

THE PREVALENCE OF *HELICOBACTER PYLORI* INFECTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE UNDERGOING HEMODIALYSIS

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ABSTRACT

The aim of this study was to analyze the prevalence of Helicobacter pylori infection and gastroduodenal lesions in Montenegrin patients with chronic kidney disease on hemodialysis. The study included 55 hemodialysis patients with dyspeptic symptoms and 50 control subjects with normal kidney function who had also dyspepsia. After dyspepsia assessment by an interview, all subjects underwent gastroduodenoscopy and histopathological analysis of biopsy specimens, taken from the corpus and antrum of the stomach. Helicobacter pylori was confirmed in 50.9% of corpus mucosa i.e. 60.6% of antrum mucosa of maintenance hemodialysis patients. There were no significant differences in endoscopic findings of the stomach and bacterial presence between the two study groups of participants ($p = 0.451$), while duodenal lesions were prevalent in control subjects ($p < 0.001$). The atrophy of corpus mucosa was more common in hemodialysis patients ($p = 0.007$), especially in those who have been on hemodialysis for a longer time ($p < 0.001$) and had lower pH ($p = 0.011$). The prevalence of Helicobacter pylori infection shown an inverse relationship with dialysis duration. Contrary, a positive relationship between Helicobacter pylori and the concentration of bicarbonate was demonstrated ($p = 0.031$). The prevalence of Helicobacter pylori and atrophic mucosal changes in Montenegrin hemodialysis patients depends on dialysis duration and acid-base balance.

Keywords: Chronic kidney disease, dialysis, *Helicobacter pylori*.

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INTRODUCTION

Chronic kidney disease (CKD) is a progressive loss of kidney function that is presented by glomerular filtration rate below 60 ml/min/1.73m² for a period longer than 3 months (1). Because of growing prevalence, it has been recognised as one of the main death causes among the chronic non-communicable diseases (2). Data from 2017 testify the age-standardised morbidity rate for Montenegrin population was 13.1% (3).

Progressive CKD has been associated with a number of serious complications including gastrointestinal disturbances (4, 5). Most often it is about dyspeptic symptoms like occasional or constant epigastric pain, early satiety, bloating, nausea, excessive belching and postprandial fullness (6, 7). The pathogenetic aspects of dyspepsia have been sufficiently unexplored. Many factors are thought to be involved in pathogenesis of this condition like uremic toxins (8), digestive hypomotility (9), amyloid protein deposition (10), sensory disturbances (11), and *Helicobacter pylori* (HP) infection (12).

The prevalence of HP infection and its relationship to gastroduodenal lesions in hemodialysis patients have been extensively studied (13). Nevertheless, the available literature data on the HP presence in hemodialysis patients are quite unequal with a wide range of variation (20-80%) (14, 15). There are also different opinions on the frequency of gastroduodenal lesions in hemodialysis CKD patients compared to non-CKD subjects (16). Some authors reported that hemodialysis patients suffered more often from gastroduodenal disorders while the others not found the differences between hemodialysis and the general population (13, 17, 18).

Thus, the aim of our study was to determine the prevalence of HP infection and gastroduodenal lesions as well as their connections with certain biochemical findings and hemodialysis quality in Montenegrin CKD patients with dyspeptic symptoms.

PATIENTS AND METHODS

Study population

The investigation has been conducted as a single center, cross-sectional study with one-time point evaluation during 2019 and early 2020s in Clinical Center of Montenegro, Podgorica. The study initially enrolled 70 patients with diagnosis of CKD undergoing hemodialysis, but further research was continued with 55 patients in whom dyspeptic symptoms have been identified for at least 3 months. The control group consisted of 50 consecutive, age and gender matched, subjects with preserved kidney function referred for endoscopic examination due to dyspepsia. The exclusion criteria for participation in the study were: (1) recent active infections, (2) chronic inflammatory or autoimmune diseases; (3) previously diagnosed gastroduodenal structural changes like inflammation or ulcer; (4) contraindications for performing

upper gastrointestinal endoscopy, (5) therapy with H₂ inhibitors, proton pump antagonists and/or nonsteroidal anti-inflammatory drugs; (6) *under 18 years of age* and (7) pregnancy.

The study was planned according to the Declaration of Helsinki. All patients and control subjects gave informed consent for the participation. The investigation has been approved by the institutional Ethical Committee according to local research regulations.

Measurements

We performed an interview about dyspeptic symptoms in all study subjects as well as physical and biochemical examination. Gastroduodenoscopy with pathohistological analysis of biopsy specimens was applied only in the cases of confirmed dyspepsia. The study also concerned to dialysis parameters such as the duration of hemodialysis (in months) and its efficiency.

Dyspepsia assessment

Dyspepsia was defined based on Roma III criteria (19): the presence of certain symptoms, which exist for the last 3 months onset and continue at least 6 months prior to diagnosis (excluding structural gastroduodenal disease). A questionnaire included the following dyspeptic symptoms: constant and occasional epigastric pain, bloating, early satiety, nausea, vomiting and heartburn.

Biochemical parameters

Biochemical parameters (hemoglobin, urea, creatinine) were investigated by standard laboratory methods, while the acid-base balance was assessed by pH and bicarbonate (HCO₃⁻) concentration.

Chemiluminescent immunoassay and *Architect Intact PTH* reagent by Abbott was used for determination of parathyroid hormone (PTH) level (range 1.6-7.2 pg/ml).

The efficiency of hemodialysis was assessed by calculation of Kt/V with dialysis machine software. Kt/V presents dialyzer clearance of urea (expressed in ml/min) multiplied by the dialysis time (expressed in minutes) and divided by volume of distribution of urea.

Gastroduodenoscopy

Gastroduodenoscopy with Olympus XQ 40 endoscope was performed in all study participants in whom the presence of dyspeptic symptoms was previously determined by the questionnaire. During the procedure, the biopsy specimens were taken from the corpus and antrum of the stomach, and stored in 4% formalin to further processing. The final diagnosis was made by endoscopic and histopathological findings of mucosal lesions regarding the degree of inflammation and its activity, the degree of atrophy, intestinal metaplasia and *Helicobacter pylori* presence.

Statistical analysis

The commercial software SPSS version 22.0 for Windows was used for the statistical analysis. Data are presented as mean $\pm$ standard deviation (SD). Differences in the parameters between the groups of patients were estimated by the Independent samples T-test or Mann-Whitney U-test (depending on the distribution). Chi-square (χ^2) test served to compare the frequency of categorical variables. For all tests described above, p values less than 0.05 were considered to be statistically significant.

RESULTS

The results of our study are presented in Tables 1-3 and Figures 1-3.

The study included 55 maintenance hemodialysis patients with dyspepsia and 50 control subjects, who underwent endoscopic examination because of dyspeptic symptoms. There were 29 (52.8%) males and 26 (47.2%) females in the group of hemodialysis patients, respectively 27 males (54%) and 23 females (46%) in the control group. The average age of hemodialysis patients was 56.48 ± 13.66 ys, while in the control group it was 54.45 ± 11.38 ys (Independent samples T test, $p = 0.311$).

Analysis of dyspeptic symptoms showed that occasional epigastric pain, bloating and nausea were the dominant symptoms in the group of hemodialysis patients, while the control group mostly showed early satiety, bloating and nausea (Figure 1). It estimated the significant difference in the frequency of constant epigastric pain ($\chi^2 = 4.335$, $p = 0.037$) and vomiting ($\chi^2 = 10.772$, $p = 0.005$) between the groups.

Data obtained by gastroduodenal examination did not confirm a statistically significant difference in endoscopic findings of the stomach between hemodialysis patients and control subjects ($\chi^2 = 5.758$, $p = 0.451$).

The most common finding in both study groups was gastritis, confirmed in 27 (49.1%) hemodialysis patients and 28 (56%) control subjects. When it comes to duodenal lesions, majority of hemodialysis patients had a normal endoscopic finding (67.9%), while in control participants duodenitis was the most frequent (42%) ($p < 0.001$) (Figures 2-3).

The results of pathohistological examination of biopsy samples taken from the corpus and antrum of the stomach are shown in Tables 1-2.

We found that atrophy of corpus mucosa was significantly more prevalent in hemodialysis patients ($p = 0.007$) compared to control subjects, who mainly showed the signs of inflammatory activity in the corpus. There was no statistically significant difference in the presence of HP infection neither in the samples of a corpus or an antrum between two study groups. HP was confirmed in 50.9% of corpus mucosa i.e. 60.6% of antrum mucosa of hemodialysis maintain patients.

In further research, we analyzed the influence of certain biochemical parameters and dialysis treatment on the occurrence of gastric atrophy and HP positivity. It has been estimated that gastric atrophy was more common to CKD patients that underwent hemodialysis for a longer time ($p < 0.001$). No influence of Kt/V ($p = 0.385$), concentration of hemoglobin ($p = 0.338$), creatinine ($p = 0.100$) and PTH ($p = 0.201$) on atrophic changes was observed. The disturbance of acid-base balance (lower pH) had a positive effect on the occurrence of gastric atrophy ($p = 0.011$).

When it comes to relationships of HP presence and the above-mentioned parameters, the data are shown in Table 3.

HP presence was higher in both corpus and antrum samples of CKD patients that underwent hemodialysis for a shorter period. Also, a positive relationship between bicarbonate concentration and HP infection was demonstrated ($p = 0.031$).

Table 1. Frequency of pathohistological categories of corpus mucosa in two study groups

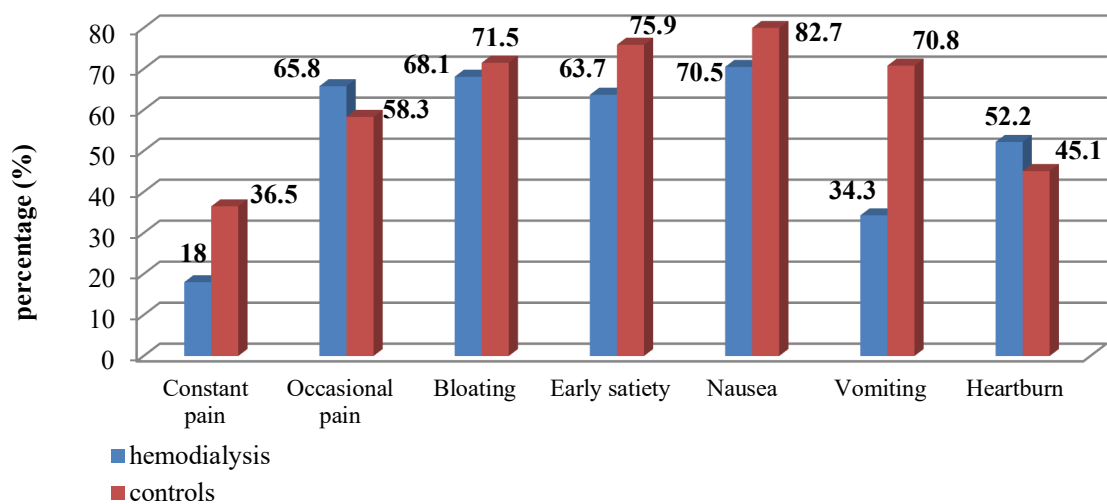
Category		Hemodialysis patients n = 55	Control patients n = 50	χ^2	significance
Inflammation activity	Yes	28 (50.9%)	31 (62.5%)	1.084	$p = 0.298$
	No	27 (49.1%)	19 (37.5%)		
Atrophy	Yes	23 (41.9%)	8 (15%)	7.274	$p = 0.007$
	No	32 (58.1%)	42 (85%)		
Intestinal metaplasia	Yes	0	0	–	–
	No	55 (100%)	50 (100%)		
Helicobacter pylori	Yes	28 (50.9%)	22 (44%)	0.315	$p = 0.574$
	No	27 (49.1%)	28 (56%)		

Table 2. Frequency of pathohistological categories of antrum mucosa in two study groups

Category		Hemodialysis patients n = 55	Control patients n = 50	χ^2	significance
Inflammation activity	Yes	39 (72.1%)	21 (42.5%)	0.485	p = 0.486
	No	16 (27.9%)	29 (57.5%)		
Atrophy	Yes	24 (44.2%)	21 (42.5%)	0.024	p = 0.877
	No	31 (55.8%)	29 (57.5%)		
Intestinal metaplasia	Yes	2 (4.7%)	0	1.906	p = 0.167
	No	53 (95.3%)	50 (100%)		
Helicobacter pylori	Yes	33 (60.6%)	26 (52.5%)	0.890	p = 0.355
	No	22 (39.4%)	24 (47.5%)		

Table 3. The relationships of HP presence and laboratory parameters

Parameter		Corpus mucosa		Antrum mucosa	
		Mean value	p	Mean value	p
Hemoglobin (g/dl)	HP-	10.47	p = 0.269	10.52	p = 0.508
	HP+	10.89		10.78	
Creatinine ($\mu\text{mol/l}$)	HP-	1017.0	p = 0.394	1024.3	p = 0.394
	HP+	963.64		969.18	
PTH (pg/ml)	HP-	473.73	p = 0.537	480.59	p = 0.568
	HP+	396.87		407.01	
pH	HP-	7.310	p = 0.133	7.309	p = 0.169
	HP+	7.323		7.322	
HCO_3^- (mmol/l)	HP-	13.70	p = 0.031	13.78	p = 0.156
	HP+	14.70		14.47	
Dialysis duration (months)	HP-	91.10	p < 0.001	106.38	p < 0.001
	HP+	31.68		33.63	
Kt/V	HP-	1.226	p = 0.447	1.199	p = 0.765
	HP+	1.190		1.213	

**Figure 1.** The prevalence of dyspeptic symptoms in hemodialysis patients and control subjects

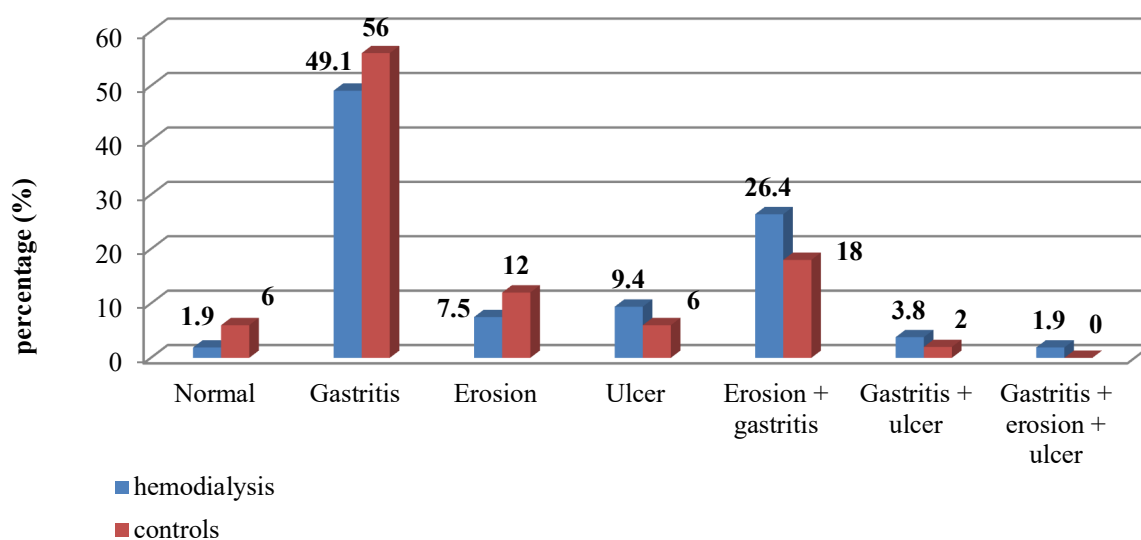


Figure 2. Endoscopic findings of the stomach in hemodialysis patients and control subjects

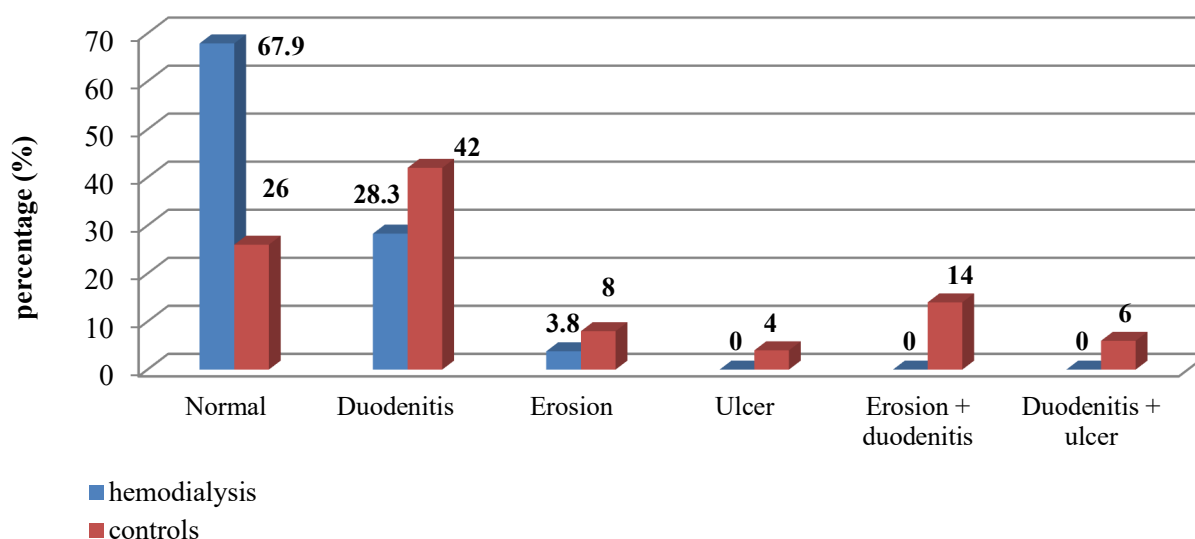


Figure 3. Endoscopic findings of the duodenum in hemodialysis patients and control subjects

DISCUSSION

The current study analyzed the presence of gastroduodenal lesions and *Helicobacter pylori* infection in Montenegrin hemodialysis patients with dyspeptic symptoms.

We estimated that CKD patients undergoing hemodialysis commonly presented as dyspepsia as occasional epigastric pain, bloating and nausea. However, dyspeptic symptoms were more pronounced in control subjects. There were no significant differences in endoscopic findings between the two study groups of participants, although control subjects had more often the lesions of the duodenum.

Pathohistological analysis demonstrated that atrophy of corpus mucosa was more prevalent in hemodialysis patients and it positively correlated with dialysis duration. Lower pH also stimulated atrophic changes. The prevalence of HP was over 50 percent so that its presence was higher in the patients that underwent hemodialysis for a shorter time.

HP is a gram-negative bacillus that inhabits the gastric mucosa and it seems to have an important role in the pathogenesis of gastroduodenal disorders in hemodialysis patients (20, 21). Namely, HP modulates gastric secretion by

increasing serum gastrin concentration and decreasing the level of somatostatin in the gastric mucosa (22). On the other hand, the inflammatory response to HP can induce the dysfunction of gastric smooth muscles and lower sensation for gastric distension (5, 23).

The results of previous studies on gastroduodenal lesions and HP infection in hemodialysis patients are quite inconsistent (13, 17). There is no single view on the frequency of endoscopic findings in CKD patients that underwent hemodialysis (existence of an equal or higher rate of lesions compared to the general population). Our investigation showed that duodenal lesions were more common in control subjects, who mainly had a histopathological finding of inflammation and a pronounced clinical presentation of dyspepsia. Contrary, atrophic mucosal changes and HP presence was higher in hemodialysis patients. These results indicate the potential effect of HP on the occurrence of mucosal atrophy. Namely, ammonia, a product of urea *hydrolysis*, formed by the action of bacterial urease, has a pro-atrophic effect on the cells of gastric mucosa (24). Additionally, it has been shown that HP could induce the apoptosis of gastric cells by increasing the expression of pro-apoptotic Bax protein (25).

Our results are in agreement with the findings of Khedmat and coworkers (13), who also reported higher prevalence of HP infection in CKD patients. Here, we must emphasize that, although higher in hemodialysis patients, the prevalence of HP did not differ significantly between two groups enrolled in the study. A meta-analysis conducted by Wijarnpreecha (26) estimated HP infection prevalence of 44% in end-stage CKD patients, which is similar to our findings in the stomach (HP confirmed in just over 50% of cases). However, current literature data indicates a wide range of variation in HP positivity in hemodialysis patients (14, 27, 28), which could be a consequence of the different design and methodology of the conducted studies.

Interestingly, we have shown the reduction of HP positivity in the patients that underwent hemodialysis for a longer time. In other words, the duration of dialysis was significantly longer in HP negative patients and *vice versa*. The association between HP infection and dialysis duration is a subject of scientific discussion (29). Thus, Nakajima et al. (30) estimated a negative correlation between the duration of dialysis and HP infection, unlike Rasmi (31) who found positive effect of hemodialysis length on HP prevalence. Undoubtedly, the duration of dialysis is an important factor affecting the HP infection. Growing evidence suggests HP eradication in CKD patients over time due to high serum concentration of urea (32), decreased gastric acid secretion and higher pH value (33), an adequate therapeutic approach (34), as well as the secretion of proinflammatory cytokines (14). It is assumed that mentioned factors induce the atrophic changes of gastric mucosa and prevent the survival of HP in altered conditions.

However, further investigations are needed to determine the association between the duration of dialysis and HP

prevalence by continuous monitoring of CKD patients at multiple time points. Previous research, including ours, have focused on HP infection in dialysis patients by single sampling and measurement of appropriate variables.

CONCLUSION

The estimated prevalence of *Helicobacter pylori* in Montenegrin hemodialysis patients was over 50%, with a somewhat greater presence in the antral mucosa. There were no significant differences in endoscopic findings between CKD patients undergoing hemodialysis and non-CKD patients with dyspepsia. Atrophic mucosal changes were more common in hemodialysis patients and they positively correlated with dialysis duration. *Helicobacter pylori* presence was reduced in the patients that underwent hemodialysis for a longer time.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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