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Helicobacter Pylori Infection and Kidney Damage: Is There An Association?

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Abstract

Objective: We aimed to investigate the association of *Helicobacter pylori* (*H. pylori*) infection with albuminuria in our study.

Methods: A total of 1398 adults who were admitted to nephrology outpatient clinics between June 2020 and August 2020 consecutively were screened. Patients who underwent upper endoscopy in our hospital within 5 years before the date of admission to nephrology outpatient clinics and who had concurrent results of serum creatinine and spot urine albumin/creatinine ratio up to 3 months before upper endoscopy were included. Patients who were shown to have any unstable condition, active infectious disease, malignancy, immunosuppressive treatments, renal transplantation, glomerulonephritis, dialysis, acute kidney injury, and liver disease were excluded. Data regarding demographic, laboratory variables [complete blood count, fasting blood glucose, urea, serum creatinine. albumin, uric acid, lipids, glycated hemoglobin, C-reactive protein, and albumin/creatinine ratio], and endoscopic/histopathologic findings were collected from electronic medical records of the patients.

Results: Ninety-six patients (42.7%, male) with a median age of 61 (interquartile range, 49.5-68) years were included in the study. Seventy-seven patients (80.2%) were diagnosed with chronic kidney disease. The prevalence of *H. pylori* infection rate in chronic kidney disease and non-chronic kidney disease patients was 39% and 42%, respectively ($P = .802$). The abnormal urine albumin/creatinine ratio was present in 65 patients (67.7%), including 63.2% (24/38) in *H. pylori*-infected patients and 70.7% (41/58) in *H. pylori*-uninfected patients ($P = .440$). There were no significant differences including patient demographics and clinical and laboratory variables between *H. pylori* (+) and *H. pylori* (–) patients. There were significant positive correlations between albuminuria and hypertension, fasting blood glucose, and glycated hemoglobin ($r = 0.211$, $P = .040$; $r = 0.318$, $P = .002$; $r = 0.222$, $P = .040$, respectively). A nearly significant positive correlation was found between albuminuria and the presence of moderate or severe *H. pylori* colonization ($r = 0.189$, $P = .065$). In the subsequent multivariate logistic regression model, no independent associations were found.

Conclusion: These results show that there is no significant relationship between *H. pylori* infection and chronic kidney disease and/or albuminuria, but there may be an association between albuminuria and the presence of moderate or severe *H. pylori* colonization.

Keywords: Albuminuria, chronic kidney disease, Helicobacter pylori, hypertension

Helicobacter pylori (*H. pylori*), a gram-negative spiral rod, colonized in gastric mucosa, is the most common chronic infection in humans and is related to various gastrointestinal diseases such as gastritis, peptic ulcer, gastric cancer, and extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue.[1-3]

In addition, several studies have revealed a link between *H. pylori* with extraintestinal associations such as insulin resistance or metabolic syndrome or ischemic heart diseases,[4-10] which may be associated with the risk of chronic kidney disease (CKD). Moreover, it has been reported that *H. pylori* is relevant to several renal diseases such as diabetic nephropathy and primary glomerulonephritis such as membranous nephropathy, immunoglobulin (IgA) nephropathy, etc.[11]

Albuminuria [urine albumin to creatinine ratio (ACR)] accurately predicts renal and cardiovascular risks in population studies, with the urine ACR test widely accepted as a key marker for kidney damage.[12]

In this study, we aimed to investigate a possible association between albuminuria and *H. pylori* infection.

Materials and Methods

Study population and data collection

All patients who were admitted to our nephrology outpatient clinics in a large tertiary care hospital between June 2020 and August 2020 consecutively were screened. Patients who underwent upper endoscopy in our hospital within 5 years before the date of admission to nephrology outpatient clinics and who had concurrent results of serum creatinine and spot urine albumin/creatinine ratio (ACR) up to 3 months before upper endoscopy were included. Patients who were shown to have any unstable condition, active infectious disease, malignancy, immunosuppressive treatments, renal transplantation, glomerulonephritis, dialysis, acute kidney injury, and liver disease were excluded.

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The source of medical records was OCTOMED (Kartal Dr. Lutfi Kirdar City Hospital Automation Program) electronic database system. We collected data for patient demographics, the presence of hypertension/diabetes mellitus, and laboratory test results. Laboratory data consisted of complete blood count, fasting blood glucose (FBG), urea, creatinine, albumin, uric acid, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glycated hemoglobin (HbA1c), C-reactive protein (CRP), and ACR in spot urine analysis. Abnormal ACR was defined as the value of ≥30 mg/g.

Moreover, we collected data regarding endoscopic findings and histopathological findings based on stomach corpus and antrum biopsies from medical records.

Patients using antihypertensive drugs were accepted as hypertensive, while those using antidiabetic drugs were accepted as diabetic. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[13] Chronic kidney disease was defined as decreased eGFR < 60 mL/min/1.73 m^2 or the presence of albuminuria, and then CKD stage was classified based on eGFR category (CKD stage 1: eGFR ≥ 90 mL/min/1.73 m^2; CKD stage 2: eGFR 60-89 mL/min/1.73 m^2; CKD stage 3-5: eGFR <60 mL/min/1.73 m^2).

Endoscopy and histopathology

All patients underwent upper endoscopy in our endoscopy center after the informed consent was signed. Upper endoscopy was performed by specialist gastroenterologists. Two samplings from the stomach antrum were obtained from all patients; however, 2 samplings from the stomach corpus were present in 73 patients. The presence of lesions was noted. Biopsies were taken with forceps from the antrum and the corpus. The biopsy sections were embedded in 10% buffered formalin. Next, hematoxylin and eosin staining was applied, while Giemsa staining was used to detect *H. pylori* species. Biopsies were examined by pathologists in our hospitals' pathology center. Histopathological classification was made according to the updated Sydney System, and chronic inflammation was reported as none (0), mild (1), moderate (2), and severe (3) The *H. pylori* colonization severity was defined as mild colonization (*H. pylori* (+)), moderate colonization (*H. pylori* (++)), and severe (*H. pylori* (+++)) based on the antrum biopsies.[14]

Statistical analysis

Continuous data were expressed as median and interquartile range (IQR). The distribution of continuous variables was determined by Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square test. Continuous variables were compared with Mann–Whitney *U* test. A Spearman's correlation analysis was used to examine the associations between albuminuria and study variables. Multivariate logistic regression analysis was performed to identify the risk factors. The dependent variable was albuminuria, and the independent variables were the other study variables. Variables were selected for regression analysis on the basis of the Spearman's correlation analysis if $P < .1$. Age and gender were adjusted for multivariate analysis. All tests were performed using Statistical Package for the Social Sciences for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). A *P* value of <.05 was considered statistically significant.

Ethics

Ethics committee approval from clinical research ethics committee of Kartal Dr. Lütfi Kırdar City Hospital was obtained (Approval Date: June 26, 2020; Approval Number: 2020/514/180/13). The study was in adherence with the Helsinki Declaration of 1975 (as revised in 1983).

Results

A total of 1398 patients were screened and 96 patients were included in the study. The flow chart of the study subjects is shown in Figure 1. Upper endoscopies were performed on a median time of 16 (IQR, 8-30.3) months before admission to nephrology outpatient clinics. The median age was 61 (IQR, 49.5-68) years and 42.7% of patients were male. Among all the participants, the prevalence of *H. pylori* infection rate was 39.6%.

Laboratory data of a median time of 29.5 (IQR, 9.3-56.8) days before upper endoscopies were recorded. There were 77 patients (80.2%) diagnosed with CKD; 18 patients with stage 1, 16 patients with stage 2, and 43 patients with stage 3-5. *H. pylori* positivity was found in 30 CKD patients (39%) and 8 non-CKD patients (42%), and there was no significant difference between the prevalence of *H. pylori* infection rate in CKD and non-CKD patients ($P = .802$). The abnormal urine ACR was present in 65 patients (67.7%), including 63.2% (24/38) in *H. pylori*-infected patients and 70.7% (41/58) in *H. pylori*-uninfected patients ($P = .440$). The demographic, clinical, and laboratory characteristics of the study patients, all patients, and patients grouped according to the presence of *H. pylori* infection are shown in Table 1. There were no significant differences in studied variables between *H. pylori* (+) and *H. pylori* (–) groups.

Endoscopic findings were present in 62 patients. The most common endoscopic findings were antral gastritis, superficial gastritis, and pangastritis, in 43.5% (27/62), 24.2% (15/62), and 22.6% (14/62), respectively. Nine patients (9.4%) had erosive gastritis and 6 patients (6.3%) had duodenitis.

The multivariate logistic regression analysis was performed to study the independent associations with albuminuria in study patients. We analyzed the correlation of albuminuria with other variables by Spearman's correlation test. There were significantly positive correlations between albuminuria and hypertension, FBG, and HbA1c ($r = 0.211$, $P = .040$; $r = 0.318$, $P = .002$; $r = 0.222$, $P = .040$, respectively). A nearly significant positive correlation was found between albuminuria and the presence of moderate or severe *H. pylori* colonization ($r = 0.189$, $P = .065$). In the subsequent multivariate logistic regression model, we explored whether hypertension, FBG, HbA1c, and moderate or severe *H. pylori* colonization were independent associations with albuminuria after adjusted for age and gender. No independent associations were found (Table 2).

Discussion

In our study, we found no statistically significant association of albuminuria with the presence of *H. pylori* infection; however, a nearly significant positive correlation was found between albuminuria and the presence of moderate or severe *H. pylori* colonization on antrum biopsies.

Albuminuria has been shown to be consistently associated with endothelial low-grade inflammation.[15] Many studies have demonstrated that elevated blood pressure, poor glycemic control, older age, and insulin resistance are associated with albuminuria in either diabetic or non-diabetic patients.[16]

H. pylori infection induces the expression of inflammatory cytokines, chemokines, growth factors, etc., causing an inflammatory microenvironment. In addition, *H. pylori* infection induces the release of cytokines and vascular-active substances, such as CRP, tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), interleukin 6, interleukin 8, and heat shock protein, arising local

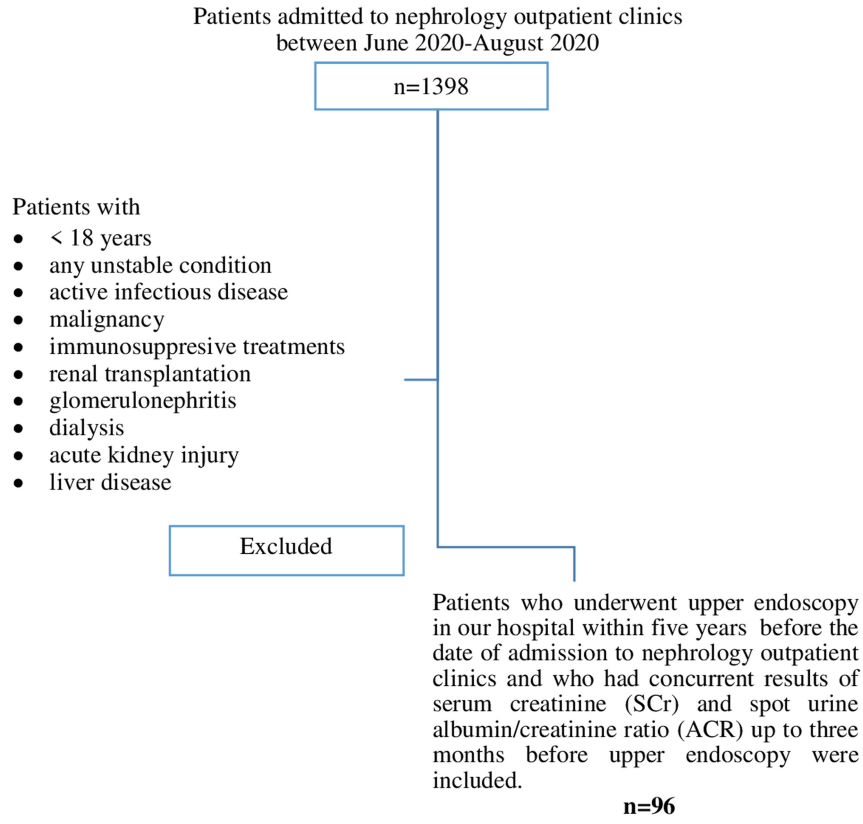

Figure 1. Flow chart of the study subjects.

and systemic immune responses, which aggravates microvascular damage.[17] Thus, *H. pylori* infection might lead to chronic kidney damage or accelerated loss of kidney function through arousing systemic inflammation.

H. pylori infection has been reported to be associated with albuminuria in diabetic patients.[18,19] In a recent meta-analysis, Shi et al[20] found that *H. pylori* infection was significantly associated with the occurrence of proteinuria in diabetes mellitus. This may be explained by several mechanisms for diabetic patients as altered gastric mucosa, overgrowth of bacteria caused by delayed gastric emptying, and dysfunction. The permeability of the glomerular basement membrane can also be changed by an increase in TNF-α and IL-1 after *H. pylori* infection, leading to proteinuria. They also speculated that immunoprecipitation could be caused by a reaction between *H. pylori* antibodies and podocyte antigens in the glomerulus.[20] In another study, in non-diabetic patients with peptic ulcer, the abnormal ACR rate data showed a significant difference between the *H. pylori*-positive group and the *H. pylori*-negative group.[21]

Several studies were conducted to assess the possible role of *H. pylori* infection in nephrotic syndrome pathogenesis.[11,22-24] Since *H. pylori*-specific antigens were found deposited along the glomerular capillary walls in patients with membranous glomerulonephritis, Henoch-Schönlein purpura nephritis or lupus nephritis,[22,25] a previous study showed that cytotoxin-associated gene A protein, one of the key virulence factors of *H. pylori,* decreased the expression and membrane distribution of tight junction protein ZO-1 and impaired the filtration barrier function of podocytes.[26] A higher prevalence of *H. pylori* infection in patients affected by membranous glomerulonephritis has been described in a few cases.[11,23] The effects of *H. pylori* eradication on the treatment response were also tested in a few cohort studies. Some authors found insignificant improvement in proteinuria after *H. pylori* eradication,[27] while others failed to prove that the improvement in proteinuria was due to *H. pylori* treatment only and not due to spontaneous remission.[24]

Thirty-nine percent of our non-dialysis CKD patients had *H. pylori* infection. Previous studies reported the prevalence of *H. pylori* infection among patients with CKD ranges between 20% and 60%.[28] The prevalence of *H. pylori* infection varied according to the population and methods used for diagnosing *H. pylori* infection. Most of the studies investigated dialysis-dependent CKD patients. In a previous study, Misra et al[29] compared both the histologic examination of antral biopsy specimens and ultra-rapid urease test for detecting *H. pylori* in pre-dialysis CKD patients, and they found the prevalence of *H. pylori* infection as 56%, and 16%, respectively. In another study, Nakajima et al[30] reported the prevalence of *H. pylori* infection in CKD patients [creatinine clearance (Cl_{Cr}) <60 mL/min without dialysis)] as 53.3% by detection of positive *H. pylori* antibody levels. Another study revealed the prevalence as 47.1% by histology and culture in patients with CKD ($10 < Cl_{Cr} < 30$ mL/min).[31] Nardone et al[32] compared 3 methods, rapid urease test (RUT), C urea breath test, and *H. pylori* stool-specific antigen (HpSA) with histology in CKD patients ($Cl_{Cr} < 40$ mL/min without dialysis). The diagnostic efficacy of RUT, C urea breath test, and HpSA were found as 85%, 95% and 88%, respectively.[32] Among a large cohort, a lower *H. pylori* prevalence rate (20.6%) was reported in CKD patients by *H. pylori* IgG antibody test.[33]

Although the urease test, histology, urea breath test, and stool antigen test have a high diagnostic value, with sensitivity and specificity exceeding 90% for the determination of *H. pylori* infection status, each diagnostic method has some considerations. False-negative results in the urease test, histology, urea breath test, and

Table 1. The Demographic, Clinical, and Laboratory Characteristics of the Study Patients; All Patients and Patients Were Grouped According to the Presence of *Helicobacter pylori* (*H. pylori*) Infection

	All Patients		*H. pylori* (+)		*H. pylori* (–)		
Variables	**n**	**Summary**	**n**	**Summary**	**n**	**Summary**	***P***
Age (years)	96	61 (49.5-68)	38	58 (45.5-66.3)	58	62 (52.5-68)	.253
Gender [male], n (%)	96	41 (42.7)	38	17 (44.7)	58	24 (41.4)	.745
HT, n (%)	96	84 (87.5)	38	36 (94.7)	58	48 (82.8)	.117
DM, n (%)	96	64 (66.7)	38	26 (68.4)	58	38 (65.5)	.768
CKD, n (%)	96	77 (80.2)	38	30 (78.9)	58	24 (81)	.802
WBC ($\times 10^3/\mu L$)	88	7.9 (6.2-9.1)	34	8.1 (6.9-9.7)	54	7.4 (6.0-10.3)	.110
Hemoglobin (g/dL)	88	12.2 (11.3-13.6)	34	11.8 (10.9-13.9)	54	12.6 (11.8-13.4)	.382
Glucose (mg/dL)	93	122 (96.5-162)	37	134 (96-173)	56	119.5 (97-153)	.572
Urea (mg/dL)	91	44 (33-63)	37	39 (34-81.5)	54	45 (31.8-62)	.435
Creatinine (mg/dL)	96	1.18 (0.8-1.56)	38	1.18 (0.8-1.79)	58	1.16 (0.85-1.44)	.319
eGFR (mL/min/1.73m^2)	96	62.8 (39.1-85.1)	38	62.5 (35.8-86.6)	58	62.8 (39.4-84.7)	.725
eGFR <60 mL/min/1.73 m^2 , n (%)	96	42 (43.8)	38	17 (44.7)	58	25 (43.1)	.873
Albumin (g/L)	75	4.3 (4.0-4.5)	28	4.3 (3.9-4.5)	47	4.3 (4.1-4.4)	.839
Uric acid (mg/dL)	63	6.4 (5.4-7.6)	25	6.3 (4.4-7.8)	55	6.5 (5.5-8.0)	.279
Total cholesterol (mg/dL)	87	209 (177-246)	34	209 (165.5-252.5)	53	209 (180.5-236)	.920
Triglycerides (mg/dL)	85	154 (113-211)	33	163 (117.5-215)	52	153 (110-214)	.516
HDL-C (mg/dL)	85	45 (39-51)	33	46 (40-51.5)	52	45 (39-50.8)	.766
LDL-C (mg/dL)	84	128 (97-166)	32	128.5 (88.3-176)	52	128 (108.5-151.8)	.730
HbA1c (%)	86	6.7 (5.8-8)	33	6.7 (5.9-9.2)	53	6.8 (5.8-7.7)	.491
CRP (mg/L)	50	4.34 (3.15-10.3)	19	3.57 (3.11-10.9)	31	4.5 (3.23-9)	.631
ACR (mg/g)	96	88.1 (19.1-635.6)	38	88.1 (16.01-1068.8)	58	90.6 (21.9-593.1)	.554

ACR, albumin/creatinine ratio; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL, low-density lipoprotein cholesterol; WBC, white blood cell.

stool antigen test can be detected when patients are taking antibiotics, proton pump inhibitors, or bismuth, which are the frequently prescribed drugs in patients with CKD. The diagnostic value of histology is higher than the other tests, but it is dependent on where the biopsies were conducted and how many specimens were obtained. The degree of atrophic gastritis or intestinal metaplasia is also important for obtaining biopsy tissue for histology, influencing the accurate determination of *H. pylori* infection status.[34]

Similar to a previous meta-analysis of both non-dialysis and dialysis-dependent patients, we could not find any association between *H. pylori* infection and CKD.[28,35,36] On the other hand, a meta-analysis of 34 studies including both non-dialysis dependent CKD and end-stage renal disease exhibited a significantly lower prevalence of *H. pylori* infection in patients with CKD compared to controls.[34] The reported risk of CKD in patients with *H. pylori* infection is still conflicting.

High levels of serum urea nitrogen can contribute to a decreased gastric acid secretion and higher gastric pH, this may be a cause of lower prevalence of *H. pylori* infection among CKD.[37] Also, inflammatory cytokines are also increased in CKD patients and they can cause gastric mucosal damage and eradicate *H. pylori*.[38] In addition, antibiotics, proton pump inhibitors, or H2 receptor antagonists are used in patients with CKD for a long time, so this may be associated with decreased *H. pylori* infection.[35]

However, in contrast, some previous reports showed the higher prevalence of *H. pylori* infection in CKD patients.[39,40] Contrary to the above theories, high urea concentration in CKD patients makes the gastric mucosa more susceptible to *H. pylori*.[38] Chronic *H. pylori* infection might induce a persistent systemic and vascular inflammation and malabsorption of folate, vitamin B6, and vitamin B12, leading to failure of methylation by 5-methyl-tetrahydrofolic acid and hyperhomocysteinemia, which causes toxicity to endothelial cells.[41] Wang et al[42] observed that *H. pylori* eradication within 90 days of diagnosis was associated with decreased rates of occurrence of CKD and mortality compared with those without early *H. pylori* eradication. Moreover, Hata et al[43] showed that the prevalence of *H. pylori* infection without atrophic gastritis was higher in CKD and might have a relationship with the risk of CKD. They speculated that *H. pylori* infection might induce renal dysfunction via reduction of ghrelin which could improve CKD

Table 2. Spearman's Correlation Analysis and Multivariate Logistic Regression Analysis Assessing Independent Risk Factors of Albuminuria

	Spearman's Correlation		Multivariate		
Parameter	***r***	***P***	**OR**	**95 %CI**	***P***
Age (years)	−0.096	0.354	0.957	0.914-1.003	.068
Gender (male)	−0.101	0.328	0.534	0.180-1.588	.259
HT	0.211	**0.040**	2.769	0.485-15.180	.252
DM	0.126	0.221			
WBC (×10³/μL)	0.150	0.161			
Hemoglobin (g/dL)	−0.167	0.121			
Glucose (mg/dL)	0.318	**0.002**	1.017	0.999-1.036	.069
Creatinine (mg/dL)	0.152	0.138			
eGFR (ml/min/1.73m²)	−0.124	0.228			
Albumin (g/L)	−0.183	0.116			
Uric acid (mg/dL)	−0.051	0.692			
Total cholesterol (mg/dL)	0.005	0.960			
Triglycerides (mg/dL)	0.098	0.373			
HDL-C (mg/dL)	−0.130	0.235			
LDL-C (mg/dL)	0.001	0.996			
HbA1c (%)	0.222	**0.040**	1.021	0.626-1.663	.935
CRP (mg/L)	0.126	0.382			
H. pylori positivity	−0.079	0.446			
H. pylori (++/+++)	0.189	**0.065**	5.680	0.602-53.623	.129

CRP, C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; HT, hypertension; *H. pylori*, *Helicobacter pylori*; LDL, low-density lipoprotein cholesterol; WBC, white blood cell.

with mechanisms including complex interactions affecting energy homeostasis, appetite, muscle mitochondrial activity, suppression of inflammation, and maintenance of the cardiovascular system.[43]

Our study has several limitations. The sample number of each group studied was small. Secondly, the cross-sectional design does not permit us to draw conclusions on casual relationships as a cause or an effect between *H. pylori* infection and CKD and albuminuria. Because of the study design, we could not reach detailed information regarding treatments that may affect *H. pylori*, albuminuria, and CKD such as proton pump inhibitors, antibiotics, angiotensin-converting-enzyme inhibitors, and angiotensin receptor blockers. We checked patients' antihypertensive treatments from the electronical prescription system; however, the quantitative data for blood pressure were missing. So hypertensive patients without antihypertensive treatments might be overlooked. Another limitation was that the study included patients with endoscopic procedures only from our hospital; however, some patients might have an endoscopy in other hospitals and cannot be included in our study, so the prevalence of *H. pylori* might be underestimated.

In conclusion, we did not find a relationship between *H. pylori* infection rate and CKD and/or albuminuria. The presence of moderate/severe *H. pylori* colonization seems to be associated with albuminuria. The local proinflammatory effect of *H. pylori* on gastric mucosa was thought to have a potential systemic effect and activate the immune response. Further investigations and randomized clinical trials are needed to verify these associations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: June 26, 2020; Number: 2020/514/180/13).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.O., E.K.; Design – M.O., E.K.; Supervision – M.O., E.K.; Resources – M.O., E.K.; Materials – M.O., E.K.; Data Collection and/or Processing – M.O., E.K.; Analysis and/or Interpretation – M.O., E.K.; Literature Search – M.O., E.K.; Writing Manuscript – M.O., E.K.; Critical Review – M.O., E.K.

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