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

Vitamin D Deficiency in Gastrointestinal Disease

by Bradley R. Javorsky, Nelly Maybee, Shetal H. Padia, Alan C. Dalkin


Bradley R. Javorsky


Nelly Maybee


Shetal H. Padia


Alan C. Dalkin

Vitamin D is an essential prohormone, primarily responsible for calcium homeostasis, though it has additional functions that go beyond bone metabolism. Calling it a vitamin is actually a misnomer, since it can be endogenously synthesized. Since its discovery in the early 1900's, which led to a cure for rickets, vitamin D has been extensively researched, detailing the molecular pathways of its synthesis and physiology, allowing for development of various therapies targeting vitamin D deficient states. Gastroenterologists and nutritionists frequently encounter patients whose medical conditions predispose them to vitamin D deficiency, such as inflammatory bowel disease, celiac disease, gastric bypass surgery and cystic fibrosis/pancreatic insufficiency. It is imperative to recognize and treat vitamin D deficiency before it manifests with its detrimental effects on the body. This overview will focus on vitamin D physiology and specific disease states associated with vitamin D deficiency commonly seen in a gastrointestinal practice. Different assays available for evaluation of vitamin D status and guidelines for treatment of vitamin D deficiency will be included.

VITAMIN D—BIOMOLECULAR CHARACTERISTICS

There are two ways of acquiring vitamin D—cutaneous irradiation and diet. In the skin, cholecalciferol is synthesized through UV irradiation of 7-dihydrocholesterol. In infants, immobile or institutionalized persons, the elderly (>70 years old), and veiled women or those living in northern latitudes, sun radiation may not be a sufficient source of vitamin D and dietary supplementation is essential. For that reason, various foods, such as milk and infant formula in the United States and other developed countries are fortified with vitamin D_3 (cholecalciferol) or D_2 (ergocalciferol), the latter being of plant derivation (Figure 1). Dietary vitamin D is absorbed through the small intestine as a fat-soluble vitamin along with

Bradley R. Javorsky, M.D., Nelly Maybee, M.D., Shetal H. Padia, M.D., Fellows, Division of Endocrinology and Metabolism; Alan C. Dalkin, M.D., Associate Professor of Internal Medicine, Division of Endocrinology and Metabolism, all at the University of Virginia, Charlottesville, VA.

dietary fat and is incorporated into chylomicrons. It is important to mention that dietary vitamin D is delivered rapidly into the circulation by way of hepatic transport of chylomicrons. As a result, one can achieve higher serum levels quicker (though more transiently) with oral supplementation rather than parenteral delivery or relying on endogenous production (1).

Whether ingested or cutaneously synthesized, vitamin D is initially inert in the form of D_2 or D_3, which is converted to its protein-bound circulating form in the liver—25-hydroxy vitamin D (calcidiol). Calcidiol is then transported to the kidney, where, under the direction of circulating PTH, it is converted by 1alpha-hydroxylase to its active form of 1,25-dihydroxy vitamin D (calcitriol).

Vitamin D degradation takes place in the liver and is controlled by a negative feedback mechanism. It is inactivated by 24-hydroxylase, a very active cytochrome P-450 enzyme that is induced by calcitriol itself; the enzyme remains inactive in states of vitamin D deficiency. Elevated PTH, as a result of hypocalcemia, can reduce enzymatic activity, thereby allowing for higher levels of calcitriol to circulate over longer periods of time (2). Vitamin D is stored primarily in the liver, but also in adipose tissue. When those sites become saturated with vitamin D, it circulates in the blood as 25-hydroxy vitamin D, at potentially toxic levels (3).

VITAMIN D—PHYSIOLOGIC FUNCTIONS

Hypocalcemia is defined by low levels of free (ionized) calcium as a result decreased entry of calcium into the circulation or increased tissue deposition. Changes in serum proteins, mainly albumin, and serum pH can alter the ionized calcium concentration and must be accounted for when evaluating a serum calcium level. In most individuals, for every 1 mg/dL change in albumin above or below 4 mg/dL, there is an inverse change in the effective calcium concentration by 0.8 mg/dL (See equation below).

$$\text{Corrected } Ca^{2+} = (\text{normal albumin} - \text{measured albumin}) \times 0.8 + \text{measured } Ca^{2+}$$

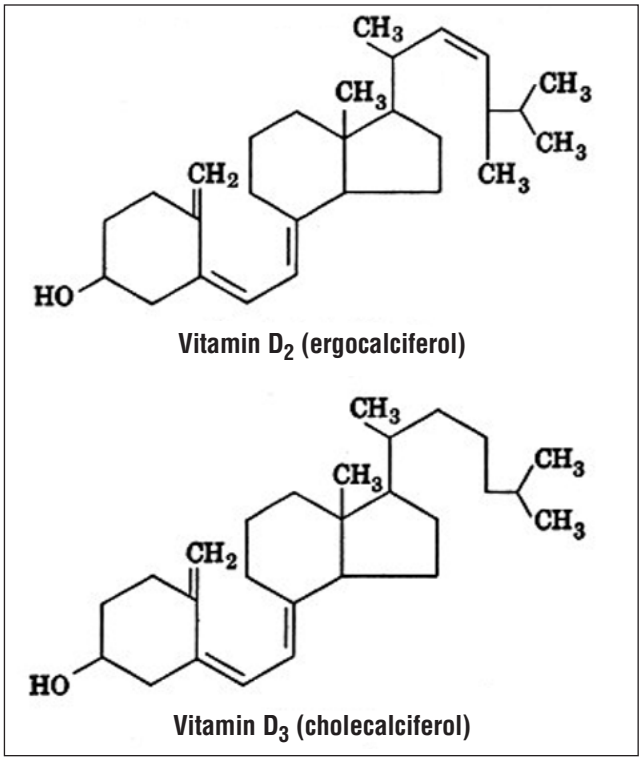

Figure 1. Molecular structure of vitamin D_2 and vitamin D_3. Used with permission from the Cyberlipid Center (http://www.cyberlipid.org/).

In some circumstances, however, this is not an accurate representation of serum calcium (4,5). Normal values for calcium may vary between centers, depending on the assay and population used for standardization.

Calcium regulation, within a fairly narrow physiologic range, involves a number of hormonal and local factors. In particular, low levels of vitamin D results in hypocalcemia that initiates a complex compensatory cascade of responses (Figure 2).

1. *Detection of hypocalcemia:* The decline in calcium concentration results in a reduction in calcium binding to the calcium-sensing G-protein coupled transporter system found on parathyroid glands (6). As a consequence, there are a number of intracellular events that increases the synthesis and secretion of PTH.

2. *PTH acts to restore eucalcemia:* PTH actions are diverse, eliciting responses at both the kidney and

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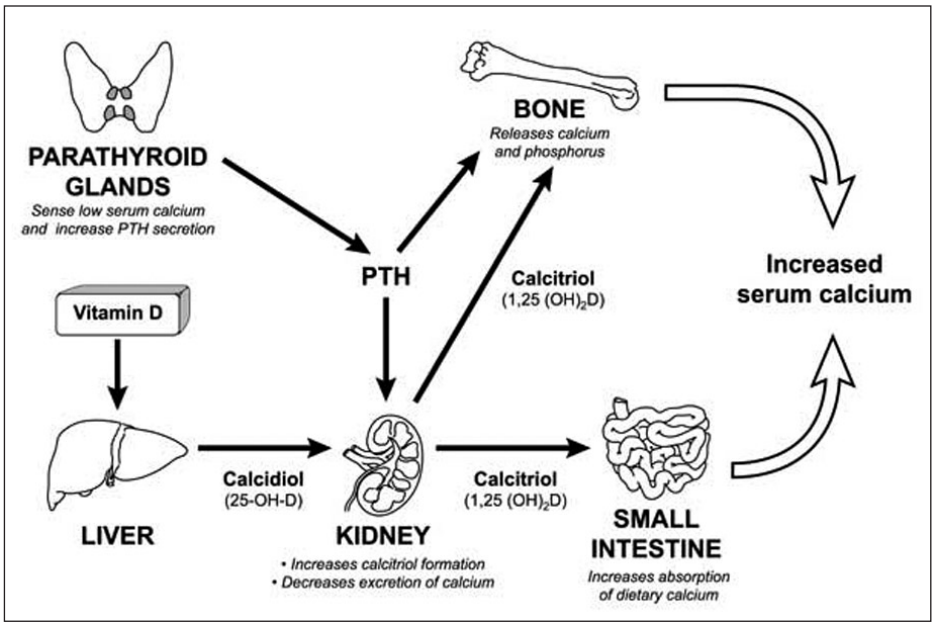

Figure 2. Reprinted with permission from: 'Vitamin D'. In: Higdon J, *An Evidence Based Approach to Vitamins and Minerals,* New York: Thieme, 2003:74.

bone. At the level of the kidney, PTH increases the conversion of calcidiol to calcitriol by 1alpha-hydroxylase, an enzyme that is activated by low phosphorus and high PTH levels. Also, under the direction of PTH, renal distal tubule reabsorption of calcium, and excretion of phosphorus, increases. Finally, via binding to cell surface PTH receptors on the osteoblast, PTH stimulates a cascade that results in increased bone turnover and calcium/phosphorus mobilization from bone.

Calcitriol actions on calcium homeostasis: In response to the increase in calcitriol, there is a stimulation of active intestinal absorption of calcium and phosphorus. Of note, along with PTH, calcitriol signals osteoblasts to enhance further osteoclast activation and bone resorption (7). Also in parallel with PTH, calcitriol can enhance distal tubule calcium reabsorption (8). As the human kidney can filter as much as 7 g of calcium over the course of the day, small changes can result in a significant contribution to total body calcium (8). Thus, the main function of vitamin D is to maintain normal serum calcium concentrations in order to preserve the process of bone mineralization. Even though most of the above actions are largely attributed to calcitriol, there is evidence that calcidiol, in its own right, promotes calcium absorption, though its contribution is less than 1% that of calcitriol (9).

VITAMIN D AND ITS NON-CALCIUM ROLE

Vitamin D receptors are not only found on enterocytes, osteoblasts and distal renal tubule cells (the main targets of vitamin D), but also on promyelocytes, keratinocytes, pancreatic islet cells, lymphocytes, colon cells, pituitary gland cells, ovarian cells, parathyroid gland cells (2). In parathyroid glands, vitamin D helps to suppress the gland by a negative feedback mechanism, which is an essential part of treating renal osteodystrophy, where the parathyroid gland hyperproliferates due to vitamin D deficiency, even in the presence of normal serum calcium (2,10).

DIETARY SOURCES OF VITAMIN D

The most abundant natural source of vitamin D is fatty fish and liver, however given the realities of the Western diet, our main dietary source of vitamin D comes from fortified foods like milk, juice, cereal and pasta. One can see how easily vitamin D deficiency is acquired even in perfectly healthy individuals, given the short list of dietary options in a setting of a limited outdoor exposure. The current RDA guidelines suggest an intake of 400–800 IU daily. However, food surveys such as those done by the NHANES III study of older women have documented that over 70% of women age 51 to 70 years do not meet that standard. Moreover, in women beyond age 70 in whom sun exposure is minimal, over 90% of individuals may have a daily vitamin D intake of <600 IU.

The high prevalence of vitamin D deficiency in the general population may serve to place patients with gastrointestinal disease at further risk to develop osteomalacia, a more severe form of vitamin D deficiency.

In a cross sectional study, patients with osteomalacia due to gastrointestinal disease were found to have a history of gastrectomy (43%), celiac disease (26%), intestinal bypass (15%), intestinal resection (8%), chronic pancreatitis (4%), and primary biliary cirrhosis (4%) (11). These conditions, while relatively infrequent among the general population, make up a large proportion of patients seen in a typical inpatient or outpatient gastroenterology practice. In light of data suggesting that measurements of muscular function in the lower extremities suggest a positive correlation between serum vitamin D levels and performance, detection of vitamin D deficiency and restoration of normal stores appears to be an essential approach to establishing optimal health (12).

SIGNS AND SYMPTOMS OF VITAMIN D DEFICIENCY

Most cases of vitamin D deficiency are asymptomatic. Vitamin D "insufficiency" is a term that has been used to describe patients with more modest reductions in vitamin D levels. Chronic deficiency complicated by osteomalacia may present with aching skeletal pain or proximal muscle weakness (13). Serum vitamin D, calcium, and phosphate levels are low, while alkaline phosphatase and PTH levels are usually elevated. Radiologic examination by DEXA and plain films reveal decreased bone density, pseudofractures (Looser's zones), and fractures. Precise diagnosis of osteomalacia requires bone biopsy after tetracycline double labeling to demonstrate increased osteoid seam width and prolonged mineralization lag time. However, with the proper biochemical and clinical settings, the need for bone biopsy is rare.

GASTROINTESTINAL CAUSES OF VITAMIN D DEFICIENCY

The pathogenesis of metabolic bone disease in gastrointestinal disorders is multifactorial and not completely understood. Malabsorptive states predispose to vitamin D, vitamin K, calcium, and protein insufficiency. Urinary losses of key minerals secondary to acidosis may lead to further mineralization defects. Inflammatory cytokines such as IL-6, TNF-α, and IL-1α, which are common in inflammatory bowel disease, may act by inhibiting osteoblast differentiation, increasing osteoclastic bone resorption, and sensitizing osteoblasts to apoptosis (14–16). In addition to the primary pathologic processes, glucocorticoids are commonly prescribed for many disease states and are well known to decrease bone mass by multiple mechanisms (17). Hypogonadism, decreased physical activity, decreased body weight, and ectopic adrenocorticotropic hormone (ACTH) or parathyroid hormone related protein (PTHrp) production are other features of some gastrointestinal disorders that may play a role in metabolic bone disease. Finally, risk factors for bone disease in the general population, such as age, heredity, and smoking, are also present in patients with gastrointestinal disease. For a more in-depth review of the other factors involved in the etiology of bone disease in gastrointestinal disorders, the reader is referred to a series of articles in the *European Journal of Gastroenterology & Hepatology* (2003, 15:841).

GASTRIC BYPASS SURGERY AND GASTRECTOMY

Gastrectomy

Vitamin D deficiency and osteomalacia are well-documented complications of gastrectomy (18–21). The severity of the deficiency appears to be directly related to the extent of anatomic modification, time since procedure, and underlying nutritional status prior to surgery (19,20). The prevalence of metabolic bone disease in postgastrectomy patients is highly variable, though a carefully done study by Bisballe, et al used detailed histomorphometric evaluation of bone biopsy after tetracycline double labeling to show that 18% of patients fulfilled the strict diagnostic criteria for osteomalacia, and 62% had some degree of histologic abnormality (19). The degree of mineralization impairment correlated directly with serum levels of 25-hydroxy vitamin D.

The pathogenesis of vitamin D deficiency after gastrectomy remains a matter of debate. Decreased intake, malabsorption (including bacterial overgrowth), accelerated catabolism, and reduced exposure to sunlight have all been implicated as etiologic mechanisms (20–25). A reduction in stomach volume due to partial or total gastrectomy may alter the quantity or type of

diet consumed. As noted previously, it is difficult for the general population to attain adequate levels of vitamin D and other nutrients essential to bone health such as calcium and vitamin K from the diet even without this added challenge. Indeed, studies by Morgan, Gertner, and Thompson support this hypothesis (22,25,26). Gertner and colleagues found that the post-absorption level of 25-hydroxy vitamin D after oral administration was normal in 5 of 6 postgastrectomy patients, while dietary intake of vitamin D was low in most of their patients with osteomalacia. Furthermore, vitamin D supplementation increased 25-hydroxy vitamin D levels and decreased the frequency of subclinical osteomalacia (19,27,28).

Malabsorption of vitamin D and calcium also likely play an important role in vitamin D deficiency. This is supported by the observation that those who have undergone Billroth II gastrectomies are at a higher risk for the development of metabolic bone disease than those who have had the Billroth I procedure, perhaps because the duodenum is excluded in the former procedure (Figure 3) (19,20,29,30). These patients may develop steatorrhea and intestinal "hurry" as a result of gastric dumping and bypass of duodenal surface area (26). Steatorrhea may also impair the reabsorption of 25-hydroxy vitamin D undergoing enterohepatic circulation, though the biological significance of this mechanism remains an area of controversy (31,32). Calcium malabsorption may result in vitamin D deficiency through a compensatory increase of PTH and 1,25-dihydroxy vitamin D. Numerous studies have shown the inverse relationship between 1,25-dihydroxy vitamin D and 25-hydroxy vitamin D (33,34). The former promotes the conversion of 25-hydroxy vitamin D to inactivation products that are excreted in bile and feces.

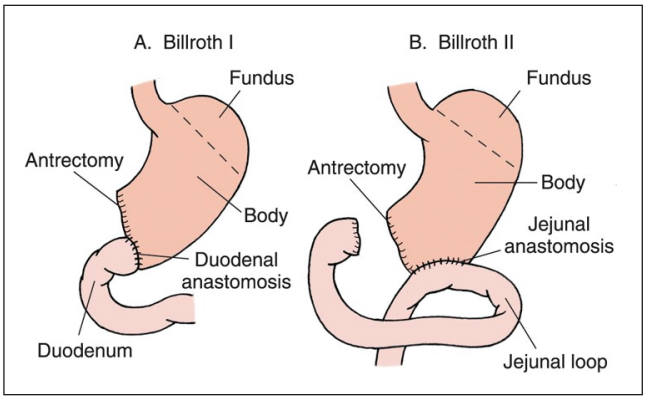

Figure 3. Anatomy of Billroth I and Billroth II gastrectomies. Used with permission from Lippincott Williams & Wilkins.

Gastric Bypass

Gastric bypass procedures for the treatment of morbid obesity are also frequently associated with vitamin D deficiency (35–41). As the rate of obesity has dramatically increased over the past twenty years, so has the demand for bariatric surgical procedures. Between 1998 and 2002 the number of gastric bypass surgeries has increased from 13,365 to 72,177, and was predicted to be 102,794 in 2003 (42). Bariatric surgery remains the only effective option for significant and sustained weight loss in the morbidly obese (43). Since the first bariatric surgery was performed in 1954 with the introduction of the jejunoileal bypass, other procedures have been developed including the Roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch, vertical banded gastroplasty, and adjustable gastric banding (Figure 4). These procedures can be categorized as restrictive, malabsorptive, or both. The prevalence of vitamin D deficiency in these patients appears to depend greatly on the particular type of surgery performed. In a cohort of patients who underwent malabsorptive surgeries, 63% were found to have vitamin D deficiency after 4 years of follow-up (40). Newbury, et al found a prevalence of 50% in patients who had undergone biliopancreatic diversion during a median follow-up of 32 months. In contrast, several studies showed no evidence of vitamin D deficiency in patients 1 and 2 years after gastric banding or vertical banded gastroplasty (44,45). It should be noted, however, that these patients still had decreased bone density at the femur and biochemical markers showing excess bone resorption.

Given that an intentional state of malabsorption or decreased intake is created in bariatric surgery patients, it is not surprising that these are the primary etiologies of vitamin D deficiency in this patient population. Malabsorption is a result of alterations in gastrointestinal anatomy with inadequate absorptive surface area, and/or dumping syndrome due to osmotic overload of the non-bypassed small intestine. Exclu-

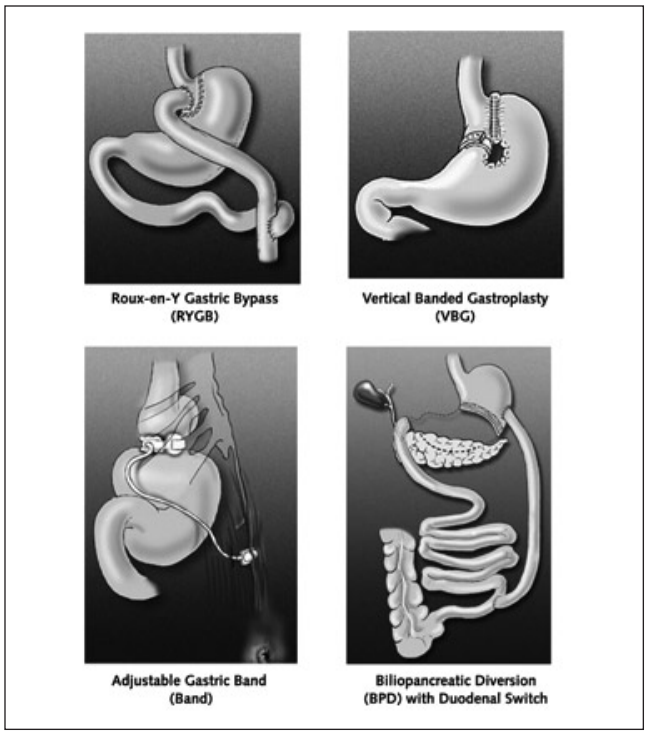

Figure 4. Common bariatric surgical procedures. Used with permission from the American Society for Bariatric Surgery.

sion of the ileum, and length of intestine that participates in digestion appear to be important factors (36,41). Studies involving treatment of vitamin D deficiency show inconsistent responses to supplementation. These data further suggest that both malabsorption and malnutrition are critical factors. Patients with osteomalacia after intestinal bypass responded to vitamin D therapy in studies by Parfitt, et al and Collazo-Clavell, et al (41,46), while another showed no improvement (47). Malabsorption of calcium, with subsequent increases in 1,25-dihydroxy vitamin D, and interruption of the enterohepatic circulation of vitamin D, may also play a role.

CELIAC DISEASE

Celiac disease is characterized by intolerance to gluten, a protein found in wheat, rye and barley, in genetically susceptible individuals. Subsequent immune-mediated enterocyte destruction with atrophic intestinal epithelium results in a decreased surface area for absorption. The prevalence of celiac disease, both symptomatic and subclinical, is higher than previously thought, and the importance of this diagnosis is becoming increasingly appreciated. It is estimated that 5% of North Americans and western Europeans suffer from celiac disease (48,49).

Given that metabolic bone disease is frequently associated with celiac disease, it is important to initiate early and effective therapy. In patients with celiac disease, Vitamin D deficiency occurs in 64% of men and 71% of women (50). Osteoporosis and osteomalacia have a prevalence of 26% and 20%, respectively (50,51). Conversely, the frequency of celiac disease is increased in patients with metabolic bone disease, and may be the only presenting manifestation (52). Of patients with gastrointestinal disease-related osteomalacia, 26% were secondary to celiac disease (11).

The primary etiology of vitamin D deficiency in celiac disease is malabsorption. Calcium, vitamin D, and other nutrients essential to bone health are poorly absorbed in untreated patients with celiac disease. Fortunately, treatment with a gluten free diet can resolve vitamin D deficiency in most patients (53). As noted with gastrectomy and gastric bypass surgeries, steatorrhea impairs the reabsorption of 25-hydroxy vitamin D undergoing enterohepatic circulation, though bile may contain only trivial amounts of vitamin D. Intake of vitamin D and calcium may also be decreased due to transient, secondary lactase deficiency in untreated celiac disease and subsequent avoidance of dairy products.

Calcium absorption is decreased in celiac disease as a result of decreased vitamin D levels and the underlying inflammatory process. Calcium is absorbed throughout the small bowel, but predominantly in the proximal portion. If enough of the small bowel is involved in the inflammatory process, calcium may be poorly absorbed resulting in compensatory secondary hyperparathyroidism. In addition, defective enterocytes have reduced levels of vitamin D dependent calcium binding proteins (54), and cannot respond to 1,25-dihydroxy vitamin D, further potentiating calcium loss and secondary hyperparathyroidism. With hyperparathyroid states, 1,25-dihydroxy vitamin D levels are increased which can further increase the metabolism and excretion of 25-hydroxy vitamin D (34).

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INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) includes a heterogeneous population of patients, making a definitive understanding of metabolic bone disease and vitamin D deficiency difficult. Crohn's disease (CD) can involve any portion of the gastrointestinal tract and includes many patients with small intestinal resection, while patients with ulcerative colitis (UC) have inflammation only of the colon. Furthermore, confounding factors that contribute to metabolic bone disease include smoking and glucocorticoid use, which differs considerably between each group.

Nevertheless, numerous investigators have demonstrated significant increases in the prevalence of metabolic bone disease in this patient population (55–59). Though study results are mixed, bone mineral density appears to be lower in patients with CD than in those with UC, likely because of the different incidence of systemic steroid use, strictures requiring intestinal resection, and extent and location of absorptive surface involved. Overall, the rate of osteoporosis for IBD is 15% (60). Jahnsen, et al found a prevalence of Vitamin D deficiency in 27% of patients with CD and 15% of patients with UC (61). Vogelsang, et al found a much higher incidence of vitamin D deficiency in patients with CD at 68% (62). A study by Tajika, et al demonstrated that 25-hydroxy vitamin D levels were correlated with CD duration and activity (63). In another study, 6 of 9 patients with CD that underwent transiliac bone biopsy were found to have osteomalacia (64). Interestingly, in animal studies, 1,25-dihydroxy vitamin D has been shown to inhibit autoimmune diseases, and vitamin D deficiency results in accelerated IBD (65).

As a result of inflammation and epithelial damage, malabsorption has been considered to play a predominant role in the etiology of vitamin D deficiency in IBD. However, only 10% of patients with CD that underwent a modified absorption test showed decreased 25-hydroxy vitamin D absorption (62). McCarthy, et al demonstrated seasonal variations in vitamin D levels, suggesting a role for sunlight exposure (58). This was further confirmed in a study by Vogelsang, et al who showed that patients with CD tended to have lower sun exposure in summer (66). Using dietary records, this study also demonstrated low dietary intake of vitamin D in CD, although it was no different from control patients. Finally, expression of 1-alpha-hydroxylase is increased in the intestinal endothelium of patients with Crohn's disease, presumably to act as a feedback inhibitor of inflammation (67). As noted previously, elevated 1,25-dihydroxy vitamin D levels are associated with decreased levels of 25-hydroxy vitamin D.

CYSTIC FIBROSIS AND CHRONIC PANCREATIC INSUFFICIENCY

Patients with cystic fibrosis (CF) and exocrine pancreatic insufficiency have a higher prevalence of metabolic bone disease and decreased bone mass (68–70). Vitamin D deficiency has also been demonstrated in numerous epidemiological studies in patients with CF and chronic pancreatic insufficiency (68–74) with prevalence reaching up to 75% in one study (75). These differences are likely a reflection of the severity and duration of the disease as well as the age of the patient (76). Unfortunately, minimal histomorphometric data exists regarding the frequency of osteomalacia in CF. A study by Haworth, et al using postmortem bone biopsies in CF patients found no evidence of vitamin D deficiency/osteomalacia, despite several case reports to the contrary (11,77,78). As progress in treating CF continues, patient longevity will continue to increase, and managing complications of CF such as metabolic bone disease will become more essential for maintaining health and preventing morbidity.

Malabsorption is the primary etiology of vitamin D and calcium depletion in patients with CF. The malabsorption is a result of exocrine pancreatic enzyme insufficiency with profound steatorrhea, rather than a defect in intestinal epithelial function as observed in patients with celiac disease and inflammatory bowel disease. Lark, et al administered oral vitamin D_2 to CF patients with exocrine pancreatic insufficiency on pancreatic enzyme replacement and compared absorption to healthy control subjects (79). In that study, on average, CF patients absorbed less than one-half the amount of vitamin D_2 that was absorbed by controls, and absorption among the CF patients varied greatly. As with other malabsorptive conditions, disruption of the enterohepatic circulation may play a role in vitamin D deficiency.

In addition to malabsorption, several other factors may contribute to vitamin D deficiency. Increased metabolism and degradation of vitamin D may occur in CF patients as a result of high cytochrome P450 enzyme activity (80). Hepatic dysfunction and cirrhosis, though an uncommon complication of CF, may worsen malabsorption or impair 25-hydroxylation of vitamin D (81). Poor nutritional intake and insufficient dietary supplementation also play important roles. For a summary of the proposed mechanisms of vitamin D deficiency in several gastrointestinal disease states, see Table 1.

Table 1
Mechanisms of vitamin D deficiency in common gastrointestinal disease states

Gastrectomy and gastric bypass
- Vitamin D malabsorption
- Reduced intake/decreased appetite
- Calcium malabsorption with increased 1,25-dihydroxy vitamin D
- Reduced sunlight exposure
- ? Interrupted enterohepatic circulation

Celiac disease
- Vitamin D malabsorption
- Reduced intake
- Calcium malabsorption with increased 1,25-dihydroxy vitamin D
- ? Interrupted enterohepatic circulation

Inflammatory bowel disease
- Vitamin D malabsorption
- Reduced intake
- Reduced sunlight exposure
- Inflammation with elevated 1,25-dihydroxy vitamin D

Cystic fibrosis
- Vitamin D malabsorption
- Insufficient supplementation
- ? Interrupted enterohepatic circulation
- Increased vitamin D metabolism

ESTABLISHING A DESIRABLE LEVEL OF 25-HYDROXY VITAMIN D IN THE BLOOD

Historically, any level of 25-hydroxy vitamin D (not 1, 25 OH vitamin D) less than 5 ng/mL was associated with osteomalacia, and a level above this was considered to be adequate. As the assays for vitamin D improved, a lower limit of 10 ng/mL has been observed. More recently, it has become clear that even at "normal" levels of vitamin D, significant reductions in calcium absorption can be observed and hence a state of vitamin D "insufficiency" (as opposed to frank depletion) has been recognized. Vitamin D insufficiency is associated with increased levels of serum PTH (secondary hyperparathyroidism), suboptimal calcium absorption, increased bone turnover, and increased fracture risk (82,83). Whether there exists a clear threshold for the 25-hydroxy vitamin D concentration at which these changes occur has been the subject of much debate.

A study of postmenopausal females in the U.S. showed that the seasonal variation in PTH was no longer observed when the serum 25-hydroxy vitamin D was higher than 90 nmol/L (36 ng/mL), indicating that the 25-hydroxy vitamin D level of this magnitude is certainly sufficient to prevent secondary hyperparathyroidism, though complete cessation of seasonal changes in PTH may not be needed to prevent bone loss (84). Furthermore, in a larger study in Amsterdam, an increase in serum PTH was only evident when the 25-hydroxy vitamin D level fell below 30 nmol/L (12 ng/mL). Climate, sunshine exposure, race/ethnicity and clothing habits can account for large differences in 25-hydroxy vitamin D levels between countries. Of note, variations have also been attributed to the differences in assays used to measure 25-hydroxy vitamin D, a concept that will be discussed in greater detail below *(see discussion on assays to follow)*.

Despite recognizing the need to identify vitamin D insufficiency, there is currently no consensus regarding the level around which 25-hydroxy vitamin D levels are low enough to result in reduced calcium absorption. Nonetheless, various authors have proposed cut-offs at which they diagnose vitamin D insufficiency and institute treatment. For example, Lips has detailed a staging system for vitamin D insufficiency where mild vitamin D insufficiency is defined by a 25-hydroxy vitamin D level of 10–20 ng/mL, which may be associated with a modest (15%) increase in PTH and a mild increase in bone turnover on histological examination (85). Moderate vitamin D insufficiency is observed at serum

25-hydroxy vitamin D levels between 5 to 10 ng/mL and is associated with a 15%–30% increase in serum PTH and high bone remodeling rates. Severe vitamin D deficiency occurs when 25-hydroxy vitamin D levels fall below 5 ng/mL at which point serum PTH is significantly increased by 30% or more leading to mineralization defects and ultimately, frank osteomalacia.

In our clinical practice, we generally use a serum 25-hydroxy vitamin D level of <30 ng/mL to diagnose and treat vitamin D insufficiency. Using this threshold, we are able to identify the majority of individuals with reduced calcium absorption (as evidenced by a reduction in urine calcium excretion) and, less commonly, increases in PTH and markers of bone turnover (e.g. alkaline phosphatase, osteocalcin and/or urine N-telopeptide. At vitamin D levels below 10 ng/mL, in our experience nearly all patients manifest some sign of secondary hyperparathyroidism and require significant doses of vitamin D for replacement.

AVAILABLE ASSAYS FOR THE MEASUREMENT OF 25-HYDROXY VITAMIN D

Currently, there are three different types of assays commercially available to measure serum 25-hydroxy vitamin D levels. The chemiluminescent assay is a protein-binding assay that uses a reagent to separate vitamin D from its binding proteins without prior chromatographic separation. This assay can report higher 25-hydroxy vitamin D levels compared to other methodologies because of the absence of preparative chromatography and hence higher molecular recovery rate. Not all chemiluminescent assays are the same, however, because different compounds are used to dissociate vitamin D from its binding proteins. The second type of assay is a radioimmunometric assay (RIA). Some antibodies recognize both 25-hydroxy vitamin D_2 (plant) and 25-hydroxy vitamin D_3 (animal), whereas others have a significantly lower affinity for 25-hydroxy vitamin D_2. Lastly, because high performance liquid chromatography (HPLC) for 25-hydroxy vitamin D purifies 25-hydroxy vitamin D_2 and 25-hydroxy vitamin D_3 separately, it has been established as the gold standard to which chemiluminescent and RIA assays are compared.

A recent study comparing measurements from 7 different laboratories using either HPLC, RIA, or automated chemiluminescent assays for measurements of serum 25-hydroxy vitamin D demonstrated that the degree of variability of the results between methods and between laboratories, even when using the same method, confounded the diagnosis of vitamin D insufficiency (86). Specifically, some chemiluminescent and RIA assays were found to underestimate the contribution of 25-hydroxy vitamin D_2 to total circulating 25-hydroxy vitamin D levels. Since the sole therapeutic form of vitamin D in the United States is ergocalciferol, or vitamin D_2, the inability to measure this compound could result in apparent laboratory failures in assessing therapeutic responses and/or lead to a misdiagnosis of vitamin D insufficiency. Increases in unmeasured vitamin D could potentially result in dose escalation and subsequent dangerous consequences such as hypervitaminosis D. As a result, we suggest ascertaining the specific assay for 25-hydroxy vitamin D used by your own laboratory, not only during diagnosis (although measurement of only D_3 in that setting would be of little harm), but also when monitoring response to treatment.

TREATMENT OF VITAMIN D INSUFFICIENCY IN PATIENTS WITH GASTROINTESTINAL OR LIVER DISEASE

When vitamin D insufficiency is not due to malabsorption, native vitamin D_2 supplementation is the best form of treatment since it permits physiologic regulation at the kidney of 1 alpha-hydroxylase and production of 1, 25-dihydroxy vitamin D levels under the stimulus of PTH. Such preparations of vitamin D_2 (ergocalciferol, Calciferol™ Drisdol®), usually given in 50,000 IU capsules, and 25-hydroxy vitamin D (calcidiol), usually given in 20 and 50 microgram capsules daily, are well tolerated in most situations. Conversely, 1, 25-dihydroxy vitamin D (calcitriol, Calcijex®, Rocaltrol®) given therapeutically is not under metabolic control, and the level of 1, 25-dihydroxy vitamin D achieved depends on the dose given and absorption from the intestinal tract. However, these preparations are better absorbed than native vitamin D and have shorter half-lives in the circulation, and are therefore more useful in the presence of fat malabsorption.

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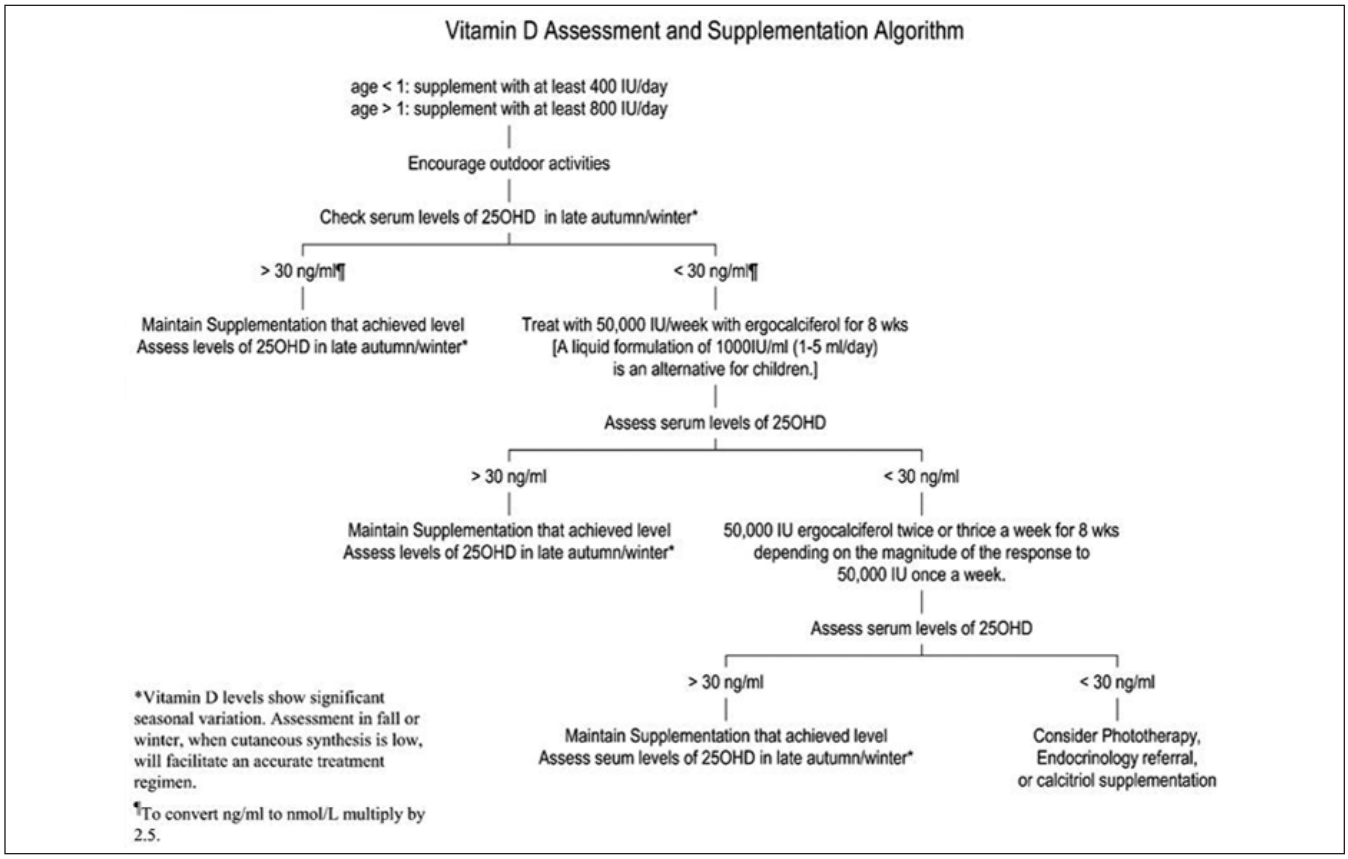

Figure 5. Algorithm for assessment and supplementation of vitamin D deficiency. Used with permission from Lippincott Williams & Wilkins.

1, 25-dihydroxy vitamin D preparations are dispensed in 0.25–1.0 microgram tablets with an equivalence of 10–40 IU. Due to its short half-life, when doses exceed 1 microgram per day, using divided doses in a b.i.d. regimen may be helpful.

In celiac disease, large doses of oral vitamin D (10,000–50,000 IU/ day) may be necessary at the time of diagnosis because of steatorrhea; however, such doses should not be given longer than one month because absorption improves with the institution of a gluten-free diet. We recommend using ergocalciferol initially in these cases, and monitoring serum 25-hydroxy vitamin D, calcium and albumin levels monthly. The dose should be adjusted to achieve a 25-hydroxy vitamin D level above 30 ng/mL and a normal serum calcium concentration (and PTH level if measured). Once intestinal absorption has normalized, we recommend oral vitamin D doses of 800 IU/ day. If oral vitamin D is not an option, parenteral vitamin D is available intramuscularly. Of note, despite repletion of vitamin D stores, secondary hyperparathyroidism may persist if there is concomitant calcium malabsorption (87). Calcium should be supplemented also, at a dose of 1–2 gm/day, which should suppress secondary hyperparathyroidism (88). At times, a higher dose of calcium may be necessary (up to 4 g/day) in patients with persistent duodenal malabsorption. We have used both calcium carbonate and calcium citrate preparations with success and find both compounds acceptable depending on patient preference. In addition, most calcium preparations can be purchased with low levels of vitamin D (e.g. 100–200 IU/tablet) if desired. At high doses, patients may find calcium carbonate produces flatus and constipation and the citrated preparations may improve tolerance.

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(continued from page 66)

Similar guidelines should be followed to treat post-gastrectomy or small bowel Crohn's disease patients with vitamin D insufficiency. In patients with chronic liver disease and impairment of 25-hydroxylation of vitamin D, preparations of 25-hydroxy vitamin D (2000 to 5000 IU/day) or 1, 25-dihydroxy vitamin D (1 µg/day in adults) may be needed (89). See Figure 5 for a vitamin D assessment and treatment algorithm.

HYPERVITAMINOSIS D

High doses of vitamin D given daily or weekly may cause vitamin D intoxication, leading to hypercalcemia, and hypercalciuria. In a study of healthy men given vitamin D_3 orally up to 50,000 IU/day for 8 weeks, no hypercalcemia was noted (90). However, the occurrence of hypervitaminosis D is unpredictable, and may be more of an issue when changes in absorptive capacity are evident as in treatment of celiac or inflammatory bowel disease. We recommend careful monthly monitoring of serum and urine calcium levels, as well as serum 25-hydroxy vitamin D levels, during treatment. Moreover, as noted earlier in this chapter, vitamin D promotes phosphorus absorption and supraphysiologic levels of vitamin D can result in hyperphosphatemia, nephrocalcinosis and ectopic calcification. Hence, routine measurement of serum phosphorus is generally suggested as vitamin D levels increase >1 mg/dL above the upper limit of normal. ■

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(continued on page 72)

(continued from page 70)

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