Helicobacter pylori *does not contribute to iron deficiency in hemodialysis patients*

T. López*, J. Almirall*, X. Calvet, M. Quesada***, I. Sanfeliú****, F. Segura*** and M. García***
*Nephrology Department. **Depatment of Digestive Diseases. ***Department of Infectious Diseases. ****Microbiology Laboratory. Hospital of Sabadell. Institut Universitari Parc Taulí. Universitat Autònoma of Barcelona.

SUMMARY

Background: *Many studies in the general population have shown a link between* Helicobacter pylori *infection and iron-deficiency, often resulting in iron-deficient anaemia. Despite the high prevalence of iron deficiency in hemodialysis patients, no studies have been performed in this population.*

Objective: *To evaluate the role of* Helicobacter pylori *infection in the appearance of anemia and the iron requirements in our hemodialysis population.*

Material and methods: *After excluding patients with severe pathology and short life expectancy and those with blood losses secondary to other causes, 79 patients were included. Iron requirements and anaemia were determined by iron serum, ferritin, and hematocrite values; and by transfusion, eritropoietin and iron requirements. The diagnosis of* Helicobacter pylori *status was stablished by the concordance of at least two of the three non invasive diagnostic methods performed (breath test, serology and fecal antigen of* Helicobacter pylori*).*

Results: *Prevalence of* Helicobacter pylori *infection was 43%. No significant differences between patients infected or not by* Helicobacter pylori *were found in any of the variables analysed: hematocrite (33.5%* versus *34.1%), serum iron (58.9* versus *63.7 pg/dl), ferritin (340.3* versus *264.2 ng/ml), transferrin saturation index (22.5%* versus *25.2%), dose of eritropoietin administred (96.6* versus *93.5 U/kg/weekly), and parenteral iron (1,389* versus *1,538 mg/year). A noteworthy finding was that patients with* Helicobacter pylori *infection had been on hemodialysis for a shorter period than those without (37.4* versus *63.7 months, p = 0.04).*

Conclusion: Helicobacter pylori *infection has no effect on anaemia (hematocrite, Eritropoietin dose or iron needs) in our hemodialysis patients. Prevalence of* Helicobacter pylori *is lower in patients with longer time on dialysis.*

We consider that the diagnosis of Helicobacter pylori *infection must be reserved for clinical peptic ulcera suspicion or patients on transplant waiting list (¿?).*

Key words: **Helicobacter pylori. *Anaemia. Hemodialysis.***

HELICOBACTER PYLORI NO CONTRIBUYE AL DÉFICIT DE HIERRO DE LOS PACIENTES EN HEMODIÁLISIS

RESUMEN

Introducción: *Estudios en determinados grupos de población han demostrado relación entre la infección por* Helicobacter pylori *y la anemia ferropénica. Se han postulado como*

Correspondence: Dra. Thaïs López Alba
Unidad de Nefrología.
Hospital de Sabadell
Institut Universitari Parc Tauli, UAB.
Parc Tauli, s/n
08208 Sabadell (Barcelona)
E-mail: tlopeza@cspt.es

mecanismos responsables las pérdidas hemáticas digestivas y la competición de la bacteria por el hierro de la dieta.

Objetivo: *Conocer si existe relación entre la infección por* Helicobacter pylori *y los requerimientos de hierro, la ferropenia o la anemia en pacientes en hemodiálisis.*

Material y métodos: *Se estudiaron 79 pacientes en hemodiálisis. Las necesidades de hierro se establecieron a partir de variables analíticas (sideremia, ferritina, índice de saturación de transferrina, hematocrito) y terapéuticas (dosis de eritropoyetina y hierro administrado) para alcanzar los objetivos. La infección por* Helicobacter pylori *se determinó mediante tres métodos diagnósticos no invasivos (test del aliento, serología y detección del antígeno en heces).*

Resultados: *La prevalencia de la infección por* Helicobacter pylori *fue del 43%. No existieron diferencias en ninguna de las variables analizadas entre los pacientes infectados por* Helicobacter pylori *y aquellos no infectados. Únicamente se observaron diferencias con respecto al tiempo de hemodiálisis, de manera que los pacientes infectados por* Helicobacter pylori *llevaban menos tiempo en hemodiálisis (37,4* versus *63,7 meses; p = 0,04).*

Conclusiones: *La infección por* Helicobacter pylori *no influye en la anemia o las necesidades de hierro o eritropoyetina en nuestros pacientes. Consideramos, por tanto, que el estudio sistemático de la infección por* Helicobacter pylori *en hemodiálisis no aporta información relevante, debiendo reservarse para situaciones clínicas específicas (sospecha de patología ulcerosa o pacientes en lista de espera para trasplante renal?).*

Palabras clave: **Helicobacter pylori.** ***Anemia. Ferropenia. Hemodiálisis.***

INTRODUCTION

Helicobacter pylori (Hp) is a spiral, flagellated, gram-negative germ, specially adapted to survive in the gastric lumen. *Hp* infection affects more than 50% of the world population[1,2] and its presence is related with the development of peptic ulcer and gastric adenocarcinoma and MALT lymphoma. Infection clearance allows curing peptic ulcer disease and may induce MALT lymphoma remission. Today, these pathologies are the main indications for eradication therapy[3].

Population-based epidemiological studies have shown a relationship between *Hp* infection and the presence of iron deficiency[4]. It has been described that *Hp* may cause iron-deficient anemia in children, adolescents[5-9], and adults[10] and in populations with a special susceptibility to gastrointestinal lesions caused by the infection[11].

The mechanisms involved in the relationship of *Hp* infection and anemia would be several. On the one hand, *Hp* would produce lesions of the gastric mucosa that could lead to losses by gastrointestinal bleeding. On the other hand, *Hp* has iron receptors on its membrane that could compete with the body for ingested iron and even affect iron metabolism or absorption generating a state of chronic iron deficiency[12-15].

It is well known that the origin of anemia in patients with end-stage chronic renal failure (ESCRF) on hemodialysis (HD) is multifactorial, but mainly due to deficient erythropoietin synthesis, to misuse of iron stores, or to blood losses through coagulations within the extracorporeal circuitry, accidental disconnections, or gastrointestinal blood losses.

In spite of the evidence that *Hp* infection is related with the presence of anemia and iron deficiency, and of the high prevalence of these conditions in ESCRF patients, to date it has not been conveniently analyzed whether *Hp* may contribute to iron deficiency or anemia in this population.

The aim of this study was to assess whether *Hp* infection is related to anemia and/or iron deficiency in ESCRF patients on HD.

PATIENTS AND METHODS

Seventy-nine clinically stable patients, older than 18 years, with at least 6 months on renal replacement therapy with HD, were selected. Patients with severe associated pathologies and low life expectancy, as well as those with any cause of non-gastrointestinal blood loss were excluded. Also excluded were those patients having received any antibiotic therapy within the last 4 weeks, and treatment with proton-pump inhibitors was discontinued and substituted by H2-antagonists within 4 weeks before the study start in order to avoid confounding factors for *Hp* determination test results. The study was approved by the Hospital local ethics committee and informed consent from all participants was obtained.

Three non-invasive diagnostic methods were used to determine *Hp* infection: the breath test with C13-labeled urea, *Hp* serologic tests, and determination of *Hp* antigen in the feces. The breath test with C13-labeled urea (Isomed; Spain) was done at the beginning of a dialysis session with the patient fasting. At the same session, a blood was drawn to determine *Hp* serology by an ELISA test (H.Pylori-IgG. Wampole Laboratories, Cranbury, NJ). A feces sample was collected to detect *Hp* antigen by Femtolab H. pylori (Connex, Martinsried; Germany).

The presence of *Hp* infection was determined by agreement of the results from the three non-invasive diagnostic tests, considering HP-infected patients those with two or three positive tests and non-*Hp* infected patients those with only one or no positive test. Iron deficient state and anemia were established by therapeutic variables (blood transfusion requirements, administered doses of erythropoietin and

iron) and laboratory parameters (total serum iron level, ferritin level, transferrin saturation index, hematocrit, hemoglobin, and mean corpuscular volume). For quantitative variables analysis, the mean of the determinations from the last 12 months was calculated. Laboratory parameters were repeated every four months, and monthly for hematocrit and hemoglobin. Erythropoietin dose was expressed as IU/kg/week, and its administration was subcutaneous divided in one or two weekly doses. Iron was administered intravenously every three months, concurrently with laboratory work-up, aiming at reaching a ferritin level equal or greater than 200 ng/mL and a transferrin saturation index greater than 20%. The relationship between these variables and the presence or absence of *Hp* infection was analyzed as well as with other parameters that could work as confounding factors such as age, gender, time on HD, presence of AHT, DM, dyslipidemia, or previous peptic ulcer disease, the use of gastro-protective therapies, NSAIDS or ASA, ESR, fibrinogen, dialysis dose expressed by the Kt/V, lipid profile, and albumin. Presence and severity of dyspeptic symptoms in patients included into the study was assessed by two tests: a symptom-severity rating scale from 0 to 55, and the Glasgow score with scored ranging 0-18. Statistical method: The Chi-squared analysis and Fisher's exact test have been used to compare ratios. The non-parametric Mann-Whitney U test has been used to compare quantitative variables. A p value < 0.05 has been considered statistically significant. Quantitative variables have been expressed as mean ± standard deviation.

RESULTS

Prevalence of *Hp* infection and patients characteristics

Seventy-nine HD patients (44 men/35 women) with a mean age of 64 years (26-88 years) were included. Renal failure etiology is summarized in table I.

Hp infection prevalence was 43% (34/79 patients). Patients characteristics were similar between patients with and without *Hp* infection (Table II). Differences were only observed for time on HD, with lower infection prevalence among patients with longer time on HD (37.4 months for infected patients versus 63.7 months for non-infected, p = 0.04).

About the vascular access for HD, 71 patients had an AVF whereas 8 patients received dialysis through a permanent catheter, 7 of them being non-*Hp* infected patients. This greater proportion of catheters among non-infected patients did not reach statistical significance (p = 0.67).

Anemia and iron requirements

About anemia study, there were no differences between infected and non-infected patients for hematocrit (33.5 *vs* 34.1%), hemoglobin (11.5 *vs* 11.4 g/dL), mean corpuscular volume (93.2 *vs* 92.3 fL), total iron level (58.9 *vs* 63.7 mg/dL), ferritin (340.3 *vs* 264.2 ng/mL), transferrin saturation index (22.5 *vs* 25.2 %), dose of administered erythropoietin (96.6 *vs* 93.5 IU/kg/week), or parenteral iron (1,389 *vs* 1,538 mg/year) (table III).

Differential analysis by type of vascular access (AVF versus permanent catheter) did not show any significant difference either between infected and non-infected patients with regards to analyzed variables, although these results should be taken carefully due to the low number of patients with permanent catheter (n = 8), of whom only one was Hp-infected.

Table I. Etiology of baseline nephropathy

	n	%
Chronic PN/interstitial nephropathy	13	17
Diabetic nephropathy	12	15
Polycystic renal disease	12	15
Nephroangiosclerosis	12	15
Chronic glomerulopathies	9	12
Unknown	7	9
Ischemic nephropathy	5	6
Malignant AHT	4	5
Obstructive uropathy	2	2
Acute tubular necrosis	2	2
Lupus nephropathy	1	1

Assessment of dyspeptic symptoms

Assessment of dyspeptic symptoms by the symptom-severity rating scale and the Glasgow score did not show differences either between Hp-infected and non-infected patients, so that infected patients had scores in the rating-scale and the Glasgow score of 5.8 ± 7.3 and 2.7± 2.9, res-

Table II. Comparison of clinical and laboratory variables between *Hp* (+) *and Hp* (-) groups

	HP (+)	*HP* (-)	p
Age (years)	63.8 ± 15.5	64 ± 12.6	ns
Gender (% male)	58.8	53.3	ns
Time on dialysis (months)	37.4 ± 41.6	63.7 ± 65.7	p = 0.04
Permanent catheter (%)	2.9	15.5	ns
AHT (%)	85.3	82.2	ns
DM (%)	23.5	20	ns
Dyslipidemia (%)	44.1	24.4	ns
Total Cholesterol (mg/dl)	176.4 ± 43.2	175.8 ± 34.9	ns
HDL - cholesterol (mg/dl)	44.1 ± 11.4	45.2 ± 12.2	ns
LDL - cholesterol (mg/dl)	99.8 ± 34	104.6 ± 28.3	ns
Triglycerides (mg/dl)	152 ± 84.6	127.9 ± 73.2	ns
ESR (mm 1st h)	48.8 ± 21,6	52.5 ± 22.7	ns
Fibrinogen (g/L)	4.42 ± 0.97	4.62 ± 1.19	ns
Albumin (g/L)	38.6 ± 3.1	38.9 ± 3.1	ns
Kt/V	0.93 ± 0.15	0.99 ± 0.15	ns
nPCR	1.05 ± 0.22	1.05 ± 0.29	ns

ESR: velocidad de sedimentación globular. Kt/V: dosis de diálisis. nPCR: tasa de catabolismo proteico.

Table III. Comparison of iron kinetics study between *Hp* (+) *vs Hp* (-) groups

	***HP* (+)**	***HP* (–)**	**p**
Hematocrit (%)	33.5 ± 2.7	34.1 ± 3.4	ns
Hemoglobin (g/dl)	11.5 ± 1.5	11.4 ± 1.3	ns
MCV (fL)	93.2 ± 3.7	92.3 ± 4.8	ns
MCH (pg)	32.2 ± 8.1	30.7 ± 1.6	ns
Total iron level (ug/dl)	58.9 ± 16.5	63.7 ± 25.5	ns
Ferritin (ng/ml)	340.3 ± 380.1	264.2 ± 17.4	ns
TSI (%)	22.5 ± 6.1	25.2 ± 8.5	ns
Erythropoietin (UI/kg/week)	96.6 ± 53.6	93.5 ± 65.7	ns
Iron (mg/year)	1,389 ± 923	1,538 ± 918	ns

MCV: volumen corpuscular medio. MCH: hemoglobina corpuscular media. TSI: índice de saturación de transferrina.

Table IV. Dyspeptic symptoms and concomitant medication by *Hp* infection status

	***HP* (+)**	***HP* (-)**	**p**
Glasgow score	2.7 ± 2.9	4.2 ± 5	ns
Symptoms scale	5.8 ± 7.3	9.3 ± 8.5	ns
Previous gastrointestinal pathology (%)	29.4	35.6	ns
Gastro-protective agents (%)	29.4	31.1	ns
Corticoids (%)	0	4.3	ns
ASA (%)	26.5	26.7	ns
NSAIDS (%)	8.8	11.1	ns

pectively, whereas non-infected patients had scores of 9.3 ± 8.5 and 4.2 ± 5, respectively. When analyzing therapeutic variables, there were no significant differences by use of aspirin, NSAIDS, or gastro-protective drugs, and there were no differences either for the presence of previous peptic ulcer disease (table IV).

DISCUSSION

Hp is specially adapted to survive in the gastric lumen, requiring metabolizing urea into ammonia. ESCRF patients present urea levels within the gastric lumen considerably higher than those for the general population, which has suggested that this may be associated with a higher predisposition to *Hp* infection[16]. However, significant differences in *HP* infection prevalence have not been observed between HD patients and controls without ESCRF, *Hp* infection rates being 30-70% depending on the diagnostic technique used and the population studied[17-20]. Some works even report an infection rate somewhat lower among dialysis patients[21,22]. Thus, in our study, *Hp* infection prevalence is 43%, similar to that observed in other studies on HD patients and a little bit lower than the one expected for the same age group in the general population.

Several population-based studies have shown a relationship between *Hp* infection and the presence of anemia or iron deficiency[23,24]. The mechanism for this association would be multifactorial, either due to the presence of gastrointestinal blood losses related to erosive lesions within the antrum or duodenum, or either due to the presence of iron receptors on the germ membrane that would compete with the body for ingested iron or affect iron metabolism or absorption.

Among the different factors that account for anemia in ESCRF patients, the main ones are erythropoietin deficiency and impairment of iron metabolism with an iron deficient state and misuse of iron stores due to the chronic inflammatory state of these patients.

Rosenblatt et al. and Wizemann et al.[25,26] showed with isotopic studies that dialysis patients had a three-fold increase in gastrointestinal blood losses as compared to individuals from the general population. These studies were done in the 1980s and did not take into account the presence of *Hp*.

In spite of the clear evidence that *Hp* infection produces blood losses and is a cause of iron deficiency in the general population, and in spite of the interest that iron metabolism in hemodialysed patients has triggered in recent years, the relationship between *Hp* infection and anemia or iron deficiency in these patients is little studied[27].

Fabbian et al.[28] carried out endoscopic studies on 57 patients on HD, assessing the presence and degree of anemia in them. With the logistic regression analysis, they observed that only age, NSAIDS abuse, and *Hp* infection were independently related with hemoglobin decrease.

On the other hand, more recent studies by Trimarchi et al.[29] on 29 HD patients have shown that Hp-infected patients present a significant reduction of vitamin B12 plasma levels when comparing them to non-infected patients (225.4 *vs* 707.9 pg/mL; $p < 0.011$), as well as an increase in the mean corpuscular volume (109.7 *vs* 91.8 fL; $p = 0.002$). They did not observe, however, any significant difference between both groups for hemoglobin and hematocrit.

Similarly to the study by Trimarchi et al., in ours we have not found significant differences between infected and non-infected patients for hematocrit or hemoglobin levels, neither for iron or erythropoietin requirements.

A relevant clinical issue was the negative correlation between *Hp* infection and time on HD. Nakajima et al.[30] observed a similar negative correlation in a group of HD patients. Although there is not a clear reason for this finding, a possible explanation would be that the decrease of stomach acid secretion observed in dialysis patients might create a more hostile environment for the microorganism. Besides, patients with longer time on HD have likely received antibiotic therapies on repeated occasions and many of them receive anti-secretory therapy. Thus, some of the patients on dialysis might have inadvertently cured the infection by combining these factors.

Some recent works have observed an association between the presence of *Hp* infection and nutritional and inflammatory status of HD and peritoneal dialysis patients. Hp-infected patients showed lower albumin and phosphorus values and higher C reactive protein values, parameters that significantly improve after clearance of this germ[31,32]. In our study, we did not observe differences between the groups

about albumin levels or the remaining inflammatory parameters analyzed (ESR, fibrinogen).

In dialysis patients the presence of dyspeptic symptoms is common presenting as nausea, vomiting, heartburn, as well as the existence of gastroduodenal pathology (gastritis and duodenitis). The origin of dyspepsia in HD patients is multifactorial, with the participation of factors related with uremia, stress, concomitant medication, and associated pathologies.

Whereas in the general population *Hp* infection may be associated with the presence of dyspeptic symptoms, the results from studies are controversial in HD patients. Whereas Ala-Kaila et al. showed a greater prevalence of dyspeptic symptoms in Hp-infected dialysis patients, other authors have not find any relationship[33,34]. In the present study, we have assessed dyspeptic symptoms by using two tests: a symptom-severity scale and the Glasgow score, with mean scores of 5.8 and 2.7, respectively, in Hp-infected patients and 9.3 and 4.2, respectively, in non-infected patients, without observing statistically significant differences, thus not being able to ascribe dyspeptic symptoms id our patients to the presence of *Hp* infection. Besides, the use of NSAIDS or ASA was similar in both groups. About the use of gastroprotective agents, either H2-blockers or proton-pump inhibitors, it was slightly higher in the group of non-infected patients, not reaching a statistical significance.

The results from this study suggest that treatment of *Hp* infection will not have an effect on anemia or iron requirements in HD patients. However, there are other reasons that may justify the search and treatment of *Hp* infection. First, there is a very clear relationship between *Hp* infection and complications of peptic ulcer disease. The cure of the infection virtually prevents both ulcers and their complications. Besides, *Hp* has an additive effect on NSAIDS and ASA use, increasing the risk for ulcer bleeding[35] and eradication prevents, at least in part, the occurrence of hemorrhagic complications[36]. Although these complications are uncommon in the patient on dialysis, when they occur they entail high morbidity and mortality because of the severe baseline pathology of these patients. This may be, therefore, a reason to preventively treat *Hp* infection, although currently there are not enough data to recommend systematic eradication in these patients.

Besides, some authors recommend routine *Hp* eradication in patients on the renal transplant waiting list because of the relationship of *Hp* infection and the presence of gastrointestinal complications after transplantation; especially in relation to malignant complications, more than gastrointestinal bleeding. Thus, there are some cases of gastric MALT lymphoma in post-transplanted renal patients carrying *Hp* with a favorable course after eradication therapy[37-38].

To conclude, the present study shows that *HP* infection prevalence in our setting is similar to that observed in other published series. The analysis also clearly suggests that the presence of *Hp* infection does not have an influence on anemia severity of iron requirements in these patients. Thus, we consider that nowadays studying the state of *Hp* infection should only be performed in those HD patients with suspected peptic ulcer disease and maybe in those on the renal transplant waiting list. There are not current data to recommend systematic determination of that infection among dialysis patients.

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