An update on *Helicobacter pylori* infection in renal failure patients

Mohammad Reza Ardalan¹, Saeed Mardani², Shahin Asgari-Savadjani², Mohamad Reza Tamadon³, Shirin Naghdifar⁴, Hamid Nasri⁵

¹Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran  
²Department of Internal Medicine, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran  
³Department of Internal Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran  
⁴Nickan Research Institute, Isfahan, Iran

**Abstract**

*Helicobacter pylori* (*H. pylori*) is a gram negative spiral rod bacterium which inhabits gastric mucosa and attaches to the gastric epithelium using specific receptor. *H. pylori* infection endures as one of the most challenging diseases triggering high mortality and morbidity. *H. pylori* infection is reported as the cause of gastric cancer, chronic gastritis, peptic ulcer and other gastrointestinal disorders. It was suggested that long-term *H. pylori* infection may aggravate chronic kidney disease (CKD) complications and cardiovascular disease (CVD) risk factors. Patients with chronic renal failure often possess gastrointestinal symptoms including decline of gastrointestinal motility, amyloid protein deposition and decreased sensory disturbance. Hence, in patients with chronic renal failure, the nutrition status is poor which usually leads to the development of malnutrition. This status will increase the morbidity and mortality of these patients. These patients in comparison to individuals with normal renal function usually have higher risks of gastric mucosal damage due to hypergastrinemia, enhanced inflammation, local chronic circulatory failure and high level of ammonia. Majority of these patients (25%–75%) usually suffer from gastrointestinal complications such as gastric erosions, gastrointestinal bleeding, peptic ulcers and angiodysplasia. The aim of the present study was to review the relation between one of the most challenging diseases, called *H. pylori* infection, and end-stage renal disease (ESRD), diabetic and chronic hemodialysis individuals as well as presenting the treatment strategies of this infection.

**Introduction**

*Helicobacter pylori* (*H. pylori*) is a gram negative spiral rod bacterium which inhabits gastric mucosa (1-4) and attaches to the gastric epithelium using specific receptor (5,6). *H. pylori* infection endures as one of the most challenging diseases triggering high mortality and morbidity (7,8). *H. pylori* infection is reported as the cause of gastric cancer, chronic gastritis, peptic ulcer and other gastrointestinal disorders (9-13). Then, bacterial infection is a basic problem in patients especially those who are hospitalized. Recently, several reports have been published reporting the relation of *H. pylori* infection and kidney failure especially chronic renal failure or diabetes diseases.

**Chronic renal failure and gastrointestinal**

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chronic renal failure, the nutrition status is poor which usually leads to the development of malnutrition. This status will increase the morbidity and mortality of these patients. These patients in comparison to individuals with normal renal function usually have higher risks of gastric mucosal damage due to hypergastrinemia, enhanced inflammation, local chronic circulatory failure and high level of ammonia. Majority of these patients (25%–75%) usually suffer from gastrointestinal complications such as gastric erosions, gastrointestinal bleeding, peptic ulcers and angiodysplasia (15). The aim of the present review paper was to review the relation between one of the most challenging diseases, called *H. pylori* infection, and end-stage renal disease (ESRD), diabetic and chronic hemodialysis individuals as well as presenting the treatment strategies of this infection.

Materials and Methods
This review article discusses recent findings on *Helicobacter pylori* infection in renal diseases. For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as chronic renal failure, end-stage renal disease, *Helicobacter pylori*, diabetic nephropathy, chronic kidney disease and hemodialysis.

*H. pylori* infection in ESRD patients
The relationship between *H. pylori* infection and ESRD events remains unknown. The risk of ESRD noticeably is increased in patients with *H. pylori* infection combined with at least one of the following concomitant comorbidities: diabetes, hypertension, hyperlipidemia and coronary artery disease (1). *H. pylori* infection is one of the main factors for dyspepsia and recently has been investigated for in end-stage its possible role in renal disease. Dyspepsia is a pain in the upper part of the abdomen which is a usual complication in chronic kidney disease (CKD) patients and dialysis patients (16). *H. pylori* infection was related to a subsequent risks of ESRD thus, it has been determined that *H. pylori*-infected patients with cardiovascular disease (CVD) or concomitant chronic kidney disease risk factors were at a higher risk of ESRD than those who had a single CVD or CKD risk factor. Hence, it was suggested that long-term *H. pylori* infection augments various complications of CKD and CVD risk factors, causing a decrease in renal function followed by ESRD, as noticed in the *H. pylori*-infected group (1). *H. pylori* also plays an important role on the aggravation of complications of chronic hemodialysis patients and its complications too (17).

*H. pylori* infection in diabetic nephropathy, hemodialysis and chronic renal failure patients
*H. pylori* infection is common in diabetics specially is higher in patients with type-2 diabetes mellitus compared to normal population. In this regard, a study was done but no significant relation was found amongst the serum *H. pylori* IgG antibody titer and magnesium levels and the age of patients, duration of diabetes and creatinine clearance. There was just a positive correspondence between *H. pylori* infection and serum magnesium. They confirmed that this correspondence might facilitate the colonization of *H. pylori* in the stomach of patients on hemodialysis but not in patients with various stages of renal failure who were not undergoing hemodialysis (18).

In studies, the value of serum *H. pylori* specific IgG antibody value could be applicable because it is as a sign of *H. pylori* infection although some authors did not find any significant difference of various biochemical parameters between females and males, diabetics and non-diabetics and serum *H. pylori* IgG antibody titer. But they found significant negative relation between serum magnesium and serum intact PTH levels and serum *H. pylori* IgG antibody titer. Otherwise, some investigators found a positive correlation between *H. pylori* infection and serum magnesium. In this regard, to understand the worsening factors of *H. pylori* infection in chronic kidney disease, particularly in hemodialysis patients, Hafizi et al conducted a study on 44 hemodialysis patients or other research on 94 type-2 diabetic patients. They found a significant positive relation of serum magnesium with *H. pylori* antibody. Thus, it seems the presence of an association of *H. pylori* infection with serum magnesium. It is clear that magnesium ion attainment is essential for *H. pylori* (19). In this regard, the high serum magnesium level in the gastric mucosa could facilitate the colonization of *H. pylori* in the stomach of patients on hemodialysis, but not in patients with different stages of renal failure that were not on hemodialysis (8, 19). Conversely, magnesium is mostly excreted by kidney and magnesium metabolism is interrupted in patients with chronic renal failure. Actually, elevated serum magnesium level can be an obstacle in patients on maintenance hemodialysis. Although, the kidneys are the major way of excretion of magnesium from the body, increased serum magnesium would be expected in hemodialysis patients and in patients with renal failure (19).

In the report of Hosseini et al, it was shown that the occurrence of *H. Pylori* infection in renal transplant patients and the normal population is the same (20). Lately, many evidences have shown that *H. pylori* is associated with extra-gastrointestinal diseases including idiopathic thrombocytopenic purpura, iron deficiency anemia and diabetes mellitus. Also, patients with chronic renal failure usually suffer from local or systemic chronic circulatory failure or both of them, high ammonia, hypergastrinemia and improved inflammation that facilitates *H. pylori* infection. Gu et al, investigated the association between infection of *H. pylori* and the different types of dialysis and then they found that *H. pylori* infection was not statistically related to hemodialysis specifically. So, their results showed that prevalence of *H. pylori* infection was similar between chronic renal failure (CRF) patients who were receiving dialysis and the control cluster with normal renal function. Some investigators, however, realized that the prevalence of *H. pylori* in CRF patients suffering dialysis was consid-
erably lower than in non-CRF controls without or with gastrointestinal symptoms (21-26). The fact is that the majority of CRF patients who receive dialysis inevitably have access to antibiotics, H2 receptor antagonists or proton pump inhibitors which then affect the H. pylori infection rate to some extent. Also, gastric atrophy progresses along with reduced secretion of acid in addition to higher levels of pro-inflammatory cytokines in CRF patients causing H. pylori infection difficult to survive (27,28).

Relation between H. pylori infection and urea concentration
H. pylori is known to change acid secretory physiology in patients with chronic infection. Subsequent acid hypersecretion and hypergastrinemia are key factors in the gastroduodenal lesions and pathophysiology of peptic ulcer disease in these patients and more evident in patients with ESRD. Therefore, detection and then treatment of gastroduodenal lesions are pretty important especially in preventing the complications after renal transplantation. Various investigations were conducted to investigate whether urea concentration or uremia in gastric secretion causes an appropriate environment for infection of H. pylori (29-33). However, on the other hand, other investigation have detected the frequency of H. pylori infection in uremia is 34%-47% and in kidney transplanted patients is 38%. Some studies have reported the frequency of H. pylori infection in patients with ESRD on hemodialysis is 34%-75% (34). The majority of patients with ESRD on hemodialysis experienced gastrointestinal discomfort. It is assumed that uremia can alter the bacterial colonization of the upper gastrointestinal tract and hence, reducing infection of H. pylori (35).

Relation between H. pylori infection and vitamin D level
25-hydroxy vitamin D (25-OH Vit D) is the main circulating metabolite of vitamin D even though the biologically active form of vitamin D is 1,25(OH)2 vitamin D, made in the kidney, it is generally accepted that the amount of circulating 25-OH vitamin D provides better information with respect to the patients vitamin D status and is used for the finding of hypovitaminosis. Generally, the presence of the vitamin D receptor shows that cells are responsive to vitamin D. Apart from enterocytes, osteoblasts and distal renal tubular cells, the vitamin D receptors is found in lots of other cell types, including parathyroid gland cells, colon cells, skin keratinocytes, ovarian cells and pituitary gland cells. The vitamin D receptor is also generally expressed in most cell types of the immune system, i.e., B cells, T cells, macrophages, monocytes, dendritic cells and NK cells. It has been detected that high blood urea nitrogen values could associated with a low occurrence of H. Pylori infection, and that patients on hemodialysis could be protected against this infection due to state of immune deficiency. We previously shown the influence of serum 25-hydroxy vitamin D levels on H. pylori infections in 36 patients with end-stage kidney failure on regular hemodialysis. The serum H. pylori specific IgG antibody values and serum 25-OH vitamin D level were assessed through an enzyme-linked immunosorbent assay (ELISA) method. The study patients were including 15 females and 21 males. The mean age of the study group was 47 (±17) years. The average level of serum 25-OH vitamin D was 0.5 ± 18.7 nmol/l (median: 3.5 nmol/l) whereas the average value of serum H. pylori specific IgG antibody titer was 7.7 (±9.9) U/mL (median: 2 U/mL). Thus an important positive association was obtained amongst the levels of serum 25-OH vitamin D and serum H. pylori specific IgG antibody titers (data adjusted for age, urea reduction rate, duration and dose of dialysis) (r = 0.36, P = 0.043). In this study, we suggested that vitamin D could positively affect the chronic inflammatory status of dialysis patients and could potentiate the immune response in such patients. According of this immuno-modulatory effect, vitamin D analogs could offer new means to control the inflammatory status in patients on upkeep dialysis (36). Moreover, in our another studies an inverse association of serum albumin with H. pylori IgG antibody level and dialysis efficacy as well as positive association of H. pylori IgG antibody level with the duration of hemodialysis treatment, were also detected which imply an inverse correlation of H. pylori infection with malnutrition and the resultant immuno-deficiency of hemodialysis patients (37-39).

H. pylori infection and kidney transplantation
Before the discovery of proton pump inhibitors and H2 blockers, usually the H. pylori infected disease would lead to serious complications following kidney transplantation. Therefore, in some centers, ulcer surgery was advocated before kidney transplant. Following the introduction and usage of ranitidine as ulcer prophylaxis following kidney transplantation, the number of serious kidney and upper gastrointestinal complications decreased substantially (40). Nowadays, H. pylori is accepted as a major etiologic factor in gastritis and gastroduodenal ulceration. During an acute rejection episode effective ulcer prophylaxis seemed to be important in patients regardless of their H. pylori status, especially in patients who were also receiving prophylactic aspirin treatment. Some centers have suggested that although H. pylori infections are common in kidney transplant patients, however these patients do not increase the risk of postoperative gastroduodenal complications (41).

H. pylori infection and anemia
Anemia is a constant finding in renal disease, affecting about more than 90% of patients, and the major role of anemia in the expansion of cardiovascular dysfunction is founded, anemia of ESRD could be accomplished relatively effectively by recombinant human erythropoietin. In this regard we previously conducted a cross-sectional study on maintenance hemodialysis patients. In this research was examined the aggravation of anemia by H. pylori on 39 patients with ESRD undergoing routine hemodialysis treatment. Average ages of patients were 46 (±18) years. All patients had dissimilar upper gastrointestinal
complaints including epigastric burning, epigastric pain, early satiety, postprandial fullness, bloating and belching. The duration of hemodialysis was 30 (±35) months (median: 18 months). Mean ± SD of hematocrit and hemoglobin level of all patients were 28 ± 6% (median: 29%) and 9 ± 2 g/dL (median: 9 g/dL) respectively. The rate of serum H. pylori particular IgG antibody titers of all patients was 7.6 (±9.9) U/mL (median: 2 U/mL). In this examination no significant difference of H. pylori IgG antibody level amongst females and males or diabetic and non-diabetic hemodialysis patients were seen. In this study in male cluster an important inverse relation amongst logarithm of H. pylori IgG antibody level and serum hematocrit and hemoglobin were understood. Furthermore, in this cluster an imperative inverse relation amongst logarithm of H. pylori IgG antibody level and serum iron were seen. Furthermore, no important relationship amongst serum H. pylori IgG antibody level and serum iron, hematocrit and hemoglobin in all patients, female, diabetic and non-diabetics hemodialysis cluster were perceived. In this research no important relationship amongst serum H. pylori IgG antibody level and serum ferritin in all clusters was seen. Thus, it was shown that presence of H. pylori infection is related to a poorer response to oral iron therapy which develops with treatment for H. pylori infection. In patients on regular hemodialysis could be shown an inverse relation amongst H. pylori infection with hematocrit and hemoglobin level in addition to with serum iron, implies further attention to infection of H. pylori in these patients which one their major problem is anemia, so aggravation of H. pylori infection with anemia needs aggressive treatment of H. pylori infection in study patients (42).

Diagnosis and treatment of H. pylori infection

H. pylori infection can be diagnosed with both noninvasive and invasive tests. Invasive tests include culture, histology and rapid urease test that require endoscopy to obtain biopsies of the gastric mucosa and noninvasive tests include analysis of samples of blood, stool or breath including urease breath test (UBT) and H. pylori stool antigen (HPSA). Noninvasive tests are beneficial for primary diagnosis, when a treatment sign previously exists, or to monitor treatment success or failure. They are also beneficial in patients who cannot tolerate endoscopy, children, and epidemiological population studies. These tests have been introduced as reliable tests to screen H. pylori infection until recently in patients with kidney failure (43). Amoxicillin (AMX) and clarithromycin (CAM) or metronidazole (MNZ) are still used for treating of H. pylori infection. However, the efficiency of legacy triple regimens has been really challenged, and they are progressively becoming ineffective. Moreover, some areas in Asia show patterns of emerging antimicrobial resistance. More effective regimens such as the bismuth and non-bismuth quadruple, sequential, and dual-concomitant (hybrid) regimens are now substituting standard triple therapies as empirical first-line treatments on the base of the understanding of the local prevalence of H. pylori antimicrobial resistance (44). The North American Society and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) proposed for first-line therapy including triple therapy with a proton pump inhibitor (PPI) and Imidazole or Clarithromycin and Amoxicillin; therapy with bismuth salt, Imidazole and Amoxicillin; or sequential therapy (45).

Conclusion

H. pylori is one of the most challenging diseases which is important for public health. H. pylori associates with ESRD, diabetic nephropathy and HD. Magnesium ion is essential for H. pylori to facilitate the colonization of this bacteria in the stomach of patients. However, urea concentration relates to H. pylori as well. Uremia can change bacterial colonization of the upper gastrointestinal tract and then reduces H. pylori infection. So, we should be aware of H. pylori infection and try to diagnose and treat this disease at least time.

Authors’ contribution

Searching the data conducted by SAS, SN and MRT. SN, SM and MRA prepared the primary draft. HN edited the manuscript. All authors read and sign the final paper.

Conflicts of interest

The authors declared no competing interests.

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