Helicobacter pylori infection and serum homocysteine in hemodialysis patient

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Abstract: Hyperhomocysteinemia is a factor that is found to be responsible for the development of atherosclerosis in the setting of chronic Helicobacter pylori (H. Pylori) infection. In the recent years, homocysteine (Hcy) has been demonstrated to be an important contributor to atherosclerosis. This study was undertaken to elucidate whether in patients with uremia on maintenance hemodialysis (HD), the infection of *H. pylori* affects the levels of Hcy. he patients were 39 HD ones with mean ages of 46±18 years. The time of hemodialysis were 30± (35) months (median: 18 months). The value of serum Hcy of all patients was 5 (±2) µmol/L (median: 4.5 µmol/L). The value of serum H. Pylori specific IgG antibody titers was 7.6 (±9.9) u/ml (median: 2 u/ml). In this study a positive correlation was found between serum homocysteine and *H. Pylori* infection. As elevation of serum Hcy is observed in the great majority (>85%) of patients undergoing maintenance dialysis, further research is needed to determine the importance of association between elevated serum homocysteine and *H. Pylori* infection. Furthermore, whether or not the treatment of *H. pylori* infection in HD patients can diminish serum homocysteine level should be elucidated.

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Introduction:

Helicobacter pylori (*H. pylori*) is a bacterium that causes infection in human stomach, and often leads to gastritis or peptic ulcer (1-3). Various data indicate a possible correlation between *H. pylori* infection and coronary heart disease (4-9). The link between *H. pylori* infection and hyperhomocysteinemia is a way to determine that this organism may be involved to the development of coronary diseases (10-13). Investigators have shown strong association between hyperhomocysteinemia and inadequate vitamin intake or insufficient vitamin concentrations in plasma, particularly vitamin B6, vitamin B12 and folate levels (14, 15). Several studies have shown that H. pylori infection has negative effects on serum vitamin B12 and folate levels (16-18). Metabolism of homocysteine (Hcy) involves a complex interaction between folate and vitamin B12 (19,22). It has been well established that chronic Helicobacter pylori infection causes gastritis (3,9,10) and decreased absorption of both folic acid and vitamin B12 has been established in patients with this condition (19-22). This study was designed to examine whether in patients with uremia on maintenance HD, the infection of H. pylori affects the serum level of Hcy.

Materials and Methods:

This cross-sectional study was conducted on patients under routin hemodialysis. The etiologies of renal failure were diabetic nephropathy, hypertension, various glomerular diseases, autosomal dominant poly cystic kidney disease (ADPKD) and also urinary tract infections (23-35). According to the severity of secondary hyperparathyroidism, each patient was treated with oral active vitamin D3 (Rocaltrol), calcium carbonate, and Rena-Gel capsules at various doses. According to the severity of anemia, patients were treated with IV iron therapy Iron Source (venofer) at various doses after each dialysis session. All

patients were under treatment with 6 mg folic acid daily, oral vitamin B-complex tablet daily. Also, 2000 U IV Eprex (recombinant human erythropoietin (rHuEPO) was given to each patient after each dialysis session routinely (35-37). All study patients had various upper gastrointestinal complaints consisting of epigastric pain, epigastric burning, post prandial fullness, early satiety, bloating and belching. Exclusion criteria for patients were using of proton pump inhibitors and antibiotics or taking aluminum hydroxide jells or having any active or chronic infection before the study. After an overnight fast, blood samples were collected. Serum homocysteine (total) was measured by enzyme-linked immunosorbent assay (ELISA) method using DRG kits (DRG Diagnostics, Berlin,Germany). Serum total Homocysteine (Hcy) has a normal range of 25-125 µmol/L. Serum H.pylori specific IgG antibody titer (titer >10 U/mL was interpreted as positive according to the kit) was measured by ELISA method using Trinity Biotech Kits (USA). For the efficacy (adequacy) of hemodialysis the urea reduction rate (URR) was calculated from pre-and post blood urea nitrogen (BUN) data (38). Body mass index (BMI) was calculated using the standard formula (post dialyzed weight in kilograms/height in square meters; kg/m²) (39). Duration and amount of hemodialysis were calculated from patients' records. The duration of each hemodialysis session was four hours. For statistical analysis, the data are expressed as the Mean ± SD and madian values. For correlations we used partial correlation test. For comparison between groups, student's t-test was used. All statistical analyzes were performed using SPSS (version 11.5.00). Statistical significance was determined at a p-value lower than 0.05.

Results:

The study was conducted on 39 (female=15, male=24) maintenance HD patients. Of 39 patients, 12 were diabetic. Mean age of patients was 46 (±18) years. The duration the patients were on HD was 30± (35) months (median: 18 months). The value of serum Hcy of patients was 5 (±2) µmol/L (median: 4.5µmol/L). Mean±SD of hemoglobin and hematocrit levels of all patients were 9±2 g/dL (median: 9 g/dL), and 28±6% (median: 29%), respectively. The value of serum H. pylori IgG antibody titer was 7.6 (±9.9) U/mL (median: 2 U/mL). Serum H. pylori antibody titer in the female and male groups were 5.9 (±8) U/mL (median: 2 u/ml) and 8.7 (±10.9) U/mL (median: 2 U/mL), respectively. In this study no significant difference of serum homocysteine and H. pylori IgG antibody level between male and female group or diabetic and non-diabetic HD patients were found (p>0.05). In non- diabetic group, a significant positive correlation between serum Hcy and anti H. pylori antibody level (r= 0.77, p=0.016) was found. Also, in male group also a significant positive correlation between serum Hcy and anti H. pylori antibody (r= 0.56, p =0.028) (adjusted for age and duration and amount of dialysis) was seen. No significant correlation between serum Hcy and H. pylori - IgG antibody in all patients, female group or diabetic HD groups was seen (p>0.05).

Discussion:

Uremia represent is associated with hyperhomocysteinemia (40-42). Hcy is a sulphur amino acid drived from methionine during transmethylation, and is either salvaged to methionine by a folate and cobalamin dependent remethylation reaction or directed toward degradation by the vitamin B6-dependent enzyme cystathionine β-synthase (41-43). Various studies have shown that moderate hyperhomocysteinemia is an independent risk factor for premature atherosclerosis and cardiovascular disease (40-43). Mild-to-moderate elevations in serum homocysteine levels are observed in the great majority (>85%) of patients with end-stage renal disease who are undergoing maintenance dialysis (43-46). Deficiency of vitamin B12 raises the serum and tissue levels of Hcy (47,48). Atrophic corpus gastritis results in impaired secretion of intrinsic factor and may lead to malabsorption of vitamin B12 in the intestine (49,50). In a study conducted by Aguilera et al. on 1313 peritoneal dialysis patients showed that infection with H. pylori was associated with anorexia, inflammation, and malnutrition in their patients (48). Eradication of H. pylori significantly improves this syndrome (49, 50). In our previous studies association of H. pylori infection with serum albumin and other nutritional parameters were shown (1, 2). To test the hypothesis that, chronic gastritis induced by Helicobacter pylori causes malabsorption of vitamin B12 and folate and lead to an increase in circulating Hcy level, Tamura et al. conducted a study on 93 patients who underwent diagnostic coronary arteriography (51). Study patients were divided into two groups according to the presence or absence of H. pylori infection. The study suggests that H. pylori - induced chronic gastritis decreases plasma vitamin B12 and folic acid levels, thereby increasing Hcy levels (51). In the study carried out by Sipponen et al. a low serum level of vitamin B12 that was associated with atrophic corpus gastritis in a sample of 12.252 men (age 51-

65 years) from two cites in Finland was found (47). Of these men, 72% (128 of 179 tested) had elevated Helicobacter pylori antibody levels. They concluded that low serum levels of vitamin B12 related to atrophic corpus gastritis is relatively common (prevalence 2.5%) among elderly male patients in the general population (47). To find, whether serum vitamin B12 levels in non-vitamin B12 deficient healthy adults correlate with serological evidence of H. pylori infection, Shuval-Sudai et al. studied 133 adults with a history of H. pylori eradication. They found that the higher prevalence of H. pylori infection among participants with serum vitamin B12 level within the lower end of the normal range, suggests a causal relationship between H. pylori infection and vitamin B12 levels in healthy adults (52). Hence, there is an association between Helicobacter pylori infection, reduced cobalamin absorption and cobalamin status. Consequently, elevated homocysteine levels, could offer an explanation why H. pylori infection is associated with coronary heart disease (53-67). However, in a meta-analysis study, testing10.000 patients, revealed no meaningful correlations between H. pylori and vascular risk factors (68). It is possible that homocysteine can directly cause endothelial damage (69-75), affect platelet function and coagulation factors (69), and increase the oxidation of low-density lipoproteins (76). Indeed in the light of these findings, a number of studies have focused on H. pylori infection as a possible cause of hyperhomocysteinemia in the general population. However, in HD patients other factors are also responsible for high serum levels of homocysteine (41,77). As noted above, in the present study we found a significant positive correlation betwee serum homocysteine and H. pylori infection. It has been well established that chronic H. pylori infection causes atrophic gastritis (1-5), and decreased absorption of both vitamin B12 and folic acid has been documented in patients with this condition (1-5). Patients with chronic H. pylori infection exhibited decreased secretion of ascorbic acid by the gastric mucosa and elevated gastric pH (78,79). It has been demonstrated that low levels of ascorbic acid in gastric juice or high pH of gastric juice could cause less folate absorption from the diet (80,81). Even in dyspeptic H. pylori - positive patients who do not exhibit gastric mucosal atrophy, complete eradication of H. pylori is associated with a significant drop in serum Hcy (65). Taken together, hyperhomocysteinemia is a factor that is suggested to be responsible for the development of atherosclerosis in the setting of chronic H. pylori infection (80,81). Homocysteine has been shown to be an important contributor to atherosclerosis as mentioned. Since in HD patients we also have hypermomocysteinemia,more researches are needed to determine the importance of this association in HD patients and whether or not treatment of H. pylori infection in hemodialysis patients can diminish serum homocysteine level.

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