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Higher Serum Levels of Vitamin D are Associated with Reduced Risk of Diverticulitis

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Abstract

Background & Aims—Recent studies have shown geographic and seasonal variation in hospital admissions for diverticulitis. Because this variation parallels differences in ultraviolet light exposure, the most important contributor to vitamin D status, we examined the association of pre-diagnostic serum levels of vitamin D with diverticulitis.

Methods—Among patients within the Partners Healthcare System that had blood drawn and serum levels of 25-hydroxyvitamin D (25-[OH]D) measured, from 1993 through 2012, we identified 9116 patients with uncomplicated diverticulosis and 922 patients who developed diverticulitis that required hospitalization. We used multivariate logistic regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) to compare serum 25(OH)D levels between these groups.

Results—Patients with uncomplicated diverticulosis had significantly higher mean pre-diagnostic serum levels of 25(OH)D (29.1 ng/mL) than patients with diverticulitis that required

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Dr. Maguire – study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript
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hospitalization (25.3 ng/mL; *P*<.0001). Compared to patients in the lowest quintile of 25(OH)D, the multivariate-adjusted RR for diverticulitis hospitalization was 0.49 (95% CI, 0.38–0.62; *P* for trend = <.0001) among patients in the highest quintile of 25(OH)D. Compared to patients with uncomplicated diverticulosis, the mean level of 25(OH)D was significantly lower for patients with acute diverticulitis without other sequlae (25.9 ng/mL; *P*<.0001; n=594), for patients with diverticulitis with abscess (25.8 ng/mL; *P*=.0095; n=124), for patients with diverticulitis requiring emergent laparotomy (22.7 ng/mL; *P*=.002; n=65), and for patients with recurrent diverticulitis (23.5 ng/mL; *P*<.0001; n=139).

Conclusions—Among patients with diverticulosis, higher pre-diagnostic levels of 25(OH)D are significantly associated with a lower risk of diverticulitis. These data indicate that vitamin D deficiency could be involved in the pathogenesis of diverticulitis.

Keywords

Vitamin D; diverticulitis; diverticulosis; risk factor; epidemiology

Background and Aims

Diverticulosis is a nearly ubiquitous colorectal condition of older individuals in the United States, reported in >70% of colonoscopies in patients over 80 years old[1]. Diverticulitis, one of its potential consequences, results in greater than 200,000 hospitalizations at a cost of more than 2 billion dollars per year[2]. Potential complications of diverticulitis, including fistula, abscess, intestinal perforation, stricture, and sepsis, generate substantial morbidity and potential mortality. In recent years, diverticulitis has been increasing in frequency, particularly among younger individuals[3].

Long-standing theories regarding the etiology of diverticulitis, such as seed and nut impaction in diverticula[4], have been undermined through etiological studies which have also highlighted novel associations between diverticulitis and lifestyle factors such as obesity[5] and use of non-steroidal anti-inflammatory drugs (NSAIDs).[6] Recently, an analysis of a national database of hospital admissions observed a seasonal variation in hospitalizations for diverticulitis.[7] Seasonal variation also reflects variation in ultraviolet (UV) light exposure, the greatest contributor to vitamin D status.

Vitamin D is a fat-soluble vitamin dependent largely on exposure of the skin to UV light for its production, with dietary sources playing an important secondary role. The active metabolite, 1,25-dihydroxy-vitamin D [1,25$(OH)_2$D], is synthesized from 25-hydroxy-vitamin D [25(OH)D] both in the kidneys and in extrarenal tissues including the colonic epithelium and many cell types in the immune system[8]. Although its role in maintaining bone health is well-characterized, compelling data support important extraskeletal effects, including an influence on the colon. Previous studies have demonstrated associations between vitamin D and other colonic disease, including colorectal neoplasia[9, 10] and inflammatory bowel disease (IBD)[11]. Based on these data, we hypothesized that a similar link might exist between pre-diagnostic levels of 25(OH)D and diverticulitis that required hospitalization.

Methods

Assembly of study cohort

We identified eligible patients through the Partners Healthcare Research Patient Data Registry (RPDR). Partners Healthcare is an integrated academic health care system that provides care for over 1.8 million patients in the greater Boston area. The RPDR is a centralized data warehouse for patient information from multiple hospital systems within

Partners Healthcare. Access is provided to demographic data, billing codes, problem lists and narrative notes generated within affiliated hospitals and outpatient facilities. Details regarding the RPDR have been previously published[12]. We queried the RPDR for individuals who had at least one measurement of serum 25(OH)D from 1993–2012 and defined a group of patients with uncomplicated diverticulosis by identifying 9,116 patients who had a code for diverticulosis (ICD-9 562.10) and did not have an associated hospitalization for diverticulitis over at least five years of follow-up after diagnosis. We also defined a group of patients hospitalized with diverticulitis as individuals with an inpatient admission associated with the ICD-9 code 562.11 or 562.13 after measurement of 25(OH)D. Within this group, we further examined subtypes of diverticulitis admissions according to the following categories: "uncomplicated diverticulitis," defined as acute diverticulitis without abscess or perforation (ICD9 562.11,562.13); "complicated diverticulitis," defined as diverticulitis with abscess or perforation (ICD9 567, 569.5, 569.83; "surgical diverticulitis" defined as diverticulitis requiring laparotomy for peritonitis or pneumoperitoneum (ICD9 17.3, 45.7, 54); and "recurrent diverticulitis," defined as more than one inpatient admission for diverticulitis with admissions separated by at least 30 days. To assess the validity of our identification of patients with diverticulosis using billing codes and patient problem lists, we examined the medical records of a randomly selected sampling of 100 patients in our control group. We were able to verify the diagnosis of diverticulosis in 95 of 100 patients. Among the 95 patients, the diagnosis was confirmed in 77 (81%) by colonoscopy or sigmoidoscopy, with the remainder confirmed by CT scan. Of the 5 patients who could not be confirmed, two had physician notes documenting diverticulosis without mention of a confirmatory study and three did not have documentation in a limited set of clinician notes. Among the 100 cases, there were no cases of diverticulitis. We also examined the medical records of a randomly selected sampling of 100 patients with diverticulitis. We were able to support the diagnosis among 92 patients. Among the 92 patients, 68 (74%) had CT evidence of diverticulitis, with the remaining patients diagnosed by history and physical exam features consistent with diverticulitis and/or elevated white blood cell count and fevers.

This study was approved by the Partners Human Research Committee.

Assessment of exposures and covariates

For our primary analyses, we examined the first measured 25(OH)D level in relation to risk of diverticulitis. In sensitivity analyses, we also examined the association of mean 25(OH)D levels with diverticulitis among patients with more than one measurement of 25(OH)D and among patients that underwent a CT scan within 7 days of diagnosis. We collected information on demographics (age, gender, race) and selected comorbidities as reported by patient providers in the medical record, including coronary artery disease, obesity, chronic renal failure, and diabetes.

Statistical analysis

In univariate analyses, we compared the group with uncomplicated diverticulosis with the group hospitalized with diverticulitis using t-tests for continuous variables and chi-squared tests for categorical variables. We also defined quintiles for serum 25(OH)D using cutoff points determined according to the distribution among patients with uncomplicated diverticulosis. We employed logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between quintiles of serum 25(OH)D and risk of hospitalization for diverticulitis. In the multivariate logistic regression, we adjusted for other potential risk factors, including age, gender, race, diabetes, chronic renal failure, obesity, coronary artery disease, and history of a prior colonoscopy. Because diverticulitis was a relatively rare outcome, we interpreted the OR as an estimate of the relative risk (RR).

P-values less than 0.05 were considered significant. We used SAS version 9.2 (SAS Institute, Inc, Cary, NC, USA) for all analyses.

Results

Table 1 demonstrates the baseline characteristics of our study population. Compared to the 9,116 patients with uncomplicated diverticulosis, the 922 patients hospitalized with diverticulitis were older, more likely to be female, and less likely to be obese or have coronary artery disease.

Table 2 compares pre-diagnostic serum 25(OH)D level between patients with uncomplicated diverticulosis and those hospitalized with diverticulitis. For individuals with more than one measurement of 25(OH)D, we used the first measured vitamin D level. Among patients with uncomplicated diverticulosis, the mean 25(OH)D was 29.1 ng/mL compared with 25.3 ng/mL among the 922 patients with diverticulitis that required hospitalization (p<.0001). Compared to patients with uncomplicated diverticulosis, mean serum 25(OH)D was significantly lower for each subtype of diverticulitis: 25.9 ng/mL (p<.0001) for acute diverticulitis without other sequelae (n=594), 25.8 ng/mL (p = 0.009) for diverticulitis with abscess (n=124), 22.7 ng/mL (p=0.002) for those who required emergent laparotomy (n=65), and 23.5 ng/mL (p<.0001) for recurrent diverticulitis (n=139). In sensitivity analyses, for individuals with more than one pre-diagnostic measurement of 25(OH)D we used the mean of all 25(OH)D levels for our comparisons and obtained similar results (Table 2). The mean vitamin D level for patients with acute, uncomplicated diverticulitis with a documented CT scan within 7 days of diagnosis (n=344) was 24.8 ng/mL compared with 27.4 ng/mL for patients with diverticulitis who did not undergo a CT scan (n=250) as part of their diagnostic evaluation (p=0.02).

We considered the possibility that our observed associations may be due to a higher prevalence of healthy behaviors among individuals with asymptomatic diverticulosis compared to those with diverticulitis. Because such health-seeking behavior may be reflected by a higher likelihood of undergoing screening colonoscopy, we performed a secondary analysis limited to individuals who also had a colonoscopy (prior to admission for case patients with diverticulitis). Among such patients, the association between 25(OH)D and risk of diverticulitis was not significantly different. (Table 3).

Table 4 shows the association between quintiles of 25(OH)D level in relation to risk of hospitalization for diverticulitis adjusting for other risk factors. Compared to patients in the lowest quintile, the age-adjusted ORs for diverticulitis hospitalization were 0.71 (95% CI, 0.59–0.87) among patients in the second quintile of 25(OH)D, 0.56 (95% CI, 0.46–0.69) among patients in the third quintile, 0.56 (95% CI, 0.46–0.69) among patients in the fourth quintile, and 0.45 (95% CI, 0.36–0.56) among patients in the highest quintile (P trend <0.0001). Additionally adjusting for available information on comorbidities and health-modifying behaviors such as presence of coronary artery disease, obesity, chronic renal failure, diabetes, and having undergone a colonoscopy did not materially alter these risk estimates (Table 4).

Compared to patients with acute diverticulitis without other sequelae, patients in the subgroups who developed abscess, required surgery, or had recurrent attacks were observed to have lower pre-diagnostic levels of vitamin D. These differences did not reach significance, with the exception of surgical patients. Surgical patients had significantly lower average levels of vitamin D as compared to patients with acute diverticulitis without other sequelae (23.9 ng/mL versus 28.1 ng/mL, p =0.01).

Conclusions

Diverticulitis is a common disease in developed countries, including the United States. However, factors that lead to diverticulitis among patients with diverticulosis are poorly understood. In this study, we demonstrate that pre-diagnostic serum 25(OH)D level is inversely associated with risk of hospitalization for diverticulitis. Compared to patients in the lowest quintile of serum 25(OH)D, patients in the highest quintile had a substantially lower risk of developing diverticulitis requiring hospitalization. The lowest levels of 25(OH)D were observed in sub-groups with more severe disease. Risk of diverticulitis fell steeply as 25(OH)D levels increased to 25–30 ng/mL, with additional small reductions in risk seen with levels greater than 30 ng/mL.

To our knowledge, our study is the first to demonstrate an association between measured circulating 25(OH)D and risk of diverticulitis. Our results extend prior indirect evidence of such an association derived from ecological studies that have shown that hospitalization for diverticulitis varies according to season of the year as well as geographic location. Both of these factors are associated with variation in exposure to UVB light, the principal contributor to vitamin D status.

Our results are biologically plausible based on prior data demonstrating the importance of vitamin D in colonic physiology. Previous studies, including those by our group, have shown that low levels of circulating 25(OH)D are associated with an increased incidence of colorectal cancer (CRC)[10,13] as well as lower colorectal cancer-specific survival[14]. At the cellular level, vitamin D has been shown to have a pro-apoptotic and anti-proliferative effect, and expression of synthetic and catabolic enzymes is altered in malignant colonocytes[15]. Vitamin D also appears to play a role in inflammatory bowel disease. We, and others, have demonstrated that patients living at lower latitudes with greater UV-B light exposure have lower risk for Crohn's disease[16]. Recently, we have also shown that a lower predicted plasma level of 25(OH)D is associated with an increase in the risk of CD[11]. In parallel, dietary supplementation with vitamin D in murine models reduces the severity of colitis, modulates the gut immune response, and improves intestinal epithelial barrier function[17]. Taken together, these data support a critical role for vitamin D in maintaining colonic homeostasis by modulating inflammation, maintaining epithelial integrity, and regulating intestinal proliferation.

Our study has several strengths. First, we examined associations between 25(OH)D levels collected prior to hospitalizations for diverticulitis, minimizing the likelihood of reverse causation (i.e. diverticular disease resulting in low vitamin D levels). Second, we utilized a large database of patients with measured 25(OH)D and follow-up for diverticular outcomes. Third, our findings were robust to a sensitivity analyses which show a strong association of both mean plasma 25(OH)D levels taken over time as well as a single assessment of 25(OH)D level in relation to risk.

This study has several limitations. First, we were unable to examine the association of 25(OH)D levels in relation to risk of milder cases of diverticulitis that did not require hospitalization. Thus, we cannot exclude the possibility that our findings are due to a higher likelihood for patients with low vitamin D levels requiring hospital admission for diverticulitis. Nonetheless, our endpoint of hospitalizations for diverticulitis is perhaps the most clinically important. Second, our reliance on billing coding likely underestimates the true incidence of uncomplicated diverticulosis. Third, we were limited in our ability to adjust for other potential diverticulitis risk factors. Although we used available information on the presence of comorbidities, such as diabetes mellitus, coronary artery disease, and obesity to reflect overall patient health, such data are likely incomplete since they required

entry and coding by treating clinicians. We were also unable to consider other important lifestyle variables within our dataset. One marker of health-promoting behaviors, receipt of colonoscopy, did not appear to alter our results materially. However, we could not consider other potentially important factors, such as diet and physical activity, that were not reliably recorded in the medical record. Physical activity has been associated with both higher 25(OH)D levels and diverticulitis. However, physical activity is unlikely to completely account for the magnitude of our observed inverse associations between 25(OH)D level and diverticulitis. Moreover, the mechanism by which physical activity may be associated with a lower risk of diverticulitis is unclear. It is plausible that such an association could, at least in part, be mediated by higher 25(OH)D levels related to greater exposure to UV light among more physically active individuals.

In summary, we show that higher pre-diagnostic serum 25(OH)D levels are associated with a lower risk of requiring hospitalization for diverticulitis. Taken together with prior studies showing an inverse association of 25(OH)D and risk of CRC and IBD, these results highlight the potential importance of vitamin D in the maintenance of colonic health. Additional studies in cohorts with more detailed information on potential confounders of this association are warranted.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
IBD	inflammatory bowel disease
CRC	colorectal cancer
UV	ultraviolet
OR	odds ratio
CI	confidence interval
RPDR	research patient data registry

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Table 1

Patient Characteristics

	Group				
	Uncomplicated Diverticulosis	**Acute Diverticulitis**	**Complicated Diverticulitis**	**Surgical Diverticulitis**	**Recurrent Diverticulitis**
	N = 9,116	**N = 594**	**N = 124**	**N = 65**	**N = 139**
Age, mean (SD), years	63.6 (11.6)	67.3 (13.7)	65.8 (11.7)	65.4 (13.0)	66.0 (12.8)
Gender, n (percentage)					
Male	3,515 (38.6)	190 (32.0)	48 (38.7)	19 (29.2)	44 (31.6)
Female	5,601 (61.4)	404 (68.0)	76 (61.3)	46 (70.8)	95 (68.4)
Race, n (percentage)					
White	7,775 (85.1)	495 (83.3)	104 (83.9)	57 (87.7)	115 (82.7)
Black	463 (5.1)	40 (6.7)	8 (6.4)	5 (7.7)	8 (5.7)
Other[a]	898 (9.8)	59 (9.9)	12 (9.7)	3 (4.6)	16 (11.5)
Comorbidity, n (percentage)					
Coronary Artery Disease	2,125 (23.3)	83 (13.9)	11 (8.9)	10 (15.4)	13 (9.3)
Chronic Renal Failure	1,062 (11.6)	61 (10.3)	14 (11.3)	19 (29.2)	9 (6.5)
Diabetes	1,497 (16.4)	101 (17.0)	17 (13.7)	14 (21.5)	17 (12.2)
Obesity	85 (9.4)	32 (5.4)	7 (5.6)	3 (4.6)	1 (0.7)

[a]"Other race" includes Hispanic, Asian, Native American, unknown, other and not documented.

Table 2

First and average vitamin D levels for each group

	Group				
	Uncomplicated Diverticulosis	**Acute Diverticulitis**	**Complicated Diverticulitis**	**Surgical Diverticulitis**	**Recurrent Diverticulitis**
	N = 9,116	**N = 594**	**N = 124**	**N = 65**	**N = 139**
First vitamin D level, mean (SD), ng/mL	29.1 (14.0)	25.9 (13.4)	25.8 (12.8)	22.7 (14.9)	23.5 (14.0)
p-value[a]		<0.0001	0.0095	0.002	<0.0001
Average vitamin D level, mean (SD), ng/mL	33.0 (12.2)	28.1 (12.7)	28.8 (12.7)	23.9 (13.9)	25.5 (13.7)
p-value[a]		<.0001	.002	<.0001	<.0001

[a] p-value compares each group to the uncomplicated diverticulosis group

Table 3

Vitamin D levels for diverticulosis and diverticulitis patients with and without colonoscopy.

	Colonoscopy		No colonoscopy	
	Diverticulosis	**Diverticulitis**	**Diverticulosis**	**Diverticulitis**
	N = 7,563	**N = 486**	**N = 1,553**	**N = 436**
First vitamin D level, mean (SD), ng/mL	29.7 (13.9)	26.4 (12.9)	26.3 (13.9)	24.1 (14.1)
p-value[a]		<0.0001		0.003
Average vitamin D level, mean (SD), ng/mL	33.7 (10.8)	29.3 (12.2)	29.4 (12.3)	25.8 (13.3)
p-value[a]		<0.0001		<.0001

[a] p-value compares diverticulitis group to diverticulosis group

Table 4

Risk of diverticulitis according to quintiles of serum vitamin D

	Quintile					
	1	**2**	**3**	**4**	**5**	**p Trend**
First 25-(OH)D						
Quintile Median ng/mL[a]	13.0	21.0	29.0	36.0	47.0	
Age-adjusted RR (95% CI)	1	0.71 (0.59–0.87)	0.56 (0.46–0.69)	0.56 (0.46–0.69)	0.45 (0.36–0.56)	<0.0001
Multivariate RR (94% CI)[b]	1	0.71 (0.58–0.87)	0.60 (0.49–0.74)	0.61 (0.49–0.76)	0.49 (0.38–0.62)	<0.0001
Average 25-(OH)D						
Quintile Median ng/mL	18.2	27.3	32.8	38.2	47.8	
Age-adjusted RR (95% CI)	1	0.41 (0.34–0.50)	0.39 (0.32–0.48)	0.31 (0.25–0.38)	0.30 (0.25–0.38)	<0.0001
Multivariate RR (94% CI)[a]	1	0.44 (0.36–0.54)	0.45(0.36–0.55)	0.36 (0.28–0.45)	0.34 (0.27–0.43)	<0.0001

[a]Quintiles based on the distribution of 25(OH)D among individuals with uncomplicated diverticulosis

[b]Adjusted for age, gender, race, diabetes, chronic renal failure, obesity, coronary artery disease, and history of a prior colonoscopy