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Can *Helicobacter pylori* Colonization Affect the Phosphate Binder Pill Burden in Dialysis Patients?

Berfu Korucu,[1] Ozant Helvaci,[1] Rezzan Sadioglu,[2] Burak Ozbas,[1] Hasan Yeter,[1] and Ulver Derici[1]

[1]*Department of Nephrology, Gazi University Faculty of Medicine and* [2]*Department of Nephrology, Ankara University Faculty of Medicine, Ankara, Turkey*

Abstract: Phosphate binder pill (PBP) burden is a significant problem in dialysis patients. Phosphate absorption through the paracellular pathway increases in relatively acidic pH. In this study, we evaluated the effect of factors contributing to duodenal pH—*Helicobacter pylori* (HP), proton pump inhibitors (PPIs), and $NaHCO_3$ capsules—on PBP burden. We evaluated 255 dialysis patients with gastric biopsies and excluded patients with low Kt/V, gastrectomy, and parathyroidectomy. Patients were divided into groups and subgroups regarding HP existence, use of PPI, or $NaHCO_3$ capsules. HP+ group had significantly higher PBP burden and PBP equivalent doses ($P < 0.001$; both). HP+ subgroup not using daily PPIs or $NaHCO_3$ capsules had the highest PBP burden and PBP equivalent doses ($P < 0.001$; both). HP− subgroups had similar PBP and PBP equivalent doses ($P = 0.446$ and $P = 0.382$; respectively). HP colonization might affect the PBP burden in dialysis patients due to a decrease of duodenal pH.
Key Words: *Helicobacter pylori*, Hemodialysis, Hyperphosphatemia, Peritoneal dialysis, Phosphate binders.

Phosphate control is one of the most compelling issues in dialysis patient management. Many patients require high amounts of phosphate binder pills (PBPs). The PBP burden negatively affects the quality of life and also is quite costly. It is usually not possible to limit dietary phosphate while attempting to prevent malnutrition. Despite adequate dialysis, dietary consultation, and patients' adherence to suggestions, failure of phosphate control without numerous PBPs is substantially common.

The PBP burden of dialysis patients is widely variable, and most of the time, lower or higher than expected. Patients' adherence to dietary prescription is a crucial point. However, the role of other physical and chemical factors could be as important, since inorganic phosphate is a negatively charged ion and its absorption through negatively charged cell surfaces is theoretically very prone to be affected by conditions.

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Address correspondence and reprint requests to Dr Berfu Korucu, Gazi Universitesi Tip Fakultesi Hastanesi, Nefroloji BD, C Blok 2. Kat, Bahcelievler, Ankara, Turkey. Email: berfukorucu@gmail.com

Phosphate absorption from the intestines occurs substantially along with diffusion paracellularly and affected by the electrochemical gradient. Another phosphate absorption pathway is active transport, and this pathway is saturable due to receptor dependency. There are numerous investigations on active transport because of its potential to be a new drug target. Conversely, little is known about paracellular absorption of phosphate and its clinical importance (1).

Phosphate is an anionic ion and presents in the gut as $H_2PO_4^-$ and HPO_4^{-2} forms. Intercellular junctions in the small intestines are highly permeable to small, positively charged ions (e.g., Na^+), but the negative charges of phosphate limit its absorption (2). $H_2PO_4^-$ form diffuses paracellularly much more effectively than the HPO_4^{-2} form. The predominant phosphate ion is HPO_4^{-2} in alkaline pH, and HPO_4^{-2} requires uptake from the lumen by an active transport system (3). Duodenum has a relatively lower pH than the rest of the small intestines, and consequently, phosphate absorption substantially occurs in the duodenum. The passive paracellular transport pathway is not saturable in contrast to the active transport system (4,5). In this aspect, gastric and duodenal pH may contribute to intestinal phosphate absorption.

In this study, possible factors that could contribute to the pH of duodenum such as, gastric *Helicobacter pylori* (HP) colonization, proton pump inhibitor (PPI), and $NaHCO_3$ capsules use and their effect on PBP burden was investigated in hemodialysis and peritoneal dialysis patients.

PATIENTS AND METHODS

Statements of ethics

The study protocol has been approved by the research institute's committee on human research.

Study design and definitions

We conducted a retrospective and observational, single-center study investigated the effects of factors altering gastric and duodenal pH on the PBP burden in dialysis patients. All follow-up dialysis patients in our institution registered for renal transplantation waiting list between January 2005 and June 2018 were evaluated. Patients who underwent upper gastrointestinal endoscopy for transplantation suitability assessment were evaluated. Patients with an endoscopic biopsy performed and medical records of at least three consecutive months prior to that gastric biopsy were included. Patients with gastric motility and pH contributing diseases (e.g., systemic sclerosis, amyloidosis) and patients with a history of gastric surgeries and parathyroidectomy were excluded. Other exclusion criteria were gastric acidity treatment medications except for PPIs, such as H_2 receptor blockers, sucralfate, alginic acid, or calcium/magnesium carbonate for standardization (Figure 1). Patients using only routine daily PPIs (recommended doses for each preparation in NICE [CG184] 2014 guideline, as follows: omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg, esomeprazole 40 mg; q.d.) and $NaHCO_3$ 500 mg capsules at least three times a day (t.i.d.), or patients with no PPI or $NaHCO_3$ medications were included for standardization (6).

Patients with at least 1 year of dialysis vintage were included. Hemodialysis patients receiving less than 12 h/week of treatment were excluded. All continuous ambulatory peritoneal dialysis (CAPD) and all automated peritoneal dialysis (APD) patients apply the daily treatment. CAPD patients apply at least four exchanges per day. HD patients with an spKt/V of <1.2 per treatment and PD patients with a Kt/V of <1.7 per week were considered as inadequately dialyzed according to KDOQI guideline and excluded (7,8). Also, in the routine monthly interrogation performed by the nephrologist, the patients whose drug and diet incompatibility was noted were excluded.

All parameters of the patients belong to the last 3 months prior to the date of the gastric biopsy. Patients' demographic features, such as age, sex, body mass index, were noted. The last blood urea nitrogen (BUN), creatinine (Cre), sodium (Na), potassium (K), albumin (alb), hemogram test, and lipid profile results prior to the gastric biopsy were analyzed. The mean value of three consecutive months' serum calcium (Ca), phosphate (P), and intact parathormone (iPTH) levels prior to the gastric biopsies were calculated for analysis. Patients' medical therapies within 3 months prior to the gastric biopsies were noted, and mean daily or weekly doses were calculated.

Daily phosphate binder pill (PBP) medications, weekly active vitamin D supplements (calcitriol), weekly active vitamin D analogs (paricalcitol), and daily cinacalcet doses of three consecutive months were evaluated. The dose of these medications in this study is given as average doses prescribed in these 3 months. For standardization, only patients on calcium carbonate (CC), calcium acetate (CA), and sevelamer hydrochloride (HCl) were included. Patients using sevelamer carbonate and lanthanum were excluded. PBP burden refers to the mean total daily pills patients use in this study. PBP equivalent doses were calculated as follows: 1.0 for 1 g of CC, 1.0 for 1 g of CA, and 0.75 for 1 g of sevelamer HCl (9).

HD and peritoneal dialysis patients were not grouped separately since the removal of phosphate with a three times per week for 4-h at a time HD treatment is up to 3000 mg a week, and similarly, CAPD or APD treatments have a weekly phosphate removal of 2000 to 3000 mg a week (10,11). Patients were initially divided into main two groups as, "HP+" (HP positive) and "HP−" (HP negative). For further analysis, subgroups were defined regarding PPI and $NaHCO_3$ use. All values were compared between and within the groups.

Statistical methods

Numeric values of the study were shown with mean and standard deviation or medians with ranges, categorical data, frequency, and percentage. For data normally disturbed; unpaired Student's *t*-test is used for comparison between two groups, and the ANOVA test with the post-hoc analysis is used for more than two groups. For abnormal distributed data Kruskal–Wallis test performed. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for

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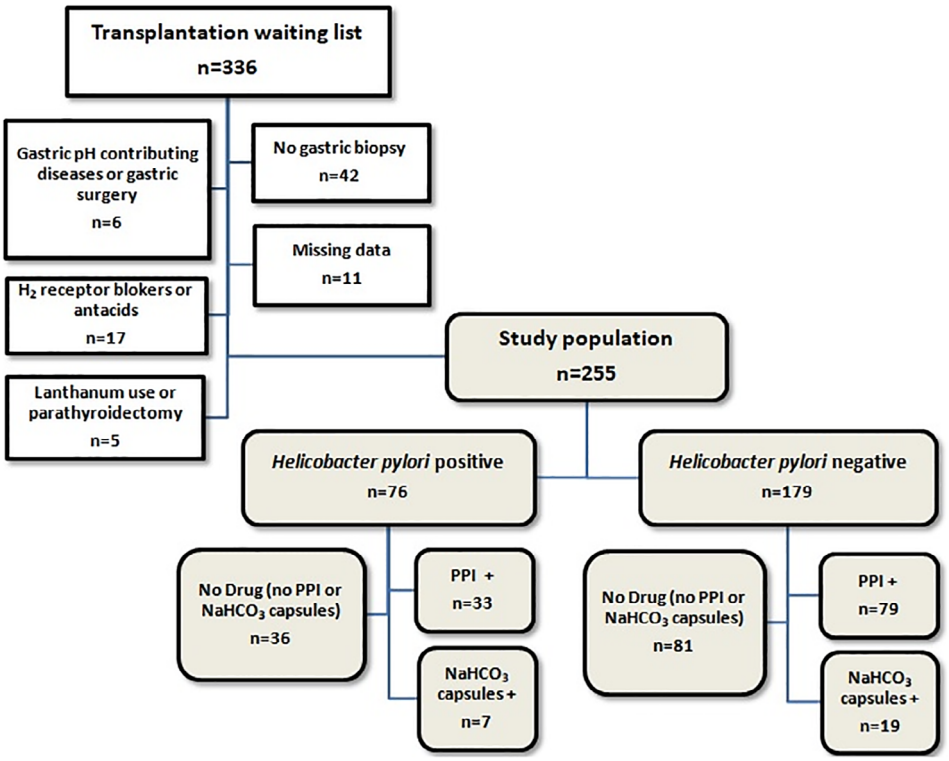


FIG. 1. Study design, study population, groups, and subgroups. $NaHCO_3$, Sodium hydrogen carbonate; PPI, proton pump inhibitor. [Color figure can be viewed at wileyonlinelibrary.com]

Social Science (SPSS, Chicago, IL, USA) for personal computers, version 21.0.

RESULTS

Baseline characteristics

Helicobacter pylori-positive and HP-negative patients' demographic features, laboratory, and health parameters were similar, except serum low-density lipoprotein (LDL)-cholesterol levels. Serum LDL-cholesterol levels were lower in the HP-positive group ($P = 0.020$). The frequency of peritoneal dialysis (PD) patients was higher in the HP-positive group ($P = 0.047$). Both groups' spKt/Vs per session or weekly Kt/Vs were similar and adequate according to guidelines. Groups had similar dialysis vintage. Frequencies of diabetic patients were similar in both groups (Table 1).

TABLE 1. *Patient characteristics and health parameters within the last month prior to gastric biopsies*

	HP positive ($n = 76$)	HP negative ($n = 179$)	P value
Female/male (n)	32/44	74/104	0.825
Age mean (SD)	51.9 (±13.2)	51.8 (±14.2)	0.748
BMI mean (kg/m^2) (SD)	24.3 (±4.3)	24.7 (±5.8)	0.577
BUN mean (mmol/L) (SD)	21.4 (±6.4)	21.7 (±6.5)	0.803
Creatinine mean (μmol/L) (SD)	618.8 (±176.8)	619.7 (±177.1)	0.612
Sodium mean (mmol/L) (SD)	138.6 (±2.4)	138.8 (±2.4)	0.637
Potassium mean (mmol/L) (SD)	4.6 (±0.7)	4.7 (±0.7)	0.614
Hemoglobin mean (g/L) (SD)	113.2 (±16.2)	112.5 (±15.3)	0.620
Albumin mean (g/L) (SD)	40 (±3.3)	41 (±3.1)	0.215
LDL mean (mmol/L) (SD)	2.9 (±0.8)	2.8 (±0.7)	**0.020**
Triglycerides mean (mmol/L) (SD)	1.8 (±0.8)	1.9 (±1.4)	0.725
	HD: 64	HD: 158	
Dialysis modality (n)	PD: 12	PD: 20	**0.047**
	HD:1.63 (±0.16)	HD:1.62 (±0.17)	0.417
Kt/V mean (SD)	PD: 1.76 (±0.36)	PD: 1.77 (±0.27)	0.569
Dialysis vintage (months) (SD)	35.9 (±33.0)	46.2(±42.1)	0.133
Diabetes mellitus n (%)	18 (23.6%)	38 (21.2%)	0.397

BMI, body mass index; BUN, blood urea nitrogen; HP, *Helicobacter pylori*; LDL, low-density lipoprotein cholesterol.

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TABLE 2. *Mean serum calcium, phosphate, intact parathormone levels, and mean daily phosphate binder pills of groups in the last 3 months prior to gastric biopsies*

	HP positive (n = 76)	HP negative (n = 179)	P value
	Mean (SD)	Mean (SD)	
Mean calcium (±SD) (mmol/L)	2.3 (±0.2)	2.2 (±0.2)	0.948
Mean phosphate (±SD) (mmol/L)	1.6 (±0.2)	1.5 (±0.2)	0.637
iPTH median (min–max) (ng/L)	247.5 (54.1–1313.0)	277.2 (39.4–1470.0)	0.061
Weekly calcitriol *n* (%)	38 (50%)	50 (27.9%)	**<0.001**
Weekly paricalcitol *n* (%)	8 (10.5%)	17 (9.5%)	0.617
Daily cinacalcet *n* (%)	5 (6.6)	20 (11.2%)	**0.021**
Daily CC (mg) median (min–max)	0.0 (0–3500)	0.0 (0–3000)	0.577
Daily CA (mg) median (min–max)	2001.0 (0–10 005)	0.0 (0–6003)	**<0.001**
Daily sevelamer HCl (mg) median (min–max)	0.0 (0–12 000)	0.0 (0–12 000)	0.094
Daily PBP burden mean (±SD)	6.5 (±4.8)	3.2 (±2.7)	**<0.001**
Daily PBP equivalent dose[†] mean (±SD)	4.1 (±3.0)	2.0 (±1.7)	**<0.001**

[†]Equivalent doses: 1.0 for 1 g of calcium carbonate, 1.0 for 1 g of calcium acetate, and 0.75 for 1 g of sevelamer hydrochloride. CA, calcium acetate; CC, calcium carbonate; HCl, hydrochloride; HP, *Helicobacter pylori*; iPTH, intact parathormone; PBP, phosphate binder pill.

Comparison of bone metabolism parameters and medications of the groups

HP-positive and HP-negative groups had similar Ca, P, and iPTH serum levels for consecutive 3 months prior to gastric biopsies (P = 0.948, P = 0.637, P = 0.061; respectively). The frequency of patients using weekly calcitriol in the HP-positive group was significantly higher ($P < 0.001$). The frequency of patients using weekly paricalcitol was similar between groups (P = 0.617). In the HP-negative group, more patients were using daily cinacalcet comparing the HP-positive group (P = 0.021). Both groups used similar mean daily CC and sevelamer HCl (P = 0.577, and P = 0.094; respectively). HP-positive group's daily CA dose was significantly higher than the HP-negative group ($P < 0.001$). Total mean PBP burden and mean PBP equivalent doses of HP-positive patients were significantly higher than the HP-negative group ($P < 0.001$; for both) (Table 2).

Comparison of bone metabolism parameters and medications of the groups excluding patients on active vitamin D or vitamin D analogs

Analyses reenacted after excluding patients on active vitamin D or vitamin D analogs (n = 143). HP-positive and HP-negative groups had similar Ca, P, and iPTH serum levels for consecutive 3 months prior to gastric biopsies (P = 0.522, P = 0.607, and P = 0.167; respectively). The frequency of patients using daily cinacalcet was similar between groups (P = 0.739). Both groups used similar mean daily CC, and daily sevelamer HCl (P = 0.654, and P = 0.222; respectively). HP-positive group's CA doses were significantly higher than the HP-negative group ($p < 0.001$). Total mean PBP burden and mean PBP equivalent doses of HP-positive patients were significantly higher than the HP-negative group ($P < 0.001$; for both) (Table 3).

Phosphate binder pill burden variability of subgroups classified according to medications altering gastric pH

Subgroups of HP-positive patients regarding PPI use and $NaHCO_3$ consumption were significantly different regarding PBP burden and PBP equivalent doses ($P < 0.001$ and $P < 0.001$; respectively). The HP-positive subgroup with no daily PPIs or $NaHCO_3$ capsules had the highest PBP burden and PBP equivalent doses. HP-negative subgroups had similar PBP and PBP equivalent doses (P = 0.446, and P = 0.382; respectively). When HP-positive subgroup without PPIs or $NaHCO_3$ (HP+no drug) were excluded, the other five subgroups (HP+PPI, HP+$NaHCO_3$, HP −no drug, HP−PPI, and HP−$NaHCO_3$) had similar PBP burden and PBP equivalent doses (P = 159 and P = 157, respectively) (Figure 2).

Comparison of HP-positive subgroups

HP-positive subgroups without PPIs or $NaHCO_3$ capsules were significantly different from the HP-positive subgroups using PPI and $NaHCO_3$ capsules regarding PBP burden ($P < 0.001$; for both), and PBP equivalent doses ($P < 0.001$, and P = 0.002; respectively). In the post-hoc analysis of HP-positive subgroups, PPI and $NaHCO_3$ groups had similar PBP burden and PBP equivalent doses (P = 0.847 and P = 0.915; respectively). [Correction added on 25 November 2019, after first online publication: in the section heading, 'HB-positive' has been updated to 'HP-positive'.]

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TABLE 3. *Mean serum calcium, phosphate, intact parathormone levels, and mean daily phosphate binder pills of groups in the last 3 months prior to gastric biopsies of patients excluding cases using calcitriol or paricalcitol*

	HP positive n = 31	HP negative N = 112	P value
	Mean (SD)	Mean (SD)	
Mean calcium (±SD) (mmol/L)	2.8 (±0.2)	2.9 (±0.2)	0.522
Mean phosphate (±SD) (mmol/L)	1.6 (±0.2)	1.5 (±0.3)	0.607
iPTH median (min–max) (ng/L)	264.7 (54.1–1313.0)	271.8 (39.4–1470.0)	0.167
Daily cinacalcet *n* (%)	3 (9.7%)	12 (10.7%)	0.739
Daily CC (mg) median (min–max)	0.0 (0–1500)	0.0 (0–3000)	0.654
Daily CA (mg) median (min–max)	2001.0 (0–10 005)	0.0 (0–6003)	**<0.001**
Daily sevelamer HCl (mg) median (min–max)	0.0 (0–12 000)	0.0 (0–12 000)	0.222
Daily PBP burden mean (±SD)	7.0 (±5.2)	3.3 (±2.7)	**<0.001**
Daily PBP equivalent dose† mean (±SD)	4.5 (±3.2)	2.0 (±1.7)	**<0.001**

†Equivalent doses: 1.0 for 1 g of calcium carbonate, 1.0 for 1 g of calcium acetate, and 0.75 for 1 g of sevelamer hydrochloride. CA, calcium acetate; CC, calcium carbonate; HCl, hydrochloride; HP, *Helicobacter pylori*; iPTH, intact parathormone; PBP, phosphate binder pill.

DISCUSSION

Helicobacter pylori is a Gram-negative, microaerophilic microorganism usually infecting the stomach. It is assumed that half of the population worldwide is colonized with HP. Colonization rates vary between countries from one-fourth to more than half of the population (12–15). HP positivity among dialysis patients is reported to be slightly less prevalent than controls with normal renal function, but clinical significance was higher in this population (15–19). Aside from its relationship with duodenal ulcers and gastric carcinoma, more than 80% of individuals colonized with HP are asymptomatic (20). Subjects with HP colonization are shown to have an increased and prolonged postprandial acid secretion and gastrin release resulting in an increase in duodenal acid load and prolongation of low pH in the duodenum (21).

The substantial amount of phosphate absorption mainly occurs in duodenum along with paracellular diffusion. However, little is known about the paracellular absorption of phosphate and its clinical importance. Phosphate presents as $H_2PO_4^-$ and HPO_4^{-2} forms. $H_2PO_4^-$ is more absorbable due to its less negative charge and is the main form in relatively acidic pH. Thus, this can be hypothesized that factors that alter duodenal pH can also alter passive paracellular phosphate absorption.

In this study, the most common and manageable factors seen in dialysis patients affecting gastric and duodenal pH and their relationship with phosphate binder pill (PBP) burden were aimed to be

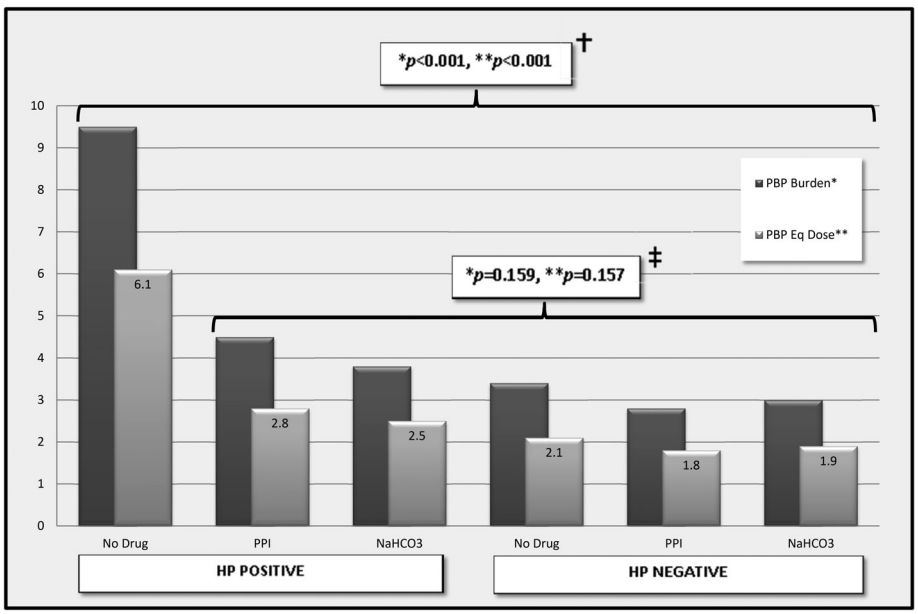


FIG. 2. Phosphate binder pill burden of subgroups. †Comparison of all subgroups; ‡Comparison of subgroups excluding HP+no drug subgroup. HP, *Helicobacter pylori*; no drug, no proton pump inhibitor or sodium hydrogen carbonate capsules; PPI, proton pump inhibitor; $NaHCO_3$, sodium hydrogen carbonate capsules; PBP, phosphate binder pill; PBP eq dose, phosphate binder pill equivalent doses: 1.0 for 1 g of calcium carbonate, 1.0 for 1 g of calcium acetate, and 0.75 for 1 g of sevelamer hydrochloride.

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evaluated. First one of these factors is HP colonization. Among various diagnostic tests for HP infection, gastric biopsy has the 100% sensitivity and specificity. The second widespread gastric and duodenal pH altering factor is the consumption of proton pump inhibitors (PPIs), H2-receptor antagonists, and antacid medications. Among these medications, more than 90% of patients in this study used PPIs. For standardization, patients using the latter classes of medications were excluded in this study. Plus, patients with irregular PPI consumption were also excluded. The third factor evaluated in this study was enteric coated $NaHCO_3$ capsules. $NaHCO_3$ capsules are widely used in dialysis patients to treat metabolic acidosis. In this study, at least three times a day (t.i.d.) use of the $NaHCO_3$ capsules is evaluated as a duodenal pH contributor. Patients using lower doses of $NaHO_3$ capsules were excluded.

The baseline characteristics of HP-positive and HP-negative patients were similar. Furthermore, mean calcium, phosphate, and intact parathormone levels of the groups were similar. HP-positive patients without PPI or $NaHCO_3$ capsule consumption significantly had a higher PBP burden. On the other hand, the number of patients using active vitamin D was significantly higher in the HP-positive group. Both calcitriol and paricalcitol increase phosphate absorption from intestines via Npt2b cotransporters. The same analyses were repeated excluding the cases using calcitriol and paricalcitol. When patients receiving these agents were excluded, there was a difference between the number of patients in the HP+ and HP– groups. We reevaluated patient characteristics and all databases and observed that this difference was far from clinical significance and was coincidental due to the limited number of the study population. After exclusion, statistics revealed similar results as presented in the Table 3. Again, HP-positive patients' PBP burden was significantly higher than the HP-negative group.

Post-hoc analyses of subgroups revealed that daily PPI use and $NaHCO_3$ capsule t.i.d. use was similarly effective in ameliorating the PBP burden in HP-positive patients presumably via restoring duodenal pH. However, this study revealed no further benefits of PPIs or $NaHCO_3$ capsules in patients without HP colonization.

The major strength of this study is the use of gastric biopsies as the HP diagnostic test. Furthermore, contributing factors, such as various antacid medications, patients with potential gastric motility and pH contributing diseases, patients with gastric surgery or parathyroidectomy were excluded for standardization. The main limitation of the study was the retrospective nature of the research and evaluation of dietary and drug compliance with the clinician's archived notes.

Rationally, it is not realistic to suggest endoscopic surveillance of all patients with PBP burden. Although there are concerns about noninvasive HP diagnostic methods such as urea breath test or stool antigen tests' suitability in dialysis patients, there is evidence that diagnostic accuracy of the urea breath test tends to improve after hemodialysis sessions and stool antigen testing results are reliable both in diagnosis and eradication confirmation (22–26). Prospective trials regarding HP surveillance of dialysis patients with poor phosphate control with noninvasive diagnostic tests would further enlighten the subject presented in this study. Further to that, among HP colonized patients, studies evaluating the contribution of HP eradication or intervention with PPIs, H2-receptor blockers, or antacid medications on phosphate control are essential to elucidate this subject.

CONCLUSIONS

Dialysis patients with *Helicobacter pylori* colonization might have increased phosphate binder pill burden, presumably due to a decrease in duodenal pH. Among *Helicobacter pylori* colonized patients, routine daily proton pump inhibitor (PPI) or $NaHCO_3$ capsules t.i.d. use was related to a lower phosphate binder pill burden. Such an association was not seen on *Helicobacter pylori*-negative dialysis patients using PPIs or $NaHCO_3$ capsules.

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CONFLICT OF INTEREST

None.

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