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## Nutrition status and *Helicobacter pylori* infection in patients receiving hemodialysis

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### Abstract

Chronic kidney disease (CKD) patients receiving hemodialysis (HD) often develop gastrointestinal abnormalities over their long treatment period. In general, prognosis in such patients is poor due to the development of protein-energy wasting (PEW). Therefore, it is important to clarify the etiology of PEW and to establish better strategies to deal with this condition. Chronic *Helicobacter pylori* (*H. pylori*) infection in the gastric mucosa has a close association with not only the development of peptic ulcer disease and gastric cancer, but is also associated with abnormal plasma and gastric mucosal ghrelin levels that are seen in malnutrition. It is unclear whether *H. pylori* infection of the gastric mucosa is directly associated with prognosis in HD patients by affecting ghrelin levels. Recent studies show that the prevalence of *H. pylori* infection in HD patients is significantly lower than in subjects with normal renal function. In the natural history of *H. pylori* infection in HD patients, the prevalence of infection decreases as the length of time on HD increases. The severity of gastric mucosal atrophy has been suggested as the major determinant of ghrelin levels in these patients, and eradication therapy of *H. pylori* improves nutritional status by increasing serum cholinesterase and cholesterol levels, especially in patients with mild-to-moderate gastric mucosal atrophy. Prompt *H. pylori* eradication to inhibit the progress of gastric atrophy may be required to prevent this decrease in ghrelin levels and subsequent PEW and improve the prognosis of HD patients by improving their nutritional status.

**Key words:** *Helicobacter pylori*; Hemodialysis; Ghrelin; Gastric mucosa; Anti-bacterial agents

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**Core tip:** Hemodialysis (HD) patients have a poor prognosis related in part to protein-energy wasting (PEW), associated with low levels of ghrelin. The severity of gastric mucosal atrophy has been suggested as the major determinant of ghrelin levels. Eradication of *Helicobacter pylori* (*H. pylori*) improves nutritional status, with serum cholinesterase and cholesterol levels stimulated by rising ghrelin levels and appetite, especially in *H. pylori* infection-positive patients with severe gastric mucosal atrophy. Although infection rates of *H. pylori* have been decreasing in HD patients, it would be preferable to eradicate *H. pylori* promptly before progression of gastric atrophy for prevention of gastric cancer and PEW.

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## INTRODUCTION

With ongoing progress in medical and dialysis machine techniques, the number of chronic renal failure patients receiving hemodialysis (HD) is increasing at a rate of 7% per year. At least 2.9 million Asians require dialysis, including Japanese, who live in an aging society and experience changes in their living environment<sup>[1,2]</sup>. HD patients often experience gastrointestinal symptoms (e.g., nausea, abdominal pain, and constipation) caused by elevated urea levels, decreased gastrointestinal motility, amyloid protein deposition, and sensory disturbances, and are at increased risk of developing gastrointestinal diseases (e.g., peptic ulcer disease, gastric antral vascular ectasia, gastroesophageal reflux disease, and gastric cancer)<sup>[3-7]</sup>. The risk of gastric mucosal damage is elevated in this population, in association with high ammonia levels<sup>[8]</sup>, systemic and/or local chronic circulatory failure<sup>[9,10]</sup>, and hypergastrinemia<sup>[11]</sup>. Gastrointestinal diseases such as peptic ulcer and gastric cancer have been linked to chronic *Helicobacter pylori* (*H. pylori*) infection<sup>[12-15]</sup>. In HD patients, the role of chronic *H. pylori* infection in their prognosis and quality of life (QOL) has not been defined.

In general, QOL in HD patients is poor. This affects their nutritional status, and thereby contributes to the development of malnutrition, which is a potent predictor of morbidity and mortality<sup>[16,17]</sup>. The state of metabolic and nutritional derangement called protein-energy wasting (PEW) has a major impact on mortality in HD patients<sup>[16,17]</sup>. Improving the prognosis of HD patients with PEW requires determination of its etiology and the development of prophylactic strategies<sup>[18,19]</sup>.

The complex interactions of gastroduodenal disease,

nutritional status, and *H. pylori* infection in HD patients (which tends to decrease with increasing time on dialysis<sup>[20]</sup>) remain to be elucidated. Here, we review the association between *H. pylori* infection and HD, and the relationship between *H. pylori* and nutritional status in this population. Finally, we review the effects of *H. pylori* eradication therapy in *H. pylori*-positive HD patients on nutritional status and plasma ghrelin levels.

## H. PYLORI INFECTION IN HD PATIENTS

*H. pylori* is a spiral-shaped, microaerophilic Gram-negative flagellate bacterium isolated in 1983 from gastric biopsy specimens of patients with chronic atrophic gastritis<sup>[21]</sup>. The gastric mucosa of approximately 50% of the world's population is infected with *H. pylori*, and the infection levels exceed 70% in some developing areas<sup>[15,22-24]</sup>.

Previously, we reported that the prevalence of *H. pylori* infection in 539 Japanese HD patients with a mean treatment period of 8.4 ± 0.3 year in 1997 was 48.6% (95%CI: 44.3%-52.9%). This was significantly lower than that in dyspepsia patients with normal renal function [78.5% (74.1%-82.4%), *P* < 0.001] and individuals receiving annual health checks [69.4% (60.3%-77.5%), *P* < 0.001]<sup>[20]</sup>. In a meta-analysis of reports investigating the prevalence of *H. pylori* in dialysis patients before 2009, the prevalence in patients receiving HD and continuous ambulatory peritoneal dialysis (CAPD) was 43.9% [(95%CI: 42.2%-45.6%), 1435/3272] and 34.8% [(29.6%-40.2%), 113/325], respectively, which was again significantly lower than that in individuals with normal renal function [49.8% (48.0%-51.7%), 1476/2961, *P* < 0.001]<sup>[25]</sup>. Although infection rates differ among different geographic populations, in East Asian countries where the prevalence of *H. pylori* infection and incidence of gastric cancer is relatively high, the latest statistics show the infection rate in HD patients to be 44.5% (41.55%-47.6%, 474/1065), which is significantly lower than that in individuals with normal renal function [54.0% (50.9%-57.1%), 560/1038, *P* < 0.001]<sup>[25]</sup>. Importantly, the prevalence in individuals with normal renal function is similar in patients receiving HD treatment for < 1 year<sup>[20]</sup>. HD treatment, but not uremia from chronic renal failure, may play an important role in the decreased prevalence of *H. pylori* infection.

Recently, infection rates of *H. pylori* have been decreasing. A large-scale Japanese epidemiological study showed that the infection rate in Japanese has declined to 30%-50%, especially in younger patients<sup>[26]</sup>. Supporting this phenomenon, an investigation of 500 Japanese HD patients with a mean treatment duration of 6.9 ± 6.6 years (2015) reported that the prevalence of infection had dramatically decreased, to 15.0% (95%CI: 12.0-18.4)<sup>[27]</sup>. Although it has not yet been proven, decreasing rates of *H. pylori* infection suggest

**Table 1 Hemodialysis treatment duration and *Helicobacter pylori* infection status in hemodialysis patients<sup>[27]</sup>, %**

	< 1 yr	1-3 yr	3-10 yr	> 10 yr	P value
<i>H. pylori</i> infection rate	23.8 (15/63)	16.7 (18/108)	15.0 (34/226)	7.8 (8/13)	0.043
Rate of <i>H. pylori</i> negatives	55.5 (35/63)	62.0 (67/108)	68.1 (154/226)	68.9 (71/103)	> 0.05

that the incidence of peptic ulcer disease and gastric cancer is expected to be decreasing in HD patients and that QOL in HD patients has improved due to decreases in *H. pylori*-related gastrointestinal disease.

## TREATMENT PERIODS OF HD AND *H. PYLORI* INFECTION

There is an inverse relationship between *H. pylori* infection and dialysis treatment duration (Table 1)<sup>[20,27-31]</sup>. We showed that the duration of HD treatment in *H. pylori*-positive patients was  $4.6 \pm 3.8$  years, which is significantly shorter than that in *H. pylori*-negatives ( $7.3 \pm 6.9$  years,  $P = 0.001$ )<sup>[27]</sup>. Interestingly, the finding of decreased *H. pylori* infection is characteristic of the prevalence of infection decreasing when the treatment period is  $\geq 2$  year<sup>[28]</sup>, and the infection rate gradually decreases up to four years after the initiation of HD and is followed by a plateau<sup>[20]</sup>. In a 4-year follow-up survey of *H. pylori*-positive patients, the prevalence of infection was 51.6% at 1 year, 42.9% at 2 year, and 38.3% at 4 year in the absence of eradication therapy. In other words, 26.7% of patients were naturally cured of *H. pylori* infection over four years<sup>[20]</sup>.

It is unknown why HD patients have a lower prevalence of *H. pylori* infection. One hypothesis is that HD patients have higher levels of pro-inflammatory cytokines<sup>[32]</sup>. As a result, gastric atrophy progresses, and finally *H. pylori* are not able to live in the gastric mucosa<sup>[33-35]</sup>. Another hypothesis is that elevated blood urea and urea nitrogen levels may inhibit *H. pylori* growth<sup>[36]</sup>. A third hypothesis is that *H. pylori* may be cured with incidental antibiotic treatment, because most HD patients suffer from an increased incidence of bacterial infections, and because plasma levels of antimicrobial agents may be higher in HD patients than in individuals with normal renal function<sup>[37]</sup>.

## PEPSINOGEN IN HD PATIENTS

Human pepsinogens (PGs) are proenzymes that act on pepsin. Serum PG levels reflect the status of the gastric mucosa, and decreased PG secretion is a marker of gastric mucosal atrophy. In patients without renal dysfunction, measurements of serum PG levels are used in screening for gastric cancer and gastric mucosal atrophy<sup>[38]</sup>. In addition, serum PG levels and the PG I/PG II ratio are useful in determining the level of gastric acid secretion<sup>[39]</sup>. Recently in Japan, a combination of the serum PG level and *H. pylori*-IgG level, namely

the ABC method, has been commonly used at health screenings as a useful marker for gastric cancer<sup>[40]</sup>. Because PG is eliminated *via* the kidney, serum PG levels are elevated in patients with renal dysfunction<sup>[41]</sup>. The value of serum PG levels as a biomarker of gastric atrophy and the capacity of gastric acid secretion in HD patients was heretofore unknown.

A recent report has demonstrated that PG I and II levels and PG I/PG II ratios in *H. pylori*-negative HD patients are significantly higher than those in *H. pylori*-positives and that PG I levels positively correlate with PG II levels and PG I/PG II ratio in *H. pylori*-negative HD patients ( $|R| = 0.849$  and  $|R| = 0.569$ ), past-infection patients ( $|R| = 0.870$  and  $|R| = 0.575$ ) and current-infection patients ( $|R| = 0.784$  and  $|R| = 0.517$ )<sup>[26,42]</sup>. In addition, a receiver operating characteristic curve using a cut-off value of 7.75 demonstrated that the sensitivity and specificity of PG I/PG II ratio in predicting the absence of *H. pylori* were 88.7% and 84.0%, respectively<sup>[26]</sup>. Therefore, serum PG I/PG II ratio may be a valid marker for *H. pylori* infection status and gastric mucosal atrophy in HD patients. Further large-scale studies are needed to verify this.

## NECESSITY OF *H. PYLORI* ERADICATION THERAPY FOR HD PATIENTS

The incidence rates of peptic ulcer and gastric cancer in HD patients are higher than those in individuals with normal renal function<sup>[7,43]</sup>. In addition, because most HD patients receive anti-thrombotic therapy and/or non-steroidal anti-inflammatory drugs (NSAIDs), the development of drug-induced ulcers and hemorrhage from gastroduodenal lesions easily occurs and often causes fatal blood loss. Therefore, prompt *H. pylori* eradication therapy is necessary for *H. pylori*-infected HD patients<sup>[12,13]</sup>, especially in HD patients with a higher risk of disease development, such as those with a past history of peptic ulcer, gastroduodenal hemorrhage, or use of anticoagulants and/or NSAIDs.

To reduce the risk of gastric cancer, the Japanese health insurance system in 2012 began covering *H. pylori* eradication therapy for all patients with endoscopic gastritis as well for peptic ulcers, gastric mucosa-associated-lymphoid tissue (MALT) lymphoma, post-endoscopic resection of early gastric cancer, and idiopathic thrombocytopenic purpura (ITP)<sup>[44-49]</sup>. In Japan, first-line eradication therapy is limited to a regimen that employs a standard dose of vonoprazan

or proton pump inhibitor (PPI) administered twice daily, amoxicillin (AMPC) 750 mg twice daily, and clarithromycin (CAM) 200 mg or 400 mg twice daily for 1 wk. Unfortunately, because the prevalence of CAM-resistant *H. pylori* strains in Japan is increasing (> 30%), the eradication rate is gradually decreasing<sup>[14,50-53]</sup>. Eradication therapy is more challenging in HD patients since they have many exposures to antimicrobial agents due to immune system impairment<sup>[54,55]</sup>. In fact, 36.4% of patients with chronic renal failure are reported to be infected with CAM-resistant strains, which is significantly higher than in patients with normal renal function (15.2%)<sup>[54]</sup>. Our recent data published in 2017 shows that rate of CAM-resistant strains in HD patients is 40.5% of infected patients<sup>[55]</sup>. Alternative regimens may be designed to use *H. pylori*-susceptible antimicrobial agents, increased dosages of antimicrobial agents and PPIs, increased dosing frequency, and longer treatment periods, according to international treatment guidelines<sup>[13,52,56-60]</sup>.

There is no optimal *H. pylori* eradication regimen in HD patients yet (Table 2). Some antimicrobial agents, especially AMPC, are known to exacerbate renal dysfunction. The maximum drug concentration of AMPC in patients with renal failure is 2-4 times higher than in patients with normal renal function, and the half-life is 5-20 times as long as that in healthy individuals<sup>[37]</sup>. Although several previous reports showed no severe adverse effects of AMPC in HD patients receiving eradication therapy<sup>[4,11,30,61-65]</sup>, the Japanese guidelines for *H. pylori* eradication therapy in the Japanese Society of Helicobacter Research recommends a reduction in AMPC dosage for HD patients<sup>[12]</sup> and the Japanese drug prescribing guidelines accordingly recommend that the dosage of AMPC for patients with renal failure should be reduced by 70%. In fact, the toxic effects of AMPC in HD patients have been reported in various studies<sup>[66-68]</sup>; for example, Sheu *et al.*<sup>[68]</sup> reported that patients with a lansoprazole-CAM-metronidazole regimen had a lower risk of acute renal failure than those with a lansoprazole-CAM-AMPC regimen (2% vs 18%; relative risk, 0.128, 95%CI: 0.016-0.979) for chronic renal failure non-dialysis patients. Overdose of drugs has to be carefully prevented. Although an optimal regimen for dosage and periods of AMPC in HD patients is not described in the Japanese guidelines for eradication<sup>[12]</sup>, an AMPC-reduced regimen may be appropriate in HD patients.

Recently, we have adopted a regimen composed of PPI and CAM, both at conventional dosage, and a dose of AMPC that is one-third of the conventional dosage (250 mg twice daily), and investigated the efficacy and safety of this regimen<sup>[55]</sup>. This regimen in HD patients provided equivalent efficacy as the standard dose in conventional therapy for non-dialysis patients in Japan (82.4% and 82.4%, respectively)<sup>[55]</sup>. Although this suggests that AMPC-reduced triple therapy is effective and safe for HD patients<sup>[55,69,70]</sup>, the sample number of these reports is small, and it is necessary to set an optimal regimen in

HD using a larger number of subjects.

Although the eradication rate with the Japanese standard triple therapy was first reported as approximately 85%-91%, it has gradually decreased year by year because of increased prevalence of CAM-resistant strains of *H. pylori*. Because the eradication rates with tailored treatments based only on CAM susceptibility are not very high (71.9%-94.3%), more advanced tailored treatment considering other factors (*e.g.*, different doses of antibiotics and PPIs, different dosages and treatment period) are required to achieve high eradication rates. A tailored *H. pylori* eradication regimen based on CAM susceptibility and maintaining acid secretion (rabeprazole, 10 mg, q.i.d.) is useful because it can achieve an eradication rate exceeding 95%, irrespective of eradication history, thus overcoming differences among CYP2C19 genotypes<sup>[52]</sup>. However, there was no report to investigate efficacy of tailored regimen in HD patients.

## H. PYLORI INFECTION AND NUTRITION STATUS IN HD PATIENTS

HD patients have many risk factors that affect mortality, such as chronic inflammation and metabolic and nutritional derangement<sup>[16,17,71]</sup>. PEW is defined as a state of decreased body stores of protein and energy fuels (body protein and fat mass) and is diagnosed if three features are present: (1) Abnormal nutrition markers (*i.e.*, low serum levels of albumin, transthyretin or cholesterol); (2) reduced body mass (*i.e.*, low or reduced body or fat mass or weight loss with reduced intake of protein and energy); and (3) reduced muscle mass (*i.e.*, muscle wasting or sarcopenia, and reduced mid-arm muscle circumference)<sup>[72]</sup>.

Ghrelin, an orexigenic peptide released primarily from endocrine cells in the stomach, is important in the pathogenesis of PEW in HD patients<sup>[71,73,74]</sup>. Ghrelin has multiple functions, including enhancement of the orexigenic effect, protein anabolism, anti-inflammatory action, and cardiovascular protection<sup>[74,75,76]</sup>. Plasma ghrelin levels increase after fasting and decrease after eating. Ghrelin levels are elevated in patients with a lean body<sup>[77]</sup>. Plasma ghrelin levels have been found to be associated with malnutrition in patients with advanced-stage cancer and anorexia nervosa<sup>[76]</sup>. In HD patients, a low ghrelin level increases the risk of cardiovascular mortality and morbidity<sup>[78]</sup>, and the utility of monitoring plasma ghrelin at fixed intervals has been proven as a biomarker for mortality in HD patients<sup>[71]</sup>.

*H. pylori* infections affect ghrelin levels. *H. pylori*-positive patients have lower gastric mucosal and plasma ghrelin levels and a smaller population of ghrelin-positive cells in the gastric mucosa<sup>[79]</sup>. Although subjects with normal renal function show a correlation between plasma ghrelin level and the severity of gastric mucosal atrophy<sup>[79]</sup>, the association between ghrelin and *H. pylori* infection and between ghrelin and gastric

**Table 2** *Helicobacter pylori* eradication therapy for chronic renal failure patients

Year	Author	Country	n	Regimen	Treatment period	Eradication rate (%)	Analytic methods
1997	Tamura <i>et al</i> <sup>[61]</sup>	Japan	14	LPZ (30) oid/ 8 wk, AMPC (500) oid/ 3 wk, plaunotol (80) tid/ 24 wk	21 d	78.6	RUT, Culture, Histology
1998	Munos de Bustillo E <i>et al</i> <sup>[30]</sup>	Spain	23	OPZ (20) bid, AMPC (500) tid	14 d	60.8	UBT
			23	plus OPZ (20) bid, CAM (500) bid	14 d	82.6	
1998	Tokushima <i>et al</i> <sup>[62]</sup>	Japan	17	LPZ (30) oid/ 8 wk, AMPC (500)	21 d	76.5	RUT, Culture, Histology
			10	LPZ (30) oid, AMPC (250), MNZ (250) bid/	7 d	90	
1999	Araki <i>et al</i> <sup>[63]</sup>	Japan	17	OPZ (20) oid/ 8 wk, AMPC (250) oid, CAM (200) oid/ 3 wk, polaprizinc (0.5) bid/ 24 wk	21 d	88.2	IgG, Histology
1999	Gur <i>et al</i> <sup>[11]</sup>	Turkey	25	FAM (40) oid, CAM (500) bid, MNZ (250) bid	15 d	80	Histology, RUT
2001	Wang <i>et al</i> <sup>[64]</sup>	China	38	OPZ (20), AMPC (1000), CAM (500) bid	7 d	86.8	Stool
2002	Mak <i>et al</i> <sup>[91]</sup>	China	21 (CRF)	OPZ (20), AMPC (1000), CAM (500) bid	7 d	90.5	RUT
2002	Tsukada <i>et al</i> <sup>[65]</sup>	Japan	39	OPZ (30) bid, AMPC (500) tid, CAM (400) bid	7 d	82.1	UBT
2003	Mak <i>et al</i> <sup>[92]</sup>	China	25 (CRF)	OPZ (20) or LPZ (30), AMPC (1000), CAM (500) bid	7 d	96	Histology
			38 (CRF)	LPZ (30), AMPC (750), CAM (500) bid	7 d	76.3	
2003	Sheu <i>et al</i> <sup>[67]</sup>	China	40 (CRF)	LPZ (30), CAM (500), MNZ (500) bid	7 d	92.5	Stool
2004	Sezer <i>et al</i> <sup>[4]</sup>	Turkey	17	OPZ (20), AMPC (1000), CAM (500) bid/	14 d	94.1	Endoscopy
2007	Tseng <i>et al</i> <sup>[93]</sup>	China	34 (CRF)	ESO (40) or OPZ (20) bid, AMPC (1000) bid, CAM (500) bid	7 d	94.1	UBT
			11	LPZ (60), AMPC (750), CAM (400)	7 d	72.7	RUT
2007	Itatsu <i>et al</i> <sup>[69]</sup>	Japan	9	LPZ (60), CAM (400)	7 d	33.3	
2010	Change <i>et al</i> <sup>[70]</sup>	Korea	12	OPZ (20), AMPC (250), CAM (250), bid	7 d	83.4	RUT, Histology
2010	Jalalzadeh <i>et al</i> <sup>[94]</sup> , Falaknazi <i>et al</i> <sup>[95]</sup>	Iran	37	OPZ (20), AMPC (1000), CAM (250), bid	14 d	81.1	IgG, UBT, Stool
2012	Seyyedmajidi <i>et al</i> <sup>[96]</sup> , Jalalzadeh <i>et al</i> <sup>[97,98]</sup> , Vafaeimanesh <i>et al</i> <sup>[99]</sup>	Iran	17	OPZ (20), AMPC (500), CAM (250), bid	14 d	82.4	UBT, Stool
			20	OPZ (40), AMPC (500), azithromycin (250), bid	14 d	80	
2014	Makhlough <i>et al</i> <sup>[100]</sup>	Iran	21	PPZ (40), AMPC (500), CAM (250), bid	14 d	66.7	RUT, Histology
			24	Sequential therapy (PPT [40] 10 d, AMPC (500) bid, 5 d and CAM (250), tinidazole (500), bid, 5 d	10 d	84	
2016	Makhlough <i>et al</i> <sup>[101]</sup>	Iran	20	PPZ (40), AMPC (500), CAM (500), bid	14 d	70	RUT, Stool
			20	Hybrid regimen PPZ (40), AMPC (500), bid, 7 d + PPZ (40), AMPC (500), CAM (500), tinidazole (500), bid, 7 d	14 d	100	
2018	Sahara <i>et al</i> <sup>[55]</sup>	Japan	18	ESO (20), AMPC (750), CAM (200) bid	7 d	77.8	IgG
			19	ESO (20), AMPC (250), CAM (200) bid	7 d	84.2	

AMPC: Amoxicillin; CAM: Clarithromycin; ESO: Esomeprazole; FAM: Famotidine; LPZ: Lansoprazole; MNZ: Metronidazole; NA: Not available; OPZ: Omeprazole; PPZ: Pantoprazole; RUT: Rapid urease test; UBT: Urea breath test; bid: Twice-daily dosing; tid: Three-times-daily dosing.

mucosal atrophy in HD patients is less well understood. In an analysis using 78 HD patients and 51 non-dialysis patients with chronic renal disease, des-acyl ghrelin levels in HD patients were significantly higher than those in non-dialysis patients, and ghrelin levels decreased with the progress of endoscopic gastric mucosal atrophy in HD patients (Table 3)<sup>[19]</sup>. Importantly, acyl-ghrelin levels in the non-*H. pylori* infection HD group (39.4 ± 23.0 fmol/mL) were significantly higher than in patients with current (24.6 ± 17.5 fmol/mL, *P* = 0.022) and past *H. pylori* infection (23.4 ± 19.9 fmol/mL, *P* = 0.007) (Table 4)<sup>[18]</sup>, suggesting that the severity of serological and endoscopic gastric mucosal atrophy is a major determinant of ghrelin levels (Table 3). In fact, multiple regression analysis shows a significant positive correlation between acyl ghrelin and PG I levels ( $\beta$  = 0.738, *P* < 0.001) and significant negative correlations between ghrelin and age, albumin, and creatinine

levels<sup>[19]</sup>. Therefore, PG level is the most influential determinant of plasma acyl and des-acyl ghrelin levels in HD patients. This suggests that plasma and gastric mucosal ghrelin levels are influenced by not only long-standing enhanced gastric mucosal inflammation induced by *H. pylori* infection but also by gastric mucosal atrophy<sup>[79]</sup>. Because plasma and gastric ghrelin levels depend on the number of ghrelin immunoreactive cells in the gastric mucosa<sup>[79-81]</sup>, plasma ghrelin levels may be influenced more by the severity of atrophy than current *H. pylori* infection in HD patients. Therefore, it is important to consider methods to prevent progression of gastric mucosal atrophy in HD patients.

HD patients with gastric mucosal atrophy have a lower normalized protein catabolic rate (nPCR) than non-atrophy patients<sup>[19]</sup>. Chronic persistent damage to the gastric mucosa and gastric mucosal atrophy in *H. pylori*-positive HD patients may contribute to

**Table 3 Clinical characteristics in hemodialysis patients between patients with and without gastric mucosal atrophy<sup>[19]</sup>**

	Atrophy (-)	Atrophy (+)	P-value
N (Male/Female)	28 (17/11)	50 (33/17)	-
Age	67.7 ± 12.3	71.6 ± 11.0	0.155
Dialysis periods (yr)	7.5 (2.4-16.8)	7.7 (3.1-12.7)	0.681
Acyl-ghrelin	38.0 (23.5-57.0)	18.0 (12.0-26.3)	< 0.001
Desacyl-ghrelin	303 (248-533)	200 (137-277)	< 0.001
BMI (kg/m <sup>2</sup> )	19.8 ± 3.2	19.6 ± 2.8	0.773
Albumin (g/dL)	3.5 ± 0.3	3.4 ± 0.4	0.273
Total cholesterol (mg/dL)	166 ± 37	154 ± 36	0.165
Cholinesterase (U/L)	245 ± 111	219 ± 68.7	0.205
Intact PTH (pg/mL)	351 ± 294	247 ± 192	0.062
Ferritin (ng/mL)	128 ± 118	128 ± 221	0.989
PG I (ng/mL)	416.2 (314.2-783.7)	196.0 (73.8-358.8)	< 0.001
PG II (ng/mL)	42.3 (31.6-60.0)	28.4 (16.8-45.7)	0.003
PG I / II ratio	10.89 (9.11-13.38)	7.31 (4.17-11.08)	0.001
nPCR (g/kg/d)	0.94 ± 0.14	0.85 ± 0.16	0.022

BMI: Body mass index; BUN: Blood urea nitrogen; PTH: Parathyroid hormone; CRP: C-reactive protein; PG: Pepsinogen; ABI: Ankle-brachial pressure index; nPCR: Normalized protein catabolic rate.

**Table 4 Plasma acyl-ghrelin and desacyl-ghrelin levels according to *Helicobacter pylori* status in hemodialysis patients<sup>[18]</sup>**

	Non-infection (n = 29)	Past-infection (n = 27)	Present infection (n = 17)
Plasma acyl-ghrelin (fmol/mL)	39.4 ± 23.0	23.4 ± 19.9 <sup>a</sup>	24.6 ± 17.5 <sup>a</sup>
Plasma desacyl-ghrelin (fmol/mL)	353.2 ± 190.2	242.1 ± 139.6 <sup>a</sup>	236.3 ± 143.6 <sup>a</sup>

<sup>a</sup>P < 0.05 vs Non-infection group.

decreased protein intake, PEW, and decreased body weight *via* decreased ghrelin production. Because ghrelin level is associated with mortality related to cardiovascular disease and PEW in HD patients, alternative management, such as *H. pylori* eradication therapy, before the progression of gastric mucosal atrophy might be necessary to prevent the decrease in ghrelin level in HD patients<sup>[74,78]</sup>.

## H. PYLORI ERADICATION THERAPY AND NUTRITION STATUS IN HD PATIENTS

*H. pylori* infection affects the incident rate of gastro-duodenal disease and nutritional status<sup>[20,25]</sup>. *H. pylori* eradication therapy often causes individuals with normal renal function to develop hyperlipidemia and hyperproteinaemia, along with an increase of body weight and BMI<sup>[80]</sup>. This phenomenon is considered to be due to increases in plasma ghrelin level followed by increased appetite and food intake after *H. pylori* eradication therapy<sup>[82,83]</sup>. In CAPD patients, *H. pylori* eradication therapy significantly improves anorexia, inflammation, and malnutrition<sup>[84]</sup>. After *H. pylori* eradication, CAPD patients with anorexia showed a significant increase in markers of nutrition and in VAS scores for almost all questions. Significant differences were also found in lymphocyte count, nPCR, prealbumin, albumin, CRP, before-lunch desire to eat, after-lunch desire to eat, hunger before lunch, hunger after lunch, fullness before lunch, consumption after lunch, and

palatability<sup>[85]</sup>. However, it is unclear whether nutritional disorders in HD patients improve after eradication therapy. It is important to answer this clinical question to improve the poor prognosis in HD patients.

At 1 year after eradication therapy, serum cholinesterase levels significantly increase compared with the level before eradication (303.2 ± 76.0 vs 287.3 ± 68.1 IU/L, *P* = 0.029). In particular, cholesterol (before, 196.6 ± 23.2 mg/dL; after, 206.1 ± 25.9 mg/dL, *P* = 0.042) and cholinesterase levels (before, 296.9 ± 70.8 IU/L; after, 316.4 ± 73.8 IU/L, *P* = 0.049) increase more in patients with mild-moderate gastric mucosal atrophy than in those with severe atrophy. This observation suggests that eradication therapy has contributed to improvement of PEW in HD patients. We therefore recommend that HD patients be checked for *H. pylori* infection and that eradication therapy should be initiated before the progression of gastric atrophy.

It is possible that the improvement in nutritional status and increase in BMI after eradication therapy depends not only on an increase in ghrelin levels but also on another biological mechanism(s), such as an improvement in gastrointestinal motility<sup>[86]</sup>, change in gut microbiome profile<sup>[87]</sup>, and/or increase in absorption ability<sup>[88]</sup>. Betrapally *et al.*<sup>[87]</sup> reported that alterations to the intestinal microbiota affect the development of nonalcoholic steatohepatitis by influencing digestion, development of obesity, immune response, and production of gut hormones. *H. pylori* eradication therapy changes the gastrointestinal microbiota<sup>[89]</sup>. A study to examine

whether the long-term prognosis of HD patients is improved by the effect of eradication therapy on the microbiota will be required to investigate this hypothesis further.

## H. PYLORI AND ANEMIA IN HEMODIALYSIS PATIENTS

*H. pylori* has been identified as a possible cause of vitamin B12 and iron deficiency in the general population. Trimarchi *et al*<sup>[90]</sup> reported that *H. pylori*-positive HD patients may present with lower vitamin B12 blood levels and that *H. pylori* should be suspected in HD patients when low or low-normal vitamin B12 levels or macrocytosis exist.

## CONCLUSION

Chronic renal failure patients receiving HD have a low prevalence of *H. pylori* infection. More than one-third of patients receiving < 4 year of dialysis had naturally cured *H. pylori* infection within the 4 year observation period. However, because chronic renal failure patients have a higher risk of gastroduodenal disorders, all HD patients are recommended to receive endoscopic check-ups to reduce the chance of developing peptic ulcer disease. Moreover, patients with *H. pylori* infection should also receive eradication therapy including AMPC 250 mg twice daily to prevent peptic ulcer, gastric cancer, and hemorrhage from gastroduodenal lesions. QOL in HD patients is usually poor and affects their nutritional status. Severity of gastric atrophy is shown to be the major determinant of ghrelin levels in HD patients and eradication treatment of *H. pylori* improves nutrition status by increasing serum cholinesterase and cholesterol levels. *H. pylori* eradication before progress of gastric atrophy may be required to prevent a decrease in ghrelin levels and improve prognosis of HD patients in relation to poor nutritional status.

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