Helicobacter pylori eradication reduces microalbuminuria in type-2 diabetic patients : a prospective study

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Abstract

Aim : **To evaluate the effect of *Helicobacter Pylori* (*H. pylori*) eradication on microalbuminuria in type 2 diabetic patients.**

Methods : **Consecutive patients with dyspepsia, type 2 diabetes mellitus and microalbuminuria were recruited. Upper gastrointestinal endoscopy and rapid urease test (*H. pylori* fast) were performed for detecting *H. pylori* infection. Patients with *H. pylori* infection were given triple treatment. Urea breath tests were performed for all patients after eradication treatment. According to the eradication status, patients were divided into two groups, as *H. pylori* negative, group 1 (successful eradication group) and H. pylori positive, group 2 (unsuccessful eradication group). Twenty-four hour urine was also collected from all patients at baseline and after *H. pylori* eradication treatment.**

Results : **A total of 69 patients were included in the study. There were no significant differences between groups for anthropometric measurements and laboratory tests at baseline ($p > 0.05$). An expected significant difference was found for microlabuminuria and fasting glucose between the two groups. Microalbuminuria and fasting glucose levels were signicantly reduced in the *H. pylori* negative group compared with the *H. pylori* positive group after eradication treatment ($p < 0.05$). Although there was no significant decline in HbA1c levels in the *H. pylori* negative group, there were relatively lower HbA1c levels compared with baseline for both groups. The rate of attaining normoalbuminuria after eradication was significantly higher in group 1 compared to group 2 ($p < 0.05$).**

Conclusion : H. Pylori **eradication was found to have a favorable effect on reducing microalbuminuria in diabetic patients.** (Acta gastroenterol. belg., **2014**, 77, **235-239**).

Key words : *H. pylori*, microalbuminuria, diabetes, endothelial dysfunction.

Introduction

There is an increasing amount of data showing the association between *H. pylori* seropositivity and extragastric conditions, such as increased coronary artery calcium scores, reduced high density lipoprotein, elevated low density lipoprotein levels, insulin resistance and microalbuminuria (1-6). Microalbuminuria, an increased urinary albumin to creatinine ratio of 30-300 μg/mg, has been defined as a strong predictor of the development of diabetic nephropathy (7,8). Microalbuminuria is thought to be the consequence of generalized endothelial damage along the vascular area including the glomerulus. Previous studies indicate several mechanisms to explain this relationship (9,10). Microalbuminuria can also be seen due to several infectious diseases in the absence of diabetes. Several microorganisms have been implicated in vascular endothelial damage, such as Hepatitis B and C virus, chlamydia, Epstein-Barr virus, cytomegalovirus, and *H. pylori* (11-15).

Our hypothesis was that if *H. pylori* infection was involved in the pathogenesis of microalbuminuria, a favorable effect on microalbuminuria might be seen after *H. pylori* eradication. Therefore, we aimed to investigate whether *H. pylori* eradication improved the microalbuminuria in diabetic patients with *H. pylori* infection.

Materials and Methods

This was a prospective, single-blind study carried out in our gastroenterology department. The person performing the endoscopy was blinded to the study patients so that the urease test results were not affected regarding the amount of tissue sampling in the biopsy or urease test checking. One hundred and seventy-one consecutive patients with dyspepsia, type 2 diabetes mellitus and microalbuminuria were recruited between July 2012 and September 2012. This study was certified by the Local Ethical Committee of the Ankara Education and Research Hospital. Informed consent was obtained from all patients.

Patients with hematologic abnormality, diabetic complications (already known diabetic nephropathy, retinopathy, neuropathy and coronary artery disease known as microvascular complications of diabetes mellitus), urinary tract infection, liver and kidney disease (creatinine higher than 1.5 mg/dL) were excluded. Patients with a history of previous *H. pylori* eradication treatment, using NSAIDs, having uncontrolled hypertension or systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 80 mmHg, using new or changing dose of antihypertensive drugs in three months, using antibiotics or proton pump inhibitors within one month were also excluded from the study. Pregnancy, lactation, alcohol consumption, and smoking were other exclusion criteria. Sixty-four patients were excluded according to these exclusion criteria (Table 1). Excluded patients were

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Table 1. — **Exluded patients with grounds for exclusion according to exclusion criteria**

Exlusion criteria and grounds	Gender
Overt nephropathy (serum creatinine > 1.5 mg/dl)	3 females, 2 males
Coronary artery disease (gastroscopy not performed due to recent myocardial infarction)	1 male
Urinary tract infection (due to contribution of albuminuria)	2 females
Kidney stones (due to serum creatinine > 1.5 mg/dl and contribution of albuminuria)	1 female, 3 males
Previous eradication treatment (due to misinterpretation of urease results)	5 females, 3 males
Uncontrolled Hypertension (due to contribution of vascular damage)	2 females, 1 male
Using NSAID within a month (due to misinterpretation of urease test)	5 females, 2 males
Using new anti-hypertensive drugs within three months (due to contribution of changes in albuminuria)	4 females, 2 males
Changing anti-hypertensive drugs within three months (due to contribution of changes in albuminuria)	5 females, 2 males
Using antibiotics within one month (due to misinterpretation of urease test)	2 females, 1 male
Using proton pump inhibitors within one month (due to misinterpretation of urease test)	7 females, 4 males
Pregnancy (gastroscopy not performed due to risk of preterm birth)	1 female
Lactation (due to patient's demand for postponed eradication therapy)	1 female
Smoking (due to contribution of eradication rates)	1 female, 4 males
TOTAL EXCLUDED PATIENTS	39 females, 25 males

referred to the gastroenterology outpatient department for appropriate diagnosis and eradication of *H. pylori*. Four patients in group 1 and 1 patient in group 2 had asymptomatic microscopic hematuria (less than five red blood cells per high-power microscopic field were seen in urinary sediment) and were included in the study. There were no statistically significant differences between the two groups according to the presence of microscopic hematuria (Table 2).

After patient approval, upper gastrointestinal endoscopy was performed. Two specimens from the incisura angularis, antrum and corpus were sampled for histological analysis during endoscopy. Rapid urease test (*H. pylori* fast) was performed on all specimens for detecting *H. pylori* infection. Thirty-eight patients (35.5%) with negative urease test were excluded from the study. Patients with urease positive test (64.5%) were eradicated with triple treatment (amoxicillin 1000 mg, clarithromycin 500 mg, lansoprazole 30 mg, twice daily) for 14 days. Lansoprazole treatment (30 mg twice daily) was continued for all patients for 4 additional weeks to complete the eradication therapy. Urea breath test was performed for all patients after 12 weeks of treatment. According to eradication status, patients were divided into two groups, as *H. pylori* negative, group 1 (successful eradication group) and *H. pylori* positive, group 2 (unsuccessful eradication group).

All patients with *H. pylori* infection were tested for fasting glucose, glycated hemoglobin (HbA1c) at baseline and 4 months after eradication treatment. Blood samples were obtained following an overnight (12 hour) fast and were used to measure glucose, total cholesterol, high and low density lipoprotein cholesterol, triglyceride and creatinine. Patients were recommended to not drink coffee and tea within thirty minutes. Systolic and diastolic artery blood pressure (SBP and DBP) was then measured in a sitting position after a 10-minute rest, twice a day. Mean values of artery tension were used for analysis. Body mass index (BMI) was calculated as body weight(kg)/height (m2) for all patients at baseline and 4 months after eradication. Also 24 hour urine was collected for all patients at baseline and after 4 months of *H. pylori* eradication treatment. Microalbuminuria was measured with a nephelometric method using a BN ProSpec System for kidney disease. Microalbuminuria was described as between 30 to 300 mg protein in a 24 hour urine collection.

Statistical analysis

Numerical values were defined as mean±standard deviation. Paired-Samples t-test was used for comparing the pre-treatment and post-teratment values of patients. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS 16 statistical package (Chicago, Illinois, USA).

Results

A total of 69 patients (female : 37, 53.6% ; male : 32, 46.4%) were included in the study. The mean age of the patients was 55.36 ± 9.15 years. Baseline demographic and laboratory findings are shown in Table 2. There was no significant differences between groups for age and gender, BMI, hematological parameters, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, creatinine, creatinine clearance, microalbuminuria, fasting glucose, glycated hemoglobin, duration of diabetes, diabetes treatment (oral antidiabetics vs insulin), lipid profiles and artery blood pressure at baseline

Table 2. — **Baseline characteristics of study patients**

	Group 1 (n = 56 ; 81.2%)	Group 2 (n = 13 ; 18.8%)	p value
Gender Male Female	 26 (46.4%) 30 (53.6%)	 6 (46,2%) 7 (53,8%)	> 0.603
Age (yr)	55.45 ± 9.11	55.00 ± 9.72	> 0.876
BMI (kg/m²)	28.76 ± 2.85	28.12 ± 2.57	> 0.459
Hb (gr/dL)	13.35 ± 1.30	13.37 ± 1.49	> 0.955
PLT (μL)	285000 ± 58300	255000 ± 51748	> 0.094
WBC (μL)	7785 ± 1187	6961 ± 1975	> 0.170
AST (U/L)	23.77 ± 6.76	26.54 ± 6.07	> 0.180
ALT (U/L)	25.54 ± 8.35	24.23 ± 4.43	> 0.438
BUN	30.58 ± 7.12	33.23 ± 8.73	> 0.253
Creatinine (mg/dL)	0.96 ± 0.21	0.95 ± 0.21	> 0.875
Creatinine clearance (ml/min)	76.29 ± 9.65	73.66 ± 12.77	> 0.409
Number of patients with microhaematuria	4 (7.1%)	1 (7.7%)	> 0.946
Microalbuminuria (mg/day)	120.98 ± 77.04	117.69 ± 60.54	> 0.546
Glycated hemoglobin (%)	7.70 ± 1.85	7.78 ± 1.32	> 0.885
Fasting glucose (mg/dL)	170 ± 69.9	171.92 ± 54.24	> 0.928
Duration of diabetes (year)	11.63 ± 2.87	10.40 ± 3.01	> 0.173
Diabetes treatment Insulin Oral antidiabetics	 9 (16.1%) 47 (83.9%)	 2 (15.4%) 11 (84.6%)	> 0.951
Triglyceride (mg/dL)	190.77 ± 70.88	175.31 ± 70.03	> 0.480
LDL (mg/dL)	120.88 ± 29.52	129.23 ± 19.62	> 0.336
HDL (mg/dL)	44.45 ± 8.32	43.77 ± 7.92	> 0.791
SBP (mmHg)	119.45 ± 7.24	120.92 ± 5.51	> 0.493
DBP (mmHg)	76.41 ± 2.58	75.15 ± 2.88	> 0.127

Values expressed as mean ± SD. BMI, Body mass index ; Hb, Hemoglobin ; PLT, Platelet count ; WBC, White blood cell ; AST, Aspartate aminotransferase ; ALT, Alanine aminotransferase ; LDL, Low density lipoprotein ; HDL, High density lipoprotein ; SBP, Systolic blood pressure ; DBP, diastolic blood pressure.

Table 3. — **Laboratory and demographic findings after eradication**

	Group 1 (n = 56, 81.2%)	Group 2 (n = 13, 18.8%)	p1, p2 values
Microalbuminuria(mg/day)	92.57 ± 77.87	106.69 ± 60.80	p1 < 0.001 p2 > 0.92
BMI (kg/m²)	28.72 ± 2.85	28.15 ± 2.58	p1 > 0.433 p2 > 0.378
Creatinine (mg/dL)	1.13 ± 0.21	0.99 ± 0.17	p1 > 0.422 p2 > 0.175
Glycated hemoglobin	7.36 ± 1.84	7.71 ± 1.13	p1 > 0.122 p2 > 0.387
Glucose(mg/dL)	151.05 ± 50.00	159.38 ± 34.02	p1 < 0.016 p2 > 0.078
SBP (mmHg)	119.98 ± 6.07	121.69 ± 5.10	P1 > 0.093 p2 > 0.086
DBP (mmHg)	76.05 ± 2.77	75.92 ± 2.43	P1 > 0.172 p2 > 0.137

Values expressed as mean ± SD. p1, p value for group 1 ; p2, p value for group 2 ; BMI, Body mass index ; SBP, Systolic blood pressure ; DBP, diastolic blood pressure.

Table 4. — **Rates of attaining the normoalbuminuria after *H. pylori* eradication**

	Group 1 (n = 56 ; 81.2%) n = 23, 41%	Group 2 (n = 13 ; 18.8%) n = 2 ; 15.3%	p
Normoalbuminuria (< 30 mg/day)	22.43 ± 5.45	24.50 ± 0.70	p1 < 0.001 p2 > 0.310

p1, p value for group 1 ; p2, p value for group 2.

(p > 0.05). Regarding the confounding factors that affect microalbuminuria, we did not find any significant differences between groups (H. pylori negative-group 1 and *H. pylori* positive-group 2) after eradication treatment (p > 0.05) (Table 3). An expected significant difference was found for microalbuminuria and fasting glucose between the two groups. Microalbuminuria and fasting glucose levels were signicantly reduced in the *H. pylori* negative group (group 1-successful eradication group) compared with the *H. pylori* positive group (group 2-unsuccessful eradication group) after eradication treatment (p < 0.05) (Table 3). Although there was no significant decline of HbA1c levels in the *H. pylori* negative group, there were relatively lower HbA1c levels compared with baseline for both groups (Table 2, 3). The rate of attaining normoalbuminuria after eradication was significantly higher in group 1 compared to group 2 (p < 0.05) (Table 4).

Discussion

This study has shown that eradication of *H. pylori* favorably decreased microalbuminuria and fasting glucose levels in type 2 diabetic patients. This result supports previous studies that established an *H. pylori* and microalbuminuria association (16,17). There are several mechanisms proposed to explain this association. First of all, *H. pylori* causes poor glucose metabolism and therefore plays a role in the development of metabolic syndrome (18). However, most previous reports placed endothelial cell damage in the center of this linkage to explain the pathogenesis and role of H. pylori in microalbuminuria. Proinflammatory or immunologically mediated mechanisms share a major part in those postulates. Proinflammatory and vasoactive substances, immunoglobulin-G antibody response, and cross-reactivity of cytotoxin-associated genA strains of *H. pylori* with endothelial antigens has been demonstrated in chronic *H. pylori* infection (19,20). On the other hand, chronic *H. pylori* infection was found to be associated with significantly higher levels of soluble intercellular adhesion molecule-1, CRP, and lower levels of flow-mediated vasodilation. Therefore, chronic infection with *H. pylori* might contribute to the pathogenesis of atherosclerosis by vascular endothelial cell damage and systemic inflammation (21). It is very well known that elevated levels of homocysteine in the blood may cause endothelial damage or vascular disease (22). Chronic *H. pylori* infection causes malabsorption of vitamin B and folate, leading to higher levels of circulating homocysteine (12). Accordingly, increased homocysteine levels due to H. pylori is claimed to play a role in endothelial dysfunction (23). Nitric oxide has a wide range of biological properties that maintain vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injurious consequences of platelets and cells circulating in blood, playing in this way a crucial role in normal endothelial function (24). So a decrease of nitric oxide due to H. pylori might obviously lead to endothelial dysfunction. Similarly, microvascular dilation with acetylcholine has been found to be significantly lower in patients seropositive for *H. pylori* resulting in endothelial dysfunction (25).

Older age, elevated blood pressure and poor glycemic control (higher HbA1c level) and gender were previously demonstrated to increase microalbuminuria in subjects with diabetes (26,27). In the present study, there was no statistically significant difference in age, blood pressure, or HbA1c level between the eradicated (group 1) group and the non-eradicated (group 2) group at the start of the study (Table 2). So the confounding effect of these factors seems to have been eliminated in our study. Therefore, a causative correlation between infection by *H. pylori* and the appearance of microalbuminuria and also the benefit of eradication for microalbuminuria has been shown in the present study.

This study has several advantages. First, to the best of our knowledge, this is the only study that shows the favorable effect of *H. pylori* eradication on microalbuminuria in diabetic patients. Previous studies have focused on the association between *H. pylori* and microalbuminuria rather than the favorable effect of *H. pylori* eradication treatment on microalbuminuria. Second, it is a prospective study and patients with type 2 diabetes were recruited so that we could establish a causative relationship between microalbuminuria and *H. pylori*. Third, gastroscopy and rapid urease test were used to document active *H. pylori* infection. Fourth, many metabolic confounding factors were also evaluated. However, this study has a limitation. We did not investigate *H. pylori*-linked inflammatory factors such as cytokines, or virulence factors such as the CagA gene. Further studies with larger patient series and involving cytokines, inflammatory markers, and antigenic molecules such as CagA are need to establish a stronger relationship between the eradication of *H. pylori* and microalbuminuria.

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