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ORIGINAL ARTICLE

Vitamin D deficiency and risk of *Helicobacter pylori* infection in older adults: a cross-sectional study

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Abstract

Background Vitamin D deficiency is known to cause increased predisposition to various infectious diseases and the addition of vitamin D to antimicrobial treatment may improve treatment responses. However, the relationship between vitamin D and *Helicobacter pylori* (*H. pylori*) remains to be determined.

Aims To assess the association between vitamin D deficiency and *H. pylori* infection.

Methods This cross-sectional study included patients aged 65 and over, who underwent gastroscopy and had gastric biopsy performed between 2010 and 2017. Of the 441 patients, 254 had available 25-hydroxyvitamin D level results and were included in the analyses. Patients were categorized into *H. pylori* (+) and *H. pylori* (−) groups, according to histopathological examination results of gastric biopsies. Serum 25(OH) vitamin D levels less than 20 ng/mL were defined as vitamin D deficiency.

Results Of all patients, 43 were *H. pylori* (+) and 211 were *H. pylori* (−). More patients had vitamin D deficiency (< 20 ng/mL) in the *H. pylori* (+) group than the *H. pylori* (−) group (86% vs 67.3%, $p = 0.014$). The proportion of *H. pylori* (+) patients decreased across increasing quartiles of 25(OH) vitamin D levels (p for trend = 0.010). In multivariable logistic regression analysis, vitamin D deficiency was associated with increased odds of *H. pylori* infection after adjustment for age, gender, and Charlson Comorbidity Index (OR = 3.02, 95% CI 1.19–7.69, $p = 0.020$).

Conclusion Vitamin D deficiency can be associated with increased risk of *H. pylori* infection. The potential protective effect of vitamin D against *H. pylori* infection and its possible role in the treatment of *H. pylori* should be evaluated in prospective trials.

Keywords Vitamin D deficiency · *Helicobacter pylori* · Aged · Gastroscopy · 25-Hydroxyvitamin D 2

Background

Helicobacter pylori (*H. pylori*) is the most common chronic bacterial infection in humans [1]. *Helicobacter pylori* is a Gram-negative, microaerophilic, and spiral microorganism. The human stomach, particularly the gastric antrum, is its main reservoir [2]. *Helicobacter pylori* is transmitted through the fecal–oral route and can infect individuals of all age groups around the world. The prevalence of *H. pylori* infection varies depending on the living environment (i.e., home or nursing home), and can be as high as 60% among older adults [3, 4]. In addition to causing gastrointestinal diseases such as peptic ulcer disease and atrophic gastritis, *H. pylori* infection is also associated with malignant diseases, including gastric adenocarcinoma and lymphoma [5, 6]. Diseases linked to *H. pylori* infection are not limited to the gastrointestinal system. It is also associated with various systemic diseases, such as coronary artery disease, Alzheimer's disease, iron-deficiency anemia, and cobalamin deficiency [7–13]. Local and systemic inflammation caused by *H. pylori* infection may be at least partly responsible for the systemic effects of *H. pylori*.

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Vitamin D deficiency is common among senior adults, which can be caused by decreased sunlight exposure, impaired cutaneous previtamin D synthesis, decreased renal hydroxylation, and insufficient dietary intake. Nursing home residency, lack of out-of-home mobility, obesity, dark skin color, presence of malabsorption, and osteoporosis put older people at high risk for vitamin D deficiency. Although there is a lack of consensus about the optimal level of serum 25-hydroxyvitamin D (25(OH) vitamin D), levels lower than 20 ng/mL are mostly considered as vitamin D deficiency [14, 15]. The American Geriatrics Society endorses higher (> 30 ng/mL) 25(OH) vitamin D levels to support bone health in older adults [16].

Vitamin D controls hundreds of genes directly or indirectly that are related to cell proliferation, differentiation, apoptosis, and angiogenesis [17, 18]. Along with osteoporosis, muscle weakness, and increased risk of fractures, vitamin D deficiency has also been shown to be associated with increased risk of various infections and autoimmune, malignant, and chronic diseases [19–25]. Recent data suggest that risk of infection such as urinary tract infections, tuberculosis, and other respiratory infections increases with vitamin D deficiency [26–28]. However, the effect of vitamin D level on *H. pylori* infection remains to be determined. In this study, we aimed to assess the association between vitamin D deficiency and risk of *H. pylori* infection.

Methods

Patients

We conducted a cross-sectional study. Patients aged 65 and over, who were admitted to our inpatient geriatrics clinic between 2010 and 2017, underwent gastroscopy, had gastric biopsies performed, and had serum 25(OH) vitamin D levels measured within 3 months of gastroscopy were eligible for the study. Patients who were on vitamin D treatment at the time of serum 25(OH) vitamin D measurements were excluded. This study was conducted in accordance with Declaration of Helsinki and approved by the ethical committee of Ankara University (#02-57-18).

Assessments

The diagnosis of *H. pylori* infection was based on histopathological examination of Giemsa-stained gastric biopsy specimens. Additional pathological findings including atrophic and non-atrophic gastritis, intestinal metaplasia, foveolar hyperplasia, adenocarcinoma, and peptic ulcers were recorded. Clinical (age, gender, comorbidities, and gastroscopic findings) and laboratory data [25(OH) vitamin D, hemoglobin, ferritin, vitamin B12, folic acid levels, and sedimentation rates] were obtained from electronic medical records. Charlson Comorbidity Index (CCI) scores were calculated [29].

Serum 25(OH) vitamin D measurements were performed using high-performance liquid chromatography (Immuchrom GmBH, Heppenheim, Germany). Intraassay and interassay coefficients of variation were < 3% and < 5%, respectively. Serum levels of 25(OH) vitamin D less than 20 ng/mL were categorized as vitamin D deficiency.

Statistical analysis

Statistical analyses were performed using the Stata software (version 14.2, Texas, StataCorp LP). Categorical variables were summarized as counts and percentages, and continuous variables were summarized as medians and interquartile ranges (IQR). Patients were categorized into *H. pylori* positive (+) and negative (−) groups. Categorical variables were compared using Chi-square test or Fisher's exact test, and continuous variables were compared with Wilcoxon rank-sum test. To adjust for possible confounding factors for the presence of *H. pylori* infection, multivariate logistic regression analysis was performed and odds ratios were calculated. *P* values lower than 0.05 were considered statistically significant.

Results

Data from 441 patients who underwent gastroscopy were reviewed and 187 were excluded due to lack of gastric biopsy and/or 25(OH) vitamin D measurement results. A total of 254 patients (152 females, 102 males) were included in the study. Median age was 77.2 (IQR 71.9–82, range 65–96) years. *Helicobacter pylori* was histopathologically positive in 43 (16.9%) patients. Median ages were 74.7 years (IQR 70.1–78) in *H. pylori* (+) and 78.2 (IQR 72–82.4) years in *H. pylori* (−) groups ($p = 0.011$). In the *H. pylori* (+) group, fewer patients were aged over 75 years (46.5% vs 63%, $p = 0.044$) and females were more frequent (74.4% vs 56.9%; $p = 0.032$). There were no significant differences in height and weight between the two groups. The distribution of body mass index categories was similar in *H. pylori* (+) and (−) patients. CCI scores were higher in the *H. pylori* (−) patients than the *H. pylori* (+) patients (median 2 vs 1; $p = 0.025$). Patient demographics, comorbidities, and medications that can potentially affect gastroscopic findings are shown in Table 1. The frequency of antibiotic use at the time of gastroscopic examination was more common in *H. pylori* (−) patients compared to *H. pylori* (+) patients (31.3% vs 16.3%, $p = 0.048$).

Overall, 44.5% of the patients underwent gastroscopy for evaluation of upper GI symptoms and 68.1% of the

Table 1 Patient characteristics by *H. pylori* infection status

	All ($n=254$)		*H. pylori* negative ($n=211$)		*H. pylori* positive ($n=43$)		p
Median age, years (IQR)	77.2	(71.9–82)	78.2	(72–82.4)	74.7	(70.1–78)	0.011
Age groups, *n* (%)							
65–75 years	101	(39.8)	78	(37)	23	(53.5)	0.044
75+	153	(60.2)	133	(63)	20	(46.5)	
Gender, *n* (%)							
Male	102	(40.2)	91	(43.1)	11	(25.6)	0.032
Female	152	(59.8)	120	(56.9)	32	(74.4)	
Height[a], cm (IQR)	161	(153–167)	162	(153–168)	158	(154–163)	0.060
Weight[a], kg (IQR)	66	(58–75)	67	(58–75)	65	(58–74)	0.543
BMI (kg/m^2)							
< 18.5	2	(0.8)	2	(1.0)	0	(0.0)	0.462
18.5–24.9	100	(39.4)	86	(40.8)	14	(32.6)	
25–29.9	97	(38.2)	79	(37.4)	18	(41.9)	
≥ 30	32	(12.6)	24	(11.4)	8	(18.6)	
Unknown	23	(9.1)	20	(9.5)	3	(7.0)	
Comorbidities, *n* (%)							
Hypertension	187	(73.6)	156	(73.9)	31	(72.1)	0.803
Type 2 diabetes	105	(41.3)	86	(40.8)	19	(44.2)	0.677
Chronic kidney disease[b]	59	(23.2)	52	(24.6)	7	(16.3)	0.236
Coronary artery disease	75	(29.5)	61	(28.9)	14	(32.6)	0.633
Alzheimer's disease	21	(8.3)	19	(9.0)	2	(4.7)	0.544
Parkinson's disease	14	(5.5)	10	(4.7)	4	(9.3)	0.266
Atrial fibrillation	33	(13)	27	(12.8)	6	(14.0)	0.837
Heart failure	30	(11.8)	29	(13.7)	1	(2.3)	0.034
Medications							
PPI	111	(43.7)	92	(43.6)	19	(44.2)	0.944
Antiaggregants	88	(34.7)	74	(35.1)	14	(32.6)	0.752
Antibiotics	73	(28.7)	66	(31.3)	7	(16.3)	0.048
Anticoagulants	35	(13.8)	29	(13.7)	6	(14.0)	0.971
NSAID	11	(4.3)	8	(3.8)	3	(7.0)	0.350
Steroids	7	(2.8)	7	(3.3)	0	(0)	0.606
Median CCI (IQR)	2	(1–3)	2	(1–3)	1	(0–2)	0.025
CCI group, *n* (%)							
< 2	125	(49.2)	100	(47.4)	25	(58.1)	0.199

BMI body mass index, *CCI* Charlson Comorbidity Index, *IQR* interquartile range, *NSAID* nonsteroidal anti-inflammatory drugs, *PPI* proton-pump inhibitors

[a]Height and weight data were missing for 23 patients

[b]Patients with an estimated glomerular filtration rate of less than 60 mL/min

patients had gastroscopy for evaluation of iron deficiency or iron-deficiency anemia. There was no significant difference in indications for gastroscopic examination between *H. pylori* (+) and (−) groups (Table 2). Histologically, atrophic (32.6% vs 13.3%, $p=0.002$), and non-atrophic gastritis (74.4% vs 9%, $p<0.001$) were more common in the *H. pylori* (+) group, whereas frequencies of foveolar hyperplasia, intestinal metaplasia, gastric adenocarcinoma, autoimmune gastritis, and peptic ulcers were similar between the groups.

Median serum 25(OH) vitamin D levels were significantly lower in the *H. pylori* (+) group compared to *H. pylori* (−) group (9 vs 13.6 ng/mL, $p=0.008$) (Fig. 1). There was an inverse linear trend between quartiles of 25(OH) vitamin D and *H. pylori* positivity. The proportion of *H. pylori* (+) patients decreased across increasing quartiles of 25(OH) vitamin D (p for trend = 0.010). Vitamin D deficiency (< 20 ng/mL) was more common in the *H. pylori* (+) group (86% vs 67.3%, $p=0.014$). Serum hemoglobin, ferritin, vitamin B12, and folic acid levels were similar among groups.

Table 2 Indications and findings of gastroscopic evaluation

	All ($n=254$)		*H. pylori* negative ($n=211$)		*H. pylori* positive ($n=43$)		p
Indications for gastroscopy[a], *n* (%)							
Upper GI symptoms[b]	113	(44.5)	92	(43.6)	21	(48.8)	0.529
Evaluation of ID/IDA	173	(68.1)	144	(68.3)	29	(67.4)	0.918
Endoscopic findings, *n* (%)							
Foveolar hyperplasia	112	(44.1)	98	(46.4)	14	(32.6)	0.095
Intestinal metaplasia	76	(29.9)	60	(28.4)	16	(37.2)	0.252
Atrophic gastritis	42	(16.5)	28	(13.3)	14	(32.6)	0.002
Non-atrophic gastritis	51	(20.1)	19	(9.0)	32	(74.4)	< 0.001
Gastric cancer	17	(6.7)	16	(7.6)	1	(2.3)	0.209
Autoimmune gastritis	13	(5.1)	13	(6.2)	0	(0.0)	0.095
Peptic ulcer	9	(3.5)	8	(3.8)	1	(2.3)	0.640
Other[c]	15	(5.9)	14	(6.6)	1	(2.3)	0.275

GI gastrointestinal, *ID/IDA* iron deficiency/iron-deficiency anemia

[a]Patients may have more than one indication; therefore, the total may exceed 100%

[b]Symptoms include dyspepsia, persistent nausea/vomiting, and gastroesophageal reflux

[c]Other endoscopic findings include gluten-sensitive enteropathy, gastric polyps, and Barret esophagus

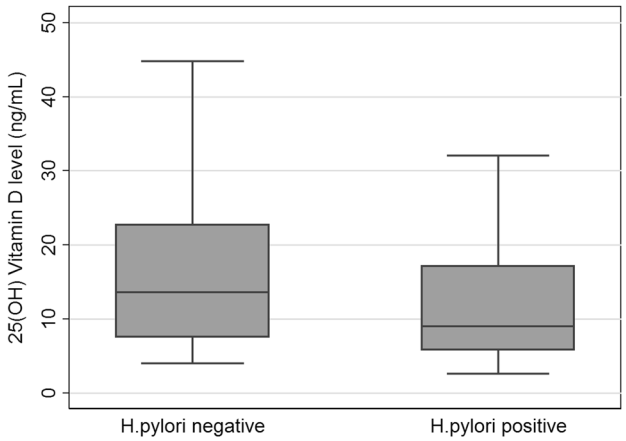

Fig. 1 Serum 25(OH) vitamin D levels according to *H. pylori* infection status

25(OH) vitamin D levels and other laboratory findings of *H. pylori* groups are shown in Table 3.

In multivariate logistic regression analysis after adjusting for age, gender, and CCI, the presence of vitamin D deficiency (< 20 ng/mL) was significantly associated with increased odds of *H. pylori* infection (OR = 3.02, 95% CI 1.19–7.69, $p=0.020$) (Table 4).

Discussion

In this study, we assessed the association between vitamin D deficiency and *H. pylori* infection in older adults. Vitamin D deficiency was more prevalent among patients with *H. pylori* infection. There was an inverse linear trend between increasing 25(OH) vitamin D quartiles and frequency of *H. pylori* infection. Patients in the *H. pylori* (+) group were younger and *H. pylori* infection was less common among patients aged over 75 years. Increased frequency of chronic atrophic gastritis and increased use of proton-pump inhibitors and antibiotics may contribute to lower *H. pylori* positivity observed with aging, as supported by the previous studies [3, 30]. In addition, comorbidity scores as measured by CCI were higher in the *H. pylori* (−) group. We think that this difference can be associated with higher rates of hospitalization and increased use of medications, particularly antibiotics, among patients with higher comorbidity scores.

In the literature, there are limited data about the association between vitamin D deficiency and *H. pylori* infection, particularly in older patients. In a study from Japan, the prevalence of *H. pylori* infection was reported to be lower among older women living in nursing homes who were receiving vitamin D treatment for osteoporosis compared to those who were not taking vitamin D [31]. In another study evaluating the association between vitamin D deficiency and atrophic gastritis, *H. pylori* infection was diagnosed more frequently among patients with vitamin D deficiency [32]. Moreover, vitamin D deficiency was also shown to be associated with worse *H. pylori* eradication rates with treatment [33]. Therefore, vitamin D seems to be important not only for protection against *H. pylori* infection, but also for the success of treatment.

Data from preclinical studies revealed possible biological mechanisms by which vitamin D modulates the immune system. Vitamin D exerts its physiological effects through intracellular vitamin D receptors, which

Table 3 25(OH) vitamin D levels and other laboratory results by *H. pylori* infection status

	H. pylori negative ($n=211$)		*H. pylori* positive ($n=43$)		p
25(OH) vitamin D, ng/mL ($n=254$)	13.6	(7.5–22.7)	9	(5.8–17.1)	0.008
25(OH) vitamin D groups, *n* (%)					
< 20 ng/mL	142	(67.3)	37	(86)	0.014
25(OH) vitamin D quartiles, *n* (%)					
1st quartile	48	(22.7)	16	(37.2)	0.010*
2nd quartile	51	(24.2)	12	(27.9)	
3rd quartile	54	(25.6)	10	(23.3)	
4th quartile	58	(27.5)	5	(11.6)	
Hemoglobin, g/dL ($n=254$)	11.1	(9.8–12.8)	11.1	(9.5–13.2)	0.840
Ferritin, ng/mL ($n=237$)	41	(12–139)	23	(11.9–81)	0.353
Vitamin B12, pg/mL ($n=251$)	327.3	(216–616)	369	(198–498)	0.455
Folic acid, ng/mL (n = 237)	8	(5.7–11.4)	8.3	(6.1–10.9)	0.855
Sedimentation rate, mm/hr ($n=251$)	36	(18–58)	30	(20–47)	0.203
Intact PTH, pg/mL ($n=172$)	55	(33–87)	52	(38–77)	0.838

Reported values are medians (IQR) or counts (percent)

IQR Interquartile range, *PTH* parathormone

*p value for trend across quartiles

Table 4 Results of univariate and multivariate analyses of predictors of *H. pylori* infection

Variable (reference group)	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age (continuous)	0.94	0.89–0.99	0.016	0.94	0.89–0.99	0.028
Gender (male)	2.20	1.06–4.61	0.035	2.26	1.05–4.88	0.036
CCI (≥ 2)	1.54	0.79–2.99	0.201	1.49	0.74–3.01	0.261
25(OH) vitamin D (≥ 20 ng/mL)	2.99	1.21–7.44	0.018	3.02	1.19–7.69	0.020

CCI Charlson Comorbidity Index, *CI* confidence interval, *OR* odds ratio

are expressed by almost all nucleated cells in the body including antigen-presenting dendritic cells, macrophages, and B and T lymphocytes [34]. After ligand binding, vitamin D receptor induces gene expression of antimicrobial peptides from monocytes, neutrophils, and epithelial cells. These antimicrobial peptides include cathelicidin and β-defensin [35]. Cathelicidins have antimicrobial effects against Gram-negative and Gram-positive bacteria, viruses, fungi, and parasites [36]. The active form of vitamin D (1,25-dihydroxyvitamin D) increases cathelicidin expression in *H. pylori*-infected gastric epithelial cells; thus, vitamin D possibly has an important role in regulation of mucosal immunity against *H. pylori* [37]. Another antimicrobial peptide, β-defensin, is also secreted from the *H. pylori*-infected gastric epithelium and exerts anti-bacterial effects on the mucosal surface [38]. Vitamin D deficiency may lead to diminished mucosal immunity because of reduced cathelicidin and β-defensin secretion; hence, the host may fail to eliminate *H. pylori*. This could at least in part explain the increased *H. pylori* infection prevalence observed among patients with low vitamin D in the present study. In addition, vitamin D can support intracellular killing of bacteria by inducing nitric oxide secretion within macrophages [39].

Our study has limitations. Although the protective effect of vitamin D against *H. pylori* is biologically plausible, we cannot infer causality due to the cross-sectional design of this study. In addition, our patient population included hospitalized patients, most of whom underwent gastroscopy for evaluation of iron-deficiency anemia to rule out gastrointestinal malignancies. The proportion of patients with *H. pylori* was lower than in former reports, possibly because few patients had gastroscopy for evaluation of dyspepsia [3, 4]. In addition, prolonged antibiotic treatment commonly administered to hospitalized patients may contribute to low *H. pylori* infection prevalence among these patients, as reported in the previous studies [30].

Conclusions

In conclusion, the results of our study suggest a relationship between vitamin D deficiency and *H. pylori* infection. The potential protective effect of vitamin D against *H.*

pylori infection and its possible role in treatment of *H. pylori* should be explored in prospective trials.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This study was approved by institutional ethical board of Ankara University and was conducted in compliance with Declaration of Helsinki.

Informed consent For this type of study, formal consent is not required.

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