Review articles

An updated view: Pathogenicity of *Helicobacter pylori* microbial infection in chronic kidney disease and End stage kidney dysfunction (ESRD) under oxidative stress

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ABSTRACT

Helicobacter pylori is a Gram-negative, flagellated, microaerophilic bacterium, which particularly found in the human stomach. Pro- as well as anti-inflammatory cytokines along with oxidative stress is a crucial factor in the progress of peptic and gastric ulceration as well as gastric carcinoma in subjects having chronic *H. pylori* microbial infection. *H. pylori* eradication from gastrointestinal tract (GIT) is liable for neuroendocrine modification because of a stressful feedback of the host and is an indication for initiating growth and pathogenic progress in body organs. The importance of *H. pylori* infection to renal dysfunction under oxidative stress condition is still unclear and almost untouched area. In a recent research study, *H. pylori* infected patients with coexistence of chronic kidney infectious disease (CKD) and cardiovascular diseases risk factors may be at surpassing risk of end stage renal disease (ESRD). However, it is hardly known about the fact whether eradication of the bacteria has any consequence on renal function under oxidative stress condition or not. Therefore, the present study anticipated this review along with extra gastric *H. pylori* infection with progressive development of chronic kidney diseases and advancement to ESRD, under oxidative stress condition.

Keywords: Extra gastric infection; end stage renal disease; oxidative stress; *Helicobacter pylori*; genetic mutation; chronic ambulatory peritoneal dialysis.

INTRODUCTION

Helicobacter pylori microbes are affecting humans for more than 58000 years but noticed when cultured by the researchers (1). It was the first bacterial species validate to cause cancer and is characterized as a group I carcinogen through the International Agency authenticated for Research on Cancer (2) are the prominent cause of gastric intestinal tract (GIT) related irregularities. In the United States, the annual expense was estimated approximately $6 billion and death rate is documented as more than 700000 people worldwide with gastric related pathogenesis in relation of colonization. The extent of *microbial* pathogens gradually elevated (> 50%) worldwide, whereas, the infection ratio was found to be descending in some developed countries. This declining ratio could be more complicated as expanding the risk of some kind of allergies, extra gastric and esophageal diseases. Infection sustains as greatest denouncing problem provoking higher mortality and morbidity rate and compelled for the pathogenesis of gastric and peptic ulcer, carcinoma and lymphoma. Although the progress from chronic gastritis to other systemic disease remains, imprecise but oxidative stress might be responsible for higher growth of microbes and release of pro and anti-inflammatory cytokines that critically play a role in the expansion of diseases. Expanding data explains that some extra-gastric problems including chronic idiopathic urticaria, iron deficiency anemia and idiopathic thrombocytopenic purpura (ITP) are also linked with *H. pylori* pathogenesis (3). This infection is the maximum reported prominent factor for dyspepsia in various research studies and a well-known reason for this discontent in end-stage renal disease (ESRD) patients. The expansion of diseases is probably growing and being noticed every day. However, realistic theory of extra gastric diseases in relation with *H. pylori* is still unclear and not much research has been done on this issue.

The focus and attention nowadays are on the correlation between microbial infection and chronic renal dysfunctions under oxidative stress are being studied. Researchers have concluded in their research studies that gastric and extra-gastric *H. pylori* infections play a remarkable role in the advancement of systemic disease mainly renal dysfunction and ESRD (4). However, other research studies have disputed, and altered results regarding the correlation between *H. pylori* microbes with kidney dysfunction. We therefore carried out a systematic evaluation, which encompassed all available information to confirm the prevalence of *infection* in kidney dysfunction and ESRD patients under high oxidative stress condition.

Pathogenicity of oxidative stress and related hormones cause higher growth of microbes

Oxidative stress can lead to the increased microbial growth in the gastric mucosal cells progress to chronic inflammation and release of stress related hormones, which are fully shown in the immune system. However, it is a new angle that indicates that generated ROS and stress-related hormones affect the infectious microorganism itself or through the interaction between host and pathogen. Recent studies showed that the neuroendocrine alteration due to host stress reactions could exploit bacteria in either the gastrointestinal tract, respiratory tract or skin as alarm of growth and pathogenicity (5). In stress, clemency of sympathetic nervous nor-epinephrine hormone can improve intestinal motility, colonic transit and trans-epithelial transportation, by galvanizing the myenteric plexus, submucosa and mucosa. The microbial population migrates from the intestinal region to other parts of the body such as kidney, heart or lungs and can be influenced by any of these effects. As commensurate bacteria restrain pathogens colonization, therefore stress-induced alteration of intestinal microbiota may be having an impact on host vulnerability to pathogens. In addition, stress may change the permeability of the intestines and modulate epithelium lining to promote bacterial growth (6). Recently in a study, *H. pylori* infection has been reported to subsidize endothelial dysfunction directly linked to progression of chronic kidney disease and declining renal function (CKD) (7). An achievable system could therefore lead to the reduction of folate, vitamin B6, and vitamin B12 by the chronic *modulation* and consequently to the failure to produce 5-methyl-tetrahydrofolic acid and hence, induce hyperhomocysteinemia which can lead to toxicity to endothelial cells. It was also concluded in research study that microbes stimulate the level and progressive metabolic changes of asymmetrical dimethyl arginine (ADMA) (8). The progression of chronic oxidative stressors, interstitial and glomerular fibrosis is closely related to endothelial impairment and advancement of CKD may be because of increased plasma ADMA levels (9). In type 2 diabetic subjects with chronic *H. pylori* microbial infections, researcher evaluated the relationship of intima-media thickened carotids (CIMT) to kidney impairment recently. Chronic infection was suggested to result in high levels of CIMT, symbiotic effect in type 2 diabetic population, as well as significant proteinuria, lipid metabolic disturbances and higher levels of inflammatory cytokines in serum (10).

Oxidative stress induced by itself

Tissue necrosis due to oxidative stress could be a generous cause of high MDA level. Furthermore, a close relationship has been observed between raised plasma MDA, nitrogen oxide levels and gastric histopathology and strains (11).

In a study, data have confirmed that microbial pathogens in infected host cells are dominant to epithelial injury and activate accumulated oxidative stress, and reactive oxygen species (ROS; 12). In addition, a notable oxidative stress and ROS have been released via excited phagocytic leukocyte cells that enter into the gastric cells during infection and proinflammatory cytokines also released by immune cells favor the release of higher amount of ROS (13). Decreased vitamin C level is also correlated to promote a pro-oxidative environment during *H. pylori* infection (14). Growth of microbes has already been announced for accelerating the expression and activity of enzyme spermine oxidase, which oxidizes polyamines and released hydrogen peroxide into the epithelial cells (15). These reports focused and stated that high *H. pylori* stimulate higher intracellular ROS indifferent cellular epithelial layers.

In other research studies, the gastritis pathogenesis via lipid peroxidation reactions was observed but there was no any correlation found with infection in these cases (16). Scientists also concluded that Cag A is, however, consistent with antioxidant expression associated with. Further, after exposure to the strains of CagA (+), total SOD activity has increased and is not greatly increased with exposure to the strains of CagA (-) (17). Studies have shown that the use of ethanol leads to increased oxidative stress, lipid peroxides, and free radicals significantly (18). In addition, binge ethanol administration intensifies endogenous lipid peroxidation significantly, and has reinforced *in vitro* lipid peroxidation susceptibility. Scientists also observed that infection is directly correlated with higher oxidative stress with significantly reduced serum nitric oxide and low glutathione levels and significantly higher serum malondialdehyde (MDA), catalase and superoxide dismutase (SOD) in subjects as correlated with normal controls in a research study (19).

Bacterial infection may cause kidney failure under oxidative stress

Bacterial infection is a basic problem in kidney failure patients mainly those who are hospitalized. Recently, published reports explain the correlation ship between higher growth of and kidney disorders. Dyspepsia is a prevalent disorder in a chronic kidney disease (CKD), preferably in routine dialysis subjects that disturb the normal and valuable lives of patients (20). *H. pylori* infection is a prominent and most stated factor for

dyspepsia that has been documented in end-stage renal disease (ESRD). However, generally seen as an extracellular microorganism but it can penetrate the plasma membrane of epithelial cells, and multiply indoor double-layer vesicles. The autophagic vesicles generated through are considered as the site of replication, and their fusion with lysosome degrades the replicated bacteria (21). The amplification of inside the cell equips a groove for antibacterial remedy resistance and has a convincing impact on its life cycle. Therefore, patients having chronic renal dysfunction repeatedly besides pathological gastrointestinal problem might be because of *H. Pylori* infection. These patients have symptoms like elevated urea levels, impaired gastrointestinal motility, amyloid protein displacement and reduced neural interruption (22). Infection is being analyzed as an extensive reason for gastric oxidative stress in dialysis patients. Although, it is obscure that elevated growth of *H. pylori* microbes is directly responsible for progressive renal failure or in prediction of advance kidney dysfunction. Previous research studies could not establish any correlation of *H. pylori* infection with chronic renal failure. History shows that the persistence of *H. Pylori* infection in hemodialysis patients decreases as dialysis proceeds, particularly in the first four years, following treatment. Besides, naturally eliminating infectious microbes is very hard and found for a long time in patients receiving dialysis.

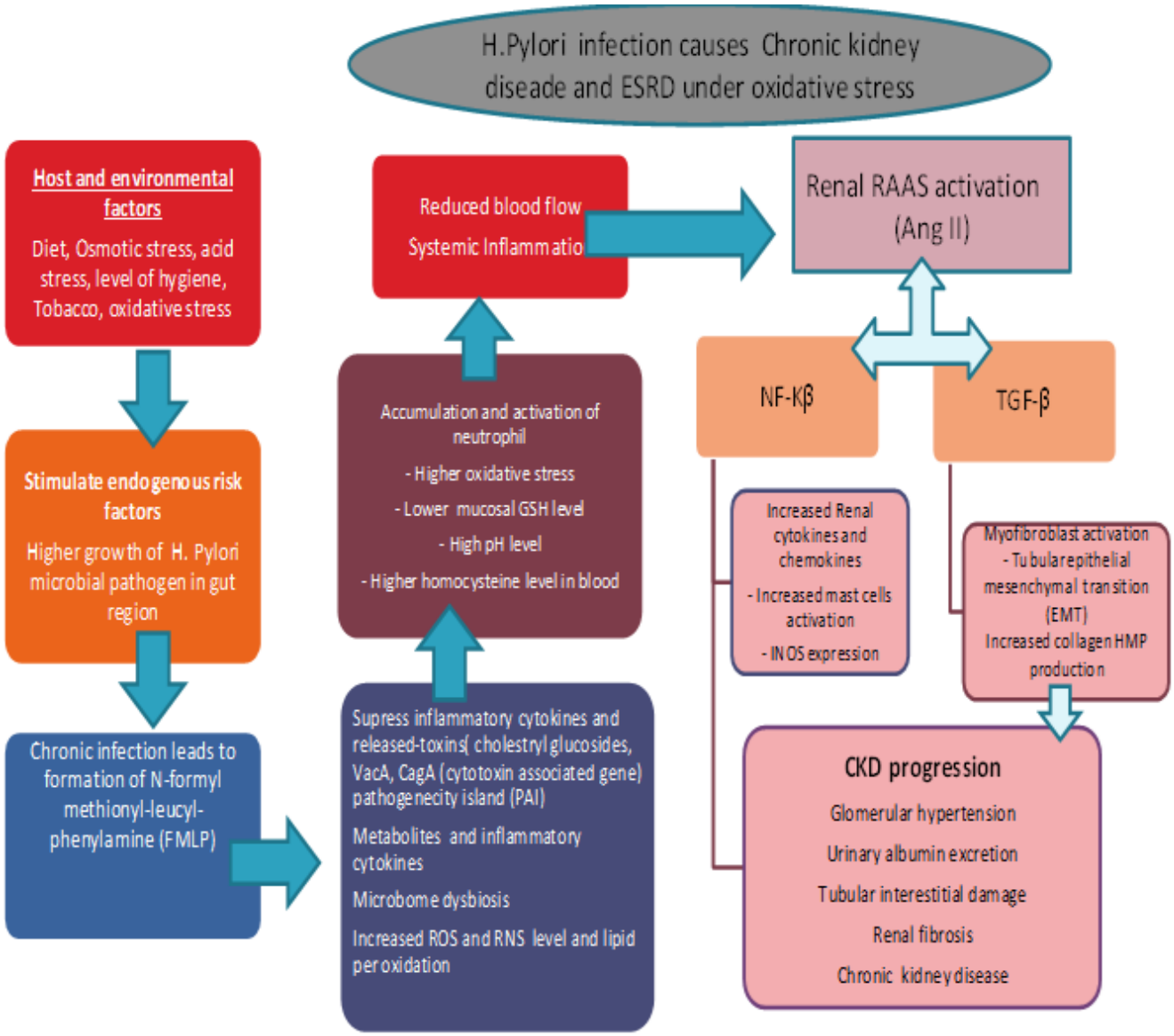

Table 1: The cross-sectional studies done in association with infection and ESRD

Sl. No.	Researcher, Year and country	Level of analysis	Study sample	Prevalence in cases of ESRD	
				Controls	Dialysis
1.	Shousha *et al.,* (29) United Kingdom 1990	Histology	Dialysis	51/120 (42%)	12/50 (24%)
2.	Gladziwa *et al.,* (26) Germany 1993	Cumulative evaluation (urease test, histology, culture and direct)	HD	Not given	12/35 (34%)
3.	Jaspersen *et al.,* (35) Germany 1995	Urease test and histology	HD	47/127 (37%)	7/34 (21%)
4.	De Vecchi *et al.,* (36) Italy 1995	Antibody	HD and PD	29/40 (72%)	37/67 (55%)
5.	Fabrizi *et al.,* (25) United States 1999	Antibody	HD	84/158 (53%)	127/228 (56%)
6.	Gür *et al.,* (45) Turkey 1999	Urease test and histology	HD	24/44 (54%)	25/45 (56%)
7.	Nakajima *et al.,* (34) Japan 2002	Urease test, histology, and culture	HD	25/45 (56%)	14/51 (28%)
8.	Khedmat *et al.,* (38) Iran 2007	Urease test	HD	106/305 (35%)	46/73 (63%)
9.	Sugimoto *et al.,* (27) Japan 2009	Antibody	HD	314/400 (79%)	262/539 (49%)
10.	Asl*et al.,* (4) Iran 2009	Histology	HD	28/40 (70%)	23/40 (58%)
11.	Genç G *et al.,* (47) Turkey 2013	Antibody	HD and PD-children	6/27 (22%)	16/27 (51.5%)
12	Chang *et al.,* (46) Taiwan 2014	Urease test and histology	ESRD	63/144 (43.7%)	81/144 (56%)

Increased level of infection may cause End-stage renal disease (ESRD)

Documented data confirm that near about 60 percent of the world community is populated with infectious agent (23). The epidemiological data related to infection in kidney dysfunctional patients are questionable. The documented data shows the frequency of microbes with renal failure patients found between 21-64% (24). Even though no scientific theory demonstrates that *H. pylori* microbial infection is related with renal disease directly. In extension, systemic infectious growth and modification in renal resistance index was notified in few research studies (25). Characterization of features of *infection* have disclosed relatively same findings in ESRD and non-numeric subjects by a few researchers. There are different interpretations for the variable prevalence. Some scientists paid attention on the greater concentration of urea in the gastric secretion of kidney dysfunctional patients, which is directly responsible for increasing gastric pH, and maintain sufficient amount of substrate for rapid growth of (26). While higher urea level in ESRD patients might be responsible for slow development and lower prevalence of microbes in these patients (27). Besides this, variation and fluctuation in the gastrointestinal blood supply reduced gastrointestinal motility, and hypo as well as hyperchlorhydria have been suggested for increased mortality rate of infection in the uremic subjects (25). In a research study, 26% of the population of was reported as having incidence of symptoms and complain of dyspepsia in chronic ambulatory peritoneal dialysis (CAPD) (28). Although very few researchers compared their findings with healthy controls and concluded that the rate of infection in peritoneal dialysis has declined in patients compared to healthy controls. In the past few years there have been regular reports identifying lower frequency of infection in kidney dialysis patients (29). These conflicting results could be based on a variety of other factors such as detection methods, the number of test patients, and the local impact on the healthy controls of the organism. The incidence of concentrations was considerably lower in hemodialysis (HD) cases in Japan in comparison of healthy peoples, however, it was found to increase over longer time when reanalyzed in a recent cross-sectional research study in 539 hemodialysis cases (27). Specifically, in this study, scientists presented three overviews: 1) Urea nitrogen

levels were elevated in the gastric secretions in dialysis patients than normal controls as higher urea concentration inhibit population in stomach. 2) May be reduced considerably and destroyed during the treatment of antibiotics as higher levels of antibiotics are commonly prescribed for patients during kidney-referenced problems. 3) Higher levels of acute phase proteins such as interleukin-1b, 6, 8 and tumor necrosis factors released from infected mucosal cells, and in filtering the gastric cells in patients who are receiving dialysis. As a result, the stomach cells atrophy steps at increased pH, and in this altering state of stomach mucosal cells, cannot survive (30). Results of a research study in 2017, summarized 35 cross-sectional studies and explained the existence of a lower population in patients with a pooled RR of 0.77 (95% CI: 0.59, 1.00) compared to the non-ESRD group (31). The meta-analysis tabulated by other researchers also showed a decrease of 0.57 RR (95 percent CI: 0.33, 1.00) *microbial* growth in patients with kidney transplant, especially in countries of high and middle incomes (32).

Prevalence of *H. pylori* infection in patients with renal dysfunction receiving dialysis and CAPD

Globally, more than 1.1 million patients with renal dysfunction are being treated for hemodialysis and this proportion is rising by 7% per year, as better dialysis technology in the medical sciences has been advanced nowadays (33). The correlation between chronic renal failures under oxidative stress in presence of microbial infection is very limited and contradictory, and this issue is yet to be explored by research. Scientists recently found a statistically significant frequency of infection (27%) in hemodialysis patients when compared with non-hemodialysis chronic renal failure (56%; 34). No correlation was found in patients getting hemodialysis treatment for less than a year when compared with healthy controls in another research study (27). In all of these studies, scientists have explained that the treatment of hemodialysis could be an important sign of low prevalence. Eight different studies conducted previously shown reduced levels of *H. pylori* colonization in patients receiving hemodialysis (22.2%) as compared with normal controls in different countries (Table1).

An additional study found that in individuals receiving CAPD was reduced (20%). Whereas, in a combined meta-analysis, the concentration of *H. pylori* in chronic hemodialysis and CAPD patients, analyzed as 43.9% ([95% CI: 42.2–45.6%], 1435/3 272) and 34.8% ([29.6–40.2%], 113/325), respectively, which is reduced in comparison to controls either healthy controls or having some impaired gastric manifestation (49.8% [48.0–51.7%], 1476/2961, $P < 0.001$) (34-37). Another research study conducted in Iran, stated that Iranian patients receiving hemodialysis showed a significant rise of infection (63.0 %) and chronic renal failure (66.2%; 38). The frequency of infection in Asian countries is significantly lower with normal renal function tests (54% [50.9–57.1%], 560/1039: P > 0,001) and 44.5% ([95% CI: 41.5–47.6%]; 474/1065%) in patients with chronic hemodialysis (39). In other countries, like South Asia, Middle East and Europe, the prevalence of *H. pylori* microbial infection in difficult to correlate with healthy one. The risk of gastric mucosa cellular impairment may be higher in patients having higher infection with dialysis than in individuals with normal renal function through chronic systemic circulatory failure high ammonia levels and increased inflammation (36).

Relevance of *Helicobacter pylori* infection in ESRD patients and impact of treatment

Microbial infection has a remarkable attachment with chronic renal failure and hemodialysis in numerous ways: 1) are responsible for the advancement of gastric and esophago-gastroduodenal erosions, and anemia. 2) It accumulates in epigastric cellular inflammation therefore may create pathological conditions like dyspepsia, anorexia, malignancies, and malnutrition in individuals and may have significant role in anemic patients (40). Increased concentration of serum gastrin is analyzed in patients with damaged renal function. The mechanisms for the hyper-gastrinemia suggested in such patients as reduced renal clearance of gastrin and the elevation in gastric G cell growth (41). It has been concluded that *in* the stomach play an imperative role in the elevation of serum gastrin concentration (42). However, scientific reports regarding the influence of infection on the serum gastrin concentration in patients with ESRD have been confined and the reports are altering. Researchers also reported that dialysis patients with *H. pylori* infection had prominently raised serum gastrin levels than those who were not infected (30), while other studies did not get any correlation (43). Furthermore, it was reported that fruitful eradication of using a combination therapy of amoxicillin, lansoprazole and plaunotol in dialysis patients, would persuade a significant low serum gastrin level (44). The restoration of normal gastrin levels was related with a distinct reduction in the gastric ammonia levels and pH value. Scientists suggested that *H. pylori* infection might be reason for hypergastrinemia in patients on dialysis (45).

CONCLUSION

In hospitalized patients, bacterial infection is a common issue. Microbes through specialized receptor cells create inflammation to gastric epithelial cells and remain element of chronic infection, and gastric

carcinoma development as responsible for generating oxidative stress. The relation of infection with extra-gastric pathogens is under oxidative stress that progresses to chronic kidney apoptosis and development of ESRD, which has been found in various research studies, and still research work is going on for the confirmation since altered results are also being reported. *H. pylori* infection is playing a crucial role in advancement of cellular inflammation therefore may create pathological conditions like dyspepsia, anorexia, malignancies, and malnutrition in individuals and may have significant role in initiation of kidney related disorders, anemia and heart related issues. Based on existing knowledge, the eradication and assessment of *H. pylori* in uremic patients should be considered in all patients with upper GI symptoms, and the effectiveness of controlled, scheduled clinical trials should be further analyzed. Furthermore, estimates of *H. Pylori* microbial concentration for all ESRD patients, regardless of symptoms, are to be considered.

Data availability

The data used to support the findings of this research study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

There is no conflict of interest for this study.

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