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Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients

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Summary

Background: Vitamin D plays a seminal role in many homeostatic mechanisms. In this study, we assessed the correlation between circulating vitamin D levels and mortality rates in critically ill patients.
Methods: All patients admitted to the intensive care units (ICUs) and internal medicine wards in a university-based hospital that required mechanical ventilation were admitted. Data collected included the underlying disease, basic hematological and biochemical blood test results, APACHE II scores and serum 25-hydroxyvitamin D [25(OH)D] levels. The primary end point was defined as all-cause mortality within 60 days from admission or from acute deterioration.
Results: Between December 2008 and June 2009, 130 patients were enrolled. Average vitamin D concentration was 14.04 ± 6.9 ng/ml; 107 patients were vitamin D deficient (< 20 ng/ml). Total mortality rate after 60 days was 44.3%. Vitamin D levels were correlated with white blood cell (WBC) count, but with no other measured variable. Among the deceased patients, survival curves indicated that survival of patients with vitamin D deficiency was significantly shorter than those whose vitamin D concentration was >20 ng/ml ($P < 0.05$); the average survival time was 15.3 ± 12.4 days for vitamin D deficient patients compared with 24.2 ± 16.5 days among those with normal vitamin D levels.
Conclusion: This study demonstrated that low vitamin D levels are common among patients admitted to ICU. We observed longer survival times among vitamin D sufficient patients. Our results indicate that vitamin D concentration may be either a biomarker of survival or a co-factor. We recommend assessing the effects of vitamin D supplementation in critically ill patients.

Introduction

Vitamin D and its metabolites, 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$], are fat-soluble pro-hormones, which are converted *in vivo* into biologically active metabolites which regulate numerous functions in various cell types. Nuclear vitamin D receptors (VDRs) have

been detected in both calcemic and noncalcemic tissues, and when activated, they control calcium metabolism and elicit a wide variety of biological responses that influence cellular growth, proliferation, apoptosis and immune system functions.[1–8] Vitamin D is known to possess anti-inflammatory and immune-modulating effects. Vitamin D hinders immune cell differentiation, restrains macrophage and monocyte interactions, and down-regulates lymphocyte activity.[9] In several inflammatory diseases, higher serum 25(OH)D levels or vitamin D supplementation has been associated with reduced levels of C-reactive protein, erythrocyte sedimentation rate and inflammatory cytokines.[10,11] Vitamin D also enhances the function of the innate immune system by stimulating formation of the macrophage-associated cathelicidin antimicrobial peptide.[12]

During the last decade, retrospective data have revealed correlations between low vitamin D levels and certain types of cancer, immune system dysfunction, diabetes, cardiovascular disease, hypertension and metabolic syndrome.[13–18]

The significance of vitamin D deficiency in critically ill patients was recently highlighted in an observational study that revealed a prevalence of vitamin D insufficiency and deficiency as high as 50% in critically ill patients, with undetectable vitamin D levels in up to 17%.[19] The role of vitamin D in critically ill patients has not yet been fully established. Epidemiological findings suggest that vitamin D insufficiency may be a risk factor for sepsis.[20] This study examined the association between circulating vitamin D levels and mortality rates in critically ill patients.

Patients and methods

This was an observational, prospective, single center study. It was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference of Harmonization and local regulatory requirements and approved by the institutional ethics committee.

Informed consent was obtained from patients' guardians. The authors were exempted from obtaining consent in cases where this was not possible, provided a physician not taking part in the study approved participation. If the patient improved and was able to consent *post factum*, approval was obtained. The patients were followed throughout their admission. The primary end point was all-cause mortality within 60 days of admission.

Study population

The study population included all severely ill patients, over the age of 18 years, requiring mechanical ventilation, hospitalized in Meir Medical Center, a university-based hospital, between December 2008 and June 2009. All of the patients were admitted either to a general, surgical or cardiac ICU or to an internal medicine ward. The only exclusion criterion was vitamin D supplementation prior to the current admission.

Patient data and biochemical analysis

Data collected included demographics, the reason for admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and basic hematological and biochemical data. Patient weight and height were not recorded for many patients; therefore, these data were not collected. All biochemical and hematological blood tests were part of the patient's routine workup and processed in the institute's laboratories. Vitamin D serum levels were collected separately, for study purposes, within 24 h of time of admission or deterioration necessitating mechanical ventilation. Serum levels of 25(OH)D were assayed using a radioimmunoassay (DiaSorin SA, Antony, France).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) as well as median for parameter not normally distributed (tests for normality of parameters was done with the Shapiro–Wilk normality test). Vitamin D deficiency was defined as levels $\leqslant 20$ ng/ml, according to the definition of depletion and repletion of vitamin D according to the Institute of Medicine (IOM).[21,22] Continuous variables were compared using the Student's *t*-test. Nominal variables such as gender or other co-morbidities were analyzed by the χ^2 test. Comparing survival between two groups of Vitamin D was done using the Kaplan–Meiers estimation. Cox regression was used in order to examine the relationship between survival and predictor variables. For all tests, a $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 18.0 statistical software (SPSS Inc., USA).

Results

Patients

During the study period, 130 patients who were admitted to an ICU or a participating internal medicine ward were enrolled. Two patients were

Table 1 Demographic characteristics of the study patients

Parameters	All patients	Vitamin D deficient (⩽20 ng/ml)	Vitamin D sufficient (>20 ng/ml)	*t*-test *P*-value*	Mann–Whitney test
Number of patients	130	107	23		
Male, *n* (%)	59 (45)	44 (41)	15 (65)	0.04	
Age, mean (SD) (years)	70.2 (16.6)	70.2 (16.3)	70.2 (18.3)	1.0	
Vitamin D, mean (SD), median (ng/ml)	14 (6.9)	11.7 (4.7), 10.9	24.9 (4.9), 23.5	0.0001	0.001
Disease severity and biochemical information					
APACHE II score	27 ± 5.7	27.1	26.3	0.55	0.666
Albumin levels, median (g/dl)	2.9 ± 0.6	2.9 ± 0.6, 2.9	3.1 ± 0.6, 3.0	0.17	0.042
Creatinine (ng/ml)	1.6 ± 1.3	1.6 ± 1.2	1.7 ± 1.5	0.73	0.444
Calcium, median (mg/dl)	8.2 ± 1	8.1 ± 1.1, 8.2	8.5 ± 1.1, 8.6	0.12	0.044
Phosphorus (mg/dl)	3.5 ± 1.4	3.5 ± 1.4	3.3 ± 1.3	0.53	0.676
WBC count (K/ml)	13.9 ± 6.5	13.6 ± 6.4	15.9 ± 6.5	0.12	0.127
Hb levels (g/dl)	12.0 ± 2.0	12.0 ± 2.0	11.9 ± 2.0	0.83	0.232
Co-morbid conditions, *n* (%) (data available for 121 patients)					
Diabetes	45 (37)	40 (39)	5 (26)	0.32	
Chronic renal failure	47 (39)	38 (38)	9 (45)	0.62	
Hypertension	74 (61)	65 (64)	9 (47)	0.21	
Ischemic heart disease	27 (22)	22 (22)	5 (26)	0.56	
Sixty-day mortality	57 (43)	47 (44)	10 (43.5)	1.0	

*The *P*-value compares patients who were vitamin D deficient or sufficient.

Table 2 Reason for intensive care admission and mechanical ventilation ($n = 130$)

Parameters	All patients, *n* (%)	Vitamin D deficient, (⩽20 ng/ml), *n* (%)	Vitamin D sufficient, (>20 ng/ml), *n* (%)	*P*-value* (χ^2 test)
Infectious diseases				
Respiratory infections	63 (48)	51 (48)	12 (52)	0.56
Abdominal infections	19 (15)	15 (14)	4 (17)	0.87
Other	10 (8)	10 (9)	0	0.13
Noninfectious causes				
Cardiovascular				
MI or CHF	14 (11)	11 (10)	3 (13)	0.65
CVA	8 (6)	6 (6)	2 (9)	0.49
Other (suicide attempt, trauma, surgical complication that are not related to infection)	16 (12)	14 (13)	2 (9)	0.59

*The *P*-value compares patients who were vitamin D deficient or sufficient.
MI: myocardial infarction; CHF: congestive heart failure; CVA: cerebrovascular accident.

excluded due to active vitamin D supplementation upon their hospitalization. All patients were mechanically ventilated, either upon admission or due to respiratory deterioration during their hospitalization. The baseline characteristics of the study subjects are shown in Table 1. Fifty-nine patients (45%) were male; the mean age of the patients was 70.2 ± 16.6 years. The most common reason for admission was infection, which was present in 91 (71%) patients, almost half of whom were mechanically ventilated due to respiratory infections. Vitamin D levels were not related to the causes of admission (Table 2).

Blood tests and outcome

The average serum vitamin D level for of the study population was 14.0 ± 6.9 ng/ml. Overall vitamin D concentration was not distributed normally (Shapiro–Wilk, $P < 0.001$), therefore we used

nonparametric tests regarding vitamin D statistical associations (Table 1). Of the 130 study patients, 107 were vitamin D deficient ($\leqslant$20 ng/ml) with an average concentration of 11.7 ng/ml. Only 23 patients had vitamin D levels >20 ng/ml, with an average level of 24.9 ng/ml. No significant differences were noted between the two groups regarding APACHE II scores, white and red blood cell count, albumin, creatinine, calcium or phosphorus levels (Table 1). Since albumin, creatinine and calcium serum concentrations as well as white blood cell (WBC) counts were not distributed normally (Shapiro–Wilk, $P<0.05$), we also applied nonparametric tests to analyze differences between their levels in the vitamin D sufficient and deficient groups and detected significant differences (Table 1).

Co-morbidities were collected using admission data that were complete for 121 patients. The vitamin D deficient patient group had higher rates of diabetes and hypertension compared with vitamin D sufficient patients, although the differences did not reach statistical significance using χ^2 test. These differences can represent the higher prevalence of vitamin D deficiency among patients with diabetes and hypertension. It was noted that women had higher rates of vitamin D deficiency, with 60% of the patients in the vitamin D deficient group being female, compared with 35% in the vitamin D sufficient group. Mortality among all patients was high, with an overall mortality rate of 44% within 60 days of hospitalization for all patients. The difference between the two groups was not significant.

The length of hospitalization or ICU stay was not collected or compared since many patients were transferred to internal medicine wards or to rehabilitation centers out of the medical center and were kept hospitalized over long periods.

Vitamin D level and survival

Although there was no difference in 60-day survival rates between the two groups ($P=0.8$), a significant difference in mean survival was observed. A longer average survival was noted among the vitamin D sufficient group. Average survival was 15.3 ± 12.4 days for the vitamin D deficient group (median survival time 9.8 days), compared with 24.2 ± 16.5 days for the vitamin D sufficient patients (median 16 days). Comparing survival time with log rank (Mantel–Cox) test retrieved a significant difference between the two groups (sig = 0.041; Figure 1).

Cox regression was applied to all parameters that differed between the groups in order to assess their contribution to overall survival. Only age and APACHE II score were found to significantly contribute to survival ($P<0.003$, $P<0.05$, respectively).

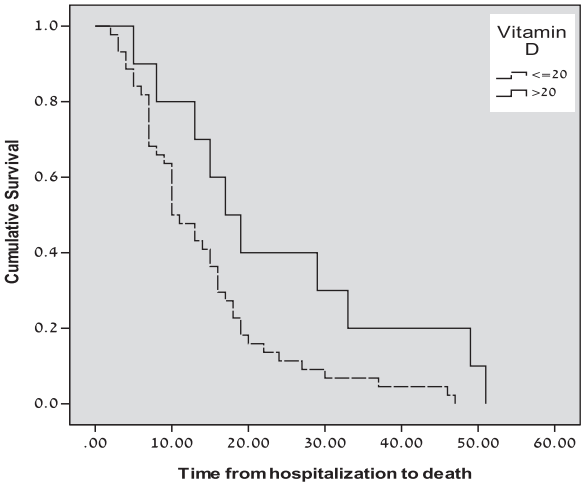

Figure 1. Comparing survival time from hospitalization or mechanical ventilation to death between two groups ($P=0.028$).

Discussion

This study sought to find if there is a correlation between vitamin D levels and survival of critically ill patients. The rationale behind the current investigation was to see if the higher morbidity and mortality rates attributed to vitamin D deficiency in the general population, and in the elderly population[23,24] also affected extremely ill patients, with high mortality rates.

The IOM committee reported guidelines stating that a level of vitamin D >20 ng/ml is needed for good bone and general health for practically all individuals.[21,22] Other consensus conferences stated that the minimum desirable serum level of 25(OH)D has been suggested to be between 20 and 30 ng/ml.[25] It is notable that there was a high rate of vitamin D deficiency among the critically ill patients. This finding is consistent with vitamin D deficiency rates discovered both in hospitalized populations and in the general population in Israel.[26,27] In Western countries, including Israel, the rates of vitamin D insufficiency and deficiency are estimated at 70–80% of the general healthy population. Due to the expected low vitamin D levels, we used the level of 20 ng/ml as the cut-off for this study. The average serum 25(OH)D level was 14 ng/ml for all patients. Low levels were observed not only among the subpopulation of patients with sepsis, but also among patients admitted due to a traumatic injury, suicide attempt, cerebrovascular event or myocardial infarction.

Vitamin D deficiency is known to be associated with many adverse systemic manifestations, such as myocardial infarction, cardiac failure, stroke, diabetes, tuberculosis and several autoimmune conditions.[13–18] The pleiotropic actions of vitamin D in immunity, endothelial/mucosal functions and glucose metabolism, as well as calcium homeostasis appear to be very important in maintaining overall health. Based, primarily, on retrospective data, it has been shown that sufficient vitamin D serum levels are associated with the prevention of cardiovascular diseases, hypertension and diabetes. Protection has also been observed for colon cancer, prostate and breast.[28,29] Recent evidence also links vitamin D deficiency with the systemic inflammatory response syndrome (SIRS), septicemia, organ failure and metabolic dysfunction in critically ill patients.[30]

Vitamin D as a mediator of the immune system in sepsis

The systemic response to an infection or to trauma is complex and only partially understood. The role of vitamin D treatment in sepsis syndrome has been evaluated in animal models of septicemia, where $1,25(OH)_2D3$ administration was associated with improved blood coagulation parameters in sepsis-associated disseminated intravascular coagulation.[31] In recent years, there has been an effort to understand possible noncalcemic roles of vitamin D, including its role in the immune system and in particular on T cell-mediated immunity. Vitamin D receptor (VDR) is found in significant concentrations in the T lymphocyte and macrophage populations. Little is known about the effect of vitamin D status on the ability of the host to fight infection. Activated vitamin D regulates the differentiation of stem cells into monocyte and macrophage immune cells by interacting with specific VDRs in myeloid tissue cells.[32] Vitamin D modulates T-cell lymphocyte, monocyte and macrophage-derived cytokine expression, which play a key role in initiation and progression of the SIRS.[33] Vitamin D also suppresses tumor necrosis factor-α (TNF-α) expression, which was demonstrated by suppression of experimental inflammatory bowel disease models.[34,35] Treatment of macrophages infected with *Mycobacterium tuberculosis* with $1,25(OH)_2D3$ *in vitro*, resulted in enhanced production of an endogenous antimicrobial peptide cathelicidin, and improved killing of the microorganisms.[12] Vitamin D also exerts a direct effect on the vasculature, causing an enhanced effect of inotropic drugs.[36,37] The hemodynamic shock response in SIRS may therefore be responsive to circulating vitamin D levels.

Vitamin D affects T cell function both directly and indirectly by regulating the function of antigen presenting cells.[38,39] In the absence of vitamin D signaling, the T-cell compartment has a potentially stronger Th1 phenotype. Activated vitamin D decreased the proliferation of purified Th cells and decreased the production of interferon-γ (IFN-γ), interleukin-2 (IL-2) and IL-5. In Th2 cells, $1,25(OH)_2D$ increased the production of IL-4. Active vitamin D also promotes inhibition of Th17, including a direct reduction of dendritic cell ability to activate Th17, a reduced ability to support Th17 polarization of naïve $CD4^+$ T cells, and inhibition of IL-17 production.[40]

Vitamin D also plays a role in macrophage regulation. It is responsible for monocytes developing into 'resident' tissue macrophages and influences their cytokine expression. It stimulates macrophages to produce prostaglandin E2, which is involved in the inflammatory process and inhibits the expression of granulocyte–macrophage colony-stimulating factor. Vitamin D deficiency impairs the ability of macrophages to mature, to produce macrophage-specific surface antigens, to produce the lysosomal enzyme acid phosphatase and to secrete H_2O_2, which is essential to their antimicrobial function.[41,42]

Vitamin D replacement is seldom considered in intensive care medicine. Standard enteral and parenteral nutrition regimes provide between 1000 and 2000 U of vitamin D per week. However, several recent studies assessing vitamin D supplementation for hospitalized patients have noted that much higher doses are needed, up to 50 000 IU/week, to maintain adequate serum levels.[43]

In this prospective study, we avoided selection bias by recruiting all patients requiring mechanical ventilation regardless of their underlying disease. It may be argued that vitamin D levels only act as a surrogate biomarker representing the general health condition of the patient. In order to assess that issue, we examined other parameters commonly used for evaluation of general well-being such as blood count, electrolytes and albumin levels. Vitamin D status did not show a correlation with any of these parameters, except for a weak correlation between vitamin D levels and WBC count (data not shown in the results).

Many single laboratory variables have been shown to represent disease severity in intensive care patients, including C-reactive protein, leukocyte and platelet counts, procalcitonin, D-dimer, IL-6 and thromboplastin time.[44] However, deficient vitamin D levels may not be merely markers, but may actually contribute to severity of the disease and to intensive care co-morbidities. The precise

nature of this association and the optimum levels of vitamin D remain to be elucidated. The potential for vitamin D therapy is important as, unlike other medications used in critical care medicine, vitamin D is inexpensive and generally safe with a wide therapeutic window.

This study suffers from several limitations. The major limitations are the small number of patients, especially in the vitamin D sufficient group, and the observational nature of the study. Many potential confounders are not explored in the study or do not show statistical significance because of the cross-sectional nature of the study and because of the small sample size. There can be alternative explanations to the lower vitamin D levels and the shorter survival, such as increased conversion of 25(OH)D to 1,25(OH) vitamin D. In this study, we have not measured the levels of 1,25 vitamin D and cannot explore that alternative explanation.

Our results provide important background information to perform larger scale, intervention-based trials of adjunctive vitamin D therapy in a variety of clinical settings, including further studies in the management of human sepsis syndrome and other critical illnesses.

Conflict of interest: None declared.

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