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Original Article

The Influence of Serum 25-hydroxy Vitamin D Levels on Helicobacter Pylori Infections in Patients with End-Stage Renal Failure on Regular Hemodialysis

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ABSTRACT. This study was designed to determine whether the serum levels of 25-OH vitamin D influence the occurrence of infection with *Helicobacter Pylori (H.Pylori)* in patients on maintenance hemodialysis (HD). The study subjects were patients with end-stage renal disease who were undergoing maintenance dialysis at the hemodialysis section, Hajar Medical, Educational and Therapeutic Center, Shahrekord, Iran. The serum 25-OH vitamin D level and serum *H. Pylori* specific IgG antibody titers were measured using an enzyme-linked immunosorbent assay (ELISA) method. A total of 36 patients were studied including 21 males and 15 females. The mean age of the study group was 47 (± 17) years. The mean level of serum 25-OH vitamin D was 0.5 ± 18.7 nmol/L (median: 3.5) while the mean value of serum *H.Pylori* specific IgG antibody titer was 7.7 (±9.9) u/ml (median: 2 u/ml). Thus, a significant positive correlation was found between 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). Our study suggests that vitamin D may positively affect the chronic inflammatory status of dialysis patients and may potentiate the immune response in such patients. Because of this immuno-modulatory effect, vitamin D analogs may offer new means to control the inflammatory status in patients on maintenance dialysis.

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Introduction

Helicobacter pylori (H. pylori) was cultivated first from human gastric mucosa in 1983 [1] and, since then, has emerged as one of the most common chronic bacterial infections in the world, affecting about 40 and 80% of the

general population in developed and developing countries, respectively. [2] *H. pylori* has been shown to play an important role in the development of gastritis and gastric ulcer .[3,4] Dyspeptic symptoms and chronic gastritis are commonly seen in patients with chronic renal failure [5] and infection with *H. pylori* has also been described in patients on dialysis. [6] However, it is yet unclear whether the occurrence of *H. Pylori* infection in dialysis patients is due to altered gastric acidity, hyper secretion of gastrin, or increased colonization of the organism. [7,8] Numerous reports are available on the factors that influence *H. Pylori* infection in patients on hemodialysis (HD). In an earlier report, we had shown the influence of serum magnesium and secondary hyper parathyroidism on *H. Pylori* infection in HD patients. [9,10]

25-hydroxy vitamin D (25-OH Vit D) is the major circulating metabolite of vitamin D. [11] Although the biologically active form of vitamin D is 1,25 $(OH)_2$ vitamin D, synthesized in the kidney, it is widely accepted that the measurement of circulating 25-OH Vit D provides better information with respect to the patients vitamin D status and is used for the diagnosis of hypovitaminosis. [11-13] In general, the presence of the vitamin D receptor (VDR) indicates that cells are responsive to vitamin D. Apart from osteoblasts, enterocytes and distal renal tubular cells, the VDR is found in many other cell types, such as parathyroid gland cells, skin keratinocytes, colon cells, pituitary gland cells and ovarian cells. The VDR is also widely expressed in most cell types of the immune system, i.e., T cells, B cells, monocytes, macrophages, dendritic cells and NK cells. [14-17] It has been reported that high blood urea nitrogen levels may correlate with a low prevalence of *H. Pylori* infection, and that patients on HD may be protected against this infection because of immune deficiency. [18, 19]

This study was designed to determine whether the blood levels of 25-OH vitamin D influence infection with *H. Pylori* in patients on maintenance HD.

Patients and Methods

Patients

This cross-sectional study was conducted on patients with end-stage renal disease (ESRD), who were on maintenance HD; dialysis was performed using acetate bath dialysate and polysulfone membrane dialyzers in all patients. According to the severity of secondary hyperparathyroidism, each patient was given oral active vitamin D_3 (Rocaltrol), calcium carbonate, and Rena-Gel capsules at various doses. According to the severity of anemia, patients were given intravenous iron sucrose at appropriate doses after each dialysis session. All patients received, in addition, 6 mg folic acid, 500 mg L - Carnitine and oral vitamin B-complex daily, and also 2000 units of intravenous recombinant human erythropoietin (rHuEPO), given after each dialysis session.

The exclusion criteria for patients were the usage of drugs that affect gastric acid secretion and/or antibiotics as well as the presence of active or chronic infection before the study. The study was carried out at the HD section of Hajar Medical Educational and Therapeutic Center of Shahrekord University of Medical Sciences in Shahrekord, Iran.

Laboratory methods

The levels of serum 25-OH vitamin D (normal range is 25 to 125 nmol/L) and serum *H. Pylori* specific IgG antibody titers (titer >10 U/ml was interpreted as positive according to the manufacturer's instructions) were measured as follows: blood samples were drawn after an overnight fast, and were centrifuged within 15 minutes of drawing. The levels were measured by an enzyme-linked

Table 1. Mean ± SD and median values of age, duration on hemodialysis, and laboratory data of the study patients.

Total patients, N=36	**Mean ± SD**	**Median**
Age (years)	47±17	43
DH* (months)	32±36	19
Dialysis (Sessions)	123±54	156
URR (%)	59±9	57.5
25-OH Vit.D (nmol/l)	10.5±18.7	3.5
Alb (g/dl)	3.8±0.5	3.95
H. Pylri-IgG u/ml	7.7±9.9	2
BMI (kg/m^2)	22 ±4.4	21.5

DH=Duration on hemodialysis

immunosorbent assay (ELISA) method using standard kits. Also, peripheral venous blood samples were collected for biochemical analysis including pre and post-dialysis blood urea nitrogen (BUN) and serum albumin (Alb) levels using standard kits after an overnight fast.

Body mass index (BMI) was calculated using the standard formula (post-dialysis weight in kilograms/height in square meters). An assessment of the efficacy of dialysis was made by calculating the urea reduction rate (URR). The duration of each session and the number of sessions of dialysis each patient had received were obtained from the patients' records.

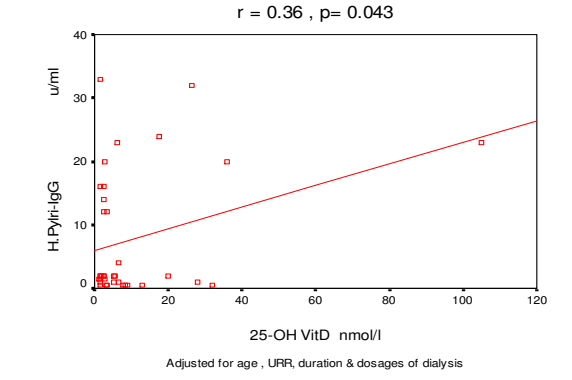

Figure 1. Significant positive correlation between serum 25-OH Vitamin D levels and serum helicobacter pylori specific IgG antibody titers.

Statistical analysis

The results are expressed as the mean ± SD and median values. A statistical correlation was assessed using a partial correlation test. All statistical analyses were performed using SPSS (version 11.5.00). The statistical significance was determined at a *p*-value < 0.05.

Results

The total number of patients involved in the study was 36 (Males = 21; Females = 15). Table one summarizes the patients' data. The mean age of the patients was 47 (± 17) years. The mean value of serum 25-OH vitamin D of the study patients was 10.5 ± 18.7 nmol/L (median: 3.5). The mean value of serum *H.Pylori* specific IgG antibody titer of the study group was 7.7 (± 9.9) u/ml (median: 2 u/ml). The correlation between the serum 25-OH vitamin D level and serum *H.Pylori* specific IgG antibody titer was statistically significant (data adjusted for age, URR, duration and doses of dialysis) (r=0.36 p=0.043; Figure 1).

Discussion

The recognition that various cell types carry the VDR has led to a wide array of studies on specific vitamin D functions unrelated to mineral metabolism. The exact mechanism by

which the activated form of vitamin D, 1,25-$(OH)_2D_3$, affects the immune system has not been elucidated, but it is clear that the immunomodulating properties are mediated at least in part by the VDR. [20-22] As mentioned above, the VDR is present in most cell types of the immune system, such as macrophages, dendritic cells and $CD4^+$ and $CD8^+$ T cells. [19-21] In these cell types, VDR ligands, such as vitamin D analogs, inhibit the expression of certain cytokines, namely, interleukin (IL)-2 in T cell lines, IL-12 in myelomonocytes, and IL-2, tumor necrosis factor (TNF)-α, interferon (IFN)-γ and GM-CSF in polymorphonuclear cells. [22-24] Indeed, 1,25-$(OH)_2D_3$ inhibits T lymphocyte proliferation and increases dendritic cell maturation and survival. [25,26] In general, 1,25-$(OH)_2D_3$ appears to primarily inhibit Th_1- while at the same time favoring Th_2-cell differentiation. [27] Activation of the VDR has been shown to inhibit IL-12 production in freshly isolated human monocytes or peripheral blood mononuclear cells primed with IFN-γ and stimulated with LPS in a dose-dependent manner. In addition, 1,25-$(OH)_2D_3$ was shown to dose dependently inhibit antigen-induced T cell proliferation and production of cytokines, such as IL-2, IL-12 and IFN-γ. [27–29] Finally, treatment of dendritic cells *in vitro* with 1,25-$(OH)_2D_3$ down-regulates the expression of co-stimulatory molecules CD40, CD80 and CD86 and decreases the production of IL-12 while, on the other hand, it enhances the expression of the anti-inflammatory cytokine IL-10. [29]

These findings suggest that vitamin D analogs may indeed positively affect the chronic inflammatory status of dialysis patients. In an earlier report, we had shown the inverse correlation between *H. Pylori* IgG antibody levels and the dose of HD. Additionally, inverse correlation between *H. Pylori* IgG antibody levels and the serum albumin and dialysis efficacy as well as positive correlation with the duration of HD treatment, were also reported in our study, [18] which indicate an inverse association of *H. Pylori* infection with malnutrition and the resultant immuno-deficiency of HD patients. [18,30,31]

In the present study, we found a significant positive correlation between serum 25-OH vitamin D levels and *H. Pylori* infection. Thus, it appears that vitamin D may indeed positively affect the chronic inflammatory status of dialysis patients and may potentiate the immune response in HD patients. Because of their immuno-modulating effects, vitamin D analogs may offer new means to control the inflammatory status in ESRD patients.

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