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Vitamin D Deficiency in Patients with Pancreatitis: Is Vitamin D Replacement Required?

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Abstract

Clinical findings have shown that approximately 40% of patients with pancreatitis, acute or chronic, have severe vitamin D deficiency; this can reach up to 60% of patients with chronic pancreatitis. These findings raise an important question: Is vitamin D deficiency a cause or a result of pancreatitis? The answer(s) to this question is clinically important given that high oral doses of vitamin D supplementation are widely prescribed for individuals with vitamin D deficiency. Considering that there is active conversion of 25(OH)D3 to 1,25(OH)2D3 by activated macrophages in tissues undergoing inflammation, that elevation of the blood levels of 1,25(OH)2D3 levels can cause hypercalcemia, that hypercalcemia can precipitate pancreatitis, that excessive use of vitamin D supplementation can cause acute pancreatitis and that sarcoidosis causes elevated blood levels of 1,25(OH)2D3, hypercalcemia and acute pancreatitis, it is reasonable to consider both 25(OH)D3 and 1,25(OH)2D3 as negative acute-phase reactants, specifically in the context of the pathogenesis of pancreatitis. Thus, down-regulation of blood levels of 25(OH)D3 and 1,25(OH)2D3 in patients with pancreatitis appears to be a protective mechanism to prevent the development hypercalcemia, which would exacerbate the pancreatitis. Therefore, it is reasonable to consider that vitamin D replacement treatment may produce more harm than benefit for patients with pancreatitis.

Keywords: Vitamin D deficiency; Inflammation; Acute pancreatitis; Sarcoidosis; Negative-Phase reactant; Hypercalcemia

Classic View of Vitamin D Metabolism

Unlike most other vitamins that are dietary essential nutrients for the human body, vitamin D is synthesized in the human body and acts like a steroid hormone [1]. As outlined in Figure 1, vitamin D metabolism in the human body starts with the UVB (ultraviolet light B) photon-stimulated structural change in 7-dehydrocholesterol to yield vitamin D3 in the epidermis of the skin. Vitamin D3 is then converted to the biologically active 1,25(OH)2D3 through two sequential hydroxylation reactions. Vitamin D3 is first hydroxylated mainly by the enzyme, CYP2R1, to become 25(OH)D3 in the liver; then 25(OH)D3 is hydroxylated to become 1,25(OH)2D3 by the enzyme, CYP27B1, in the epithelial cells of the proximal convoluted tubule in the kidney [1]. PTH (parathyroid hormone), which is released by the parathyroid glands in response to decreasing blood calcium level, stimulates CYP27B1 activity in the epithelial cells of the proximal convoluted tubules in the kidney, thereby regulating the rate of renal conversion of 25(OH)D3 to 1,25(OH)2D3 [1]. The PTH-regulated renal production of 1,25(OH)2D3 is the primary source of the 1,25(OH)2D3 in the blood circulation because individuals with renal failure have decreased blood levels of 1,25(OH)2D3 [2]. The biologically active 1,25(OH)2D3 binds to and stimulates the transcription activity of the nuclear VDR (vitamin D receptor) in target cells to regulate expression of genes, thus changing cellular activities [1]. Specifically, 1,25(OH)2D3 stimulates VDR-mediated expression of calcium transporters in the small intestine and kidney to stimulate intestinal absorption of calcium and renal reabsorption of calcium for the maintenance of blood calcium homeostasis and bone

health [3,4]. Therefore, chronic, excessive renal production of 1,25(OH)2D3 is a major cause of hypercalcemia.

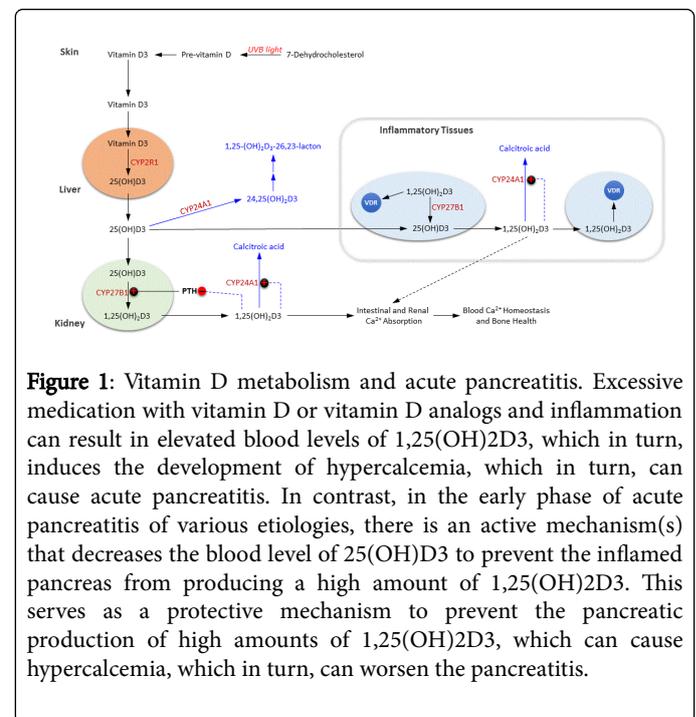


Figure 1: Vitamin D metabolism and acute pancreatitis. Excessive medication with vitamin D or vitamin D analogs and inflammation can result in elevated blood levels of 1,25(OH)2D3, which in turn, induces the development of hypercalcemia, which in turn, can cause acute pancreatitis. In contrast, in the early phase of acute pancreatitis of various etiologies, there is an active mechanism(s) that decreases the blood level of 25(OH)D3 to prevent the inflamed pancreas from producing a high amount of 1,25(OH)2D3. This serves as a protective mechanism to prevent the pancreatic production of high amounts of 1,25(OH)2D3, which can cause hypercalcemia, which in turn, can worsen the pancreatitis.

To prevent hypercalcemia, there are multiple feedback mechanisms to regulate the renal synthesis of 1,25(OH)2D3: 1,25(OH)2D3 induces suppression of PTH release by the parathyroid glands; 1,25(OH)2D3 induces suppression of CYP27B1 activity in the kidney, thus inhibiting

its own synthesis; 1,25(OH)₂D₃ stimulates the expression of CYP24A1, which is the enzyme that degrades 1,25(OH)₂D₃ and 25(OH)D₃ to biologically inactive calcitric acid and 1,25-dihydroxyvitamin D₃-26,23-lactone, respectively [1,5]. The importance of CYP24A1-mediated degradation of vitamin D for the maintenance of the homeostasis of blood 1,25(OH)₂D₃ is underscored by the fact that humans and animals with deficiencies of CYP24A1 have abnormally high blood levels of 1,25(OH)₂D₃, which causes recurrent hypercalcemia and complications of hypercalcemia [6-10].

The 25(OH)D₃ circulates in the blood at ng/mL concentrations with a half-life of 15 days or longer, whereas 1,25(OH)₂D₃ circulates at pg/mL concentrations with a half-life of approximately 15 hours [11,12]. Although it has been reported that 25(OH)D₃ has biological activity [13], 1,25(OH)₂D₃ is generally considered to be the biologically active vitamin D [1]. However, serum levels of 25(OH)D₃, but not 1,25(OH)₂D₃, are often measured for the determination of the vitamin D status in patients. Furthermore, although different investigators may use different cut-off values to define the vitamin D status, the Endocrine Society defines vitamin D deficiency as a serum 25(OH)D₃ level of 20 ng/mL (50 nmol/L) or less, vitamin D insufficiency as a serum 25(OH)D₃ level of 21-29 ng/mL (52.5-72.5 nmol/L), and vitamin D sufficiency as a serum 25(OH)D₃ level of 30 ng/mL (75 nmol/L) or higher [14].

Vitamin D Metabolism in Extrarenal Tissues

Besides kidney, CYP27B1 is also expressed in various extrarenal tissues, such as the colon, parathyroid gland, prostate gland, breast, brain, placenta and pancreas, for local production of 1,25(OH)₂D₃ [15]. The extrarenal synthesis of 1,25(OH)₂D₃ is not regulated by PTH and is uncoupled from the maintenance of the blood calcium homeostasis [16]. It is important to note that there is accelerated CYP27B1-catalyzed conversion of 25(OH)D₃ to 1,25(OH)₂D₃ by activated macrophages in the extrarenal tissues undergoing inflammation [16]. This explains why patients with different inflammatory diseases, such as sarcoidosis [17-21], rheumatoid arthritis [22-25], pulmonary tuberculosis [26-29], inflammatory bowel disease [30-32] and leprosy [33], have elevated blood levels of 1,25(OH)₂D₃ and develop hypercalcemia.

It should be noted that the synthesis of 1,25(OH)₂D₃ in extrarenal tissues is not intended to raise the systemic level of 1,25(OH)₂D₃. Instead, the 1,25(OH)₂D₃ molecules produced in these tissues act through intracrine and paracrine mechanisms to regulate VDR-dependent activities of the local cells. However, excessive production of 1,25(OH)₂D₃ in extrarenal tissues can result in spilling over of 1,25(OH)₂D₃ to the blood circulation, thus raising blood levels of 1,25(OH)₂D₃, which in turn can cause hypercalcemia [18-32]. Therefore, extrarenal production of 1,25(OH)₂D₃ can have deleterious consequences, such as the development of acute pancreatitis as discussed below.

Hypercalcemia and Acute Pancreatitis

Dysregulation of the blood level of 1,25(OH)₂D₃ is a major cause of excessive intestinal calcium absorption, renal calcium reabsorption and bone reabsorption [34-36]. Thus, hypercalcemia often develops in individuals with dysregulated blood levels of 1,25(OH)₂D₃. Hypercalcemia is an established risk factor for pancreatitis [37,38]. The process starts with hypercalcemia-caused increases in the cytosolic concentration of calcium of susceptible pancreatic acinar cells. This

leads to activation of proteases intracellularly and necrotic death of these cells. The proteases released from the necrotic cells and the continuous presence of hypercalcemia cause damage and necrotic death of more acinar cells, thus perpetuating the process. Eventually, given enough necrotic cell death, pancreatitis ensues [37,38]. Therefore, primary hyperparathyroidism, a major cause of hypercalcemia [39], is a known cause of acute pancreatitis (Table 1). In addition, individuals who use excessive amounts of vitamin D or biologically active synthetic analogs of vitamin D may not only develop hypercalcemia, but also acute pancreatitis (Table 1).

Given that inflammation in various tissues is a major cause of extrarenal synthesis of 1,25(OH)₂D₃ [16,18-32], it is not surprising that epidemiological studies have found high incidence of acute pancreatitis in patients with rheumatoid arthritis or systemic lupus erythematosus disease [49-52].

Sarcoidosis is another inflammatory disorder that is characterized by the presence of granulomas, mainly in lymph nodes and pulmonary tissues, that serve to “quarantine” infectious microorganisms and/or other foreign particles when the immune system fails to eliminate them [53]. The granulomas contain large numbers of activated macrophages that use CYP27B1 to actively convert 25(OH)D₃ to 1,25(OH)₂D₃ [18-21]. This is independent of PTH and is not subjected to feedback inhibitory regulation [54,55]; therefore, there is excessive synthesis of 1,25(OH)₂D₃ in patients with sarcoidosis, and the “spilling over” of the 1,25(OH)₂D₃ from the granulomas into the blood circulation results in elevated blood levels of 1,25(OH)₂D₃, thus causing hypercalcemia (Figure 1) [17-21].

Therefore, it is not surprising that there are well-documented cases of acute pancreatitis in patients with sarcoidosis (Table 1). However, it should be mentioned that not all patients with sarcoidosis develop acute pancreatitis.

In short, at the present time there is a body of strong evidence to indicate that elevated blood levels of 1,25(OH)₂D₃ is a risk factor for acute pancreatitis.

Severe Vitamin D Deficiency in Patients with Chronic and Acute Pancreatitis

Several different investigators initiated studies of the vitamin D status in patients with chronic pancreatitis by different investigators and produced the startling finding that the majority of their patients had vitamin D deficiency as their serum levels of 25(OH)D₃ were lower than 20 ng/ml (Table 2). Furthermore, a large number of the patients have severe vitamin D deficiency since their serum levels of 25(OH)D₃ were 10 ng/ml or lower (Table 2).

Strikingly, Mann et al. [67] also found that there is a 40% to 60% reduction in the serum 1,25(OH)₂D₃ level in patients with chronic pancreatitis in comparison to healthy subjects (Table 2). Although the vitamin D status in patients with acute pancreatitis has not received wide attention, studies by Parrish et al. [68] and Bang et al. [69] have found convincing evidence of high rates of vitamin D deficiency in patients with acute pancreatitis. Parrish et al. [68] found that up to 74.4% of their patients had less than 20 ng/ml of blood 25(OH)D₃, and, furthermore, approximately 34% of their patients had severe vitamin D deficiency since their blood levels of 25(OH)D₃ were lower than 10 ng/ml (Table 2) [68]. Similarly, Bang et al. [69] found the following: 23% of patients had less than 5.2 ng/ml of serum 25(OH)D₃, 20% of patients had less than 10 ng/ml of serum

25(OH)D3 and 20% of patients had less than 20 ng/ml of serum 25(OH)D3 at the time of admission (Table 2) [69]. Therefore, these investigators independently found that up to 40% of patients with acute pancreatitis had severe vitamin D deficiency at the time of admission.

Causes of pancreatitis	Reference
Hyperparathyroidism	[40]
	[41]
	[42]
	[43]
	[44]
Excessive use of vitamin D supplements	[45]
	[46]
Topic use of 22-oxacalcitriol for psoriasis	[47]
Topic use of Tacalcitol for psoriasis	[48]
Rheumatoid arthritis	[49]
	[50]
Systemic lupus erythematosus disease	[51]
	[52]
Hypercalcemia secondary to sarcoidosis	[56]
	[57]
	[58]
	[59]
	[60]
	[61]
	[62]
	[63]
[64]	

Table 1: Acute pancreatitis in patients with Hypercalcemia, intoxication with vitamin D and vitamin D analogs or with inflammatory disorders.

Additionally, Bang et al. [69] found that there was a significant progressive decrease in the blood level of 25(OH)D3 in a linear fashion from day 0 to day 2 in their patients. This decrease was associated with increasing C-reactive protein concentration in the blood, indicating that the acute pancreatic inflammatory condition is intimately associated with a significant reduction in the blood 25(OH)D3 level. Strikingly, Bang et al. [69] found that the blood levels of 25(OH)D3 in these patients began to progressively increase, starting on day 3, in the absence of vitamin D replacement therapies, suggesting that a recovery aspect from acute pancreatitis is normalization of the blood 23(OH)D3 level. Unfortunately, Parrish et al. [68] and Bang et al. [69] did not report the blood levels of 25(OH)D3 prior to the admission or the blood levels of 1,25(OH)2D3 and PTH in patients with acute pancreatitis at any time.

Syndrome	No. of Patients	Vitamin D Status	Reference
Chronic Pancreatitis	37	-62% of patients had vitamin D deficiency	[65]
		-32 % of patients had <10 ng/ml 25(OH)D3	
Chronic pancreatitis	111	-32.4% of patients had 10-20 ng/ml 25(OH)D3	[66]
		-49.5% of patients had <10 ng/ml 25(OH)D3	
Chronic Pancreatitis	42	-16.6% of patients had a mean of 13.6 ng/ml 25(OH)D3 and 44% reduction in the level of 1,25(OH)2D3 in comparison to control subjects	[67]
		-35.7% of patients had a mean of 9.76 ng/ml 25(OH)D3 and 61.5% reduction in the level of 1,25(OH)2D3 in comparison to control subjects	
		-47.6% of patients had a mean of 10.3 ng/ml 25(OH)D3 and 60% reduction in the level of 1,25(OH)2D3 in comparison to control subjects	
Acute Pancreatitis	78	-74.4% of patients had <20 ng/ml 25(OH)D3	[68]
		-37% of patients had <10 ng/ml 25(OH)D3	
Acute Pancreatitis	76	-66% of patients had vitamin D deficiency	[69]
		-23% of patients had <10 ng/ml 25(OH)D3	
		-23 % of patients had <5.2 ng/ml 25(OH)D3	

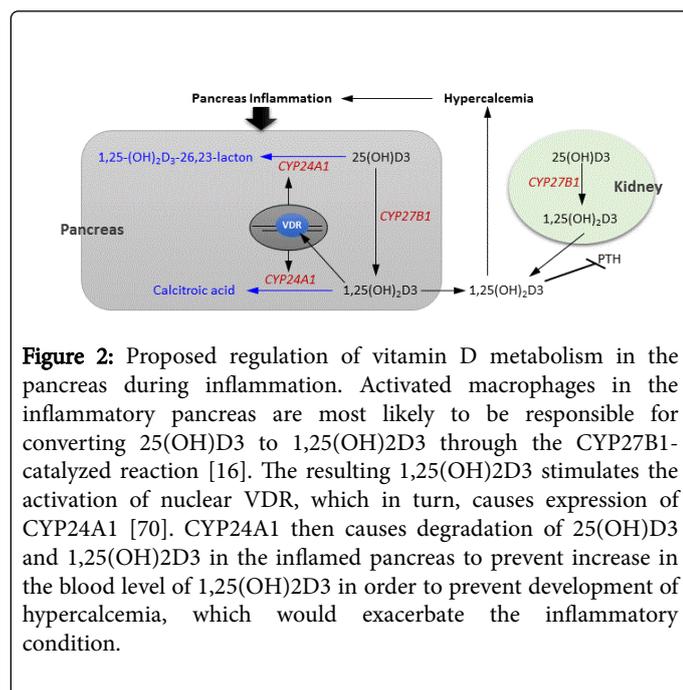
Table 2: Vitamin D status in patients with chronic pancreatitis.

Discussion

Decreased synthesis of 25(OH)D3 in the liver could explain the low levels of blood 25(OH)D3 and 1,25(OH)2D3 in patients with chronic pancreatitis. However, it is unlikely that even a lack of 25(OH)D3 synthesis in the liver could cause the observed very low blood levels of 25(OH)D3 in the patients with acute pancreatitis since the half-life of 25(OH)D3 in the blood is at least 15 days [11,12]. Therefore, there must be an alternative mechanism(s), such as CYP24A1-mediated degradation of both 25(OH)D3 and 1,23(OH)2D3 (see discussion below), that is responsible for causing the low levels of 25(OH)D3 and 1,25(OH)2D3 in patients with pancreatitis.

Considering the fact that loss-of-function mutations in CYP24A1 causes elevated blood levels of 1,25(OH)2D3, hypercalcemia and complications of hypercalcemia [6-9], it is important to note the study of pancreas biopsies from patients with chronic pancreatitis by Hummel et al. [70]. In this study, Hummel et al. [70] found elevated levels of CYP24A1 enzyme and co-expression of CYP24A1 and VDR in various locations in the inflamed pancreas [70]. Since there is active CYP27B1-catalyzed conversion of 25(OH)D3 to 1,25(OH)2D3 in tissues undergoing inflammation [16] and 1,25(OH)2D3 induces VDR-mediated expression of CYP24A1 in target cells as a feedback mechanism to regulate its own level [1], the following series of events related to vitamin D metabolism seems possible in the pancreas during a pancreatitis flare.

The inflamed pancreas is a site of CYP27B1-catalyzed conversion of 25(OH)D₃ to 1,25(OH)₂D₃. The 1,25(OH)₂D₃ then causes activation of nuclear VDR. The active VDR induces the expression of CYP24A1, among other genes. The presence of a high level of CYP24A1 results in rapid degradation of both 25(OH)D₃ and 1,25(OH)₂D₃ in the inflamed pancreas, thus causing reduced levels of both 25(OH)D₃ and 1,25(OH)₂D₃ in the blood circulation (Figure 2). These events are highly likely because degradation of 25(OH)D₃ reduces the substrate availability for the production of 1,25(OH)₂D₃, and degradation of 1,25(OH)₂D₃ prevents a buildup of the blood level of 1,25(OH)₂D₃, which would cause hypercalcemia, which can exacerbate the pancreatitis.



Future research using isogenic wild type and *cyp24a1*-knockout mice [St-Arnaud] to study the relationship between CYP24A1 and pancreatitis under various conditions will no doubt produce invaluable information. This work could further elucidate whether CYP24A1 is involved in the down-regulation of blood levels of vitamin D during a pancreatitis flare. And also, whether down-regulation of blood level of vitamin D is indeed a protective mechanism to prevent hypercalcemia in order to protect the already inflamed pancreas from further damage.

However, CYP24A1-mediated degradation of vitamin D₃ does not explain how blood levels of 25(OH)D₃ in many patients with acute pancreatitis began to progressively increase, starting on day 3 after admission, in the absence of vitamin D replacement therapies [69]. Given that CYP2R1 is the primary enzyme that converts vitamin D₃ to 25(OH)D₃ in the liver, it is plausible that in the early phase of an acute pancreatitis there is also down-regulation of CYP2R1, resulting in a reduction in the blood level of 25(OH)D₃. The combined down-regulation of CYP2R1 in the liver and up-regulation of CYP24A1 in the inflamed pancreas should reduce the blood level of 25(OH)D₃ faster and more efficiently, thus causing the severe vitamin D deficiency seen in patients. Then, during the recovery phase, the expression of CYP2R1 in the liver is restored (and perhaps the level of CYP24A1 in the pancreas is being decreased), allowing production of 25(OH)D₃ for the normalization of the blood 25(OH)D₃ level.

Nevertheless, future investigations are needed to investigate the expression of CYP2R1 in the liver during a pancreatitis flare.

Given that there is active synthesis of 1,25(OH)₂D₃ in inflamed tissues and that elevated blood levels of 1,25(OH)₂D₃ can cause hypercalcemia, which in turn can precipitate pancreatitis, active down-regulation of the blood levels of 25(OH)D₃ and 1,25(OH)₂D₃ during pancreatic inflammation should serve as a protective mechanism against potential development of hypercalcemia, which would further damage the already inflamed pancreas. Therefore, it is reasonable to consider both 25(OH)D₃ and 1,25(OH)₂D₃ as negative acute-phase reactants, specifically in the context of acute pancreatitis of various etiologies.

In the future, careful investigations will be needed to determine whether 25(OH)D₃ and 1,25(OH)₂D₃ are indeed negative acute-phase reactants specifically in the context of pancreatitis. If they are indeed negative-phase, then it will present a challenging dilemma for physicians to manage patients with chronic pancreatitis because it is estimated that over 60% of patients with chronic pancreatitis have osteopenia or osteoporosis [71]. If these patients are treated with vitamin D supplementations, it might produce more harm than benefit because it might cause hypercalcemia, which should be avoided in patients with pancreatitis. Therefore, future research is needed to investigate the safety and benefits of vitamin D replacement treatment for patients with chronic pancreatitis. Meanwhile, patients with chronic pancreatitis may be treated with anti-resorptive agents, such as bisphosphates and RANKL inhibitors [72].

Also, if future investigations confirm that 25(OH)D₃ and 1,25(OH)₂D₃ are indeed negative acute-phase reactants in the context of pancreatitis, then patients with acute pancreatitis plus vitamin D deficiency at the time of admission should not be treated with vitamin D. Doing so would provide more substrate for the inflamed pancreas to produce more 1,25(OH)₂D₃, thus possibly worsening the disease activity. However, it will be important to investigate if treatment of patients with acute pancreatitis in later days following admission with low or moderate doses of vitamin D would produce any benefits.

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