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Chapter

Extraskeletal Effects of Vitamin D Deficiency in Intensive Care Patients

Edward T. Zawada

Abstract

There has been a progression of investigations of the biology and pharmacology of vitamin D. Original work proved the importance of this axis on bone and skeletal homeostasis. Subsequent knowledge of basic cellular physiology led to studies of the role of vitamin D in other tissues where calcium flux is important to cellular functions. This was the beginning of exploration of vitamin D in extraskeletal health. Next came investigations into extraskeletal diseases which appeared to be more prevalent in vitamin D-deficient individuals. It was surprising that not only was there higher mortality from those diseases associated with low vitamin D levels, but also all-cause mortality was higher as well. Cellular pathophysiology of these findings was explored. Finally, studies have focused on outcomes in seriously ill patients with those diseases when hospitalized in the intensive care unit (ICU). Inverse correlations have been seen of several common ICU outcomes with levels of vitamin D at entry to the ICU, but the current effort is now in clarifying a role for routine measurement of these levels and the possible role of at least vitamin D replacement or even supplementation in the ICU patient with multiple organ pharmacologic or mechanical life support.

Keywords: vitamin D, extraskeletal, supplementation

1. Introduction

The important role of vitamin D in calcium homeostasis which in turn is so important to the cellular functions of diverse organs naturally led to interest in studying its role in extraskeletal health [1]. Calcium ions play an important role in signal transduction pathways where they act as a second messenger, in neurotransmitter release from neurons, in contraction of all muscle cell types, and in fertilization. It was natural for studies to begin to explore the impact of vitamin D on vascular tone, cardiac contractility, neuron function, and hormone release and function. As mentioned in the introductory chapter, my observations led to further studies on the role of vitamin D and calcium on vascular tone, blood pressure, and hypertensive states [2, 3]. It was not surprising when Framingham data and the National Health and Nutrition Examination Survey (NHANES 2001–2004) suggested that individuals with low levels of vitamin D were more likely to have a cardiovascular event, a higher prevalence of angina and myocardial infarction, and higher prevalence of heart failure and peripheral arterial disease [4, 5]. Reports of the consequences of vitamin D on mortality in a variety of serious illnesses and even

all-cause mortality were furthering this expanded role for vitamin D [5]. The purpose of this chapter is to review the evidence for and against the impact of deficiency of vitamin D on the most seriously ill patients, those in the intensive care unit (ICU).

2. Extraskeletal dysfunction in vitamin D deficiency

A brief menu of organ dysfunction previously reported is now presented as a prelude to understanding possible contribution to prolonged recovery or higher mortality in seriously ill ICU patients [1].

a. Muscle weakness: some descriptive studies have associated muscle weakness with vitamin D deficiency. For example, vitamin D-deficient children have severe muscle weakness. However, randomized studies of supplementation have only led to some improvement in these series.

b. Falls due to musculoskeletal dysfunction has been reported to be associated with increased vitamin D-deficient elders with benefit of supplementation seen in many studies, especially in those patients with the lowest 25-hydroxy vitamin D levels, < 25 nmol/L.

c. Cancer incidence is associated with vitamin D deficiency for patients with colon cancer and breast cancer in postmenopausal women, but not prostate cancer. There are many small series of worsening outcomes in hematologic malignancies, especially in children, in vitamin D-deficient individuals, but supplementation has not been clearly shown to improve outcomes. Since many of these patients are admitted to the ICU for short-term management of emergency complications of their diseases or treatments, surveillance of vitamin D may be important to the management of these patients. A very recent report on the subject of vitamin D supplementation and colorectal cancer will be presented in the Conclusion section of this chapter.

d. Immune system: vitamin D has effects on all cells of the immune system, and there are reports of deficiency associated with such immune-mediated diseases as diabetes, multiple sclerosis, and inflammatory bowel disease. Certainly in patients with these medical problems, complications develop requiring admission to the ICU. So it would seem that more studies and larger numbers of patients in these series are needed in the monitoring and at least maintenance of normal levels in patients with these common immune-mediated diseases.

e. Asthma: severe bronchospasm is a common reason for admission to the ICU, often in a younger or pediatric patient. The data on the role of vitamin D in this problem thus far is considered inconclusive. There has also been no good evidence of the need to aggressively search or supplement vitamin D in patients with chronic obstructive pulmonary disease (COPD).

f. Infection: despite the evidence for vitamin D on the immune system, no specific infections have required correction or supplementation with Vitamin D to improve success in the management of seriously ill patients.

g. CV system: in my introduction to this book, I review my previous work on the role of calcium and vitamin D in vascular tone and blood pressure [2, 3]. Despite these reports, no conclusive evidence has led to routine screening,

correction, or supplementation of vitamin D to prevent or control hypertension. In the Framingham Study [4], a relationship of vitamin D deficiency and risk of cardiovascular events was raised. This concern was furthered by data from the National Health and Nutrition Education Survey (NHANES) data [5].

h. Diabetes: as alluded previously there have been studies of increased incidence and severity of type 1 diabetes mellitus (T1DM) in vitamin D populations, but the evidence has not been conclusive. Diabetes is likely the most common comorbidity in intensive care unit patients.

i. Neuropsychiatry: despite the relationship of calcium and vitamin D to membrane transport and neurohumoral secretion, the impact of vitamin D or its supplementation or augmentation on ICU neurologic diseases such as stroke or seizures has not been proven.

j. Pregnancy: there are reports of more complications with vitamin D-deficient mothers. No definitive studies suggest a role for monitoring or replacement or augmentation in ICU syndromes in pregnancy such as preeclampsia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

3. Studies of vitamin D specific to patients in the ICU

There are multiple publications concerning vitamin D deficiency affecting mortality in seriously ill patients [6, 7]. Whereas these studies are prospective and controlled, the numbers of patients have not been great. In a report by Han et al. [7] high-dose vitamin D administration was studied in ventilated intensive care unit patients. This was a small pilot double-blinded randomized controlled trial. Twelve subjects were in each group. The levels were low in 43% of patients. The groups were given 50,000 vs. 1,000,000 units daily enterally vs. placebo for 5 days. High-dose vitamin D3 increased levels of 25OHD and led to decreased numbers of hospital days without any other improved clinical outcomes. The decrease in hospital length of stay not ICU days or ventilator days or hospital-acquired infections, hospital mortality, or mortality at day 84 was seen.

There are additional reports of the role of vitamin D in patients with specific major organ dysfunction. These reports have studied heart, lung, or kidney failure in the ICU. Those studies which have dealt with vitamin D supplements to assist with patients to be liberated from the ventilator because of respiratory failure have shown no benefit of supplementation to reduce time on the ventilator and speed liberation [7].

There are a considerable number of journal articles dealing with cardiac function in patients with disturbed calcium metabolism [8] and improvement of heart failure with vitamin D administration [9]. Renal failure is another common organ failure developing in seriously ill patient who requires often intensive care. There is a long tradition of vitamin D administration to dialysis patients due to their impaired renal activation of 25OH vitamin D to 1,25 dihydroxyvitamin D. New findings from a real-world study of 52,757 patients confirmed that vitamin D improves survival in hemodialysis patients [10].

4. Contradictory recent major studies

In the past few decades, there appeared to be a crescendo of possible multisystem benefits from vitamin D supplementation reported throughout the world

medical literature. However, the crescendo has been halted by several recent negative studies. In a long-awaiting randomized, double-blinded, controlled trial, Manson studied vitamin D dosing of 2000 units of D3 daily in 25,000 adults with a mean age of 67 followed for a mean of 5.3 years [11]. He did not show difference in the occurrence of cardiovascular diseases or outcome of patients with invasive cancer or incidence of death from cancer, cardiovascular disease, or any cause which did not differ from those treated with placebo.

However, another recent prospective placebo-controlled report by Witte et al. [12] still suggests usefulness of vitamin D supplementation in patients with heart failure which likely contributes to morbidity in many if not most ICU patients. This is the vitamin D treating patients with chron***ic*** he***ar t*** failur**e** trial (VINDICATE). In this trial, there was no improvement in a 6-min walk but had beneficial effects on left ventricular structure and function in 229 patients with vitamin D levels <50 nmol/L or which is <20 ng/mL treated with 4000 units daily who had already been on contemporary optimal medical therapy for their heart failure with optimal medical therapy. Left ventricular structure was assessed by changes in stroke volume, and remodeling was assessed from improved left ventricular systolic diameter and end-diastolic diameter. One of the most recent issues of JAMA reported that high-dose vitamin D vs. standard-dose vitamin D when added to standard chemotherapy had no benefit for the outcome of median progression-free survival but did reduce the hazard ratio for progression or death. [13].

Just when the pendulum in the world's literature seems to swing in one direction, new publications are reported for the opposite conclusions about vitamin D and extraskeletal health. The pendulum right now has swung against routine screening or supplementation in the treatment or prevention of extraskeletal organ dysfunction. But then Witte and the recent studies in dialysis patients suggest that the patients with heart and kidney dysfunction do benefit not only in organ function but also overall survival.

5. Conclusions and recommendations

There is some evidence that deficiency of vitamin D at the time of entry to the ICU is associated with worse outcomes. There are weak correlations between vitamin D levels and outcomes during the course of the ICU stay. Vitamin D is not recommended at this time to be routinely checked in ICU patients unless part of several large studies is ongoing worldwide such as the VINDICATE trial described above. Supplementation with vitamin D is routine in patients with renal failure and does improve outcomes in that group of patients commonly hospitalized in the ICU. There appears some benefit to supplementation of vitamin D in patients with heart failure, another group commonly hospitalized in the ICU. Studies are ongoing in this subgroup of patients. There appears no evidence for measurement or supplementation of vitamin D to patients with COPD exacerbations, asthma, and pneumonia or to assist with liberation from the ventilator. More large-scaled, multicenter, prospective, randomized, and controlled trials are needed. Dosing duration and correction of deficiency vs. creation of elevated levels by low- or high-dose treatments are all variables which need systematic study.

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