin resistance in these patients.[23] It is also believed that the chronic inflammation induced by HP infection is strongly associated to the pathogenesis of diabetes, which is related to a general activation of the immune system.[24] On the other hand, altered glucose metabolism may produce chemical changes in the gastric mucosa which invites bacterial colonization and individuals with diabetes are more frequently exposed to pathogens than their healthy counterparts as they have more frequent healthcare contact. It is also well known that diabetic patients are prone to chronic infections because of cellular and humoral immune deficiency.[25, 26]

In the present study, detection of active *H. pylori* infection was done using a non invasive antigen detection method in stool. It is well demonstrated that serum testing for presence of specific IgG antibodies against the CagA is a sensitive method for detection of the CagA-positive strains.[27] That's why we chose to use these two non-invasive tests to screen for virulent infections.

The reported prevalence of *H. pylori* infection in type 2 diabetic patients in our study was 60%. The prevalence of *H. pylori* infection has been reported to range between 20%-90% in diabetic patients in previous studies.[12, 13, 28, 29] The overall seroprevalence of anti-*H. pylori* CagA IgG antibodies in our study was 38.9%. This rate was in accordance with the study of Ibrahim A et al which reported a prevalence of 40.8%[14], while in contrast to the study of Jafarzadeh et al. and Pietroiusti A et al which reported a prevalence of 78.9% and 68% respectively.[15, 30]

We reported a significant association between CagA positive diabetic patients and Malb (< 0.001). The significant relationship of *H. pylori* CagA-positive with Malb has also been reported in other studies.[12, 14, 15] Furthermore, there are studies which report that Malb is significantly higher in *H. pylori* positive patients, regardless of the development of diabetes.[31]

We claim that the most interesting finding in our study is the significant progressive increase in UACR mean values and thus in Malb comparing *H. pylori* negative/CagA seronegative, *H.pylori* positive/CagA seronegative, *H. pylori* negative/CagA seropositive, and *H. pylori* positive/ CagA seropositive groups. We also found that Malb has a significant positive correlation with anti-CagA IgG titer ($r=0.497$, $p<0.001$). These results may emphasize the role of CagA antibodies per se in the pathogenesis of Malb in diabetic patients.

The mechanisms underlying increased urinary albumin excretion are complex. Chronic *H. pylori* infection causes an increased production of cytokines which may alter the permeability of the glomerular basement membrane resulting in the urinary loss of albumin and immunoglobulins, and they are mainly stimulated in the CagA-positive *H.pylori* infected patients. CagA positive strains have antigenic sequences common to endothelial cells. The formed CagA antibody can react with endothelial antigens and consequently causes

vascular lesions and leakage of albumin.[17, 18, 19] Moreover, Prasad et al.[32] showed that the immunoglobulin-G antibody response to pathogens was an independent risk factor for endothelial dysfunction and coronary atherosclerosis.

Considering inflammatory markers in patients with CagA positive H. pylori infection, they were also significantly higher (p<0.001). Our results are similar to previous studies[15, 33, 34] which have concluded that H. pylori infection may cause a systemic inflammatory response; therefore, it is considered to be a risk factor for the progression of diabetic nephropathy.[13]

We reported a positive association between *H. pylori* CagA positivity and fasting blood sugar as well as HbA1c levels. Other researchers found a poor glycemic control in type 2 diabetic patients who were infected by *H. pylori*. [14, 35, 36] The significant decrease in the glycemic control in patients infected with CagA-positive *H. pylori* could be explained by its ability to increase insulin resistance [37], and decrease serum concentration of somatostatin which has an inhibiting effect on insulin release.[38] Also, CagA-positive strains are associated with increased production of cytokines such as tumor necrosis factor (TNF alpha), interleukin (IL)-1, -6, and -8 which may affect carbohydrate metabolism.[24] In contrast, other studies did not find any association between infection by H. pylori and glycemic control.[10, 39]

In the present study, we also demonstrated a significant increase in total cholesterol, triglycerides, and LDL-C; (P= 0.005, <0.001, 0.026 respectively) as well as a significant decrease in HDL-C (p=0.001) in CagA positive group. El Hadidy M et al.[40] also provided evidences that *H. pylori* seropositivity was associated with atherogenic modified lipid profile among patients with type 2 DM. *H. pylori* infection was associated with significant increase in triglyceride level, significant decrease in HDL level and non significant effect on levels of both LDL and total cholesterol. Association of *H.pylori* infection with modified atherogenic lipid profile may be due to the bacterial cell wall lipopolysaccharides which stimulate the production of many cytokines including TNF- α which inhibit lipoprotein lipase activity leading to mobilization of lipids from the tissues and elevated serum triglycerides, lowered HDL cholesterol levels.[41]

There is no clear relationship between *H. pylori* and obesity.[42] Diabetes and obesity are multifactorial disorders that involve environmental, lifestyle, genetic, and social factors.[35] The body mass index mean in CagA positive patients was lower than CagA negative group (24.74 ± 1.82 vs 29.89 ± 1.55 respectively).

Nevertheless, the study has several limitations. First, we did not include a control non-diabetic group for comparison. Second, the study does not prove the type of causative association between CagA and Malb as it is a cross-sectional study. Third, the study was limited to a certain population (military males) and the results could not be generalized. Fourth, the study doesnot provide data on influence of specific genotype of *H. pylori* in the development of Malb.

Conclusion

In conclusion, our study found a significant correlation between the *H. pylori* CagA serpositivity and the severity of Malb in type 2 diabetic patients. The study also showed a possible association between *H. pylori* CagA seropositivity and increased inflammatory response, poor glycemic control, and disturbed lipid profile in diabetic patients. Infection with virulent *H. pylori* (CagA +) strains may play a role in the pathogenesis of diabetic nephropathy, where CagA antibodies per se may take the upper hand. Further study about the effect of *H. pylori* eradication in such patients to reverse these complications is mandatory. The results of this study may provide data for early detection and prevention of Malb in diabetic patients.

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