Review

Role of Vitamin D in Adults Requiring Nutrition Support

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The major and most well-known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. However, recent evidence suggests that vitamin D may be important for a variety of nonskeletal outcomes. The review synthesizes the available evidence for the role of vitamin D in skeletal health as well as its novel roles in medical conditions such as muscle function, falls, immunity, glucose homeostasis, and cardiovascular diseases. The article reviews methods for assessing vitamin D status and suggests strategies to restore vitamin D status in patients requiring enteral or parenteral nutrition who are at particularly high risk of hypovitaminosis D. Screening for hypovitaminosis D with plasma total 25-hydroxyvitamin D should be a routine part of the care of the patient requiring enteral or parenteral nutrition. Restoration of optimal vitamin D status with high-dose supplemental vitamin D is required in most cases, whereas exposure to sunlight or an ultraviolet B radiation–emitting device is most effective in patients with severe malabsorption or those requiring long-term parenteral therapy. Given the emerging role of vitamin D for a variety of acute and chronic conditions, the optimal vitamin D status in acutely ill patients as well as in patients requiring long-term nutrition therapy warrants further investigation. (*JPEN J Parenter Enteral Nutr.* 2010;34:70-78)

Keywords: vitamin D; nutrition support; nutrition therapy

The major and most well-known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. However, recent research has revealed that optimal vitamin D status may be important for a variety of nonskeletal outcomes. The purpose of the review was: (1) to synthesize the available evidence on the role of vitamin D in medical conditions such as muscle function and falls, fractures, compromised immunity, glucose intolerance, and cardiovascular disease in inpatient populations, including those requiring nutrition support; (2) to review methods for assessing vitamin D status; and (3) to suggest strategies to restore vitamin D status in patients requiring enteral nutrition (EN) or parenteral nutrition (PN).

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Literature Search and Data Synthesis

We searched MEDLINE for English-language literature from 1966 through December 2008 for: (1) observational studies on the association between vitamin D status and outcomes, (2) interventional studies of the effect of vitamin D supplementation, and (3) systematic reviews or comprehensive narrative reviews on the role of vitamin D in inpatient populations with special focus among those requiring nutrition support. Search terms included *diabetes, hyperglycemia, glucose, metabolic syndrome, cardiovascular disease, metabolic bone disease, fracture, falls, immune system, infection, autoimmunity, inpatient, hospital, nutrition therapy, enteral nutrition, parenteral nutrition, vitamin D,* and related terms. Additional publications were identified from citations from the recovered articles, review articles, and personal reference lists, and we selected those we judged relevant.

Review of Vitamin D Homeostasis

The sources of vitamin D include cutaneous synthesis (in the form of cholecalciferol [D_3]) and intake (from diet and/or supplements in the form of D_3 or, less frequently, ergocalciferol [D_2]). Upon exposure to solar ultraviolet B radiation (UVB), 7-dehydrocholesterol in the skin is converted to previtamin D_3, which is immediately converted to vitamin D_3 in a heat-dependent process. Humans have evolved to derive the majority of their vitamin D requirement from cutaneous synthesis, so vitamin D is found in high amounts in only a few foods (hereafter "D" represents D_2 or D_3) (Table 1). The most important dietary sources of vitamin D are commonly consumed foods that are fortified with vitamin D, such as milk and breakfast cereals, or supplements containing vitamin D (Table 1). Whether endogenously synthesized or ingested, vitamin D is bound to the vitamin D binding protein and is transported to the liver, where it is converted to 25-hydroxyvitamin D (25[OH]D), its major circulating form. This form of vitamin D has limited biological activity. Under the influence of parathyroid hormone (PTH) and vitamin D status, 25(OH) D is converted primarily in the kidney to its most active circulating metabolite, 1,25-hydroxyvitamin D (1,25[OH]$_2$D), by the enzyme CYP27B1 (formerly 25[OH]D-1α-hydroxylase). The primary action of 1,25(OH)$_2$D is through the vitamin D receptor to enhance intestinal calcium absorption and promote the maturation of osteoclasts, thereby maintaining calcium and phosphorus homeostasis and bone health. However, it has been increasingly recognized that vitamin D has pleiotropic effects in a variety of extraskeletal tissues, suggesting an important role in health and prevention of disease.

Assessment of Vitamin D Status

Because of its long half-life (approximately 3 weeks), plasma 25(OH)D concentration is considered the best measure for assessing vitamin D status.[1,2] Low 25(OH)D concentration has been correlated with classic conditions of vitamin D deficiency such as hypocalcemia, secondary hyperparathyroidism, rickets, and osteomalacia, whereas improvements in circulating 25(OH)D have been correlated with recovery from these conditions.[3,4] The most widely used method to quantify 25(OH)D is radioimmunoassay. Automated direct detection methods, such as chemiluminescence, high-performance liquid chromatography, and liquid chromatography–mass spectroscopy assays have become increasingly common, especially in large medical centers. The latter 2 methods quantify and report 25(OH)D_2 and 25(OH)D_3 separately. However, it is not clear whether this separation is useful in clinical practice, as nearly all patients tested will have no detectable circulating 25(OH)D_2 unless they have been treated with ergocalciferol (D_2). Because there is evidence that separate reporting may confuse interpretation by physicians,[5] it is recommended that in routine clinical practice the total 25(OH)D be reported and evaluated.[6]

Vitamin D binding protein decreases with injury or trauma, and reduced concentrations appear to reflect severity of illness and predict eventual morbidity or mortality.[7,8] However, following an initial decrease shortly after an acute illness, synthesis of vitamin D binding protein increases.[9] Reductions in this protein may in part reflect its role as an actin scavenger, with increased consumption associated with injury. Whether changes in vitamin D binding protein that accompany acute illness affect measured 25(OH)D concentrations is unclear. Free vitamin D concentration appears to be well maintained in patients with reduced vitamin D binding protein secondary to chronic malabsorption or liver disease, indicating that the total 25(OH)D level is accurate as an indicator of vitamin D status among those with severe illness.[2] In general, 1,25(OH)$_2$D should not be measured to assess vitamin D status because those with hypovitaminosis D may have normal 1,25(OH)$_2$D concentration as a result of secondary hyperparathyroidism, which results in increased CYP27B1 activity. Additionally, the elimination half-life of 1,25(OH)$_2$D is very short; therefore, 1,25(OH)$_2$D concentration does not reflect long-term vitamin D status.

Measurement of 25(OH)D is sometimes accompanied by measurement of serum calcium and PTH concentrations. In healthy populations and in many chronic conditions, PTH elevations reflect secondary hyperparathyroidism in response to hypovitaminosis D (low 25[OH]D and 1,25[OH]$_2$D concentrations). However, provision of PN may complicate the relationship between measured vitamin D, calcium, and PTH. In patients receiving nocturnal PN infusions that contain calcium, the evening diurnal increase in PTH is blunted. If calcium is removed from PN, the normal diurnal increase will no longer be suppressed.[10]

Another factor complicating interpretation of 25(OH)D among those requiring nutrition support may be the accelerated bone resorption seen in immobilized patients. In a study of patients who were chronically disabled with stroke, concentrations of both 25(OH)D and 1,25(OH)$_2$D were low, and there was no correlation between 25(OH)D and PTH. Decreases in serum ionized calcium were associated with reduced concentrations of 1,25(OH)$_2$D but were not associated with concentrations of 25(OH)D. In addition, 25(OH)D deficiency did not predict 1,25(OH)$_2$D concentration.[11] Therefore, treatment of 25(OH)D deficiency in those with accelerated bone resorption due to immobilization may not necessarily lead to expected increases in the active 1,25(OH)$_2$D.

In general, biochemical markers that are routinely measured in acutely or chronically ill patients are likely to be of little value in suggesting the presence of hypovitaminosis D. Serum measurements of calcium and phosphorus are influenced by many factors. In hospitalized ill patients, hypoalbuminemia has been a predictor of hypovitaminosis D in some but not all studies.[12-15] Hypophosphatemia with initiation of enteral feeding is not uncommon in hospitalized patients, especially in those at risk for refeeding syndrome. Hypovitaminosis D may impair phosphate absorption from food, EN products, and supplements. Hypophosphatemia seen during enteral feeding should stimulate consideration of assessment of vitamin D status.

Vitamin D Status in the Population

As described below, there is controversy as to the optimal 25(OH)D plasma concentration; however, most experts agree that a plasma concentration <20 ng/mL (50 nmol/L) is considered "deficiency," whereas a plasma concentration <30 ng/mL (75 nmol/L) is considered "insufficiency."[16,17] Data from National Health and Nutrition Examination Survey III (NHANES III) show that vitamin D insufficiency may affect the majority of the noninstitutionalized population in the United States, even in the southern latitudes during the winter.[18-21] Additional studies have shown a prevalence of hypovitaminosis D ranging from 36% to 100% in a variety of populations worldwide, from healthy young adults to hospitalized elderly individuals.[12,20,22-29] As expected, vitamin D deficiency is much more common in high-risk populations, such as homebound elderly and hospitalized persons who are sun-deprived and have suboptimal nutrition,[12,24,30] overweight/obese individuals, and those with dark skin such as non-Hispanic blacks and Hispanics.[19,31,32]

Risk Factors for Hypovitaminosis D

There are multiple risk factors for hypovitaminosis D, as outlined in Table 2. Approximately 80% of the variation in vitamin D status among individuals can be explained by differences in cutaneous synthesis as a function of UVB exposure and skin color.[33] As 25(OH)D concentration is inversely related to body weight and body fat,[34,35] excess body weight is another important predictor of vitamin D status. In obese patients with hypovitaminosis D, vitamin D status does not necessarily normalize after bariatric surgery, and these patients remain at risk for vitamin D deficiency, secondary hyperparathyroidism, and metabolic bone disease.[36,37] The risk for vitamin D deficiency may be related, in part, to the degree of systemic inflammation.[38]

Hospitalized patients, especially those with prolonged hospitalizations or in long-term care facilities, including those who require short-term or long-term EN or PN, are at particularly high risk for vitamin D deficiency because they exhibit many of the major risk factors, including lack of exposure to UVB light, suboptimal vitamin D intake, advanced age, and diseases or medication influencing vitamin D metabolism.

Similar to healthy individuals, hospitalized patients have an increased risk for hypovitaminosis D because of lack of sun exposure,[12,39,40] especially those with prolonged hospital stays. Although dietary intake of vitamin D is less important than UVB exposure in healthy individuals, the association between poor intake of vitamin D and hypovitaminosis D is heightened with inpatients.[12,13,40] Chronic illness prior to hospitalization may contribute to both poor intake and reduced sun exposure.

Vitamin D absorption is influenced by a number of gastrointestinal diseases. Patients with Crohn's disease[41,42] and celiac disease[41] are at risk for hypovitaminosis D as well as long-term metabolic bone disease Vitamin D status is impaired by cholestatic liver disease such as primary biliary cirrhosis[43] and pancreatic insufficiency with its associated malabsorption (eg, cystic fibrosis[44,45]). Noncholestatic cirrhosis may be associated with impaired vitamin D status because loss of hepatocytes may result in reduced synthesis of 25(OH)D. However, not all studies have confirmed reductions in 25(OH)D in these patients,[14,46] probably reflecting less advanced disease with preserved 25-hydroxylase function. Chronic kidney disease is commonly associated with hypovitaminosis D, at least in part due to reduced activity of 25(OH)D-1α-hydroxylase. Nephrotic syndrome may lead to increased urinary losses of vitamin D and vitamin D binding protein.

Table 1. Dietary and Supplemental Sources of Vitamin D[a]

	Amount	
	IU	μg
Natural foods		
Cod liver oil	400–1,000/tsp	10–25
Oily fish (3.5 oz)		
Salmon		
Fresh, wild	600–1,000	15–25
Fresh, farmed	100–250	2.5–6.75
Sardines, canned	300	7.5
Mackerel, canned	250	6.25
Tuna, canned	230	5.75
Egg yolk	20	0.5
Fortified foods	100/serving	2.5
Milk		
Orange juice		
Most cereals		
Some yogurt		
Supplements		
Cholecalciferol (D_3)		
Multivitamin	400	10
Vitamin D–only pill	400, 800, 1,000, 2,000, 5,000, 10,000	10, 20, 25, 50, 125, 250
Vitamin D–only liquid	1,000, 4,000/serving	25, 100
Ergocalciferol (D_2)		
Prescription pill	50,000/capsule	1,250/capsule
Intramuscular[b]	300,000–600,000/injection	7,500–15,000

[a]Vitamin D_3, unless specified.
[b]Intramuscular vitamin D is not available in the United States as a standard formulation.

Vitamin D, Health Outcomes, and Implications for Hospitalized Patients

Emerging data demonstrate that the health implications of impaired vitamin D status are widespread and of potentially great clinical significance.

Table 2. Major Risk Factors for Vitamin D Deficiency

Risk Factor	Example
Reduced skin synthesis	
Limited UVB exposure	Latitude >37° N or S, season, time of day, weather
	Protective clothing, sunscreen
	Physical inactivity, homebound
	Repeated UVB exposure/tanning
	Air pollution
Skin pigmentation	Dark skin
Decreased intake	Unhealthy diet/limited supplement intake
	Intestinal malabsorption syndromes
	Parenteral nutrition
Decreased bioavailability	Sequestration of vitamin D (not conclusively shown to occur in humans)
Increased catabolism	Glucocorticoids, antiepileptic drugs (carbamazepine, phenytoin)
Aging	All of the above (eg, physical inactivity)
	Other (decreased cutaneous synthesis, lactose intolerance)
Decreased synthesis of 25(OH)D	Liver failure
Reduced synthesis of $1,25(OH)_2D$	Chronic kidney disease

UVB, ultraviolet B radiation.

The discovery that nearly all tissues in the body express the vitamin D receptor and that several tissues also express CYP27B1 enzyme, which allows for local production of $1,25(OH)_2D$ with a paracrine effect, has provided new insights into the role of vitamin D in several medical conditions. Hypovitaminosis D has been associated with increased all-cause and cardiovascular mortality,[47] whereas a recent meta-analysis of randomized trials showed that intake of ordinary doses of vitamin D supplements was associated with a modest decrease in total mortality.[48] However, because the risk factors for vitamin D deficiency are also risk factors for many acute and chronic medical conditions, vitamin D status is an excellent marker of overall health; therefore, the observational studies linking hypovitaminosis D with suboptimal health may not reflect a true association because of potential residual or unmeasured confounding.

Musculoskeletal function

Musculoskeletal disability and falls are serious undesirable events among patients in hospitals and long-term care facilities.[49-51] Several observational studies have reported an association between vitamin D insufficiency and poor lower-extremity muscle performance, gait imbalance, and increased risk of falls.[52-54] Randomized trials have shown improvements in muscle performance after vitamin D supplementation in these patients.[55-59] A meta-analysis that assessed the effectiveness of vitamin D in preventing falls concluded that vitamin D supplementation reduces the risk of falls among ambulatory or institutionalized older individuals by >20%.[59] Recent trials have supported a beneficial role of supplemental vitamin D in falls[60,61]; however, other trials found no effect.[62-64] Two of the trials with neutral results were conducted in the outpatient setting, where the baseline incidence of falls is low. Vitamin D is thought to improve muscle function via a direct effect on myocytes, which express vitamin D receptors.[65]

Evidence of the effect of vitamin D on bone health and fractures varies between studies. An evidence-based review combining data from 13 trials found a nonsignificant reduction in fractures but significant heterogeneity between studies.[66] The effect appears to be maximal when high-dose vitamin D (700–800 IU [17.5–20 μg]/d) is given in older persons living in institutionalized settings.

Vitamin D deficiency is associated with osteomalacia, which in adults presents with nonspecific complaints of malaise, fatigue, and body aches, and can be debilitating to the patient and frustrating for the clinician to diagnose. Restoring vitamin D status can reverse symptoms of osteomalacia.[67]

Metabolic bone disease

A chronic complication in patients receiving PN is the occurrence of metabolic bone disease. This has been reported in the majority of patients receiving long-term home PN.[68] Several factors have been implicated in the cause of PN-associated metabolic bone disease, including calcium deficiency, aluminum toxicity, and the contribution by crystalline amino-acid solutions. The role of vitamin D in the pathogenesis of PN-associated metabolic bone disease has been controversial. It has been suggested that in the absence of a requirement for enteral calcium absorption, the amount of exogenous vitamin D found in the injectable multivitamin package may be toxic to the bone. It has been hypothesized that in those patients with suppressed PTH, provision of parenteral vitamin D contributes to metabolic bone disease.[68] In 2 studies, withdrawal of vitamin D from PN was associated with improvement in the clinical and biochemical indices of bone mineralization.[69,70] In these studies, vitamin D status, as assessed by 25(OH)D level, was suboptimal by current criteria. No reports in the last decade have confirmed these findings. In a recent study, bone mineral loss in patients receiving long-term PN was similar in age- and gender-matched controls,[71] suggesting that underlying disease itself may be responsible for metabolic bone disease and PN is less likely to promote metabolic bone disease.

Immune system, infections, and autoimmunity

Hospital-acquired infections are prevalent in hospitals and long-term facilities. Hospitalized patients are exposed to a large number of pathogens, and the risk of acquiring an infection increases when immunity is compromised. Several lines of evidence suggest an important role of vitamin D as a regulator of the immune system.[72] Therefore, a patient's preadmission vitamin D status may affect the risk and severity of hospital-acquired infections. In observational studies, vitamin D deficiency has been found to be associated with development of infections, including influenza and tuberculosis.[73,74] Infants with rickets are at increased risk for respiratory infection.[75,76] There are limited data from randomized trials to suggest that vitamin D supplementation may prevent infections.[77,78] A direct role of vitamin D in immunity is suggested by the expression of the vitamin D receptor by the majority of immune cells, including antigen-presenting cells like macrophages and dendritic cells, as well as activated CD4 and CD8 T lymphocytes.[79] Moreover, macrophages express CYP27B1, which allows local synthesis of the active form of vitamin D.[72,80] These findings suggest a fundamental role of vitamin D in the innate immune system and a potentially important role in preventing infections among susceptible individuals, including those who required long-term EN or PN therapy. Finally, several studies have reported an association between hypovitaminosis D and a variety of autoimmune diseases, including type 1 diabetes mellitus, multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis.[81-84] Vitamin D is thought to act as an immunomodulator by suppressing T-helper type 1 cytokine profile, which favors suppressor T cells (T-helper type 2).[85]

Glucose homeostasis and cardiovascular disease

Diabetes and cardiovascular disease (hereafter termed *cardiometabolic disease*) are major causes of morbidity and mortality in the industrialized world. On the basis of evidence from animal and human studies, vitamin D has emerged as a potential modifier of cardiometabolic risk.[86] Vitamin D insufficiency has long been suspected to be a risk factor for type 1 diabetes.[87] Accumulating evidence suggests that altered vitamin D homeostasis may play a role in the development of type 2 diabetes and cardiovascular disease. Observational studies have reported a consistent association between hypovitaminosis D and incident type 2 diabetes[88] or cardiovascular disease.[47,89,90] Evidence from randomized trials on cardiometabolic disease is limited. A posthoc analysis of a trial designed for bone-related outcomes showed a beneficial effect of combined vitamin D_3 (700 IU [17.5 μg]/d) and calcium (500 mg/d) supplementation on preventing the worsening of glucose intolerance among nondiabetic adults with altered glucose homeostasis at baseline.[91] However, a posthoc analysis from the large Women's Health Initiative trial showed no effect of combined vitamin D_3 (400 IU [10 μg]/d) and calcium (1,000 mg/d) supplementation on incident cardiovascular disease[92] or self-reported diabetes.[93] In the Women's Health Initiative, the neutral results may be explained by the low dose of supplemental vitamin D_3, which is considered insufficient for both skeletal and nonskeletal outcomes. Congestive heart failure has been associated with increased risk for hypovitaminosis D.[94,95] Patients with congestive heart failure supplemented with 2,000 IU of vitamin D_3 showed reduced concentrations of inflammatory cytokines, although it remains unclear whether this could translate to improved myocardial function or delayed disease progress.[96] Several ongoing trials are expected to offer further insights into the role of vitamin D on cardiometabolic disease. The potential effects of vitamin D on the cardiometabolic system are thought to be mediated by a variety of mechanisms, including improving pancreatic β-cell function, enhancing insulin action in insulin-sensitive tissues, ameliorating systemic inflammation, regulating smooth muscle function, and inhibiting the renin-angiotensin system.[91]

Vitamin D Supplementation

The Food and Nutrition Board of the Institute of Medicine set the adequate intake of vitamin D at 200–600 IU (5–15 μg)/d based on age.[3] In the Nurses' Health Study, a large prospective observational cohort, it was found that only 3% of female nurses reported the recommended vitamin D intake for their age. However, there is growing consensus that vitamin D intakes above these levels are associated with better health outcomes. Optimal plasma 25(OH)D concentration is highly debatable. But for a variety of skeletal and nonskeletal outcomes, most experts agree that a plasma concentration >30 ng/mL (75 nmol/L) is required to improve outcomes.[97] To achieve this desired level of 25(OH) D, an intake of at least 1,000 IU [25 μg]/d of vitamin D is needed.[97,98] Plasma concentrations of 25(OH)D much higher than 30 ng/mL (75 nmol/L) need to be individualized because the risk of nephrolithiasis increases and hypercalcemia may be unmasked in patients with granulomatous disease or asymptomatic primary hyperparathyroidism. Oral formulations of vitamin D are available either as D_3 or D_2 (Table 1). Supplementation with vitamin D_3 is usually preferred over D_2 because the latter may be less bioactive and may have lower affinity for the vitamin D receptor,[99] although data are conflicting.[100] However, which type of vitamin D is preferred may not be relevant in clinical practice because nearly all over-the-counter dietary supplements and foods fortified with vitamin D contain vitamin D_3, whereas the only high-dose vitamin D available as a prescription formulation is vitamin D_2 (Table 1). Vitamin D_2 is the only vitamin D form available as a pharmaceutical preparation because it predated certain regulations by the U.S. Food and Drug Administration and thus was grandfathered as a pharmaceutical instead of a dietary supplement. Vitamin D_3 has not been approved as a pharmaceutical agent in the United States.[100] Effective supplementation can be achieved on a daily, weekly, or monthly basis.[101] The amount of vitamin D in commonly used EN formulations (Table 3) is consistent with the official recommendations by the Food and Nutrition Board.[3] However, ill patients will likely need much higher intakes of vitamin D because of aging, lack of sun exposure, and other factors such as malabsorptive syndromes or renal disease.

Our recommendation is to first confirm hypovitaminosis D (plasma 25[OH]D <30 ng/mL [75 nmol/L]) and then administer 50,000 IU (1,250 μg) of vitamin D_2 weekly for 12 weeks, followed by 1,000 IU (25 μg) of vitamin D_3 daily. Alternatively, as high-dose vitamin D formulations (>10,000 IU) become available, the initial high (loading) dose of vitamin D_2 may be substituted for an equivalent dose of vitamin D_3. This regimen raises 25(OH)D concentration to >30 ng/mL (75 nmol/L) in most patients. However, in patients with severe malabsorption syndromes, doses as high as 50,000 IU (1,250 μg) per day may be needed to adequately raise and maintain plasma 25(OH)D concentration. Frequent monitoring for hypercalcemia (preferably with measurement of ionized calcium) is recommended, especially when daily high-dose regimens (>2,000 IU daily) are prescribed. To avoid hypercalciuria, a 24-hour urine collection for measurement of calcium and creatinine may be considered; results of 24-hour urine excretion of calcium in patients maintained by oral nutrition or EN can be interpreted by use of current normal ranges, but interpretation in patients receiving PN may be influenced by a number of factors that render interpretation more difficult.

Given the lack of requirement for calcium absorption, patients who are exclusively receiving PN do not require vitamin D for calcium absorption; however, given the direct effects of vitamin D on parathyroid cells and osteocytes, and its pleiotropic effects on tissues not involved in calcium homeostasis, maintaining optimal vitamin D levels is important in this population as well. The difficulty with patients requiring PN is determining the optimal level of $25(OH)_2D$ concentration. In patients requiring long-term PN, frequent (eg, monthly) measurements of 25(OH)D, $1,25(OH)_2D$, PTH, and calcium and maintenance of these markers as close to normal as possible are important. Vitamin D supplementation in patients who require PN is also challenging because of the lack of a high-dose (eg, 50,000 IU) parenteral formulation of vitamin D. Currently, patients receiving PN receive a daily multivitamin injection that contains 200–400 IU (5–10 μg) of vitamin D_2 or D_3, depending on the product. There is an intramuscular form of high-dose vitamin D_2, but it is not available in the United States. The intramuscular form may not provide consistency in solubility and absorption profile to result in a predictable clinical response and can cause significant discomfort; therefore, it is not recommended. An alternative and quite effective method to improve vitamin D status in individuals with malabsorption syndromes and those on long-term PN is exposure to sunlight or UVB radiation from a tanning bed or other UVB-emitting device.[102] On rare occasions such as with hypercalcemia or hypervitaminosis D, elimination of vitamin D from PN may be desired; however, vitamin D is included as a standard component of parenteral multivitamins and there is no known multivitamin preparation for infusion that does not contain vitamin D.

Table 3. Vitamin D Content in Selected Total Enteral Nutrition Preparations

Selected Enteral Nutrition Preparations	Vitamin D_3, IU/L[a]
2CalHN (Abbott Laboratories[b])	425
Promote (Abbott Laboratories)	400
Promote with Fiber (Abbott Laboratories)	400
Peptamen AF (Nestlé Nutrition[c])	328
Jevity 1 Cal (Abbott Laboratories)	305
Osmolite 1 Cal (Abbott Laboratories)	305
Glucerna 1.2 Cal (Abbott Laboratories)	285
Peptamen (Nestlé Nutrition)	272
Nepro with Carb Steady (Abbott Laboratories)	85
Renalcal (Nestlé Nutrition)	0

[a]40 IU = 1 μg.
[b]Abbott Park, IL.
[c]Minnetonka, MN.

Conclusions

Vitamin D deficiency or insufficiency is very common, especially among hospitalized patients requiring long-term EN or PN, and it is associated with increased risk for a variety of acute and chronic medical conditions, including musculoskeletal disease, fractures, infection, and cardiometabolic disease. Screening for vitamin D deficiency with plasma 25(OH)D concentrations should be a routine part of the care of the patient requiring EN or PN support. Restoration of optimal vitamin D status with high-dose supplemental vitamin D is required in most cases, whereas exposure to sunlight or UVB-emitting device could be most effective in patients with severe malabsorption or those requiring long-term PN. Several unresolved questions need further investigation, including the role of vitamin D in the pathogenesis of PN-associated metabolic bone disease; the optimal plasma 25(OH)D concentration in patients requiring nutrition support, especially among those exclusively on long-term PN; and the best modality for restoring vitamin D status. Given the emerging roles for vitamin D in inflammation and glucose homeostasis, the influence of vitamin D status and vitamin D provision on outcomes in hospitalized patients deserves further attention.

References

1. Hollis BW. Assessment of vitamin D nutritional and hormonal status: what to measure and how to do it. *Calcif Tissue Int*. 1996;58:4-5.
2. Zerwekh JE. Blood biomarkers of vitamin D status. *Am J Clin Nutr*. 2008;87:1087S-1091S.
3. Standing Committee on the Scientific Evaluation of Dietary Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academy Press; 2003.
4. Holick MF. Vitamin D: a millenium perspective. *J Cell Biochem*. 2003;88:296-307.
5. Binkley N, Drezner MK, Hollis BW. Laboratory reporting of 25-hydroxyvitamin D results: potential for clinical misinterpretation. *Clin Chem*. 2006;52:2124-2125.
6. Hollis BW. Measuring 25-hydroxyvitamin D in a clinical environment: challenges and needs. *Am J Clin Nutr*. 2008;88:507S-510S.
7. Dahl B, Schiodt FV, Ott P, et al. Plasma concentration of Gc-globulin is associated with organ dysfunction and sepsis after injury. *Crit Care Med*. 2003;31:152-156.
8. Meier U, Gressner O, Lammert F, Gressner AM. Gc-globulin: roles in response to injury. *Clin Chem*. 2006;52:1247-1253.
9. Dahl B, Schiodt FV, Rudolph S, Ott P, Kiaer T, Heslet L. Trauma stimulates the synthesis of Gc-globulin. *Intensive Care Med*. 2001;27:394-399.
10. Goodman WG, Misra S, Veldhuis JD, et al. Altered diurnal regulation of blood ionized calcium and serum parathyroid hormone concentrations during parenteral nutrition. *Am J Clin Nutr*. 2000;71:560-568.
11. Sato Y, Kuno H, Asoh T, Honda Y, Oizumi K. Effect of immobilization on vitamin D status and bone mass in chronically hospitalized disabled stroke patients. *Age Ageing*. 1999;28:265-269.
12. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338:777-783.
13. Hochwald O, Harman-Boehm I, Castel H. Hypovitaminosis D among inpatients in a sunny country. *Isr Med Assoc J*. 2004;6:82-87.
14. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol*. 2007;5:513-520.
15. Gonzalez EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease: a single center observational study. *Am J Nephrol*. 2004;24:503-510.
16. Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr*. 2006;136:1117-1122.
17. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266-281.
18. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone*. 2002;30:771-777.
19. Yetley EA. Assessing the vitamin D status of the US population. *Am J Clin Nutr*. 2008;88:558S-564S.
20. Jacobs ET, Alberts DS, Foote JA, et al. Vitamin D insufficiency in southern Arizona. *Am J Clin Nutr*. 2008;87:608-613.
21. Binkley N, Novotny R, Krueger D, et al. Low vitamin D status despite abundant sun exposure. *J Clin Endocrinol Metab*. 2007;92: 2130-2135.
22. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med*. 1992;93:69-77.
23. van der Wielen RP, Lowik MR, van den Berg H, et al. Serum vitamin D concentrations among elderly people in Europe. *Lancet*. 1995;346:207-210.
24. Gloth FM III, Gundberg CM, Hollis BW, Haddad JG Jr, Tobin JD. Vitamin D deficiency in homebound elderly persons. *JAMA*. 1995;274:1683-1686.
25. Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care*. 2006;29:650-656.
26. Hanley DA, Davison KS. Vitamin D insufficiency in North America. *J Nutr*. 2005;135:332-337.
27. Binkley N, Krueger D, Drezner MK. Low vitamin D status: time to recognize and correct a Wisconsin epidemic. *WMJ*. 2007;106: 466-472.
28. Lips P, Hosking D, Lippuner K, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med*. 2006;260: 245-254.
29. Bakhtiyarova S, Lesnyak O, Kyznesova N, Blankenstein MA, Lips P. Vitamin D status among patients with hip fracture and elderly control subjects in Yekaterinburg, Russia. *Osteoporos Int*. 2006;17:441-446.
30. Foote JA, Giuliano AR, Harris RB. Older adults need guidance to meet nutritional recommendations. *J Am Coll Nutr*. 2000;19: 628-640.
31. Harris SS. Vitamin D and African Americans. *J Nutr*. 2006; 136:1126-1129.
32. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr*. 2002;76: 187-192.
33. Armas LA, Dowell S, Akhter M, et al. Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol*. 2007;57:588-593.
34. Looker AC. Body fat and vitamin D status in black versus white women. *J Clin Endocrinol Metab*. 2005;90:635-640.
35. Snijder MB, van Dam RM, Visser M, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab*. 2005;90:4119-4123.
36. Goode LR, Brolin RE, Chowdhury HA, Shapses SA. Bone and gastric bypass surgery: effects of dietary calcium and vitamin D. *Obes Res*. 2004;12:40-47.
37. Youssef Y, Richards WO, Sekhar N, et al. Risk of secondary hyperparathyroidism after laparoscopic gastric bypass surgery in obese women. *Surg Endosc*. 2007;21:1393-1396.
38. Compher C, Pazianas M, Benedict S, Brown JC, Kinosian BP, Hise M. Systemic inflammatory mediators and bone homeostasis in intestinal failure. *JPEN J Parenter Enteral Nutr*. 2007;31:142-147.
39. Romagnoli E, Caravella P, Scarnecchia L, Martinez P, Minisola S. Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients. *Br J Nutr*. 1999;81:133-137.
40. Chatfield SM, Brand C, Ebeling PR, Russell DM. Vitamin D deficiency in general medical inpatients in summer and winter. *Intern Med J*. 2007;37:377-382.
41. Bikle DD. Vitamin D insufficiency/deficiency in gastrointestinal disorders. *J Bone Miner Res*. 2007;22(suppl 2):V50-V54.
42. Goh J, O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2003;17:307-320.
43. Kaplan MM, Elta GH, Furie B, Sadowski JA, Russell RM. Fat-soluble vitamin nutriture in primary biliary cirrhosis. *Gastroenterology*. 1988;95:787-792.
44. Gordon CM, Anderson EJ, Herlyn K, et al. Nutrient status of adults with cystic fibrosis. *J Am Diet Assoc*. 2007;107:2114-2119.
45. Rovner AJ, Stallings VA, Schall JI, Leonard MB, Zemel BS. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. *Am J Clin Nutr*. 2007;86:1694-1699.
46. Duarte MP, Farias ML, Coelho HS, et al. Calcium-parathyroid hormone-vitamin D axis and metabolic bone disease in chronic viral liver disease. *J Gastroenterol Hepatol*. 2001;16:1022-1027.
47. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med*. 2008;168:1340-1349.

48. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007;167:1730-1737.
49. von Renteln-Kruse W, Krause T. Incidence of in-hospital falls in geriatric patients before and after the introduction of an interdisciplinary team-based fall-prevention intervention. *J Am Geriatr Soc*. 2007;55:2068-2074.
50. Boufous S, Finch C. Estimating the incidence of hospitalized injurious falls: impact of varying case definitions. *Inj Prev*. 2005;11:334-336.
51. Brophy M, Zhang X, Xiang H. Injuries among US adults with disabilities. *Epidemiology*. 2008;19:465-471.
52. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr*. 2004;80:752-758.
53. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab*. 2007;92:2058-2065.
54. Dharmarajan TS, Akula M, Kuppachi S, Norkus EP. Vitamin D deficiency in community older adults with falls of gait imbalance: an under-recognized problem in the inner city. *J Nutr Elder*. 2005;25:7-19.
55. Bunout D, Barrera G, Leiva L, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. *Exp Gerontol*. 2006;41:746-752.
56. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res*. 2003;18:343-351.
57. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res*. 2000;15:1113-1118.
58. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis*. 2005;20:187-192.
59. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC. Effect of vitamin D on falls: a meta-analysis. *JAMA*. 2004;291:1999-2006.
60. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc*. 2007;55:234-239.
61. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc*. 2005;53:1881-1888.
62. Burleigh E, McColl J, Potter J. Does vitamin D stop inpatients falling? A randomised controlled trial. *Age Ageing*. 2007;36:507-513.
63. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium OR vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365:1621-1628.
64. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BML*. 2005;330:1003.
65. Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *Am J Clin Nutr*. 2008;88:537S-540S.
66. Cranney A, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *Am J Clin Nutr*. 2008;88:513S-519S.
67. Lorenzo JA, Canalis E, Raisz LG. Metabolic bone disease. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, Polonsky KS, Wilson JD, eds. *Williams Textbook of Endocrinology*. Philadelphia, PA: Saunders; 2008.
68. Buchman AL, Moukarzel A. Metabolic bone disease associated with total parenteral nutrition. *Clin Nutr*. 2000;19:217-231.
69. Shike M, Sturtridge WC, Tam CS, et al. A possible role of vitamin D in the genesis of parenteral-nutrition-induced metabolic bone disease. *Ann Intern Med*. 1981;95:560-568.
70. Verhage AH, Cheong WK, Allard JP, Jeejeebhoy KN. Harry M. Vars Research Award. Increase in lumbar spine bone mineral content in patients on long-term parenteral nutrition without vitamin D supplementation. *JPEN J Parenter Enteral Nutr*. 1995;19:431-436.
71. Haderslev KV, Tjellesen L, Haderslev PH, Staun M. Assessment of the longitudinal changes in bone mineral density in patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2004;28:289-294.
72. Adams JS, Liu PT, Chun R, Modlin RL, Hewison M. Vitamin D in defense of the human immune response. *Ann N Y Acad Sci*. 2007;1117:94-105.
73. Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. *Epidemiol Infect*. 2006;134:1129-1140.
74. Chan TY. Vitamin D deficiency and susceptibility to tuberculosis. *Calcif Tussue Int*. 2000;66:476-478.
75. Karatekin G, Kaya A, Salihoglu O, Balci H, Nuhoglu A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *Eur J Clin Nutr*. 2009;63:473-477.
76. Najada AS, Habashneh MS, Khader M. The frequency of nutritional rickets among hospitalized infants and its relation to respiratory diseases. *J Trop Pediatr*. 2004;50:364-368.
77. Avenell A, Cook JA, MacLennan GS, MacPherson GC. Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people. *Age Ageing*. 2007;36:574-577.
78. Grant WB, Garland CF. The role of vitamin D3 in preventing infections. *Age Ageing*. 2008;37:121-122.
79. Veldman CM, Cantorna MT, DeLuca HF. Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Arch Biochem Biophys*. 2000;374:334-338.
80. Monkawa T, Yoshida T, Hayashi M, Saruta T. Identification of 25-hydroxyvitamin D3 1-αhydroxylase gene expression in macrophages. *Kidney Int*. 2000:559-568.
81. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*. 2001;358:1500-1503.
82. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med (Maywood)*. 2004;229:1136-1142.
83. Ponsonby AL, Pezic A, Ellis J, et al. Variation in associations between allelic variants of the vitamin D receptor gene and onset of type 1 diabetes mellitus by ambient winter ultraviolet radiation levels: a meta-regression analysis. *Am J Epidemiol*. 2008;168:358-365.
84. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog Biophys Mol Biol*. 2006;92:60-64.
85. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. *J Nutr*. 1995;125(6 suppl):1704S-1708S.
86. Peechakara SV, Pittas AG. Vitamin D as a potential modifier of diabetes risk. *Nat Clin Pract Endocrinol Metab*. 2008;4:182-183.
87. Mathieu C, Badenhoop K. Vitamin D and type 1 diabetes mellitus: state of the art. *Trends Endocrinol Metab*. 2005;16:261-266.
88. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes: asystematic review and meta-analysis. *J Clin Endocrinol Metab*. 2007;92:2017-2029.
89. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008;168:1174-1180.

90. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117:503-511.
91. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care*. 2007;30:980-986.
92. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115:846-854.
93. de Boer IH, Tinker LF, Connelly S, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care*. 2008;31:701-707.
94. Pilz S, Marz W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab*. 2008;93:3927-3935.
95. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol*. 2003;41:105-112.
96. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83:754-759.
97. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr*. 2006;84:18-28.
98. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr*. 2005;135:317-322.
99. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. *Am J Clin Nutr*. 2006;84:694-697.
100. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab*. 2008;93:677-681.
101. Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J Clin Endocrinol Metab*. 2008;93:3430-3435.
102. Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. *Gastroenterology*. 2001;121:1485-1488.