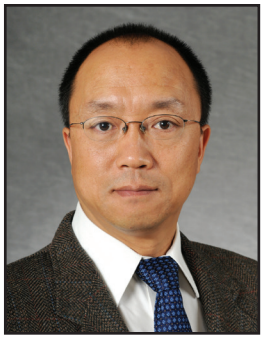
Carol Rees Parrish, M.S., R.D., Series Editor

Vitamin D Deficiencies in Patients with Disorders of the Digestive System: Current Knowledge and Practical Considerations



Zhiyong Han

Samantha L. Margulies

Divya Kurian

Mark S. Elliott

There is a considerably high prevalence of vitamin D deficiency in patients with various disorders of the digestive system, including cystic fibrosis, acute and chronic pancreatitis, celiac disease, short bowel syndrome and inflammatory bowel disease. There are different causes of the vitamin D deficiency, and accordingly, there are different strategies for normalization of the vitamin D status in patients. In general, vitamin D normalization is beneficial for most patients. However, because there is evidence suggesting that vitamin D may be a negative acute-phase reactant, and as such is down-regulated during acute pancreatitis, it may be prudent to hold off on supplementing during the acute phase (and perhaps wait until the acute phase passes before checking levels) until there is evidence supporting benefit.

BRIEF INTRODUCTION TO VITAMIN D METABOLISM

Vitamin D had been considered as a dietary essential nutrient for the human body until it became obvious that it is a natural hormone of the human body. That is, vitamin D is synthesized in the human body and acts in ways that are no different from a steroid hormone.[1]

However, vitamin D synthesis is unique in that it depends on the irradiation of the epidermis of the skin by UV-B (ultraviolet B) light. Briefly, the energy of UV-B photons causes a structural change in 7-dehydrocholesterol, yielding pre-vitamin D3. The pre-vitamin D3 then spontaneously isomerizes to vitamin D3 (also called cholecalciferol). Vitamin D3 is exported to the blood circulation from the skin and is sequentially metabolized to:

- 25(OH)D3 (25-hydroxyvitamin D3, or calcidiol) mainly by the enzyme, CYP2R1 (25-hydroxylase), in the liver
- then to $1,25(OH)_2D3$ (1,25-dihydroxyvitamin D3, also called "calcitriol") by the enzyme, CYP27B1 (1-α-hydroxylase), in the epithelial cells of the proximal convoluted tubules in the kidney.[1]

Of the different forms of vitamin D, only $1,25(OH)_2D3$ has biological activity.[1] The $1,25(OH)_2D3$

Zhiyong Han PhD[1] Samantha L. Margulies[2] Divya Kurian[2] Mark S. Elliott PhD[1] [1]Department of Biochemistry and Molecular Medicine, [2]MD Class of 2016, The George Washington University School of Medicine and Health Sciences, Washington, DC

in the blood circulation acts as an endocrine hormone to stimulate vitamin D receptor (VDR)-dependent gene regulation for intestinal absorption of Ca^{2+} and renal reabsorption of Ca^{2+} for the maintenance of a healthy blood Ca^{2+} level.[1] PTH (parathyroid hormone) and reduced serum ionized calcium concentration induce renal CYP27B1 activity, thereby stimulating the renal production of $1,25(OH)_2D3$; increased concentrations of $1,25(OH)_2D3$, serum calcium or phosphorus have the opposite effect (reduce CYP27B1 activity).[1]Similar to other hormone systems, $1,25(OH)_2D3$ has a negative feedback effect on PTH production. Therefore, patients with chronic kidney disease have reduced production of $1,25(OH)_2D3$ and are likely to have increased PTH secretion and secondary hyperparathyroidism.

Although proximal tubules of the kidneys are the primary site of $1,25(OH)_2D3$ production, activated macrophages in extrarenal tissues have also been shown to possess CYP27B1.[2] Thus conditions such as sarcoidosis can result in increased production of $1,25(OH)_2D3$ in macrophages which can lead to hypercalcemia.[2] The $1,25(OH)_2D3$ produced in these tissues acts locally in an intracrine or paracrine fashion to stimulate VDR-dependent expression of genes to affect the functions of these cells.[2] This explains the potential immunomodulatory effects of VDR-activating synthetic vitamin D analogs shown in some studies.[3,4] The production of $1,25(OH)_2D3$ in extrarenal tissues is independent of the blood levels of Ca^{2+} and PTH.

Vitamin D Deficiencies in Patients with Disorders of the Digestive System

The 25(OH)D3 circulates in the blood at ng/mL concentrations with a half-life of approximately 15 days whereas the $1,25(OH)_2D3$ circulates at pg/mL concentrations with a half-life of approximately 15 hours.[5] Therefore, blood levels of 25(OH)D3 are commonly used for the determination of vitamin D status in the body because of convenience for technique reasons. Although controversy exists in the literature, vitamin D status is defined by the Endocrine Society as follows:

- Vitamin D deficiency is defined by a serum 25(OH)D3 level of $\leq$20 ng/mL
- Vitamin D insufficiency by a serum 25(OH) D3 level of 21-29 ng/mL
- Vitamin D sufficiency by a serum 25(OH) D3 level of $\geq$30 ng/mL.[6]

Given the above definition of vitamin D deficiency, vitamin D deficiency occurs in 40-60% of patients with various intestinal disorders, including celiac disease, short bowel syndrome, cystic fibrosis, Crohn's disease and ulcerative colitis.[7] In addition, up to 70% patients with acute or chronic pancreatitis develop vitamin D deficiency.[8-11] Strikingly, it appears that over 40% of the patients with acute pancreatitis at the time of admission had severe vitamin D deficiency – that is, their serum

Table 1. Major Causes of Vitamin D Deficiency in Patients with Intestinal Disorders*

Cause	Mechanism
Insufficient solar UV-B exposure	Reduced conversion of 7-dehydrocholesterol to vitamin D3 in the epidermis due to insufficient UV-B photons
Dark skin colors (high melanin)	Reduced conversion of 7-dehydrocholesterol to vitamin D3 in the epidermis due to absorption of UV-B photons by melanin
Winter in high latitude locations (35^0 North or South)	Reduced conversion of 7-dehydrocholesterol to vitamin D3 in the epidermis due to significant reduction in the solar UV-B
Intestinal Inflammation	Increased CYP27B1-catalyzed conversion of 25(OH)D3 to $1,25(OH)_2D3$ in the inflamed intestine, independent of PTH
Hyperparathyroidism secondary to hypocalcemia due to calcium wasting	Increased PTH-dependent, CYP27B1-catalyzed renal conversion of 25(OH)D3 to $1,25(OH)_2D3$

*For detailed information, please see reference 7

Table 2. Causes of Reduced Vitamin D Absorption Capacity of the Small Intestine in Patients with Disorders of the Digestive System*

Disease	Mechanism
Small bowel resection	Reduced intestinal surface area for vitamin D absorption
Cystic fibrosis	Malabsorption and steatorrhea-mediated wasting of vitamin D due to indigestion and malabsorption of fat
Crohn's disease	Reduced intestinal surface area for vitamin D absorption due to villous atrophy
Chronic pancreatitis Pancreatic cancer	Malabsorption and steatorrhea-mediated wasting of vitamin D due to indigestion and malabsorption of fat
Quiet Crohn's disease	Unknown

*For detailed information, please see references 7, 8 and 9

levels of 25(OH)D3 were less than 10 ng/ml.[10,11]

The high rates of vitamin D deficiency in patients with intestinal disorders and chronic pancreatitis are closely correlated with increased incidence of osteopenia and osteoporosis or low-trauma fracture .[7,12]

Except in cases of acute pancreatitis, the causes of vitamin D deficiency in patients with disorders of the digestive system appear to include:

1. Insufficient cutaneous synthesis of vitamin D
2. Hyperparathyroidism secondary to hypocalcemia that results from calcium wasting
3. Inflammation-associated conversion of 25(OH)D3 to 1,25$(OH)_2$D3 (Table 1).[7]

However, vitamin D deficiency in patients with acute pancreatitis at the time of admission is likely an acute event caused by an as-of-yet unidentified mechanism that actively down-regulates the blood 25(OH)D3 level during pancreatic inflammation.[10,11]

Insufficient cutaneous synthesis of vitamin D in patients due to inadequate solar UV-B exposure is a major cause of vitamin D deficiency.[7] The rate of pre-vitamin D synthesis in the epidermis is inversely related to the amount of melanin in the skin as melanin is an excellent UV-B absorbent, hence, the rate of vitamin D deficiency is higher in patients with darker skin than in those with fair skin in the same season (Table 1). Furthermore, since the solar UV-B doses are substantially reduced in geographical locations of high latitudes (>35° North [ex. Albuquerque, Memphis, Charlotte] or < 35° South [Adelaide, Auckland, Melbourne]) in the winter as a result of the solar zenith angle,[13] the rate of vitamin D deficiency is much higher during the winter months than during the summer months of the same patient population.[7] The significance of solar UVB exposure for the maintenance of a sufficient serum level of 25(OH)D3 is further highlighted by the fact that sunlight exposure, but not fat malabsorption, is a more important determinant of vitamin D levels in preadolescent children with cystic fibrosis,[7] and that the amount of sunlight exposure, but not even an oral supplementation of up to 800 IU vitamin D/day, was the key determinant to the serum vitamin D level over a period of four years in a cohort of patients with cystic fibrosis.[14]

Hyperparathyroidism secondary to hypocalcemia, which can result from gastrointestinal loss of calcium, often develops in patients with celiac disease and gastrectomy,[7] and possibly in others with steatorrhea. Thus, excessive renal conversion of 25(OH)D3 to 1,25$(OH)_2$D3 due to hyperparathyroidism can cause a reduction in the serum levels of 25(OH)D3 in patients with celiac disease and gastrectomy.[7]

Active intestinal conversion of 25(OH)D3 to 1,25$(OH)_2$D during an inflammatory flare is independent

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of blood levels of PTH and calcium and appears to be primarily induced by the inflammatory cytokine, TNFα, because neutralization of TNFα with therapeutic antibody can effectively restore the blood level of 25(OH)D3 in individuals with different inflammatory conditions.[7] Thus, conversion of 25(OH)D3 to $1,25(OH)_2D3$ in the inflamed intestine "drains" 25(OH) D3 from the blood circulation to the inflamed intestine, and hence reduces the blood 25(OH)D3 level. The significance of the intestinal production of $1,25(OH)_2D$ during an inflammatory flare is that $1,25(OH)_2D3$ acts locally to activate a biofeedback mechanism to enhance antimicrobial activity of macrophages and promote the intestinal epithelial barrier and tissue healing,[15] and additionally, to cause suppression of the activities of pro-inflammatory T helper cells (i.e., Th1 and Th17 cells) in the intestine to prevent excessive inflammatory damage to the intestine.[2]

The severe vitamin D deficiency in patients with acute pancreatitis[10,11] deserves special attention. In an observational study, 74.4% (58/78) of patients admitted with acute pancreatitis were found to be vitamin D deficient (< 20ng/mL) the first 2 days of their admission.[10] In a prospective study, patients not only had documented vitamin D deficiency at the time of admission, there was a progressive decrease in the blood level of 25(OH)D3 from day 0 to day 2 as a result of pancreatic inflammation.[11] Given that inflammation is known to cause macrophage-mediated conversion of 25(OH)D3 to $1,25(OH)_2D3$,[2] which may lead to hypercalcemia,[16] which can cause acute pancreatitis,[17] it seems active down-regulation of the blood 25(OH)D3 level is beneficial for patients with acute pancreatitis: it would reduce the substrate available for the production of $1,25(OH)_2D3$ to a level that is high enough to cause hypercalcemia, which can exacerbate acute pancreatitis. Thus, it is reasonable to suspect 25(OH)D3 as a negative acute-phase reactant, specifically during the process of acute pancreatitis.

Normalization of Vitamin D Status in Patients with Disorders of the Digestive System

Not counting vitamin D supplements, there are two sources of vitamin D for the human body: vitamin D present in foods and vitamin D3 synthesized in the epidermis upon UV-B irradiation. Most natural foods, except certain fatty fish (e.g. salmon, bluefish, mahi-mahi and swordfish) and a few species of edible mushroom, are poor sources of vitamin D.[7] There are few types of vitamin D-fortified food, such as milk, orange juice and breakfast cereals.[7] Given the fact that a minimal daily intake of 600 IU of vitamin D is needed for individuals with minimal sunlight exposure to maintain vitamin D,[18] it is unrealistic for many to rely on eating vitamin D-fortified foods to acquire adequate vitamin D3.

Therefore, it is important to inform patients that having sufficient solar UV-B exposure can result in cutaneous synthesis of the amount of vitamin D that the body needs. For the determination of sunlight exposure time to avoid sun burn, physicians could teach patients how to use the solar UV-B calculator (http://zardoz.nilu.no/~olaeng/fastrt/VitD_quartMED.html) developed by Webb and Engelsen.[19] Alternatively, physicians could use short-term UV-B light therapy to stimulate cutaneous synthesis of vitamin D in patients.[20,21] However, the UV-B light treatment seems ineffective for patients with chronic pancreatitis;[22] in addition, patients should be warned that UV-B exposure has added health risks, such as skin cancer.

Vitamin D absorption occurs mainly in the jejunum and terminal ileum.[23] Therefore, patients with ulcerative colitis, which rarely involve the small intestine, may still have normal intestinal vitamin D absorption capacity. However, patients with active Crohn's disease or short bowel syndrome have reduced intestinal surface area for vitamin D absorption (Table 2). Patients with cystic fibrosis and chronic pancreatitis have fat maldigestion and malabsorption and consequently malabsorption- and diarrhea-mediated wasting of vitamin D (Table 2). The reduced intestinal absorption of vitamin D or wasting of vitamin D explains why daily intake of up to 800 IU vitamin D is ineffective in normalization of the vitamin D status in these patients,[14] and it also explains why normalization of the vitamin D status in these patients require long term treatments with higher doses of oral vitamin D3 supplementation (Table 3).

In addition to vitamin D3 supplements, vitamin D2 (ergocalciferol) supplements are also widely used by patients. However, the blood level of 25(OH)D2 (25-hydroxyvitamin D2) cannot be accurately measured by certain commonly used methods, and thus the effect of vitamin D2 treatment on the blood vitamin D level cannot be accurately determined.[24] In addition, it has been suggested that the use of vitamin D3 is preferable because vitamin D2 treatment is considered by some

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investigators to be less effective than vitamin D3 treatment.[25]

The Cystic Fibrosis Foundation guideline recommends that all patients maintain a serum 25(OH) D level of at least 30 ng/ml.[26] Hall et al. reviewed available evidence and recommend to treat patients with cystic fibrosis less than five years old with 12,000 IU vitamin D3 bi-weekly and for older patients with 50,000 IU vitamin D3 bi-weekly.[27]

For most patients with celiac disease, adhering to gluten-free diets for 6 months or longer can result in the normalization of the vitamin D status (Table 3).[7,28]

For patients with chronic pancreatitis, long-term supplementation of extremely high oral doses of vitamin D, 20,000 – 60,000 IU/week or even 140,000 IU/week (20,000 IU/day), are required (Table 3).[8]

For patients with short bowel syndrome, very high doses of vitamin D3 may be needed. In addition, an intake of 1,500 mg calcium/day should be considered if the patients develop bone metabolic disorders (Table 3).[29,30]

For patients with Crohn's disease, it is recommended that the blood level of 25(OH)D3 be raised to above 30 ng/ml.[31,32] Numerous studies have demonstrated that treatment of patients with 2000 IU vitamin D3/day over a prolonged period of time is necessary to raise the blood levels of 25(OH)D3 to above 30 ng/ml (Table 3).[7] In particular, the study by Raftery and colleagues[31] demonstrated that if the blood level of 25(OH)D3 in patients with Crohn's disease in remission is raised to above 30 ng/ml, it can reduce the rate of relapse and promote the maintenance of intestinal permeability and cause elevated serum levels of LL-37 (cathelicidin, an antimicrobial peptide that promotes intestinal healing and reduces intestinal inflammation) and higher quality of life score.

However, it should be noted that normalization of the vitamin D status in some patients may not be achieved even with super high oral doses of vitamin D3 supplementation (e.g., 10,000 to 50,000 IU vitamin D3 daily). Therefore, the symptoms of vitamin D deficiency of these patients may be treated with calcitriol (0.5 mg) or synthetic, biologically active vitamin D analogs, such as paricalcitol (1 mg) twice daily, daily or less frequently.[3,4,33] However, there is no guarantee that calcitriol and vitamin D analogs would be easier to absorb. Also, it would be prudent for physicians to monitor the blood levels of calcium, phosphate and PTH in patients to prevent possible development of hypercalcemia.

CONCLUSION

It appears that elevation of the blood levels of 25(OH) D3 to >30 ng/ml is beneficial to patients with various disorders of the digestive system. To achieve this, it is reasonable to first start patients on clinically tried regimens, depending on the disorder, for 2-3 months (Table 3). If the treatment fails to achieve the goal, then different forms such as tablets (crushed),

Table 3. Oral Vitamin D Supplementations for Normalization of the Vitamin D Status in Patients.

Disorder	Treatment	Reference
Cystic fibrosis	1,200 IU vitamin D3 every two weeks for patients < 5-year-old 5,000 IU vitamin D3 every two weeks for other patients	(7)
Crohn's disease	2,000 IU vitamin D3/day	(7)
Celiac disease	Gluten-free diets + 1,000 mg calcium/day + 32,000 IU vitamin D3/week	(7, 28)
Chronic pancreatitis	20,000 – 60,000 IU vitamin D3/week (140,000 IU vitamin D3/week if necessary)	(8)
Short bowel syndrome	50,000 IU vitamin D3 every other day until normalization 20,000-40,000 IU vitamin D3/week	(29, 30)

liquid, or higher doses and longer treatment may be needed; intramuscular injections of high-dose vitamin D3 ("Arachitol", Solvay Pharmacia) may also be considered.[34-36] Nevertheless, patients must be individually monitored on a regular basis to ensure that adjustment of dose, form, or route of administration of vitamin D is made in a timely manner.

Finally, even though it is not conclusive at the present time that 25(OH)D3 is truly a negative acute-phase reactant in the context of acute pancreatitis, given that inflammation-associated production of $1,25(OH)_2D3$ can cause hypercalcemia,[16] which is an established cause of acute pancreatitis,[17] it is critical that physicians conduct thorough investigations before deciding to give patients with acute pancreatitis vitamin D replacement therapy simply because their serum 25(OH)D3 levels are low at the time of admission. ■

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