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CLINICAL PERSPECTIVE

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Vitamin D deficiency in the intensive care unit: an invisible accomplice to morbidity and mortality?

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Abstract The association between vitamin D deficiency and chronic illness is well-known. Vitamin D deficiency has been associated with increased mortality in the general population. Despite this knowledge, vitamin D insufficiency is seldom considered and rarely replaced adequately, if at all, in critically ill patients in intensive care. We present a hypothetic model demonstrating how vitamin D deficiency may be an unrecognized contributor to adverse outcome in intensive care patients.

Keywords Endocrine disorders · Electrolyte disorders · Multiple organ failure · Nutrition · Systemic diseases · Cardiovascular issues in the ICU · Vitamin D deficiency · Hypocalcaemia

Critically ill patients in the intensive care unit have a high mortality. Modern critical care provides comprehensive life support for patients with multi-organ failure. The association between vitamin D deficiency and chronic illness, and its likely progressive decline with intensive care unit stay due to sunlight and dietary depletion is well-known. Despite this knowledge, vitamin D deficiency is seldom considered and rarely replaced adequately, if at all, in critically ill patients. We present a hypothetic model discussing how vitamin D deficiency may be an unrecognized contributor to adverse outcome in intensive care patients.

Contrary to the view that vitamin D deficiency is a mild chronic condition, recent reports associating vitamin D deficiency with severe hypocalcaemia in intensive care [1, 2] highlight how vitamin D deficiency may contribute to acute complications. In a recent observational study, the prevalence of vitamin D insufficiency (serum 25-hydroxyvitamin D (25-OH D) between 30 to 60 nmol/L) and deficiency (serum 25-OH D <30 nmol/L) was estimated to be as high as 50% in critically ill patients, with undetectable vitamin D levels in 17% of patients [3]. Mortality rate predicted by the simplified acute physiologic scores was close to 3 times higher in vitamin D deficient patients compared to those who were sufficient (25-OH D >60 nmol/L). While the study was small ($N = 42$) and could be subject to a referral selection bias, it raised the question of whether vitamin D deficiency is a potentially important contributor to worse outcomes and replacement could be beneficial in critically ill patients.

The classic role of vitamin D relates to its maintenance of calcium homeostasis. Hypocalcaemia, even after

adjustment for protein and pH (i.e. ionized calcium), is common in critically ill patients and has been found in 15–88% in adults in intensive care units [4–7]. Risk factors include sepsis, burns, pancreatitis and rhabdomyolysis [5, 7]. As calcium is important in many physiological processes, it is not surprising that hypocalcaemia may be associated with disease severity [5] and mortality [8]. However, parenteral calcium supplementation has not been shown to improve the outcome of intensive care patients, as noted in a recent Cochrane review [9]. The reasons for this lack of benefit are unclear but hypocalcaemia may be a sign of disease severity rather than a causal factor per se. Indeed, in one study hypocalcaemia was not an independent predictor of day-30 all cause mortality [7]. In addition, although various mechanisms have been proposed to explain how hypocalcaemia occurs in critical illness, including intracellular sequestration of calcium and relative hypoparathyroidism, it is unclear why hypocalcaemia occurs.

Severe hypocalcaemia is an uncommon finding in non-critically ill patients, due to the presence of multiple compensatory mechanisms to maintain normocalcaemia. The ability to maintain calcium homeostasis is dependent on a sufficient and responsive parathyroid hormone (PTH)-vitamin D axis. Calcium-sensing receptors in the parathyroid glands are exquisitely sensitive to changes in serum calcium concentration. Hypocalcaemia is prevented by increase in intestinal calcium absorption, renal calcium re-absorption and release of calcium from the skeleton through bone resorption, mediated by 1,25-$(OH)_2$-vitamin D (1,25-$(OH)_2$D). The skeleton is an important reservoir for calcium. Hypocalcaemia therefore does not occur unless PTH action is insufficient, as in hypoparathyroidism or PTH resistance (e.g. hypomagnesaemia, renal failure resulting in inadequate renal 1α-hydroxylation), or if vitamin D is severely deficient not allowing adequate formation of 1,25-$(OH)_2$D despite maximal PTH stimulation [1, 2].

Although hypocalcaemia and higher parathyroid hormone have both been found to relate to worse outcomes in intensive care patients, vitamin D metabolites have not been examined in these studies [5–8, 10]. Yet these may represent an important link between hypocalcaemia and morbidity and mortality in intensive care patients. Critically ill patients in the intensive care unit have a high mortality that increases with duration of stay [11]. Higher mortality is also associated with vitamin D deficiency in population studies [12], and in patients with coronary [13] and renal diseases [14]. Vitamin D deficiency has been associated with myocardial infarction, cardiac failure, stroke, diabetes, tuberculous infections, inflammatory bowel disease and autoimmune conditions [15–23]. The pleiotropic actions of vitamin D in immunity, endothelial/mucosal functions and glucose metabolism, as well as calcium homeostasis, may be fundamental to the common morbidities seen amongst critically ill patients, including the systemic inflammatory response syndrome, septicaemia, organ failure and metabolic dysfunction (Table 1).

For example, the critical role of vitamin D in glucose and calcium homeostasis may explain the association between vitamin D deficiency and diabetes and osteomalacia or osteoporosis in the general population; in critically ill patients, however, vitamin D deficiency may lead to hyperglycaemia and hypocalcaemia. At an organ level, vitamin D deficiency is associated with cardiac failure and chronic airway diseases [24] in ambulatory patients, but may result in the cardiac dysfunction and acute lung injury seen in some critically ill patients. On a

Table 1 Potential manifestation amongst critically ill patients of known association of vitamin D deficiency seen in the general population

Known functions of vitamin D	Known association in general population	Potential manifestation of association in critically ill patients
Cardiac function	Myocardial infarction, cardiac failure	Cardiogenic shock
Neuronal/cognitive function	Stroke, Alzheimer's disease, diabetic neuropathy	Coma, slow neurological recovery, critical illness polyneuropathy
Glucose metabolism	Diabetes	Hyperglycaemia
Calcium homeostasis	Osteomalacia, osteoporosis	Hypocalcaemia
Mucosal barrier function	Inflammatory bowel disease	Mucositis, translocation of bowel flora
Lung function	Chronic obstructive airway disease	Acute lung injury, Respiratory failure
Endothelial function	Atherosclerosis, hypertension	impaired microcirculation, organ failure
Innate immunity	Tuberculosis	Nosocomial infections, sepsis, septic shock
Adaptive immunity	Autoimmune disease, neoplasm	Systemic inflammatory response syndrome
Muscle function	Myopathy, myalgia	critical illness myopathy
Consequence →	Increased mortality →	Multi-organ dysfunction and increased mortality

whole body level, vitamin D deficiency leads to immune dysfunction [25] and has been implicated in the pathogenesis of systemic infection such as tuberculosis and autoimmune diseases. In critically ill patients, such immunopathy may manifest as increased susceptibility to nosocomial infections such as ventilator associated pneumonia and central line infections, sepsis and the systemic inflammatory response syndrome. Indeed a recent study demonstrated a strong positive correlation between 25-OH D concentrations and levels of cathelicidin (LL-37), an endogenous antimicrobial peptide produced by macrophages, suggesting defense against infection in septic critically ill patients may be regulated by vitamin D status [26].

Formation of 1,25-$(OH)_2$D from 25-OH D is under both endocrine and paracrine regulation by PTH (Fig. 1). 25-OH D is the hepatic metabolite of vitamin D and substrate of 1α-hydroxylase. Serum level of 25-OH D is the best marker of overall vitamin D status. In addition to its classic location in the kidneys, the activating enzyme, 1α-hydroxylase, is found in almost all mammalian cells. While renal 1α-hydroxylase activation may be important for circulating 1,25-$(OH)_2$D levels; locally, 1,25-$(OH)_2$D formed by tissue 1α-hydroxylase may be critical in mediating the pleiotropic actions of vitamin D. Circulating vitamin D sufficiency is required for both the endocrine and paracrine arms of the PTH-vitamin D axis to function effectively. Critical illness is characterized by different degrees of local and systemic inflammation, as well as metabolic and immune dysfunction; functions over which vitamin D exerts important regulatory actions [27]. In states of normal circulating vitamin D level, individual target tissues are possibly able to increase local formation of 1,25-$(OH)_2$D to meet tissue demand during critical illness (Fig. 2a). Also, failure to up-regulate PTH-vitamin D axis due to circulating vitamin D insufficiency may contribute to metabolic and immune dysfunction and ultimately multi-organ failure, which is the cause of morbidity and mortality in intensive care patients (Fig. 2b).

While vitamin D insufficiency does not pose immediate health hazards in otherwise well individuals, deficient states may prove detrimental during critical illnesses, if the circulating vitamin D pool functions as an important reservoir for conversion to their active metabolites at a tissue level during stress. We therefore hypothesize that vitamin D deficient/insufficient states may worsen existing organ dysfunctions in critically ill patients, leading to worse outcomes. In other words, the observed association between increased mortality and vitamin D deficiency in the general population may be magnified during critical illnesses, translating into excess morbidity and mortality [12, 13]. While at this stage, the role of vitamin D deficiency in adverse outcomes in the critically ill is speculative, the concepts discussed above as well as preliminary work lead us to believe that causation

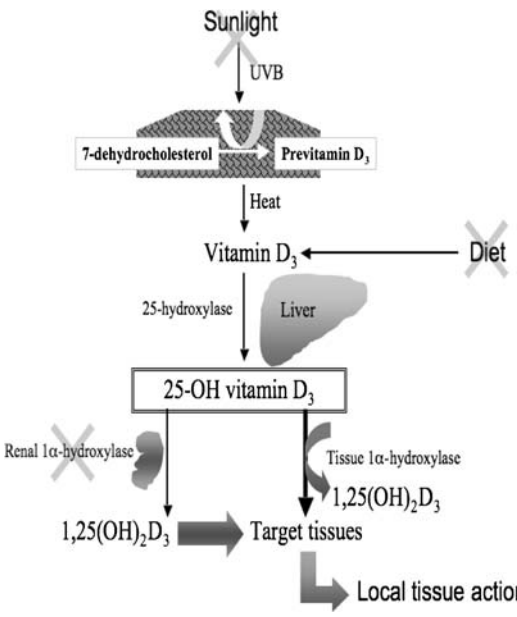

Fig. 1 Schematic diagram illustrating the mismatch of "supply and demand" of vitamin D in the intensive care unit: reduction of vitamin D availability from sunlight and dietary depletion, decreased renal formation of 1,25-$(OH)_2$D from renal failure versus increased tissue conversion of 25-OH D to 1,25-$(OH)_2$D during acute stress

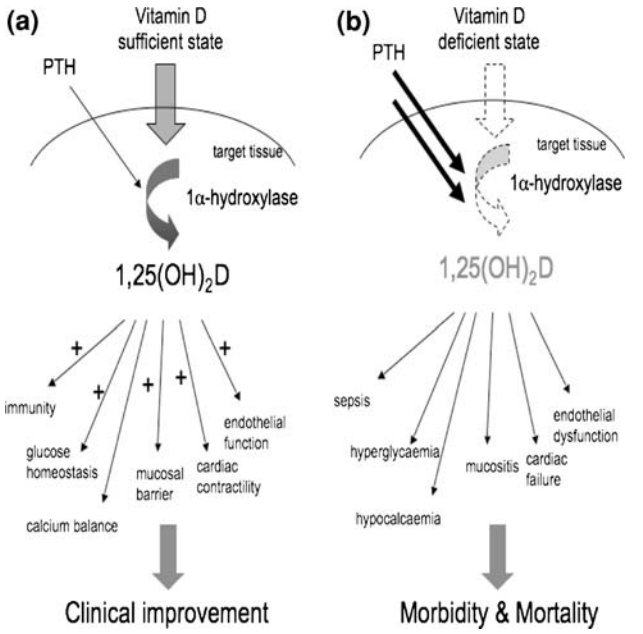

Fig. 2 Proposed mechanisms of the role vitamin D in intensive care patients: **a** vitamin D sufficiency enhances metabolic, immune and organ functions due to sufficient up-regulation of tissue PTH-vitamin D axis and **b** vitamin D insufficiency leads to break down of various tissue homeostatic mechanisms resulting in morbidity and mortality

between vitamin D deficiency and adverse outcomes is more likely than purely an association. We propose performing further studies in this area to gain further understanding into the effect of adequate supplementation of vitamin D in the intensive care unit.

Vitamin D replacement is seldom considered in intensive care medicine. Standard enteral as well as parenteral nutrition (TPN) regimes provide between 1,000 and 2,000 Units of vitamin D per week [26, 28–30]. However, in one study in which the nutritional efficacy of a TPN regimen, designed to provide 2,100 Units of vitamin D per week, was evaluated in a group of cancer patients, the mean serum 25-OH D concentration 4 weeks after initiation of TPN was 36% lower than baseline level, implying inadequate replacement and possibly increased demand during active illness, in support of our hypothesis [31] (Fig. 2). In another study, daily administration of 500 IU of vitamin D failed to normalise vitamin D status during the course of admission in 22 critically ill patients in intensive care [32]. In addition, obesity is associated with hypovitaminosis D and there is recent evidence that obese individuals may require larger replacement dosage [33].

Our concept of intensive care vitamin D insufficiency explains why hypocalcaemia and hyperparathyroidism relate to disease severity but why calcium replacement would not improve outcome. Both hypocalcaemia and hyperparathyroidism are markers of vitamin D insufficiency, but it is vitamin D insufficiency, the cause of hypocalcaemia, which leads to wide spread tissue dysfunction. In addition, vitamin D has benefits on bone health. Vitamin D supplementation may reduce bone loss, which is common in immobile intensive care patients frequently treated with high dose steroids [34].

Although the current model is hypothetical, improved understanding of the PTH-vitamin D axis and its relationship to morbidities in intensive care patients may shed light on therapeutic possibilities for vitamin D metabolites. Many single laboratory variables have been shown to predict disease severity in intensive care patients, including C-reactive protein, leucocyte and platelet counts, procalcitonin, D-dimer, interleukin-6 and thromboplastin time [35–37]. However, deficient vitamin D levels may not only predict disease severity and outcomes but due also, to its pleotropism, may contribute to intensive care co-morbidities. The potential for vitamin D therapy is important as, unlike other modern therapeutics used in critical care medicine, vitamin D is inexpensive and safe with a wide therapeutic window; thus it is critical that its potential role in this situation is clarified. This model aims to improve the care of critically ill patients, and may finally bring "light" into intensive care units.

References

1. Lee P, Milliken S, Center JR (2008) Hypocalcaemic cardiac failure post BMT secondary to unrecognized vitamin D deficiency. Bone Marrow Transplant 42:363–364
2. Lee P, Samaras K, Glanville A, Center JR (2009) Transplant recipients on the edge of the hypocalcaemia abyss. J Heart Lung Transplant 28:93–95
3. Lee P, Eisman A, Center JR (2009) Vitamin D deficiency in critically ill patients. N Engl J Med 30:1912–1914
4. Zaloga GP, Chernow B, Cook D, Snyder R, Clapper M, O'Brian JT (1985) Assessment of calcium homeostasis in the critically ill surgical patient. The diagnostic pitfalls of the McLean-Hastings nomogram. Ann Surg 202:587–594
5. Zaloga GP, Chernow B (1986) Hypocalcemia in critical illness. JAMA 256:1924–1929
6. Zivin JR, Gooley T, Zager RA, Ryan MJ (2001) Hypocalcemia: a pervasive metabolic abnormality in the critically ill. Am J Kidney Dis 37:689–698
7. Hästbacka J, Pettilä V (2003) Prevalence and predictive value of ionized hypocalcemia among critically ill patients. Acta Anaesthesiol Scand 47:1264–1269
8. Desai TK, Carlson RW, Geheb MA (1988) Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. Am J Med 84:209–214
9. Forsythe RM, Wessel CB, Billiar TR, Angus DC, Rosengart MR (2008) Parenteral calcium for intensive care unit patients. Cochrane Database Syst Rev 8:CD006163
10. Burchard KW, Gann DS, Colliton J, Forster J (1990) Ionized calcium, parathormone, and mortality in critically ill surgical patients. Ann Surg 212:543–549
11. Gruenberg DA, Shelton W, Rose SL, Rutter AE, Socaris S, McGee G (2006) Factors influencing length of stay in the intensive care unit. Am J Crit Care 15:502–509
12. Melamed ML, Michos ED, Post W, Astor B (2008) 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 168:1629–1637
13. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W (2008) Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med 168:1340–1349
14. Mailliez S, Shahapuni I, Lecaque C, Massy ZA, Choukroun G, Fournier A (2008) Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int 74:389
15. Giovannucci E, Liu Y, Hollis BW, Rimm EB (2008) 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 168:1174–1180
16. Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, Boehm BO, Dobnig H (2008) 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 93:3927–3935

17. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, März W (2008) Low vitamin d levels predict stroke in patients referred to coronary angiography. Stroke 39:2611–2613
18. Danescu LG, Levy S, Levy J (2009) Vitamin D and diabetes mellitus. Endocrine 35:11–17
19. Nnoaham KE, Clarke A (2008) Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol 37:113–119
20. Pappa HM, Grand RJ, Gordon CM (2006) Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. Inflamm Bowel Dis 12:1162–1174
21. Kamen DL, Aranow C (2008) The link between vitamin D deficiency and systemic lupus erythematosus. Curr Rheumatol Rep 10:273–280
22. Zold E, Szodoray P, Gaal J, Kappelmayer J, Csathy L, Gyimesi E, Zeher M, Szegedi G, Bodolay E (2008) Vitamin D deficiency in undifferentiated connective tissue disease. Arthritis Res Ther 10:R123
23. Arnson Y, Amital H, Shoenfeld Y (2007) Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis 66:1137–1142
24. Janssens W, Lehouck A, Carremans C, Bouillon R, Mathieu C, Decramer M (2009) Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. Am J Respir Crit Care Med 179:630–636
25. Adorini L, Penna G (2008) Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin Pract Rheumatol 4:404–412
26. Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR, Tangpricha V (2009) Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med 23:28
27. Bikle D (2009) Nonclassic actions of vitamin D. J Clin Endocrinol Metab 94:26–34
28. Lowry SF, Goodgame JT Jr, Maher MM, Brennan MF (1978) Parenteral vitamin requirements during intravenous feeding. Am J Clin Nutr 31:2149–2158
29. Nichoalds GE, Meng HC, Caldwell MD (1977) Vitamin requirements in patients receiving total parenteral nutrition. Arch Surg 112:1061–1064
30. Bradley JA, King RF, Schorah CJ, Hill GL (1978) Vitamins in intravenous feeding: a study of water-soluble vitamins and folate in critically ill patients receiving intravenous nutrition. Br J Surg 65:492–494
31. Kirkemo AK, Burt ME, Brennan MF (1982) Serum vitamin level maintenance in cancer patients on total parenteral nutrition. Am J Clin Nutr 35:1003–1009
32. Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R (2003) Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab 88:4623–4632
33. Lee P, Greenfield JR, Seibel MJ, Eisman JA, Center JR (2009) Adequacy of vitamin D replacement is dependent on body mass index. Am J Med (in press)
34. Hollander JM, Mechanick JI (2009) Bisphosphonates and metabolic bone disease in the ICU. Curr Opin Clin Nutr Metab Care 12:190–195
35. Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K (1999) Outcome prediction by traditional and new markers of inflammation in patients with sepsis. Clin Chem Lab Med 37:363–368
36. Arbarth S, Holeckova K, Froidevaux C et al (2001) Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 164:396–402
37. Pettilä V, Pentti J, Pettilä M et al (2002) Predictive value of antithrombin III and serum C-reactive protein concentration in critically ill patients with suspected sepsis. Crit Care Med 30:271–275