Optimizing Vitamin D Status Improves Outcomes in Critical Ill and Injured Patients

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Abbreviations: ICU: Intensive Care Unit; BMD: Maximal Bone Density; VDR: Vitamin D Receptors; ARDS: Acute Respiratory Distress Syndrome

Introduction

In 2008, Giovanucci et al. [1] showed that men with low vitamin D levels suffered 2.42 times more myocardial infarctions than those with normal vitamin D status [1]. Alternatively, a sufficient amount of serum 25-hydroxyvitamin D3, [25(OH)D], appears to improve the risk of almost every disease of aging. Dobnig et al. [2] similarly demonstrated people with an inadequate vitamin D status have twice the likelihood of death over seven years [2,3]. Vitamin D sufficiency, define as serum 25(OH)D levels of 30ng/mL (75nmol/L) and above, improves various health outcomes, including bone mineral density, fractures, and colorectal cancer, based on analysis of observational studies [4]. Vitamin D levels of 21-29ng/mL delineates insufficiency and a concentration of 20ng/mL or less defines vitamin D deficiency [4]. When vitamin D levels are inadequate, and particularly fall below 17.8ng/mL, mortality risk increases by as much as 26% from all-cause mortality in the general population [3,5]. Current data suggests hypovitaminosis D plays a significant role in the development of numerous common chronic diseases and inflammatory conditions, including coronary artery disease, cerebrovascular disease, diabetes mellitus, autoimmune disorders, such as systemic lupus erythematosus, scleroderma and multiple sclerosis and 17 different forms of cancer [6-12]. Vitamin D deficiency is arguably one of the most prevalent but underrated nutritional deficiency worldwide [6,7]. It continues to be associated with increased overall mortality risk in several studies [8-12]. Several observational studies on hypovitaminosis D over the past decade support the persistent existence of a high prevalence of vitamin D insufficiency and deficiency in as many as 50 to 90% of hospitalized patients, with a particular predilection in the setting of critical illness [6-9, 12-14]. Although full elucidation of the role vitamin D status plays in patients requiring admission to the intensive care unit (ICU) is an area undergoing active investigation, epidemiological data supports the findings that vitamin D sufficiency may decrease the risk of systemic inflammatory from all causes as well as sepsis in general [12,15]. Investigations by our group examining the prevalence and effects of insufficient or deficient serum vitamin D levels on our critically-ill and/or severely-injured trauma patients revealed increased risk of unfavorable outcomes when serum vitamin D levels fell below a level of 30ng/mL (75nmol/mL) in SICU trauma patients who survived their initial injury and resuscitative efforts [6,16]. According to some of the world’s leading vitamin D experts, optimal serum levels of 25(OH)D range between 30 and 50ng/mL. Those individuals with 25(OH)D levels below 30 ng/mL are considered to have vitamin D insufficiency as noted above [5,6, 8,15,16] looked at the risk of 30-day and in-hospital mortality after initiation of critical care services in patients with severe vitamin D deficiency. There was a 1.9-fold higher risk of death than in those patients with vitamin D levels of ≤30ng/mL [7]. Inadequate levels of 25(OH)D in the insufficient cohort remained a significant predictor of increased likelihood of mortality, even after multivariate adjustment [7].

Under normal circumstances, vitamin D is a hormone produced principally by the skin in response to natural sunlight. However,
when the sun hits the northern hemisphere below 45 degrees in the spring and summer; it cannot produce UVB rays of the proper wavelengths from 290 to 315 nm, which is required for the production of vitamin D in the skin between 10:00 a.m. and approximately 3:00 p.m. [6,17]. At latitudes of 32 degrees or above, vitamin D levels are the lowest, particularly during the winter months and early spring, due to the lack of sunlight at the suitable wavelength [6,17]. During the fall and winter months, vitamin D stores decrease by approximately 20 to 30%. Furthermore, vitamin D deficiency is very common in Western society as it is nearly impossible to get adequate amounts of vitamin D from diet alone without purposeful exogenous supplementation [6,7,17]. Therefore, reversal of hypovitaminosis D may not be quick or easy without supplementation.

There is a suggestion by researchers that vitamin D deficiency is present in at least 50% to 80% of critically ill patients admitted to surgical and medical ICUs. Nevertheless, based on the definition of normal and subtherapeutic vitamin D status, vitamin D insufficiency in western society may be grossly underestimated [6-14,16]. The true prevalence and extent of vitamin D deficiency might be much worse. This understanding is particularly pertinent considering we have entered the season of increased risk for acute respiratory illness, where a robust immune system is of paramount importance for fighting off upper respiratory tract infections. This underappreciation of vitamin D deficiency may be associated with increased relative risk of adverse outcomes in fragile and critically ill patient populations [6-14,16]. In our prior investigations, we evaluated a cutoff ≥40 ng/mL as a surrogate marker to define a normal vitamin D level, and levels of <40 ng/mL to represent a relative insufficiency in our ICU patients [6]. We found higher 25(OH)D levels improved outcomes in surgical ICU patients [6,8,16]. There is other evidence that supports the body functions better at this higher vitamin D level. Other authors have suggested that maximal bone density (BMD) can only be achieved when the 25-hydroxyvitamin D level reaches 40ng/mL or greater [17]. As fractures are very common in critically injured elderly trauma patients, achieving adequate vitamin D levels becomes increasingly important in this fragile, at-risk patient population. Based on prior observations demonstrating the need for calcidiol levels ≥ 40ng/mL to adequately suppress serum parathyroid hormone levels and achieve maximal bone density in the hips and lumbar spine patients, it is plausible to suggest that higher vitamin D levels may portend a protective effect in the other severely injured and/or critically ill individuals [5,6,15,18-20].

To achieve a vitamin D of 30 to 50ng/mL and maintain it long term, investigators have found that it takes over 4,000 to 5,000 units of 25-(OH) vitamin D supplementation per day [18,20]. This amounts to over 5 to 10 times the current recommended daily intake [20]. The importance of this recommendation is that optimal local concentrations of serum 25-(OH) D ≥30 ng/mL [6,24,25] are required for optimal paracrine conversion to 1,25-(OH)2-vitamin D (calcitriol) by macrophages and other immune cells. The serum concentration needs to be ≥ 30 (>75 nmol/L) [6,7,21-24] to activate the vitamin D receptors (VDR) that regulates the immune response. Activation of the VDR by bioactive vitamin D up-regulates the anti-inflammatory cytokines IL-8 and IL-10, which promotes the expression of a T-suppressor cell lineage and helps to turn off the adaptive immune response once the job is complete [23-25]. Thus, it is understandable that patients with moderate to severe vitamin D deficiency syndromes are less capable of mounting a successful immune response to severe insults, injury, and acute viral and bacterial infections. Furthermore, they have higher risk of ICU-related septic complications, acute respiratory distress syndrome (ARDS) and death.

### Conclusion

Published data suggests critically-ill patients with inadequate serum vitamin D stores may enter into a vicious inflammatory cycle due to low levels of the bioactive form of vitamin D, calcitriol, which leads to increased production of pro-inflammatory cytokines, which may not be easily reversed with vitamin D supplementation [6,8,24]. This review may provide a plausible link between the excess mortality observed in people during an acute outbreak of novel acute respiratory syndromes in the general population and especially patients in the ICU setting who are at a higher risk of frankly deficient vitamin D levels. Therefore, we recommend checking serum 25-OH vitamin D levels on all hospitalized ICU patients, and particularly those with acute respiratory or unexplained infectious/inflammatory illness. Although it is difficult to prove clinical effectiveness in the setting of acute infectious illness, supplementation of vitamin D stores to augment the immune system using cholecalciferol (Vitamin D3) at doses of 4,000 to 5,000 units daily may not be unreasonable, especially during this uncharacteristically aggressive flu season, and more so in light of the worldwide coronavirus [COVID-19] epidemic.

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