Editorial

Vitamin D: Way More Important in Critical Care Than We May Have Recognized

Critical care nurses are familiar with the role of Vitamin D in maintaining skeletal integrity, but may not be aware of its importance in numerous other physiologic activities relevant to our patient populations. Much of the attention to vitamin D has come to light indirectly, as the ill effects of vitamin D deficiency (VDD) related to cardiovascular disease (CVD), immunity, infection, cognition, and mortality were uncovered.[1] Vitamin D's physiologic contributions to health and the potentially detrimental effects of its deficiency are gradually being acknowledged as a major public health concern.[2]

Vitamin D Physiology

Vitamin D, a fat-soluble vitamin, exists in different forms, the most important of which are vitamin D_2 (ergocalciferol), which is synthesized by plants and found in foods such as eggs and fortified milk, and vitamin D_3 (cholecalciferol), which is generated by human skin exposed to sunlight (ultraviolet B light), causing photolytic conversion of 7-dehydrocholesterol to cholecalciferol. Epidermal synthesis of vitamin D_3 is the primary source of vitamin D for humans. Cholecalciferol binds with vitamin D–binding protein and is hydroxylated to 25-hydroxyvitamin D (25[OH]D), its serum circulating form, in the liver. Renal tissues process bound 25(OH)D, producing calcitriol (1,25-dihydroxyvitamin D). Calcitriol is found in endothelial, endocrine, brain, immune, and colon tissues.[3] Calcitriol binds to vitamin D receptor (VDR) for some effects, while local tissue activates unbound 25(OH)D to calcitriol to drive a wide array of additional effects.[4] Both VDR and the enzyme that converts vitamin D to its active form exist in all body organs,[5,6] including endothelium, vascular smooth muscle, endothelium, cardiomyocytes, macrophages, and beta-pancreatic cells, enabling vitamin D's widespread physiologic influences.

Table Cut-points for vitamin D adequacy, inadequacy, and deficiency

Vitamin D status	nmol/L[a]	Institute of Medicine[8] ng/mL[a]	Endocrine Society[9] ng/mL
Adequate	≥50	≥20	≥30
Inadequate	30 to <50	12 to <20	21 to 29
Deficient	<30	<12	≤20

[a] 1 nmol/L = 0.4 ng/mL

Definition of VDD

The best indicator of vitamin D status is serum concentration of 25(OH)D,[7] measured in either nanomoles per liter (nmol/L) or nanograms per milliliter (ng/mL). There are no universally accepted definitions to distinguish vitamin D adequacy, inadequacy, or deficiency, as illustrated by the contrasting cut-points in the Table and by the wide variation of values employed in research studies.

Prevalence

Vitamin D deficiency is the most common nutritional deficiency globally for adults and children.[10] The combined prevalence of vitamin

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D insufficiency and VDD is estimated at 42% of US adults, 69% of Hispanic and 82% of African Americans, owing to differences in diet and skin pigmentation.[11] Worldwide, an estimated 1 billion people have VDD,[12] suggesting this problem represents a pandemic.[13,14] For Americans older than 65 years, VDD prevalence is 50%, and rises to 70% to 90% among those cognitively impaired.[15]

Potentially Detrimental Effects of VDD

A substantial volume of emerging evidence underscores the health problems attributable to a lack of sufficient vitamin D. An overview of the adverse outcomes related to VDD follows.

Increased Complications for Kidney Transplant Patients

Patients with chronic kidney disease requiring kidney transplant frequently have VDD, owing to impaired renal function. In these patients, low calcidiol levels are associated with poor graft survival, type 2 diabetes mellitus, metabolic and cardiovascular disorders, and higher mortality. Vitamin D_3 supplementation has helped mitigate acute rejection episodes.[16]

Diminished Muscle Development, Increased Falls and Fractures

Vitamin D assists in regulating calcium flux in muscle cells and in regulating muscle cell differentiation and proliferation, suggesting its enhancement of muscle development and contraction. In laboratory models, global deletion of VDR causes muscle atrophy, supporting its role in motor function.[17] Separate meta-analyses[18,19] of randomized controlled trials confirm that vitamin D improves lower limb muscle strength and reduces falls and fractures, particularly for those older than 65 and those with VDD.[18]

Role of Vitamin D in Cardiovascular Health

Vitamin D appears to bestow protective effects on cardiovascular health that are diminished or lost with VDD, resulting in a higher prevalence of cardiovascular risk factors, morbidity, and mortality. Some of the mechanisms proposed to explain these outcomes include loss of vitamin D's protective vascular and endothelial effects through its influence on nitric oxide, the renin-angiotensin-aldosterone system, inflammatory cytokines, and mediators of thrombus formation.[20]

Higher CVD Morbidity and Mortality

Longitudinal study meta-analysis reveals a strong, virtually linear, inverse association between vitamin D concentration and CVD risk (total CVD, CVD mortality, coronary heart disease, stroke). In general, the lower the vitamin D, the higher the CVD risk.[21] Similar results were reported for type 2 diabetes, where the association of VDD is considered a prognostic factor for cardiovascular morbidity and mortality.[22] There is also abundant evidence of an inverse relationship between serum vitamin D and many of the risk factors for CVD. This link may be at least partly explained by VDR presence in the myocardium and vascular tissues.[23-25]

Increased Prevalence of CVD Risk Factors

Numerous studies demonstrate that VDD contributes to development of hypertension,[26,27] diabetes,[28-30] obesity,[31] and metabolic syndrome.[32] Low vitamin D is inversely correlated with elevated systolic blood pressure (SBP),[33] type 2 diabetes,[34] and obesity.[31] SBP can even be predicted using the vitamin D level.[33] The high prevalence of VDD in obesity is attributed to dilution or sequestration of vitamin D in adipose tissue.[31]

Higher Prevalence of Metabolic Syndrome

Metabolic syndrome (MS) identifies persons at heightened risk for CVD owing to their combination of risk factors: obesity, hypertension, elevated triglycerides, hyperglycemia (insulin resistance), and reduced high-density lipoprotein cholesterol.[35] A recent study found a high prevalence of VDD associated with MS: 60% of MS patients had VDD, 27% vitamin D insufficiency.[33] This same study confirmed that vitamin D is inversely correlated with SBP, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and glycemic control (HbA1c) and directly correlated with pancreatic β cell function.[33] Unfortunately, a meta-analysis of 51 vitamin D supplementation studies failed to improve lipids, SBP, stroke, or myocardial infarction.[36]

Greater Incidence, Morbidity and Mortality for Acute Myocardial Infarction

Several important associations exist between VDD and acute myocardial infarction (AMI): VDD is highly prevalent in AMI[37-43]; risk of AMI is significantly higher and inversely proportional to the degree of VDD[37]; and AMI patients with VDD fare significantly worse with

greater morbidity, postinfarction complications, and higher mortality.[39-41,43] One study found rates of major cardiovascular events were 50% higher with vitamin D insufficiency and 80% higher with VDD.[44] At a 10-year follow-up of more than 18 000 men, those with low vitamin D levels had twice the risk of AMI as those with adequate vitamin D.[45] A larger meta-analysis confirmed that VDD constitutes a unique risk factor for AMI and CVD.[46] Longer-term outcomes support that finding, with the lowest vitamin D levels linked to greater rehospitalizations for acute heart failure (HF) and subsequent acute coronary syndrome,[40] higher 1-year mortality,[39] and deaths from HF and sudden cardiac death.[47]

Reduced Exercise Capacity and Higher Mortality in HF

One of the definitive manifestations of HF, often considered a prognostic marker, is diminished exercise capacity, measured via peak oxygen consumption ($\dot{V}O_2$). A recent study found that 87% of HF patients had VDD (<20 ng/mL) and 25% had severe VDD (<10 ng/mL); those with severe VDD had significantly lower $\dot{V}O_2$, peak $\dot{V}O_2$%, and higher brain natriuretic peptide compared with those with higher levels.[48] These findings support other reports[49] that low vitamin D is associated with muscular impairment and poor prognosis in HF with limited improvement from cardiovascular rehabilitation.[50]

Increased Risk and Poor Outcomes for Ischemic Stroke

A recent study discerned that VDD correlates with increased inflammatory markers, risk of ischemic stroke, and poor short-term outcomes.[51] Patients with ischemic stroke had lower levels of vitamin D, higher prevalence of VDD, and higher high-sensitivity C-reactive protein than controls. Three months later, stroke patients with poor outcomes had lower VDD levels than those with good outcomes, suggesting that vitamin D has an important role in the inflammatory response, pathophysiology, and recovery from acute ischemic stroke.[51]

Increased Immune Dysfunction: Inflammation, Infection, and Sepsis

The role of vitamin D in regulation of the innate and adaptive immune systems has been recognized for some time.[52] The mechanisms responsible are believed to include direct expression of antimicrobial peptides, stimulated production of suppressive T cells, and suppression of proinflammatory T_H17 cells.[53] VDD <50 nmol/L represents a serious risk factor for infection, sepsis, and mortality in critically ill patients, as it increases susceptibility for severe infections and mortality.[54] This link between VDD and inflammatory biomarkers is also found in patients with multiple sclerosis, rheumatoid arthritis, and advanced age.[55]

An interesting link among vitamin D, immunity, insulin resistance, and CVD was revealed in laboratory mice when researchers genetically eliminated macrophage VDRs and the mice developed arterial atherosclerotic plaques and insulin resistance due to hepatic and vascular inflammation. Eliminating monocyte VDR led to monocyte adherence to vascular walls, cholesterol deposition, and release of inflammatory mediators that caused diabetes and heart disease. When bone marrow transplants restored VDRs to macrophages and monocytes, the laudatory benefits of vitamin D appeared: atherosclerosis suppression, insulin sensitivity, and lack of macrophage accumulation.[56]

More Severe Traumatic Brain Injury and Lower Quality of Life

In a study of the relationship between vitamin D levels and severity of head injury, patients with severe traumatic brain injury (TBI) had significantly lower vitamin D levels than those with mild TBI. In addition, self-reported quality of life was better for patients with optimum vitamin D compared with those with VDD, even after controlling for injury severity. The authors recommend active screening of TBI patients to identify when VDD occurs and to prevent its detrimental effects on healing, morbidity, and CVD.[57]

Increased and Accelerated Cognitive Decline

Low vitamin D levels are strongly associated with diminished cognitive performance and future cognitive decline, especially among the elderly.[58] In a large, ethnically diverse, longitudinal study, VDD (<12 ng/mL, 26%) and insufficiency (12 to <20 ng/mL, 35%) were prevalent among participants (mean age, 76 years) at the outset. Over 5 years, the cognitive performance of those with vitamin D levels less than 20 ng/mL declined at a rate 3 times faster than for those with adequate vitamin D levels (20-49 ng/mL). These substantial cognitive losses, especially in episodic and semantic memory and

executive function (problem-solving, following directions, reasoning) related to dementia and Alzheimer disease, were independent of baseline cognitive ability, race, ethnicity, or other risk factors.[59]

Some of the neurosteroid actions of vitamin D that may account for its notable effects on cognition include clearance of amyloid-β peptide and antioxidant, anti-inflammatory effects that may protect against the neurodegeneration associated with Alzheimer disease. Some researchers consider supplemental vitamin D as crucial to slow, prevent, or improve neurocognitive decline.[60] Comparable findings were reported in China, where individuals with lower baseline vitamin D were 2 to 3 times more likely to have significant cognitive decline within 2 years compared to those with adequate levels.[61]

Loss of Antineoplastic Protection

There is some evidence that low vitamin D concentrations may be associated with greater risk of colorectal cancer,[62] though vitamin D supplementation has not demonstrated any benefit for prevention.[63] Although it may not reduce the incidence of cancer, there is evidence that vitamin D may lower its mortality.[64]

Increased Risk of All-Cause Mortality

The protective functions afforded by vitamin D can be perceived as culminating in perhaps its most important attribute: its capacity to reduce mortality. In addition to single reports suggesting that higher vitamin D levels confer mortality benefits,[39-41,43,47,66,67] a number of randomized controlled trial meta-analyses demonstrate the consistency of the inverse relationship between vitamin D level and mortality from any cause.[68-72]

Closing

The detrimental physiologic effects of VDD are widespread and can wreak multisystem morbidity before inflicting lethality. Assessing, monitoring, and optimizing serum vitamin D may be a lifesaving intervention that we can no longer overlook. CCN

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