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BRIEF ARTICLE

Helicobacter pylori seropositivity in diabetic patients is associated with microalbuminuria

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Abstract

AIM: To investigate the relationship between *Helicobacter pylori* (*H. pylori*) seropositivity and the presence of microalbuminuria.

METHODS: Between December 2003 and February 2010, asymptomatic individuals who visited the Seoul National University Healthcare System Gangnam Center for a routine check-up and underwent tests for *H. pylori* immunoglobulin G antibodies and urinary albumin to creatinine ratio (UACR) were included. All study subjects completed a structured questionnaire, anthropometric measurements and laboratory tests. Anti-*H. pylori* immunoglobulin G was identified using an enzyme-linked immunosorbent assay kit. A random single-void urine sample, collected using a clean-catch technique, was obtained to determine the UACR. The presence of microalbuminuria was defined as a UACR from 30 to 300 μg/mg. The presence of diabetes mellitus (DM) was defined as either a fasting serum glucose level greater than or equal to 126 mg/dL or taking anti-diabetic medication. Multiple logistic regression analysis was performed to identify the risk factors. The dependent variable was microalbuminuria, and the independent variables were the other study variables.

RESULTS: A total of 2716 subjects (male, 71.8%; mean age, 54.9 years) were included. Among them, 224 subjects (8.2%) had microalbuminuria and 324 subjects (11.9%) had been diagnosed with DM. Subjects with microalbuminuria had a significantly higher *H. pylori* seropositivity rate than subjects without microalbuminuria (60.7% *vs* 52.8%, $P = 0.024$). Multivariate analysis after adjustment for age, body mass index (BMI), waist circumference, and glucose and triglyceride levels showed that *H. pylori* seropositivity was significantly associated with microalbuminuria [odds ratio (OR), 1.40, 95% CI, 1.05-1.89, $P = 0.024$]. After the data were stratified into cohorts by glucose levels (⩽ 100 mg/dL, 100 mg/dL < glucose < 126 mg/dL, and ⩾ 126 mg/dL or history of DM), *H. pylori* seropositivity was found to be significantly associated with microalbuminuria in diabetic subjects after adjusting for age, BMI and serum creatinine level (OR, 2.21, 95% CI, 1.20-4.08, $P = 0.011$). In addition, the subjects were divided into five groups. Those without microalbuminuria (an UACR of < 30 μg/mg) were divided into four groups in accordance with their UACR values, and subjects with microalbuminuria comprised their own group. Notably, *H. pylori* seropositivity gradually increased with an increase in UACR ($P = 0.001$) and was highest in subjects with microalbuminuria (OR, 2.41, 95% CI, 1.14-5.11). This suggests that *H. pylori* seropositivity is positively associated with microalbuminuria in diabetic subjects.

CONCLUSION: *H. pylori* seropositivity was independently associated with microalbuminuria, and the prevalence of *H. pylori* seropositivity was associated with the severity of UACR in diabetic subjects.

Key words: *Helicobacter pylori*; Seropositivity; Microalbuminuria; Atherosclerosis; Diabetes

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection has been implicated in various extragastric conditions, including coronary heart disease and ischemic cerebrovascular disorder caused by predisposing chronic inflammation and atherosclerosis[1-5]. The association between *H. pylori* seropositivity and coronary artery calcium scores was recently reported[6]. Moreover, *H. pylori* infection was found to be associated with reduced high density lipoprotein and elevated low density lipoprotein levels in serum[7,8]. Furthermore, a prospective single-center study showed that *H. pylori* eradication had beneficial effects on insulin resistance, lipid abnormalities and low-grade inflammation[9]. These findings suggest a role for *H. pylori* infection in subjects with metabolic syndrome, including diabetes.

In contrast, microalbuminuria, which is defined as an increased urinary albumin to creatinine ratio (UACR) of 30-300 μg/mg[10], has been known to be a strong predictor of the development of diabetic nephropathy[11]. It has also been demonstrated that microalbuminuria is a risk factor for cardiovascular disease in the general and diabetic populations[12-14]. Although the mechanism linking microalbuminuria to cardiovascular morbidity remains unclear, one possible explanation is that the increased urinary leakage of albumin reflects vascular damage, i.e., endothelial dysfunction or low-grade chronic inflammation[15]. In addition, some studies have reported a relationship between microalbuminuria and metabolic syndrome, suggesting that insulin resistance underlies the pathogenesis of microalbuminuria[16-18].

Our hypothesis was that if *H. pylori* infection is involved in the pathogenesis of atherosclerosis, a significant association might exist between *H. pylori* infection and microalbuminuria, which is an early marker of atherosclerosis. Therefore, we aimed to investigate the relationship between *H. pylori* infection and microalbuminuria in subjects presenting for a routine health check-up.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted at the Seoul National University Hospital Gangnam Healthcare Center between March 2003 and February 2010. During the study period, a total of 2737 asymptomatic individuals visited our center for a routine check-up, including *H. pylori* serology and UACR tests. Among them, 21 subjects who showed macroalbuminuria exceeding 300 μg/mg were excluded. Accordingly, 2716 individuals comprised the study population. The presence of diabetes mellitus (DM) was defined as either a fasting serum glucose level greater than or equal to 126 mg/dL or taking anti-diabetic medication. This study was approved by the Institutional Review Board of Seoul National University Hospital, which waived the requirement for informed consent.

Clinical and laboratory assessments

All study subjects completed a structured questionnaire and underwent anthropometric measurements and laboratory tests. A current smoker was defined as a subject who had smoked 100 or more cigarettes during his lifetime and smoked daily at the time of the examination[19]. 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). Systolic and diastolic blood pressures were measured in a sitting position after a 5-min rest, twice a day; mean values were used in the analysis. Blood samples were collected after at least a 12 h of fasting and used to determine glucose, triglyceride, high density lipoprotein cholesterol, and creatinine levels. Serum creatinine concentrations were determined using the Jaffe rate reaction. Anti-*H. pylori* immunoglobulin G was identified using an enzyme-linked immunosorbent assay kit (*H. pylori*-EIA-Well, Radim, Italy) and an automatic analyzer, Alisei® (Seac, Italy). The cut-off values were set according to the manufacturer's instructions.

A random single-void urine sample using a clean-catch technique after at least 12 h of fasting was obtained to determine the UACR (μg/mg). Urinary albumin excretion was measured using an immunoturbidimetric assay, and urinary creatinine was measured using the Jaffe rate reaction. Microalbuminuria was defined as a UACR from 30 μg/mg to 300 μg/mg.

Statistical analysis

Analyses were performed using the SPSS statistical package (Version 17.0, SPSS, Inc., Chicago, IL, United States). A Pearson χ^2 test was used to examine associations between microalbuminuria and the study variables, and P values of < 0.05 were considered statistically significant. Multiple logistic regression analysis was performed to identify risk factors. The dependent variable was microalbuminuria, and the independent variables were the other study variables. Odds ratios (OR) and the relevant 95% CI are presented for all of the potential risk factors.

RESULTS

Clinical characteristics of the study population

The mean age of the 2716 study subjects was 54.9 years, and 71.8% were men. Of the subjects, 224 (8.2%) had

Table 1 Baseline characteristics

	Normal (n = 2492)	Microalbuminuria (n = 224)	P value
Male	1 781 (71.5)	170 (75.9)	0.159
Age[1] (yr)	54.6 (9.1)	57.7 (10.5)	< 0.001
BMI[1] (kg/m^2)	24.2 (2.8)	25.5 (3.4)	< 0.001
Waist circumference[1] (cm)	86.9 (7.6)	89.8 (8.8)	< 0.001
Glucose[1] (mg/dL)	102.4 (19.5)	118.3 (33.2)	< 0.001
Triglyceride[1] (mg/dL)	129.1 (78.2)	161.2 (117.2)	< 0.001
HDL cholesterol[1] (mg/dL)	52.7 (12.3)	50.2 (12.6)	0.005
Creatinine[1] (mg/dL)	1.0 (0.2)	1.0 (0.2)	0.026
SBP[1] (mmHg)	119.0 (14.7)	119.2 (15.6)	0.899
DBP[1] (mmHg)	78.6 (11.2)	78.1 (11.8)	0.577
Hypertension	259 (10.4)	24 (10.7)	0.880
Diabetes mellitus	256 (10.3)	68 (30.4)	< 0.001
Current smoking	364 (16.6)	40 (20.4)	0.170
H. pylori seropositivity	1317 (52.8)	136 (60.7)	0.024

[1]Data are presented as the mean ± SD. BMI: Body mass index; HDL: High density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *H. pylori*: *Helicobacter pylori*.

Table 2 Univariate and multivariate analysis assessing independent risk factors of microalbuminuria

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
H. pylori seropositivity	1.38	1.04-1.82	0.024	1.40	1.05-1.89	0.024
Age (yr)	1.04	1.02-1.05	< 0.001	1.04	1.02-1.06	< 0.001
Sex	1.28	0.91-1.73	0.159	-	-	-
BMI	1.15	1.09-1.20	< 0.001	1.15	1.04-1.27	0.005
WC	1.05	1.03-1.07	< 0.001	0.98	0.94-1.01	0.213
Glucose	1.02	1.02-1.03	< 0.001	1.02	1.01-1.12	< 0.001
Triglyceride	1.00	1.00-1.005	< 0.001	1.00	1.00-1.00	0.001
HDL cholesterol	0.98	0.97-0.99	0.004	1.00	0.99-1.01	0.959
Creatinine	2.87	1.38-5.96	0.005	1.57	0.71-3.51	0.267
Smoking	1.29	1.86-1.87	0.171	-	-	-
Hypertension	1.04	0.67-1.61	0.880	-	-	-
SBP	1.00	0.99-1.01	0.894	-	-	-
DBP	1.00	0.98-1.01	0.558	-	-	-

H. pylori: *Helicobacter pylori*; OR: Odds ratio; BMI: Body mass index; WC: Waist circumference; HDL: High density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

microalbuminuria, and 324 (11.9%) met the criteria for DM, either by taking diabetic medications or showing fasting serum glucose level in the diabetic range (≥ 126 mg/dL). BMI and the serum glucose, triglyceride and creatinine levels were found to be significantly higher in subjects with microalbuminuria than in those without microalbuminuria. In addition, subjects with microalbuminuria had a significantly higher *H. pylori* seropositivity rate than subjects without microalbuminuria (Table 1).

Risk factors of microalbuminuria

The results of the univariate and multivariate analyses of the risk factors for microalbuminuria are shown in Table 2. Multivariate analysis after adjustment for age, waist circumference, glucose, triglyceride and BMI showed that *H. pylori* seropositivity was statistically associated with microalbuminuria (OR, 1.40, 95% CI, 1.05-1.89, P = 0.024; Table 2). Because serum glucose level is the most well-known factor determining microalbuminuria, we performed the analysis after stratifying the cohort by glucose levels (≤ 100 mg/dL, 100 mg/dL < glucose < 126 mg/dL, and ≥ 126 mg/dL or history of DM) to reduce the confounding effect of serum glucose level. As a result, *H. pylori* seropositivity was significantly associated with microalbuminuria in diabetic subjects after adjusting for age, BMI and serum creatinine level (OR, 2.21, 95% CI, 1.20-4.08, P = 0.011). However, the relation between *H. pylori* seropositivity and microalbuminuria was not statistically significant in non-diabetic subjects.

Helicobacter pylori infection and microalbuminuria in diabetic subjects

The seropositivity rates for *H. pylori* in diabetic subjects and non-diabetic subjects were 50% (162/324) and 54% (1291/2392), respectively. Because *H. pylori* seropositivity was found to be significantly associated with an increased prevalence of microalbuminuria in diabetic subjects, we evaluated the relation between the severity of UACR and *H. pylori* seropositivity. The subjects were divided into five groups. Those without microalbuminuria (an UACR of < 30 μg/mg) were divided into four groups in accordance with their UACR values, and subjects with microalbuminuria comprised their own group. The percentage of *H. pylori* seropositivity was found to gradually increase with UACR (P = 0.001; Figure 1), and the highest rate was observed in subjects with microalbuminuria (OR, 2.41, 95% CI, 1.14-5.11; Table 3), suggesting that *H. pylori* seropositivity is positively associated with microalbuminuria in diabetic subjects.

DISCUSSION

This study shows that *H. pylori* seropositivity is independently associated with the presence of microalbuminuria, and the prevalence of *H. pylori* seropositivity shows a positive correlation with the severity of urine albumin creatinine ratio in diabetic subjects. These findings suggest that *H. pylori* infection might affect microvascular damage and possibly contributes to pathogenesis of early atherosclerosis in diabetes.

The mechanisms underlying increased urinary albumin excretion are complex, but endothelial cell dysfunction appears be a major pathogenic contributor[20]. Moreover, microalbuminuria is known to be associated with atherogenic risk factors, such as hypertension, hyperglycemia, central obesity and hyperinsulinemia[21]. In the present study, we consistently found that metabolic variables, such as glucose, triglyceride and BMI were significantly associated with microalbuminuria. In particular, *H. pylori* seropositivity was found to be positively related to microalbuminuria after adjusting for other variables, which suggests that *H. pylori* infection might participate in the pathogenesis of endothelial dysfunc-

Table 3 Relationship of the severity of the urine albumin to creatinine ratio to *Helicobacter pylori* seropositivity in diabetes subjects

Urine albumin-creatinine ratio (μg/mg)	*n*	*H. pylori* seropositivity (%)	OR (95% CI)	*P* for trend
Q1 (< 4.9)	64	50.0	Reference	0.001
Q2 (5.0-7.9)	63	46.0	0.86 (0.42-1.01)	
Q3 (8.0-13.9)	64	51.6	1.10 (0.36-2.23)	
Q4 (14.0-29.9)	65	61.5	1.55 (0.75-3.19)	
Microalbuminuria	68	72.1	2.41 (1.14-5.11)	

H. pylori: *Helicobacter pylori*; OR: Odds ratio.

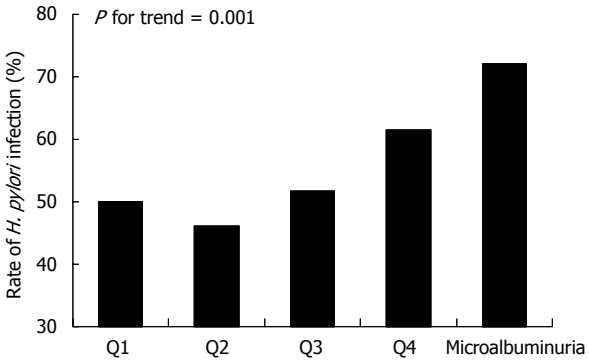

Figure 1 The rate of *Helicobacter pylori* seropositivity according to the urinary albumin to creatinine ratio in diabetic subjects. The subjects were divided into five groups: subjects without microalbuminuria were divided into four groups in accordance with their urine albumin to creatinine ratio values, and subjects with microalbuminuria comprised their own group: Q1, < 4.9 μg/mg; Q2, 5.0-7.9 μg/mg; Q3, 8.0-13.9 μg/mg; Q4, 14.0-29.9 μg/mg and microalbuminuria, > 30 μg/mg. *H. pylori*: *Helicobacter pylori*.

tion. There have been some studies suggesting the association between *H. pylori* infection and endothelial dysfunction; Oshima *et al*[22] reported that *H. pylori* seropositivity was associated with elevated C-reactive protein and soluble intercellular adhesion molecule-1. This indicates that chronic *H. pylori* infection might be involved in the pathogenesis of atherosclerosis. Prasad *et al*[23] showed that the immunoglobulin-G antibody response to pathogens was an independent risk factor for endothelial dysfunction and coronary atherosclerosis.

A possible mechanism linking *H. pylori* infection and endothelial dysfunction is the association between *H. pylori* infection and insulin resistance. Recently, a systematic review has reported a positive association between *H. pylori* infection and a homeostatic model of assessing insulin resistance[24]. *H. pylori* infection was significantly associated with metabolic syndrome in a large Japanese population[25]. Furthermore, Gunji *et al*[26] found that *H. pylori* infection significantly increases insulin resistance in the asymptomatic population. A recent prospective study showed the beneficial effect of *H. pylori* eradication on insulin resistance, serum lipid and low-grade inflammation[27]. It remains uncertain how the presence of *H. pylori* affects the pathogenic process of insulin resistance. The disturbance of proinflammatory and vasoactive substances, such as tumor necrosis factor-α, interlukin-6 and c-reactive protein, may be involved in the pathogenesis of insulin resistance[28,29]. Moreover, the reactive oxygen species caused by an *H. pylori* infection also affects insulin resistance[30,31].

Many studies have demonstrated that elevated blood pressure, poor glycemic control, older age and insulin resistance are associated with microalbuminuria in subjects with diabetes[32,33]. In this study, we stratified the study population according to glucose levels to reduce the confounding effect, and the association between *H. pylori* seropositivity and microalbuminuria was more potent in diabetic subjects than in non-diabetic and pre-diabetic subjects. Diabetic patients are known to have impaired function of cellular and humoral immunity, and consequently, the direct invasion of the arterial wall by bacteria might be more frequent in these patients than in non-diabetic ones. Indeed, some previous studies have found a higher prevalence of *H. pylori* infection among diabetic patients[34,35]. On the other hand, other studies did not detect an association between *H. pylori* infection and diabetes[36,37], and these contradictory results among studies might have resulted from differing methods used by the studies and from the uneven epidemiological distribution of *H. pylori* infection.

This study has several advantages. First, to the best our knowledge, this is the only study of the association between *H. pylori* infection and microalbuminuria. Second, it utilized a large study population, and we constructed a multiple regression model containing many metabolic confounding factors. Third, subjects in this study were an apparently healthy population that presented for screening, and such populations seems to approximate the general population.

Nevertheless, the study has several limitations. First, it does not provide details regarding the nature of the causative relation between *H. pylori* seropositivity and microalbuminuria because of the cross-sectional study design. Second, although the *H. pylori* seropositivity does not indicate current *H. pylori* infection, seropositivity for *H. pylori*-specific immunoglobulin G antibody was taken as a surrogate of *H. pylori* infection status in the present study. Thus, there might be some false-positive or false-negative subjects. Third, we did not evaluate *H. pylori*-induced inflammatory and virulence factors, such as the *cag A* gene, which could contribute to the pathogenesis of *H. pylori*-induced early atherosclerosis.

In conclusion, *H. pylori* seropositivity was independently associated with the presence of microalbuminuria, and the prevalence of *H. pylori* seropositivity was positively correlated with the severity of urine albumin creatinine ratio in diabetic subjects. Our findings suggest that *H. pylori* infection might be involved in the pathogenesis of early atherosclerosis in diabetes.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) infection has been implicated in various extragastric conditions including coronary heart disease and ischemic cerebrovascular

disorder, caused by predisposing chronic inflammation and atherosclerosis. On the other hand, microalbuminuria is a known early marker of renal and cardiovascular diseases. Their hypothesis was that if *H. pylori* infection is involved in the pathogenesis of atherosclerosis, a significant association might exist between *H. pylori* infection and microalbuminuria, which is an early marker of atherosclerosis.

Research frontiers

Recent studies have reported the association between *H. pylori* infection and endothelial dysfunction. *H. pylori* infection significantly increases insulin resistance in the asymptomatic population and it also associated with metabolic syndrome in a large Japanese population. Moreover, the beneficial effect of *H. pylori* eradication on insulin resistance was reported.

Innovations and breakthroughs

This study showed that *H. pylori* seropositivity is independently associated with presence of microalbuminuria and the prevalence of *H. pylori* seropositivity showed a positive correlation with the severity of the urine albumin creatinine ratio in diabetic subjects.

Applications

This study suggests that *H. pylori* infection might affect microvascular damage and possibly contributes to the pathogenesis of early atherosclerosis in diabetes.

Peer review

The authors have studied the relationship between the occurrence of *H. pylori* and microalbuminuria in a healthy population. The association between *H. pylori* and microalbuminuria has only recently been reported and has not been studied in a larger setting. Thus, the paper is of importance and novel. The paper is well written and well presented. Regarding ethics, the local review board had waived the need for written consent.

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