ORIGINAL ARTICLE

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Association of *Helicobacter pylori* infection with microalbuminuria in type 2 diabetic patients

Özgür TANRIVERDİ[1, 2]

Department of [1]Internal Medicine, Palu Government Hospital, Elazığ
Department of [2]Internal Medicine and Emergency Service, Safak Health Group Göztepe Hospital, İstanbul

Background/aims: *As default, Helicobacter pylori infection may cause systemic inflammation and vascular endothelial damage. Therefore, it can be assumed that the glomerular damage as a result may lead to an increase in urinary albumin excretion. In this study, this hypothesis was set, and the relationship between Helicobacter pylori infection and microalbuminuria was examined.* ***Methods:*** *Ninety-three patients with type 2 diabetes were included in the study. These patients were divided into two groups as Helicobacter pylori infection-positive (Group 1) or -negative (Group 2). In all infected and non-infected patients, urinary albumin excretion and other parameters were compared.* ***Results:*** *The presence of Helicobacter pylori infection was detected in 53 of 93 diabetic patients (56.98%). Diabetic patients infected by Helicobacter pylori (Group 1; 186.7±24.2 mg/24 h) showed significantly higher microalbuminuria than non-infected patients (Group 2; 131.2±11.6 mg/24 h) (p=0.012). Diabetics infected with Helicobacter pylori had significantly higher inflammation marker levels than non-infected patients (p<0.05). It has been concluded that the relation between microalbuminuria level and Helicobacter pylori infection in diabetics is independent from other study variables.* ***Conclusions:*** *Helicobacter pylori infection, because of the systemic inflammatory response, may play an important role in the progression of diabetic nephropathy or its development. In this study, demonstrating the relationship between Helicobacter pylori infection with diabetic microalbuminuria, due to the small number of patients, is inadequate. Therefore, clinical and molecular studies involving more patients should be supported.*

Key words: *Helicobacter pylori,* microalbuminuria, diabetes mellitus, systemic inflammation

Tip 2 diyabetik hastalarda *Helikobakter pilori* infeksiyonu ile mikroalbuminüri arasındaki ilişki

Amaç: *Helikobakter pilori ile oluşan infeksiyonun sistemik inflamasyona ve vasküler endotelyal hasara yol açabileceği düşünülmektedir. Bu nedenle, idrarla atılan albumin düzeyindeki artışın bu infeksiyon sonucu meydana gelen glomerular hasara bağlı olabileceği varsayılabilir. Bu çalışmada, Helikobakter pilori infeksiyonu ile mikroalbuminüri arasındaki ilişki bu hipoteze dayanılarak incelendi.* ***Yöntem:*** *Tip 2 diyabetes mellitus tanılı 93 hasta çalışmaya dahil edildi. Bu hastalar Helikobakter pilori infeksiyonu varlığına gore; infekte olanlar (Grup 1) ve olmayanlar (Grup 2) şeklinde iki gruba ayrıldı. Tüm hastalarda idrarla atılan albumin miktarı ile çalışmanın diğer değişkenleri karşılaştırıldı.* ***Bulgular:*** *Diyabetik 93 hastanın 53'ünde (%56.98) Helikobakter pilori infeksiyonu saptandı. İnfekte olan diyabetiklerde, infekte olmayanlara gore mikroalbuminüri düzeyinin anlamlı olarak daha yüksek olduğu saptandı (sırasıyla, 186.7±24.2 mg/24h ve 131.2±11.6 mg/24h, p=0.012). Benzer şekilde infekte diyabetiklerde inflamasyon göstergelerinin infekte olmayanlara oranla anlamlı olarak daha yüksek olduğu belirlendi (p<0.05). Diyabetik hastalarda Helikobakter pilori infeksiyonu ile mikroalbuminüri arasındaki ilişkinin çalışmanın diğer değişkenlerinden bağımsız olduğu saptandı.* ***Sonuç:*** *Helikobakter pilori infeksiyonu, oluşturduğu sistemik inflamatuvar yanıt nedeniyle, diyabetik nefropatinin gelişmesinde veya ilerlemesinde önemli bir rol oynayabilir. Bu çalışma, diyabetik mikroalbuminüri ile Helikobakter pilori infeksiyonu arasındaki ilişkiyi göstermede, hasta sayısının azlığı nedeniyle yetersizdir. Bu nedenle, daha fazla sayıda hastayı kapsayan klinik ve moleküler çalışmalarla desteklenmesi gerekmektedir.*

Anahtar kelimeler: *Helikobakter pilori,* mikroalbuminüri, diabetes mellitus, sistemik inflamasyon

Address for correspondence: Özgür TANRIVERDİ
Muğla University Education and Research Hospital,
Department of Medical Oncology and Internal Medicine,
48000 Muğla, Turkey
Phone: + 90 256 444 12 56
E-mail: ozgurtanriverdi@hotmail.com

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INTRODUCTION

Microalbuminuria (Malb) is a confirmed marker of diabetic nephropathy (1). The appearance of albumin in urine is thought to be the consequence of generalized endothelial damage along the vascular area including the glomerulus (1). Various infectious diseases may be listed among the etiologic factors related with this vascular endothelial damage and consequently developing atherosclerosis. Hepatitis B and C virus, chlamydia, Epstein-Barr virus, cytomegalovirus, and as shown in recent studies, *Helicobacter pylori (H. pylori),* are these microorganisms (2-5). *H. pylori,* particularly notable in developing countries, and affecting approximately 50% of the world population, is a gram-negative, spiral and microaerophilic bacterium (3,5). Its inflammatory response models have not been elucidated yet (3).

We performed a cross-sectional case control study to investigate a possible association between Malb and infection by *H. pylori* in a population of type 2 diabetic patients.

MATERIALS AND METHODS

Patients

The subjects of the present study were selected from patients attending the outpatient department during the period April 2004 to August 2004 in the first center and September 2005 to November 2006 in the second center. A population of 93 diabetic outpatients was analyzed through a review of clinical records and personal interview. Subjects diagnosed as suffering from type 2 diabetes mellitus according to the report of the Expert Committee for the Diagnosis and Classification of Diabetes Mellitus were included in the study (6). Diabetes mellitus was defined as diabetes treated by diet alone or by diet combined with oral hypoglycemic agents or as treatment with insulin in a case of diabetes onset after the age of 40 years. Inclusion criteria were the following parameters: age of onset >40 years, duration of diabetes <4 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 the other exclusion criteria.

The subjects were divided into two groups according to *H. pylori* infection as Group 1 (*H. pylori*-positive) and Group 2 (*H. pylori*-negative).

Ethics

The protocol of this study conformed to the local ethical guidelines and informed written consent was obtained from each participant. The study began following approval of the Academic Ethics Committee on March 12, 2004 in first center and on September 19, 2005 in second center.

Exclusion Criteria Used in the Study

Exclusion criteria were as follows: (i) those previously diagnosed to have *H. pylori* infection or those who had undergone or were currently undergoing *H. pylori* eradication, (ii) those receiving anti-ulcer treatment in the last three months and still receiving proton-pump inhibitors (PPI) or H_2 receptor blockers, (iii) diabetic patients with poor glucose regulation diagnosed previously and detected in laboratory parameters as having nephropathy, retinopathy, neuropathy, or ischemic cardiovascular disease, and diabetics having >120 mmHg systolic blood pressure and >85 mmHg diastolic blood pressure, (iv) those with vascular or inflammatory disease, those obliged to continue antibiotic treatment for various reasons, and those suspected for or diagnosed as rheumatoid or immunological disease, (v) diabetics with periodontal disease diagnosed by a dentist and requiring intensive treatment and those with poor oral hygiene, (vi) smokers, (vii) those not providing consent for the study, and (viii) those with poor socioeconomic level unable to return for follow-ups regularly.

Parameters and Measurement Methods Used Throughout the Study

Demographic and clinical parameters of the study were age (years), gender (male or female), anti-diabetic treatment (diet or oral anti-diabetics or insulin), body mass index (BMI, kg/m^2), duration of diabetes (years), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). Laboratory parameters were total cholesterol (mg/dl), blood glucose (mg/dl), triglyceride (mg/dl), high-density lipoprotein-cholesterol (HDL-C, mg/dl), low-density lipoprotein-cholesterol (LDL-C, mg/dl), glycosylated hemoglobin (HbA1c, %), leukocyte ($10^3/mm^3$) and platelet ($10^3/mm^3$) counts, erythrocyte sedimentation rate (ESR, mm/hour), C-reactive protein (CRP, mg/dl), fibrinogen (mg/dl), lipoprotein (a) (LPa, mg/dl), and Malb levels (mg/24 hours). The presence of *H. pylori* infection was also assessed.

Outcome Data and Assays

Body mass index (BMI) was calculated by using the Quetelet index (weight/length^2=kg/m^2) (7). Blood pressure was calculated based on Korotkoff Phase-I and Phase-V sounds through both arms with a mercury sphygmomanometer after 10 minutes rest while sitting. A systolic pressure of over 120 mmHg and a diastolic pressure of over 85 mmHg were accepted as hypertension (7). Plasma glucose (hexokinase method), total cholesterol (enzymatic method), triglyceride (enzymatic method without glycerol blocking), and HDL-C (dextran sulfate- MgCl2 precipitation) were measured on a Hitachi 911 automated analyzer using reagent kits supplied by the manufacturer of the analyzer. LDL-C was calculated by the Friedewald equation (7). HbA1c was measured by an automated ion-exchange chromatographic method, and the reference range was 5.1-6.4%. The CRP level was determined by the immunoturbidimetric method, and a Cobas Integra auto-analyzer was used for the measurement. Measurement of fibrinogen was realized in citrated plasma on a Behring Nephelometer Bien 100 instrument (Dade Behring Diagnostic, Liederbach, Germany). This method developed to measure fibrinogen (mg/dl) in plasma depends on immune complex formation of plasma factors by specific antibodies through an immunochemical reaction, radiation of light beam passing through these complexes, and proportional change of radiated light with the protein being measured. Serum LPa level (mg/dl) was measured using the enzyme immunoassay kit (Boehringer-Mannheim Biochemica).

The presence of cerebrovascular disease was documented with a central nervous system computed tomography and consultation with a neurologist. Peripheral vascular disease was clinically defined by the presence of intermittent claudication, absent or weakened peripheral pulses, or both. Retinopathy was documented by standard fundus examination. Clinical neuropathy was defined by an abnormal examination, consistent with the presence of peripheral sensorimotor neuropathy. Coronary heart disease was clinically assessed and supported with electrocardiographic findings. Advanced nephropathy was defined by the presence of urinary albumin excretion ≥300 mg per 24 hours and a rate of creatinine clearance <70 ml/min.

Determination of Malb

Urinary albumin excretion was measured by nephelometric test for the measurement of Malb in urine. Three consequent Malb measurements were performed in three months and those with 24-hour urinary albumin excretion between 30-300 mg on at least two measurements were accepted as micro-albuminuric (1,2). Since heavy exercise, excessive protein ingestion, fluid overlaod, and urinary tract infections increase the urinary protein excretion, these conditions were discarded during Malb measurements.

Assessment of *Helicobacter pylori* Infection

Three endoscopic biopsy samples were obtained from the antral mucosa of each patient. Two biopsy samples were placed into 10% formol solution and dyed by Giemsa and hematoxylin-eosin, and investigated for *H. pylori*. Another tissue sample was used for rapid urease test, also known as the Campylobacter-like organism (CLO) test. The CLO test was monitored for color change up to 24 hours after the addition of the gastric tissue. A pink coloration was interpreted as positive. Histology-positive patients were those with curved organisms seen in hematoxylin and eosin-stained sections under the microscope. When either the histopathology or the urease tests were positive, the *H. pylori* infection was confirmed (8). *H. pylori* infection was shown in all patients with histopathological results. Urease test was negative in only 8 patients. Since the diagnosis of *H. pylori* has a sensitivity of 93–99% and specificity of 95-99%, the diagnosis was established by the histopathological method accepted as the "gold standard" (8). Due to financial difficulties, specific strain identification directed towards *H. pylori* could not be performed. The endoscopic findings obtained from all patients were recorded. The relationships between these findings and study variables were investigated and it was attempted to determine any effect(s) on inflammation indicators.

Statistical Evaluation

All data were expressed as mean±SD or median range as appropriate. The distribution of variables was analyzed with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, independent Student's t test. Nonparametric variables were analyzed with the Mann-Whitney U test. However, qualitative parameters were analyzed with the chi-square test and Fisher's test. Kruskal-Wallis test was used while making comparisons between endoscopic findings and study variables. The relati-

onship between urine albumin excretion and other study variables was made by using Spearman correlation coefficient and logistic regression analysis. Results were evaluated in 95% confidence interval, at p<0.05 significance level. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.

RESULTS

The demographic, clinical and laboratory characteristics of patients in this study (Groups 1 and 2) are displayed in Table 1.

The presence of *H. pylori* infection was detected in 53 of 93 diabetic patients (56.98%). Diabetic patients infected by *H. pylori* (Group 1; 186.7±24.2 mg/24 h) showed significantly higher Malb than non-infected patients (Group 2; 131.2±11.6 mg/24 h) (p=0.012) (Table 2). Infected diabetics with *H. pylori* had significantly higher leukocyte and platelet counts, ESR, serum CRP, fibrinogen, and LPa levels than non-infected diabetics (p=0.011, p=0.041, p=0.024, p=0.019, p=0.027, respectively) (Table 2).

The endoscopic findings detected for all patients participating in the study are given in Table 3. No relationship between endoscopic findings and urine albumin excretion or other study variables was detected.

It has been concluded that the relation between Malb level and *H. pylori* infection in diabetics is independent from other study variables (sex, diabetes duration, HbA1c, blood pressure, lipid profile, diabetes treatment) (p=0.025; OR=3.32, CI 95% 1.16- 9.50).

DISCUSSION

The Malb levels were higher in patients with *H. pylori* infection than in those without *H. pylori* in-

Table 1. The demographic, clinical and laboratory characteristics of patients in the infected (Group 1) and non-infected (Group 2) patients

Parameters	Group 1 (infected with *H. pylori*)	Group 2 (non-infected with *H. pylori*)	P*
Patients (n)	53	40	-
Age (year)	58±11	52±8	-
Male/female (n)	28/ 25	21/19	-
Blood glucose level (mg/dl)	126.4±8.3	115.6±5.1	>0.05
HbA1c (%)	6.9±1.2	6.1±1.4	0.055[ɣ]
Total cholesterol level (mg/dl)	192.2±13.1	187.4±10.2	>0.05
Triglycerides level (mg/dl)	199.4±13.1	195.6±11.4	>0.05
HDL-cholesterol level (mg/dl)	28.5±6.4	27.2±4.1	>0.05
LDL-cholesterol level (mg/dl)	121.7±7.1	126.3±5.4	>0.05
Body mass index (kg/m^2)	29.1±2.7	27.1±2.3	>0.05
Systolic blood pressure (mmHg)	104.3±11.4	105.2±8.2	0.056[ɣ]
Diastolic blood pressure (mmHg)	88.4±6.2	86.2±4.3	>0.05
Oral anti-diabetics/insulin	28/ 25	16/ 24	>0.05
Diabetic duration (year)	2.9±0.8	2.8±0.5	>0.05

* A two tailed p value of <0.05 was considered statistically significant, [ɣ]not statistically significant for each group.

Table 2. The inflammation markers and urine protein excretion levels of patients in the infected (Group 1) and non-infected (Group 2) patients

Parameters	Group 1 (infected with *H. pylori*)	Group 2 (non-infected with *H. pylori*)	P*
Urine protein excretion (mg/24 h)	186.7±24.2	131.2±11.6	P<0.05
Fibrinogen level (mg/dl)	532.2±46.4	498.5±23.3	P<0.05
C-reactive protein (mg/dl)	32.4±9.7	27.5±9.3	P<0.05
Lipoprotein-a level (mg/dl)	39.1±8.2	31.3±5.2	P<0.05
Leukocyte count (10^3/mm^3)	12.1±1.9	9.8±2.4	P<0.05
Platelet count (10^3/mm^3)	512.45±98. 4	467. 51±78.6	P<0.05

* A two tailed p value of <0.05 was considered statistically significant.

Table 3. Endoscopic findings for all patients

Endoscopic findings	Group 1 (infected with *H. pylori*)	Group 2 (non-infected with *H. pylori*)	P*
Patients (n)	53	40	-
Normal endoscopy n, (%)	30 (56.61%)	24 (60%)	>0.05
Abnormal endoscopy n, (%)	23 (43.39%)	16 (40%)	0.057[ɣ]
Pangastritis n, (%[£])	3 (13.04%)	2 (12.5%)	>0.05
Atrophic gastritis n, (%[£])	2 (8.69%)	1 (6.25%)	>0.05
Antral gastritis n, (%[£])	6 (26.08%)	3 (18.75%)	>0.05
Duodenitis n, (%£)	4 (17.39%)	3 (18.75%)	>0.05
Duodenal ulcer n, (%[£])	1 (4.34%)	1 (6.25%)	>0.05
Gastric ulcer n, (%[£])	1 (4.34%)	1 (6.25%)	>0.05
Esophagitis n, (%£)	6 (26.08%)	5 (31.25%)	>0.05

* A two-tailed p value of <0.05 was considered statistically significant, [ɣ]not statistically significant for each group; [£]shows the ratio of patients with an abnormal endoscopy.

fection. This study is the first to describe any relationship with *H. pylori* in a diabetic population with Malb. The prevalence of *H. pylori* infection has been reported to range between 30%-80% in diabetic patients (9-18). In this recent study of our institute, the prevalence of *H. pylori* infection in diabetics was found to be 56.98%, and this rate was concordant with the values observed in other studies.

Malb has been shown to be consistently associated with endothelial low-grade inflammation (19). Ross (20) has proposed that dysfunction of the vascular endothelium and chronic systemic low-grade inflammation are the key features in the pathophysiology of atherothrombosis and Malb. Although a certain value has not been determined about the frequency, it has been demonstrated that persistent systemic inflammatory response related with *H. pylori* increases the vascular injury in diabetics and predisposes them to pulmonary, cardiovascular and cerebral diseases (9,10,21). *H. pylori* infection has been hypothesized to contribute to a strong inflammatory response, atherogenesis and plaque instability (22). It is thought that pro-inflammatory factors are produced at excessive amounts in this infection, and cross-reaction between the released mediators and host antigens causes gastric injury and extra-digestive manifestations (21). Studies have demonstrated a significant relation between LPa, HDL-C, oxidant lipids, LDL-C, thrombotic activation-related anti-thrombin (AT)-III, von-Willebrand factor, interleukin-1, tumor necrosis factor, and interleukin-6 and *H. pylori* infection (23-25). Unfortunately, certain evidence has not been presented on the predicted changes in renal microvascular structure of *H. pylori*, accepted to have a notable relation with atherosclerosis and particularly with coronary artery disease. In the present study, inflammation markers (CRP and fibrinogen levels, ESR and leukocyte count) and thrombotic activation markers (LPa level) were found to be significantly increased in infected diabetic patients. Nevertheless, the microalbuminuric process related with endothelial dysfunction that forms the first step of systemic vascular response and vascular injury, particularly in diabetics, and the relationship with *H. pylori* infection have not been sufficiently emphasized in recent studies. In a limited number of studies, no definite result regarding the relation between diabetic nephropathy and *H. pylori* infection was obtained. In a study by Pietroiusti et al. (21), infections produced by cytotoxin-associated gene-A (cagA), thought to cause cross-reaction with endothelial antigens carrying *H. pylori* strains, were shown to be related with diabetic Malb.

This present study is inadequate for drawing a conclusion regarding a definite relationship between *H. pylori* infection and diabetic Malb, primarily because of the small number of patients.

In conclusion, further studies with large patients' series and involving many inflammatory markers and antigenic molecules may put forth a discussion on another absolute indication of *H. pylori* eradication.

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