Review

Role of Vitamin D in Adults Requiring Nutrition Support

Anastassios G. Pittas, MD, MS1; Ursula Laskowski, MD1; Luke Kos, MD1; and Edward Saltzman, MD2,3

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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

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 [D3]) and intake (from diet and/or supplements in the form of D3 or, less frequently, ergocalciferol [D2]). Upon exposure to solar ultraviolet B radiation (UVB), 7-dehydrocholesterol in the skin is converted to
previtamin D₃, which is immediately converted to vitamin D₃ 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 D₂ or D₃) (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]₂D), by the enzyme CYP27B1 (formerly 25[OH]D-1α-hydroxylase). The primary action of 1,25(OH)₂D 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.³⁻² 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 of patients who were chronically disabled with stroke, concentration of 1,25(OH)₂D but were not associated with concentrations of 25(OH)D. In addition, 25(OH)D deficiency did not predict 1,25(OH)₂D 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)₂D.

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 disease41,42 and celiac disease41 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 cirrhosis41 and pancreatic insufficiency with its associated malabsorption (eg, cystic fibrosis44,45). 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.

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 1. Dietary and Supplemental Sources of Vitamin D*

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural foods</td>
<td></td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>400–1,000/tsp</td>
</tr>
<tr>
<td>Oily fish (3.5 oz)</td>
<td></td>
</tr>
<tr>
<td>Salmon</td>
<td>600–1,000</td>
</tr>
<tr>
<td>Fresh, wild</td>
<td>100–250</td>
</tr>
<tr>
<td>Fresh, farmed</td>
<td></td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>300</td>
</tr>
<tr>
<td>Mackerel, canned</td>
<td>250</td>
</tr>
<tr>
<td>Tuna, canned</td>
<td>230</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>20</td>
</tr>
<tr>
<td>Fortified foods</td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>100/serving</td>
</tr>
<tr>
<td>Orange juice</td>
<td></td>
</tr>
<tr>
<td>Most cereals</td>
<td></td>
</tr>
<tr>
<td>Some yogurt</td>
<td></td>
</tr>
<tr>
<td>Supplements</td>
<td></td>
</tr>
<tr>
<td>Cholecalciferol (D₃)</td>
<td></td>
</tr>
<tr>
<td>Multivitamin</td>
<td>400</td>
</tr>
<tr>
<td>Vitamin D–only pill</td>
<td>400, 500, 1,000</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
</tr>
<tr>
<td>Vitamin D–only liquid</td>
<td>1,000</td>
</tr>
<tr>
<td>Ergocalciferol (D₂)</td>
<td></td>
</tr>
<tr>
<td>Prescription pill</td>
<td>50,000/capsule</td>
</tr>
<tr>
<td>Intramuscularb</td>
<td>300,000–600,000</td>
</tr>
</tbody>
</table>

*Vitamin D₃, unless specified.

bIntramuscular vitamin D is not available in the United States as a standard formulation.
increased all-cause and cardiovascular mortality, whereas a conditions. Hypovitaminosis D has been associated with insights into the role of vitamin D in several medical potential residual or unmeasured confounding.

Observational studies linking hypovitaminosis D with subop-

status is an excellent marker of overall health; therefore, the risk factors for vitamin D deficiency are also risk factors for many acute and chronic medical conditions, vitamin D intake of ordinary doses of vitamin D supplements was associated with a modest decrease in total mortality. 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 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. Several observational studies have reported an association between vitamin D insufficiency and poor lower-extremity muscle performance, gait imbalance, and increased risk of falls. Randomized trials have shown improvements in muscle performance after vitamin D supplementation in these patients. 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%. Recent trials have supported a beneficial role of supplemental vitamin D in falls, however, other trials found no effect. 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.

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. 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.

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. 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. In 2 studies, withdrawal of vitamin D from PN was associated with improvement in the clinical and biochemical indices of bone mineralization. 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, 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. Therefore, a patient’s pre-admission 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. Infants with rickets are at increased risk for respiratory infection. There are limited data from randomized trials to suggest that vitamin D supplementation may prevent infections. 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. Moreover, macrophages express CYP27B1, which allows local synthesis of the active form of vitamin D. 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. 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).

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. Vitamin D insufficiency has long been suspected to be a risk factor for type 1 diabetes. 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 or cardiovascular disease. 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 D₃ (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. However, a posthoc analysis from the large Women’s Health Initiative trial showed no effect of combined vitamin D₃ (400 IU [10 µg/d]) and calcium (1,000 mg/d) supplementation on incident cardiovascular disease or self-reported diabetes. In the Women’s Health Initiative, the neutral results may be explained by the low dose of supplemental vitamin D₃, which is considered insufficient for both skeletal and nonskeletal outcomes. Congestive heart failure has been associated with increased risk for hypovitaminosis D. Patients with congestive heart failure supplemented with 2,000 IU of vitamin D₃ showed reduced concentrations of inflammatory cytokines, although it remains unclear whether this could translate to improved myocardial function or delayed disease progression. 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.

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) based on age. 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 intake 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. 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. 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 D₃ or D₂ (Table 1). Supplementation with vitamin D₃ is usually preferred over D₂ because the latter may be less bioactive and may have lower affinity for the vitamin D receptor, although data are conflicting. 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 D₃, whereas only high-dose vitamin D available as a prescription formulation is vitamin D₂ (Table 1). Vitamin D₂ 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 D₃ has not been approved as a pharmaceutical agent in the United States. Effective supplementation can be achieved on a daily, weekly, or monthly basis. The amount of vitamin D in commonly used EN formulations (Table 3) is consistent with the official recommendations by
the Food and Nutrition Board. 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$_1$ 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 hypercalcioria, 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)$_2$D concentration. In patients requiring long-term PN, frequent (eg, monthly) measurements of 25(OH)D, 1,25(OH)$_2$D, 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. 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

<table>
<thead>
<tr>
<th>Selected Enteral Nutrition Preparations</th>
<th>Vitamin D$_3$, IU/L$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2CalHN (Abbott Laboratories$^b$)</td>
<td>425</td>
</tr>
<tr>
<td>Promote (Abbott Laboratories)</td>
<td>400</td>
</tr>
<tr>
<td>Promote with Fiber (Abbott Laboratories)</td>
<td>400</td>
</tr>
<tr>
<td>Peptamen AF (Nestlé Nutrition$^c$)</td>
<td>328</td>
</tr>
<tr>
<td>Jevity 1 Cal (Abbott Laboratories)</td>
<td>305</td>
</tr>
<tr>
<td>Osmolite 1 Cal (Abbott Laboratories)</td>
<td>305</td>
</tr>
<tr>
<td>Glucerna 1.2 Cal (Abbott Laboratories)</td>
<td>285</td>
</tr>
<tr>
<td>Peptamen (Nestlé Nutrition)</td>
<td>272</td>
</tr>
<tr>
<td>Nepro with Carb Steady (Abbott Laboratories)</td>
<td>85</td>
</tr>
<tr>
<td>Renalcal (Nestlé Nutrition)</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$40 IU = 1 µg.
$^b$Abbott Park, IL.
$^c$Minnetonka, MN.

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

27. Binkley N, Krueger D, Drezer MK. Low vitamin D status: time to recognize and correct a Wisconsin epidemic. WMJ. 2007;106:466-472.


