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Low serum vitamin D is associated with failure of Helicobacter pylori treatment

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ABSTRACT

Background and Aims: *Helicobacter pylori* are the most common gastrointestinal infection worldwide. Determination of contributing factors for successful eradication of Helicobacter pylori is important for better infection control. Therefore, this study was conducted to investigate the association between serum vitamin D deficiency and Helicobacter pylori eradication rate.

Materials and Methods: In this nested case control study in Loghman Hospital in Tehran in 2018 and 2019, 200 consecutive patients with Helicobacter pylori infection using amoxicillin, pantoprazole, bismuth, and metronidazole for 4 weeks were enrolled. The serum vitamin D level was compared across the groups with successful (n=153) versus unsuccessful (n=47) eradication of infection. Finally, data analysis was performed using SPSS statistical software version 25 and the mean, standard deviation, frequency, percentage and statistical test of Chi-square were used to describe and analyze the data and the significance level in this study was less than 0.05.

Results: The results of this study demonstrated that before-treatment vitamin D level was between 10 and 20 ng/dL in majority of unsuccessful cases (40.4%) and it was more than 30 ng/dL in majority of successful cases (83.7%) showing statistically significant difference ($P < 0.001$).

Conclusion: This study showed a significant association between vitamin D deficiency and Helicobacter pylori eradication and low vitamin D level resulted in failure of treatment; Hence in unsuccessful cases, assessment of vitamin D level and possible supplementation in those with hypovitaminosis D is recommended.

INTRODUCTION

Helicobacter pylori (Hp) is a gram-negative, microaerophilic, and spiral bacterium that colonizes the stomach of humans. The prevalence of this bacterium is very high, from 25% in developed countries to 90% in developing countries [1, 2]. The bacterium causes some diseases involving the gastrointestinal tract, including chronic gastritis, peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer [3]. Concerning ulcers, 76%–95% of gastric ulcers and 90% of duodenal ulcers are associated with Hp infection [4]. Hp infection treatment and eradication is significantly effective in the treatment of gastric ulcer and gastric lymphoma, so successful eradication of this pathogen can prevent gastric cancer [5, 6]. According to previous studies, factors influencing the eradication failure of Hp include low drug compliance, antibiotic resistance, microbial virulence factors, genetic factors in the host, smoking, alcohol consumption, and diabetes [7-9]. Besides, it is clear that, like other infections, host immunity plays an essential role against Hp infection. Many of recent studies have shown that vitamin D, in addition to its known role in calcium and phosphorus metabolism, acts as an anti-inflammatory agent and immune system regulator. This vitamin plays a role in reducing the risk of chronic diseases such as some common cancers, autoimmune, cardiovascu-

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lar, and infectious diseases. Infections of the urinary tract, respiratory tract and tuberculosis and deficiency of vitamin D can lead to an increase in immune system disorders and be risk factors for the development of infectious diseases, including urinary tract and respiratory infections and tuberculosis [10-14]. Laboratory studies have shown that vitamin D binds to its receptor (vitamin D Receptor: VDR), activating a signal pathway that triggers several immune responses. This vitamin is involved in the regulation of the immune response in many infectious diseases by regulating the expression of a number of endogenous antimicrobial peptides [15-17]. Laboratory studies have also shown that vitamin D and its decomposition products have an antimicrobial effect, specifically against Hp bacterium, and play a role in homeostasis of gastric mucosa and protection of host against this pathogen. Also, VDR is up regulated in the gastric epithelium in the presence of Hp [18-20]. However, there are few clinical studies on the effect of vitamin D on Hp eradication treatment, some of which have been performed on specific populations such as the elderly or diabetic people, and the presence of intervening factors that are effective on the results is not fully known [21, 22]. Considering the high prevalence of Hp infection and the importance of its eradication, it is important to eliminate the factors that increase the likelihood of treatment failure. Also, according to laboratory studies, it seems not only Vitamin D deficiency (VDD) may have an effect in increasing the eradication failure rate, but also treatment of such deficiency and supplementation may have direct antimicrobial or protective effects on the gastric mucosa against Hp infection. Therefore, considering the importance of the subject matter, the present nested case-control study investigated the association of VDD with Hp eradication therapy.

MATERIALS and METHODS

The present study was performed on 200 patients aged 18-80 years who underwent endoscopy at Loghman Hospital from June to March 2019, and the presence of Hp infection was confirmed based on histopathological samples. Patients with previous history of Hp eradication, renal and hepatic failure, systemic inflammatory or autoimmune disease, and history of antibiotic use, vitamin D supplementation, antacid or anti-inflammatory drug, and corticosteroid / immunosuppressive therapy in the previous two months have been excluded from the study. Prior to treatment, serum vitamin D levels were determined in all patients, and they were divided into four categories, including vitamin D<10, 10-20, 21-30, and > 30 ng /dL. All patients underwent four-week bismuth-based quadruple Hp eradication treatment (two amoxicillin 500 mg b.d, two metronidazole 250 mg b.d, two bismuth250 mg b.d, and pantoprazole 40 mg b.d.) To confirm the eradication of HP, the urea breath test was performed for all patients for four weeks after the treatment. Accordingly, patients were divided into two groups: failed treatment and successful treatment, and vitamin D levels were compared between two groups. All participants gave informed written consent prior to the study. All the patients in study have not taken vitamin D in the past year. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1398.197).

Data analysis method

Finally, data analysis was performed using SPSS ver. 25. The mean and standard deviations were used to describe quantitative variables and the number and percentage were used to describe qualitative variables. The inter-group comparison was carried out using chi-square test and P-value < 0.05 was considered as the significance level.

RESULTS

In this study, 200 patients with Hp infection who underwent Hp eradication therapy using amoxicillin, metronidazole, bismuth, and pantoprazole for four weeks were divided into following groups based on the urea breath test: optimal therapeutic response (n=153 people) and treatment failure (n=47 people).

In the group with positive urea breath test, 18, 13, and 16 people, and in the group with negative urea breath test, 51, 64, and 38 people were in the <35, 35-55, and >55 age groups, respectively. There was no significant difference between the two groups in terms of age group distribution (P = 0.2).

There were 33 (2.70%) and 95 females (1.62%), respectively, in the groups with and without treatment failure, and the rest were male. There was no significant difference between the two groups in terms of sex distribution (P = 0.4). Table 1 shows the distribution of the two groups with and without treatment failure based on body mass index (BMI). There was also no significant difference between the two groups in terms of this variable (P = 0.6).

Table 1. Distribution of two groups with and without treatment failure based on body mass index.(BMI= Body Mass Index)

BMI	Urea Test		P-value
	Positive N=47 (%)	Negative N=153 (%)	
18.5< (Underweight)	16(34.0)	47(30.7)	0.6
18.5-25 (Normal)	17(36.2)	55(35.9)	
25-30 (Overweight)	13(27.7)	39(25.5)	
30≤ (Obese)	1(2.1)	12(7.8)	

Table 2. Distribution of two groups with and without treatment failure based on vitamin D levels.

Serum Vitamin D	Urea Test		P-value
	Positive N=47 (%)	Negative N=153 (%)	
<10 ng/dL	8 (17.0)	6 (3.9)	<0.001
10-20 ng/dL	19 (40.4)	15 (9.8)	
21-30 ng/dL	4 (8.5)	4 (2.6)	
30 ng/dL <	16 (34.0)	128 (83.7)	

At the beginning of the treatment, vitamin D levels in the majority of patients (40.4%) of the treatment failure group was 10-20 ng/dL, but it was more than 30ng/dL in the majority of patients (83.7%) of the group with optimal therapeutic response. Such a difference was statistically significant ($P < 0.001$) (Table 2).

DISCUSSION

CConsidering the high prevalence of H. pylori infection (HP) and the importance of its eradication, it is important to eliminate the factors that increase the likelihood of treatment failure. Laboratory studies suggest the role of vitamin D in host immunity against Hp infection as well as the specific antibacterial effects of this vitamin against Hp pathogen. Therefore, the present study investigated the effect of VDD on the success rate of eradication treatment in Hp-positive patients. The results showed that vitamin D level was 10-20 ng/dL in the majority of patients (40.4%) in the treatment failure group at the beginning of treatment, but it was more than 30 ng/dL in the majority of patients (83.7%) in the group with optimal therapeutic response at the beginning of treatment, which was statistically different.

A retrospective study (2018) was carried out on 160 patients with type 2 diabetes who underwent Hp eradication treatment from 2015 to 2017 and had their baseline vitamin D levels checked. Patients were divided into two groups: successful eradication therapy (n=124 people) and failed eradication treatment (n=36 people). The statistical analysis showed that the mean vitamin D level in the treatment failure group was significantly lower than the successful eradication group, which is consistent with the results of the present research [16].

A study was carried out on 220 patients diagnosed with Hp gastritis using endoscopic biopsy in 2017, and vitamin D levels were measured in all of them before the eradication treatment. Patients were treated with bismuth-based quadruple Hp eradication treatment for 14 days and were then divided into two groups based on vitamin D levels: vitamin D <10 ng / dL and vitamin D ≥ 10 ng / dL. Hp eradication was successful in 77.2% of cases. VDD was prevalent among 30.5% of the studied population. The mean vitamin D levels in the eradication failure group were significantly lower. Also, the number of patients with VDD in the treatment failure group was significantly higher than the successful treatment group, and the results of the mentioned study, similar to the present research, showed that VDD is a risk factor for the failure of Hp eradication therapy [15].

A case-control study (2018) was carried out on 150 patients diagnosed with Hp gastritis using endoscopy and confirmed by stool antigen tests (SATs). Patients were divided into two groups based on their vitamin D levels: <20 ng/dL (VDD) and ≥ 20 ng/dL. Results showed that vitamin D levels in the treatment failure group were significantly lower than in the successful treatment group. Besides, the number of patients with VDD was significantly higher in the treatment failure group, which is consistent with the results of the present research [17].

A cross-sectional study (2018) was conducted on 254 patients aged above 65 years who underwent endoscopy between the years 2010 and 2017 and were examined for Hp infection. Of the total patients, 23 were Hp-positive and 211 were Hp-negative. Most patients with VDD were in Hp-positive group. Also, multivariate regression analysis showed that VDD was significantly associated with an increased risk of Hp infection after the removal of age, sex, variables and Charlson comorbidity index (CCI). This suggests that VDD has an effect on increasing both the risk of Hp infection and treatment failure [18].

In a study in 2012, the mean vitamin D level in 36384 outpatients was measured and determined, and the results of statistical analysis showed the role of hypovitaminosis D (VDD) as a risk factor for autoimmune diseases. It was also found that lower vitamin D levels in Hp patients can be influential factors for more severe invasion of gastric mucosa, which can be the main justification for the results obtained in the present study [20].

In a cross-sectional study on 208 patients with upper gastrointestinal symptoms in 2018, they were genotyped for VDR polymorphism and the results were compared between Hp-positive and Hp-negative individuals. Results showed a significant relationship between VDR gene polymorphism and Hp infection, which justifies our research findings at the molecular level [22].

A case-control study (2014) investigated the role of VDR in intrinsic immunity against Hp infection. A total of 17 Hp-positive patients and 16 controls were included in the study, and the results showed overexpression of VDR and Cyclic Adenosine Monophosphate in the gastric mucosa in cases of Hp infection. The results also showed that VDR plays an important role in the gastric mucosal hemostasis and protection against Hp infection, which is consistent with the findings of the present research [23].

A laboratory study in 2015 showed that the combination of vitamin D decomposition products had antibacterial effects only against Hp, but not other bacteria. Therefore, the results of the present research cannot be generalized to other bacteria. A laboratory study in 2018 showed that some compounds derived from vitamin D, including VDP1 [(1R,3aR,7aR)-1-[(1R)-1,5-dimethylhexyl]octahydro-7a-methyl-4H-inden-4-one], have completely specific and very strong antibacterial effects against Hp and they can be used to produce medicine against this bacterium in the future, and the results of the present research also support this theory [24].

CONCLUSION

Overall, the results of the present case-control study revealed a significant statistical relationship between serum vitamin D deficiency level and H. pylori eradication rate. Vitamin D deficiency increases H. pylori treatment failure, so measuring serum vitamin D levels in cases of treatment failure and the use of vitamin D supplements are recommended in peo-

ple with vitamin D deficiency to improve the eradication treatments of H. pylori.

CONFLICT OF INTERESTS

We do not have conflict of interests.

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