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ASSOCIATION BETWEEN DURATION OF DIALYSIS AND HELICOBACTER PYLORI INFECTION IN DIALYSIS PATIENTS AT THE UNIVERSITY CLINICAL HOSPITAL MOSTAR

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SUMMARY

Introduction: *Association of Helicobacter pylori (HP) infection with the length of dialysis in dialysis patients is contradictory. This study was conducted in order to determine the association between the duration of dialysis and the HP infection status in the dialysis patients. Furthemore, biochemical parameters were monitored in two subject groups that were included in this study.*

Subjects and methods: *The study included 51 patients on chronic hemodialysis program who had gastrointestinal symptoms. The subjects were divided in two groups per the length of dialysis treatment. In this study we analyzed age, gender, the time period since the onset of the chronic hemodialysis program, body mass index, biochemical parameters, and whether the patients have arterial hypertension and/or diabetes. The presence of HP antigen was determined in the stool samples with use of he UlcoGnost AG test plate.*

Results: *The incidence of HP infection in hemodialysis patients, with some of the gastrointestinal symptoms, was 25.5%. Patients on hemodialysis for less than 24 months had lower incidence of HP infection than those on hemodialysis program for more than 24 months. HP positive and HP negative subjects were also compared by gender, age, biochemical parameters and body mass index. There was no statistical significant difference between the groups in any of those characteristics. When comparing the HP status of the subjects with the presence of arterial hypertension and diabetes, no statistically significant difference was found between the groups.*

Conclusion: *This study showed negative correlation between HP infection and the length of hemodialysis program. Analysis of age, gender, body mass index, biochemical parameters, presence of arterial hypertension and/or diabetes showed no statistically significant difference was found between the hemodialysis patients who were HP positive and those who were HP negative. Additional studies are needed to elucidate the correlation mechanism between the HP infection and the duration of dialysis, in order to examine how long the dialysis time period is the most susceptible to HP infection, and then to improve the prognosis of patients with renal disease.*

Key words: *dialysi - helicobacter pylor - hemodialysis*

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INTRODUCTION

Helicobacter pylori (HP) an infectious organism, is present in about 50% of the global population, and the infection level exceed 70% in some developing areas (Rocha et al. 1992). Infection with HP has been implicated not only in the etiopathogenesis of gastrointestinal disease, such as gastritis, ulcerative diseases, low-grade mucosa-associated lymphoid tissue lymphoma, and gastric malignancies, but also in various extra-gastrointestinal conditions, among them chronic renal disease (Huang et al. 2000, Van Vlem et al. 2000). To 75% of patients with chronic renal failure (CRF) who receive hemodialysis for a long time have gastrointestinal disorders (Araki et al. 1999). It is assumed that the high concentration of urea makes more of the gastric mucosa of these patients susceptible to HP colonization (Hazell and Lee 1986). Many factors seem to contribute to inhibit the growth of HP in the stomach by CRF patients (eg higher levels of pro-inflammatory cytokines,weakened immune system, increased pH, higher blood urea levels and antibiotic treatment) (Jaspersen et al. 1995, Sugimoto et al. 2009, Suzuki & Mori 2018).

Magnesium, as well as calcium, are thought to be important factors in the regulation of gastric acid secretion as well as for the survival and virulence of HP. Some studies have concluded that high magnesium concentrations in plasma and probably its higher concentrations in gastric mucose may facilitate HP colonization in the stomach of hemodialysis patients (Marušić et al. 2006, Gatta et al. 2004). Many studies have been conducted comparing the relationship between the length of dialysis treatment and the incidence of HP infection, but the results are inconsistent. Some studies have shown that

the length of dialysis treatment and HP colonization are inversely proportional, while others have shown that the incidence of HP infection increases with time spent on dialysis (Marušić et al. 2006, Gatta et al. 2004, Warren & Marshall 1983, Katičić et al. 2014, Rocha et al. 1992, Cancer & Organization 1994, Huang et al. 2000). In some studies, however, there was no association between the length of dialysis treatment and HP infection (Marušić et al. 2006, Gatta et al. 2004, Warren & Marshall 1983, Katičić et al. 2014, Rocha et al. 1992, Cancer & Organization 1994, Huang et al. 2000, Tamadon et al. 2013, Filipec et al. 2002).

The present study is the analysis, with the main objective to clarify the prevalence of HP in CRF patients as well as the relationship between the lenghth of dialysis and the prevalence of HP. In addition, HP status in CRF patients and the course of dialysis will be discussed

SUBJECTS AND METHODS

The study was conducted at the Dialysis Center of the University Clinical Hospital Mostar. The study included 51 patients in the chronic hemodialysis program. All subjects had the gastrointestinal symptoms (bloating, nausea, belching, heartburn, loss of appetite, epigastric pain) and/or signs of gastrointestinal bleeding. The patients were divided in two groups, and the start of the hemodialysis program was taken as the criterion for forming the groups. The first group consisted of the patients on the hemodialysis program which lasted from 3 to 24 months, while the second group consisted of the patients who were on the hemodialysis program for more than 24 months. Patients from the Dialysis Center who had already undergone triple therapy for HP eradication were excluded from the study, as well as the patients who were on continued therapy with some of the proton pump inhibitors or H2 receptor blockers. The Dialysis Center patients who were temporarily dialyzed due to the acute kidney damage were also excluded from the study.

Presence of HP antigen was determined in stool samples with the UlcoGnost AG test plate. The UlcoGnost AG test plate is the rapid immunochromatographic test for qualitative detection of the specific HP antigen in human stool samples. This test for bacterial antigens detects current HP infection, unlike the serological test for antibodies in the serum. The antibodies specific to HP antigens were applied on the cellulose membrane of the test. During the testing, the sample of homogenized stool bonds to the colored particles, coated with anti-HP antibodies. Thus connected sample travels chromategraphically to the detection site or the test zone. If the sample is positive, specific antibodies which are bound to the membrane react with the conjugates, and the pink colored line appears in the test zone, in case of positive result to HP antigens. Regardless to the the presence of HP antigens in the tested sample, the pink colored line always appear in the control zone of the procedure as the confirmation of correctly performed test, which shows that enough sample was applied and that the flow was good.

Patients have their blood samples regularly taken for hematological and biochemical tests. In this study we analyzed the age, gender, time since the onset of the chronic hemodialysis program, body mass index, biochemical tests required for the study, and whether the patients have arterial hypertension and/or diabetes.

Analyzed biochemical tests included the following: urea, creatinine, uric acid, hemoglobin, C-reactive protein (CRP), calcium, phosphorus, magnesium, cholesterol and triglycerides. The analysis of biochemical tests was performed in the Department of Laboratory Diagnostics of the University Clinical Hospital Mostar, with the following methods:

- urea (reference range 1.7-8.3 mmol/l): UV-kinetic method;
- creatinine (reference range 71-116 μmol/l): continuous photometric method with alkaline picrate;
- uric acid (reference range 212-482 μmol/l): enzyme-colorimetric method (uricase / PAP);
- hemoglobin (reference range 119-175 g/l): volumetric impedance principle automatic hematology counter;
- CRP (reference range 0-5 mg/l): immuneturbidimetric method;
- calcium (reference range 2.02-2.60 mmol/l): spectrophotometric method;
- phosphorus (reference range 0.8-1.5 mmol/l): enzyme-colorimetric method;
- total magnesium (reference range 0.65-1.05 mmol/l): spectrophotometric method;
- cholesterol (reference range 3.4-6.2 mmol/l): enzyme photometric method with cholesterol oxidase;
- triglycerides (reference range 0.6-2.2 mmol/l): enzyme-colorimetric method

Statistical analysis

For the analysis of nominal variables the χ^2 test was applied. The symmetry of the distribution of continuous variables was analyzed with the use of the Kolmogorov-Smirnov test. For the display of main valuea and the measure of dispersion we used arithmetic mean ± standard deviation (SD) for variables whose distribution was normal and median (interquartile range) for continuous variables whose distribution deviated from normal. Student's t-test or Mann-Whitney U test was used in order to compare the continuous variables, depending on the symmetry of the distribution. P value less than 0.05 was considered statistically significant.

For statistical analysis of the data, the SPSS software system for Windows (version 20.0, SPSS Inc, Chicago, Illinois, USA) was used.

RESULTS

The study included 51 subjects in chronic hemodialysis program in the Dialysis Center of the University Clinical Hospital Mostar, out of which 13 (25.5%) were female and 38 (74.5%) male. The presence of HP antigen in the stool sample was found in 13 (25.5%) subjects. The characteristics of the tested sample are presented in the Table 1.

Patients on hemodialysis for less than 24 months had statistically significant lower rate of HP infections (Table 2).

HP positive and HP negative subjects were also compared with biochemical tests, age, time spent on hemodialysis and body mass index. There was no statistically significant difference between the groups for any of those characteristics (Table 3).

Table 1. The tested sample characteristics according to analyzation

Characteristics	
Women, n (%)	13 (25.49)
Helicobacter Pylori +, n (%)	13 (25.49)
Arterial hypertension, n (%)	34 (66.66)
Diabetes, n (%)	17 (33.33)
Age, years	61 (20.5)
Dialysis, months	28 (61)
C-reactive protein, mg / l	5.6 (24.9)
Phosphorus, mmol / l	1.55 (0.64)
Calcium, mmol / l	2.2±0.22
Magnesium, mmol / l	0.96±0.15
Urea, mmol / l	18.5±6.4
Creatinine, µmol / l	665.04±203.7
Uric acid, µmol / l	298.6±83.5
Hemoglobin, g / l	106±20.2
Total cholesterol, mmol / l	4±1.3
Triglycerides, mmol / l	1.4±0.7
Body mass index, kg / m^2	23.9±3.6

Table 2. Comparison of HP status for the patients who were on hemodialysis for up to 24 months with those who were on hemodialysis for more than 24 months

	≤24 months on hemodialysis	>24 months on hemodialysis	χ^2	s. s.	*P*
HP+	3	10	5.436	1	0.020
HP-	22	16			

HP - Helicobacter pylori

Table 3. Comparison of HP positive and HP negative patients on hemodialysis according to continuous variables

Characteristics	HP+ (n=13)	HP- (n=38)	Test value*	*P*
C-reactive protein, mg / l	5.6 (22.6)	4.3 (23.6)	224.5**	0.945
Age, years	65 (14)	58 (26)	166.5**	0.082
Dialysis, months	68 (73)	22 (61)	187**	0.194
Phosphorus, mmol / l	1.73 (0.7)	1.55 (0.8)	212**	0.719
Calcium, mmol / l	2.2±0.22	2.2±0.22	0.691	0.493
Magnesium, mmol / l	0.9±0.13	0.9±0.15	1.587	0.121
Urea, mmol / l	17.2±4.03	18.9±7.14	0.817	0.418
Creatinine, olmol / l	646.8±165.48	669.3±219.88	0.335	0.739
Uric acid, µmol / l	289.5±88.68	301.2±83.9	0.406	0.687
Hemoglobin, g / l	113±21.52	104±19.27	1.403	0.167
Total cholesterol, mmol / l	3.73±1.3	4.13±1.4	0.857	0.396
Triglycerides, mmol / l	1.18±0.6	1.54±0.72	1.545	0.130
Body mass index, kg / m2	24.6±3.4	23.6±3.7	0.862	0.394

Table 4. Comparison of HP positive and HP negative patients on hemodialysis by presence of arterial hypertension and diabetes and by gender

	HP+	HP-	χ^2	s. s.	*P*
HTA yes	9	25	0.087	1	0.768
HTA no	4	9			
DM yes	5	12	0.041	1	0.840
DM no	8	22			
Female	2	11	0.938	1	0.333
Male	11	27			

HTA - arterial hypertension; DM - diabetes mellitus

As for the comparison of HP status in the subjects with presence of arterial hypertension and diabetes, there was no statistical significant difference between the groups.

Also, there was no statistical significant difference in comparison of the HP status of the subjects in relation to their gender (Table 4).

DISCUSSION

In this study, University Clinical Hospital Mostar, Dialysis Center patients who were on hemodialysis for less than 24 months had statistically significant lower rate of HP infections than those who were on hemodialysis for more than 24 months. The study by Rasmi et al. also pointed out that the incidence of HP infection was significantly higher for the patients on hemodialysis for more than 3 years (Rasmi et al. 2012). However, it should be noted that their study only partially coincides with ours, since the presence of HP infection in hemodialysis patients was found with serological test

A meta-analysis conducted by Li and Chen showed that the rate of HP infection was negatively associated with cumulative dialysis time, and HP detection methods did not affect the association between HP infection and cumulative dialysis time. In this study, age was a risk factor for HP infection in dialysis patients, which is not consistent with our study (Li & Chen 2019).

Other studies showed that the patients on hemodialysis program for a short period of time had higher incidence of HP infection and vice versa (time spent on dialysis and HP colonization were inversely proportional) (Nakajima et al. 2002, Nakajima et al. 2004, Antoniou et al. 1997, Mortazavi and Rafeey 2008). In a meta-analysis conducted by Gu et al. there was no association between the time spent on dialysis and HP infection (Gu et al. 2013). Inconsistency in the results can be explained to the certaom extemd with various factors ithat influence the study such as the differences in the diagnosis of HP infection, sample size, and local incidence of HP in a healthy population, clinical or demographic characteristics, and other unknown factors (Fabrizi et al. 1999).

When assessing the relationship between HP infection in hemodialysis patients and their urea and creatinine concentrations, no statistically significant difference was found. This implies that the increased concentration of urea and creatinine do not inhibit the HP colonization in this population. This is supported by the research conducted by Loffeld et al. (Loffeld et al. 1991). Tsukada et al. have published the opposite results showing how high serum urea concentration of hemodialysis patients can act as an inhibitory factor for the HP colonization in these patients stomach (Tsukada et al. 2003).

Although the research of Nasri (Nasri 2007) showed that increased concentration of magnesium in plasma and probably its higher gastric mucosal concentration may facilitate HP colonization in the stomach of hemodialysis patients, in this study there were no findings about the difference between the HP status in hemodialysis patients and their magnesium concentration.

The reason for the discrepancy in the results are probably related to the different characteristics of the analyzed samples, as well as the difference in diagnosing the HP infection (in the study by Nasri, serological test was used to prove HP infection) (Nasri 2007). The number of available papers in the literature on the association between plasma magnesium concentration and HP infection in hemodialysis patients is modest, and the most of them have been conducted in the last ten years. It would certainly be good to conduct additional research in order to clarify this issue.

CONCLUSION

The incidence of HP infection in hemodialysis patients who have some of the digestive problems was 25.5%. The patients who were on hemodialysis for less than 24 months had lower incidence of HP infections than those who were on hemodialysis for more than 24 months.

Serum urea and creatinine concentrations have not been found as the HP colonization inhibitors in hemodialysis patients.

In this study, there was no difference in serum magnesium concentration of hemodialysis patients regardless to their HP status. Analisy of other characteristics (age, gender, biochemical tests, body mass index, time from the beginning of hemodialysis, diabetes, arterial hypertension) showed there was no statistically significant difference between hemodialysis patients who were HP positive compared to those who were HP negative.

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Contribution of individual authors:

Anđela Penavić: written the first draft of the manuscript, literature searches, approval of the final version.

Ivona Tomić, Ante Mandić, Ivan Tomić: writening of the manuscript, literature searches, approval of the final version.

Marta Mandić, Ivan Zeljko, Mirna Sabljo: comments on the concept and design of article, approval of the final version.

Monika Tomić: original idea, design of the study, literature searches, approval of the final version.

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