The Role of Vitamin D in Elderly Inflammatory Bowel Disease Patients

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Abstract: The role of vitamin D has long been discussed in many chronic diseases, and its significance in inflammatory bowel disease has recently gained attention. This article reviews vitamin D homeostasis, the involvement of vitamin D in the pathophysiology of inflammatory bowel disease, and vitamin D deficiency as a result of inflammatory bowel disease. In addition, this article explores the possibility of age, specifically in the elderly population, as a risk factor for developing vitamin D deficiency in patients with inflammatory bowel disease.

Inflammatory bowel disease (IBD), although present in all age groups, is most common in young adults. However, there is an emerging occurrence of IBD in the elderly and pediatric populations.[1] Although the definition of elderly varies among studies, it is usually defined as over 60 to 65 years of age. The proportion of elderly patients with IBD has been increasing over the past 30 years in Western countries.[2] In comparison to younger patients, elderly patients with IBD often present with more subtle abdominal symptoms but similar extraintestinal manifestations.[3,4] Elderly patients with IBD compose a unique patient population to study the role of vitamin D, as these patients are currently not well studied. This article reviews the role of vitamin D in IBD and the possible association between advancing age and vitamin D levels among patients with IBD.

Sources of Vitamin D

Several forms of vitamin D exist, including ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D initially enters the body through gut absorption or subcutaneous synthesis. Of the total synthesized vitamin D, 80% is a product of skin exposed to ultraviolet B radiation, and the resultant 7-dehydrocholesterol is converted into vitamin D3.[5] When absorbed through the gut, vitamin D is predominantly absorbed in the jejunum and ileum[6] and then transported to the liver, where it is transformed into 25-hydroxyvitamin D (25[OH]D) via the 25-hydroxylase enzyme. 25(OH)D is subsequently converted to 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) in the kidneys via the 1-hydroxylase enzyme (Figure).[7] Most circulating vitamin D in the body is in the form of 25(OH)D due to the short half-life of $1,25(OH)_2D$ compared to 25(OH)D.

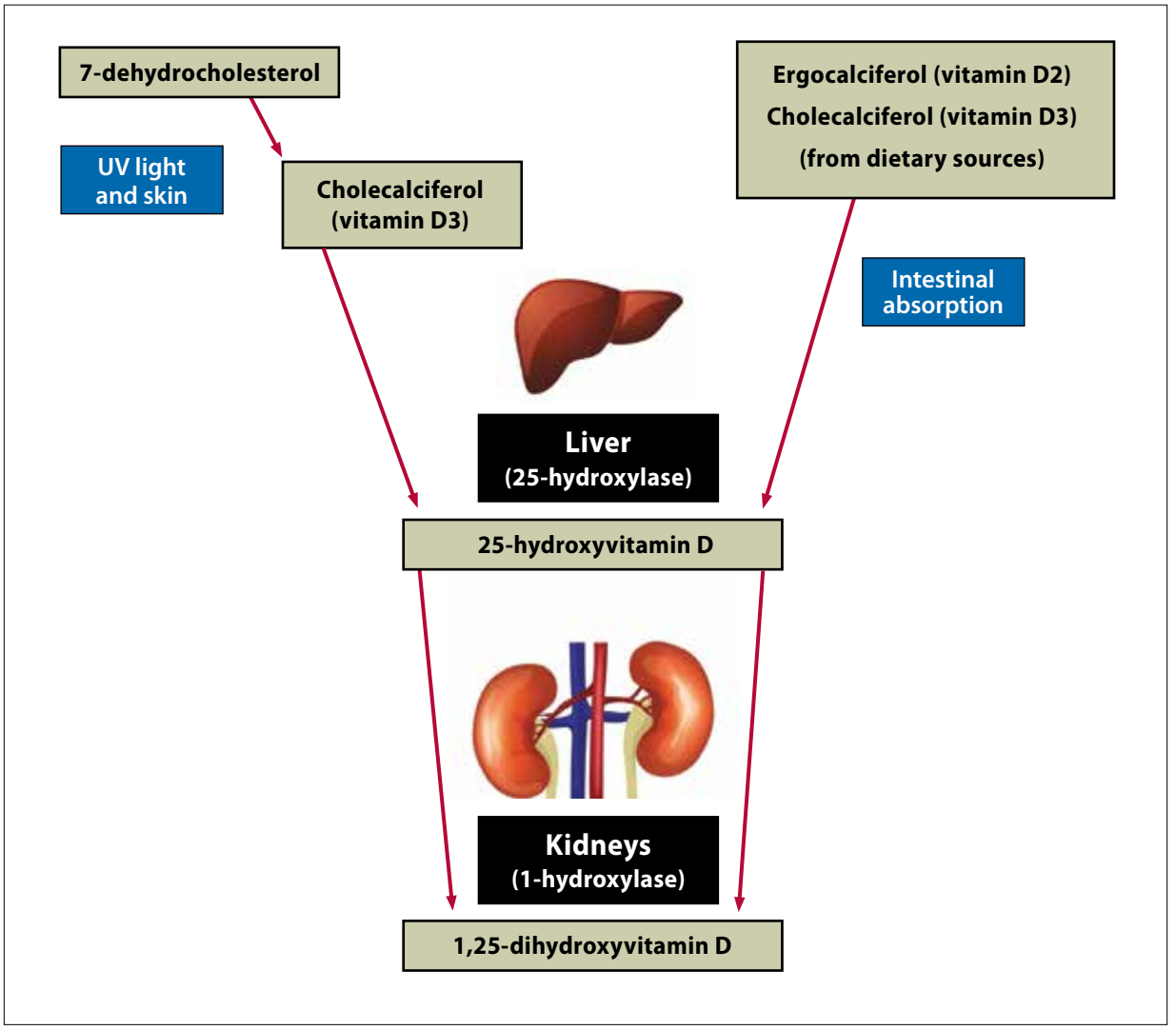

Figure. Synthesis of vitamin D.

UV, ultraviolet.

Physiologic Role of Vitamin D

$1,25(OH)_2D$ is integral to maintaining homeostasis of calcium via intestinal absorption, and further increases calcium levels by stimulating bone resorption and reducing renal calcium excretion. $1,25(OH)_2D$ levels are increased by the parathyroid hormone. Upon detecting inadequate calcium levels, the parathyroid gland secretes parathyroid hormone to increase the 1-hydroxylase enzyme and thereby increase $1,25(OH)_2D$ levels. Additionally, $1,25(OH)_2D$ promotes intestinal phosphate absorption and decreases renal phosphate excretion. Research suggests that vitamin D has a probable role as an anti-inflammatory agent with potential activity against microbes via vitamin D receptors (VDRs) located in most nucleated cells.[8] Recent studies support vitamin D's role through these mechanisms in cancer, depression, dementia, cardiovascular disease, and gastrointestinal diseases.[9,10]

Importance of Vitamin D in Inflammatory Bowel Disease

IBD is a chronic relapsing-remitting inflammatory disease of unclear etiology thought to result from a complex interaction between genetic predisposition, a dysregulated immune response, and an environmental trigger, central to which now appears to be the gut microbiome and its interaction with these factors. Vitamin D has a

protective role in IBD by maintaining the intestinal epithelial barrier through immune interactions that favorably affect the gut microbiome. Furthermore, vitamin D has been noted to influence the gut's immune system by modulating the innate and adaptive immune systems.[11,12] Vitamin D deficiency as a result of IBD has been increasingly recognized to contribute to a dysregulated intestinal immune response.

Pathophysiologic Role of Vitamin D in Inflammatory Bowel Disease

VDRs play a significant role in maintaining the intestinal epithelial barrier between the host commensal microbes and the immune system. Research has shown that VDRs sustain the tight intercellular epithelial junctions and prevent apoptosis of these epithelial cells, thereby preventing the entry of luminal antigens and foreign bacteria as well as the resulting inflammation.[13] In addition, vitamin D helps maintain the intestinal microbiome, which further supports the gut's innate immune system. Cathelicidin peptide acts as an antimicrobial when stored in macrophages and neutrophils. Vitamin D preserves gut homeostasis as an antimicrobial by promoting the expression of cathelicidin peptide. Furthermore, activated VDRs increase CYP3A activity, improving the detoxification of harmful bile acids.[12]

On the other hand, vitamin D may play a proinflammatory role in the development of IBD. In genetically predisposed individuals, vitamin D has been shown to promote the synthesis of CD8 cells. Through the interleukin-17 and interferon-γ pathways, these cells promote inflammation and may play a role in the development of IBD.[14]

Defining Vitamin D Deficiency

The definitions of vitamin D sufficiency, insufficiency, and deficiency vary in the literature. Commonly, 25(OH)D levels of 21 ng/mL and below are considered to be vitamin D–deficient, levels over 21 ng/mL up to 30 ng/mL are considered to be vitamin D–insufficient, and levels of 30 ng/mL up to 75 ng/mL are considered to be vitamin D–sufficient.[15] Using 21 ng/mL as a cutoff has found support in research demonstrating decreased all-cause mortality, as well as cardiovascular disease mortality, above levels of 21 ng/mL.[16] Mechanisms that may explain the increased mortality seen in vitamin D deficiency include suppression of smooth cell proliferation and overstimulation of the renin-angiotensin-aldosterone pathway, leading to higher blood pressure and cardiac muscle hypertrophy.[17] However, other authors have argued for a higher cutoff for vitamin D deficiency. A study suggested that there is a lower risk of colorectal cancer among patients with vitamin D levels above 40 ng/mL,[18] which could be considered sufficient. Of note, there is some evidence that vitamin D deficiency incurs a protective effect on the development of cancer, although this finding is questionable.[19]

Vitamin D Deficiency in Elderly Patients

Elderly patients, including those with IBD and those who are healthy, are assumed to be at an increased risk for vitamin D deficiency. This generalization may be due to decreased sun exposure, lower metabolic activity in aging skin, and decreased consumption of vitamin D–fortified foods. Additionally, decreased muscle mass is considered to be a reservoir of vitamin D, low VDR levels, and hepatic and renal dysfunction in elderly patients, compared to younger patients, further predisposing elderly patients to vitamin D deficiency.[20,21]

Vitamin D Deficiency in Inflammatory Bowel Disease

Significant controversy exists within the literature regarding a possible association between vitamin D deficiency and IBD. If an association does exist, it remains challenging to prove causality (ie, whether IBD causes vitamin D deficiency or whether vitamin D deficiency results in IBD).

Association Between Vitamin D Deficiency and Inflammatory Bowel Disease

Mouli and Ananthakrishnan first noted a correlation between IBD and vitamin D deficiency.[22] The authors used this observation to further explain the north-south gradient among IBD patients because IBD prevalence seems to parallel ultraviolet exposure and vitamin D levels.[22] Additionally, Ananthakrishnan and colleagues noted a 6% relative risk reduction in Crohn's disease and a 4% relative risk reduction in ulcerative colitis per 1 ng/mL increase of serum vitamin D level.[23] They also noticed a risk reduction in ulcerative colitis among women taking vitamin D supplementation.[23] However, the study used predicted vitamin D serum levels in place of measured levels, which may be a limitation. Another study noted VDR polymorphisms to be associated with increased susceptibility to Crohn's disease.[24]

In contrast to the above studies, Opstelten and colleagues found no association between serum vitamin D levels and the risk of Crohn's disease and ulcerative colitis among patients of all ages.[25] However, in patients 60 years and older, low 25(OH)D serum concentrations were slightly associated with the development of ulcerative colitis (odds ratio, 0.84; 95% CI, 0.70-1.00; *P*=.05). This analysis was based on categories of vitamin D concentrations, as shown in the Table. Elderly patients

60 years of age and older who had Crohn's disease did not show any such association when 25(OH)D concentrations were analyzed as a categorical variable based on subcategories of vitamin D deficiency, insufficiency, and sufficiency.

Inflammatory Bowel Disease as a Risk Factor for Vitamin D Deficiency

Few studies have focused on IBD as a risk factor for vitamin D deficiency. Atia and colleagues demonstrated that veterans with Crohn's disease, compared to ulcerative colitis, were more likely to have vitamin D insufficiency and deficiency.[24] Several potential mechanisms can explain the development of vitamin D deficiency in IBD patients, specifically Crohn's disease patients. Intestinal inflammation of the jejunum and ileum during active disease, prior abdominal surgeries, bacterial overgrowth, and disease in the small bowel will result in malabsorption and may hinder vitamin D absorption from dietary sources.[25-27] Additionally, avoidance of dairy products and food aversion result in decreased dietary intake of vitamin D.[26,27] Lastly, medications for IBD management can also lead to vitamin D deficiency. Although IBD patients may already feel disabled due to their disease, thiopurines' possible interaction with sunscreen products may discourage the patients from participating in outdoor activities.[28]

Vitamin D Supplementation in Inflammatory Bowel Disease

Given the risk factors for vitamin D deficiency in IBD, and the possibility that vitamin D deficiency furthers disease progression, several studies have analyzed vitamin D supplementation as a treatment modality in IBD. Jorgensen and colleagues demonstrated that among patients with Crohn's disease in remission, vitamin D supplementation with 1200 IU daily significantly increased serum vitamin D levels.[29] Additionally, relapse rates were lower among treated patients. Although these results did not reach statistical significance, they highlight the possibility of supplementation as a treatment modality.[29] Research has shown that the active form of vitamin D ($1,25[OH]_2D$), when compared to 25(OH)D, incurred these disease improvements, as measured by the Crohn's Disease Activity Index and a decrease in C-reactive protein level.[30] These results were replicated in ulcerative colitis patients as well.[31]

Although the above studies did not specifically target IBD patients with vitamin D deficiency, and treated all patients with IBD, Mathur and colleagues specifically treated vitamin D–deficient (defined as <30 ng/mL) ulcerative colitis patients with vitamin D supplementation (2000 or 4000 IU daily).[32] Among the 18 patients randomized, the authors found that the higher dose (4000 IU daily) was more effective at increasing serum vitamin D levels above 30 ng/mL. However, no statistically significant improvement was noted in the Mayo Ulcerative Colitis Score, although the results did trend toward improvement with the higher dose.[32] In contrast, among 10 patients with active Crohn's colitis or ulcerative colitis, Garg and colleagues found that the improved serum levels of vitamin D among IBD patients treated with vitamin D supplementation did not correlate with objective measures of intestinal or systemic inflammation.[33]

Vitamin D Deficiency in Elderly Patients With Inflammatory Bowel Disease

With this background, a priori, it might be suspected that elderly IBD patients are more at risk for vitamin D deficiency, given the double risk factors of IBD as well as age. Interestingly, there are a very limited number of studies addressing this association.

In a retrospective study, Juneja and colleagues assessed vitamin D deficiency and IBD severity in the elderly population.[26] They found that 15.3% of elderly IBD patients had overt vitamin D deficiency, defined as 25(OH)D less than 9 ng/mL (11.3% in Crohn's disease; 17.7% in ulcerative colitis). Although the study did not have a comparative younger cohort, the authors noted that vitamin D deficiency rates were lower than in the published literature of IBD patients of all ages, suggesting that elderly IBD patients are less at risk of developing vitamin D deficiency compared to younger IBD patients. Notably, the definition of vitamin D deficiency that was used is a lower level of vitamin D compared to that used in most studies. However, the authors reported significant correlation between the duration of Crohn's disease and vitamin D deficiency. The average length of disease noted in the patients with vitamin D deficiency was 28.9 years, compared to 12.8 years (P=.003) in patients without vitamin D deficiency. There was no similar correlation in elderly patients with ulcerative colitis.

Kabbani and colleagues evaluated vitamin D levels and IBD status in elderly patients.[34] The study compared elderly patients (>65 years) to middle-aged (45-65 years) and young (<45 years) patients with IBD. Older patients were less likely to have vitamin D deficiency (19.4%) when compared to the younger population (34.8%). Of note, the elderly cohort was only 9% of the entire IBD cohort.

Assessing Age as a Risk Factor for Vitamin D Deficiency in Inflammatory Bowel Disease

Evidence Against Age as a Risk Factor

Separate from viewing elderly patients in isolation, the following studies have analyzed age as a risk factor for developing vitamin D deficiency among IBD patients. Frigstad and colleagues reported that, among 408

Table. Aggregate of 25(OH)D Levels in IBD Patients in Various Studies

Study	Number of Patients		Age, yrs	25(OH)D Status		
	CD	UC		Deficient	Insufficient	Sufficient
Ananthakrishnan et al[23,a]	122	123	53 (median)			
Opstelten et al[25,b]	72	169	≥60	32% (CD) vs 40% (control) 52.5% (UC) vs 39.8% (control) (<30.05 ng/mL)		16% (CD) vs 22% (control) 18.6% (UC) vs 22% (control) (≥30.1 ng/mL)
Atia et al[24]	43	80	64 (mean)	51.2% (CD) 30.0% (UC) *P*≤03 for all data	83.7% (CD) 57.5% (UC) *P*≤03 for all data	
Juneja et al[26,c]	150	243	≥65	15.3% (<9 ng/mL) 11.3% (CD) 17.7% (UC)		
Kabbani et al[34]	597	367	<45	34.8% (<29 ng/mL)		
			45-65	28.4%		
			>65	19.4% *P*=.005 for all data		
Frigstad et al[35]	230	178	40 (median)	53% (CD) 44% (UC)		
Han et al[36]	34	49	32 (mean)	39.8% (<10 ng/mL)	49.4% (10-19 ng/mL)	
			<40	47.1%		
			≥40	28.1%		
Pallav et al[37]	139	98	≥65	15.4% (≤20 ng/mL)	38.5% (21-29 ng/mL)	46.2% (≥30 ng/mL)
Venkata et al[21]	196	0	45[d] 54	58.7% (<30 ng/mL)		41.3% (≥30 ng/mL)
Ulitsky et al[38,e]	403	101	43 (mean)	49.8%		24.4%
Leslie et al[39,f]	56	45	47 (mean)	5.9% (<10 ng/mL)	72.3% (10-29 ng/mL)	21.8% (≥30 ng/mL)

25(OH)D, 25-hydroxyvitamin D; CD, Crohn's disease; IBD, inflammatory bowel disease; OR, odds ratio; UC, ulcerative colitis.

[a]Median age at diagnosis of IBD and median 25(OH)D levels are shown. The average 25(OH)D levels are 22.9 ng/mL (range, 7.3-24.9) in quartile 1, 26.3 ng/mL (range, 24.9-27.6) in quartile 2, 28.7 ng/mL (range, 27.6-30.0) in quartile 3, and 27.6 ng/mL (range, 7.3-38.6) in quartile 4.

[b]OR of serum 25(OH)D concentrations associated with development of IBD. Serum concentrations are converted from nmol/L to ng/mL. The 25(OH)D status is ≤15 ng/mL and OR, 1.00 for quartile 1; 15.01-22.0 ng/mL and OR, 1.86 (range, 0.72-4.83) for quartile 2; 22.01-28.1 ng/mL and OR, 0.97 (range, 0.35-2.69) for quartile 3; and ≥28.2 ng/mL and OR, 0.71 (range, 0.25-2.04) for quartile 4.

[c]Average length of IBD in patients with vitamin D deficiency is 28.9 years and 12.8 years in patients without vitamin D deficiency.

[d]45 years is the average age of patients in the group with low vitamin D levels (<30 ng/mL) and 54 years is the average age of patients in the group with vitamin D sufficiency (≥30 ng/mL).

[e]Patients with vitamin D deficiency had a later onset of disease than those who were sufficient and insufficient (30.2 years vs 27.3 years; *P*=.03).

[f]The mean serum 25(OH)D concentration is 24.4 ng/mL for patients younger than 50 years and 22.6 ng/mL for patients over 50 years. 51 patients were younger than 50 years and 50 patients were over 50 years.

Norwegian patients with IBD, age was not significantly associated with vitamin D concentrations.[35] Han and colleagues described similar findings in Korean patients.[36] Using univariate binary logistic regression analysis, the authors found that patients younger than 40 years were at risk for vitamin D deficiency; however, a multivariate logistic regression analysis showed only female sex and the presence of Crohn's disease to be associated with vitamin

D deficiency.[36] Among American patients, Pallav and colleagues found only African-American race and body mass index greater than 30, but not age, to be associated with vitamin D deficiency among IBD patients.[37]

In Support of Age as a Risk Factor

Different results were reported by Kabbani and colleagues, who found that elderly IBD patients were less likely to have vitamin D deficiency, concluding that younger age was a risk factor.[34] Similarly, Venkata and colleagues found younger age to be associated with vitamin D deficiency.[21] The authors divided 196 patients with IBD into cohorts based on vitamin D levels and assessed risk factors for hospital admission. Upon review of baseline characteristics of the 2 cohorts, the authors noted that the vitamin D–deficient cohort was significantly younger than the vitamin D–sufficient cohort, supporting younger age to be associated with vitamin D deficiency among IBD patients.

Alternatively, 2 studies have demonstrated that increasing age may be a risk factor for vitamin D deficiency in IBD. Ulitsky and colleagues retrospectively divided 504 IBD patients into cohorts based on vitamin D levels.[38] The authors found that vitamin D–deficient patients were statistically significantly older than vitamin D–sufficient patients, although the age difference may not be clinically significant (44.6 years vs 40.6 years; P=.004).[38] Leslie and colleagues reported that patients younger than 50 years had slightly higher vitamin D levels compared to patients above 50 years (60.8 ng/mL vs 56.4 ng/mL).[39] However, because both studies only showed modest results, it cannot be concluded that they support the possibility of age being a significant contributor to vitamin D deficiency.

Summary

The role of vitamin D in IBD remains poorly understood. Vitamin D may play a role as a risk factor for disease pathogenesis and/or a consequence of the disease. It might be assumed that elderly patients are particularly vulnerable to developing vitamin D deficiency due to decreased absorption, activation, and storage of vitamin D, yet conflicting data exist regarding age as a risk factor. Few clinical studies are dedicated to elderly patients with IBD, and contradictory data exist regarding the likelihood of elderly IBD patients having vitamin D deficiency. Currently, there are no specific recommendations for vitamin D supplementation in IBD patients. Further studies and guidelines are necessary to elucidate the optimal vitamin D level among elderly IBD patients, as well as to determine whether supplementation significantly alters disease development, disease progression, or quality of life.

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