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Title page

Vitamin D severe deficiency in patients admitted to the Emergency Department with severe sepsis is associated with an increased hospital mortality

Malinverni S, Ochogavia Q, Lecrenier S, Scorpiniti M, Cotton F, Preiser JC, Mols P, Bartiaux M.

Authors affiliations:

Stefano MALINVERNI, MD. Emergency Department, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium. Adress : Rue Haute 322 , 1000 Brussels, Belgium. Telephone : +320471268267. Email : stefano.malinverni@stpierre-bru.be (Corresponding author) https://orcid.org/0000-0003-3840-0491

Queitan OCHOGAVIA, MD. Emergency Department, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium. https://orcid.org/0000-0003-1726-7070

Sarah LECRENIER, MD. Emergency Department, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium. https://orcid.org/0000-0002-0871-0774

Margherita SCORPINNITI, MD. Emergency Department, San Donato Hospital, Arezzo, Azienda USL Toscana Sud Est, Arezzo, Italy. https://orcid.org/0000-0001-7290-0727

Jean-Charles PREISER, MD, Ph.D. Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium. https://orcid.org/0000-0003-3163-039

Frédéric COTTON, PharmD Ph.D. Clinical Chemistry, LHUB-ULB, Université Libre de Bruxelles. https://orcid.org/0000-0002-7356-7417

Pierre MOLS, MD Ph.D. Emergency Department, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium. https://orcid.org/0000-0001-8320-1171

Magali BARTIAUX, MD. Emergency Department, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium https://orcid.org/0000-0001-9877-9240

Abstract

Background

The role of vitamin D in the response to infection has been increasingly acknowledged. However, the influence of severe vitamin D deficiency on the outcome of patients admitted for severe sepsis is unknown. Hence, this study aimed to investigate the association between severe vitamin D deficiency and sepsis-related outcomes in patients presenting to the Emergency Department (ED).

Methods

This single center prospective study included patients presenting to the ED with severe sepsis from April 2014 until December 2017. 25-hydroxy vitamin D (25(OH)D) was measured in a blood sample drawn within 24 hours of admission to the ED, and severe vitamin D deficiency was defined as 25(OH)D < 12 ng/mL. 90-day mortality was compared between the two groups by a multivariable analysis adjusting for confounders and according to a Kaplan-Meier survival analysis.

Results

263 patients were initially screened and 164 patients with severe sepsis were included in this study, 18% of whom had septic shock. Severe vitamin D deficiency was present in 46% of patients. The overall 90-day mortality rate was 26.2% and the median length of stay was 14 days. In a logistic regression accounting for sepsis severity and age-adjusted comorbidities, severe vitamin D deficiency was associated with increased mortality (odds ratio [OR]=2.69 (1.03–7.00), p=0.043), and lower chances of hospital discharge (sub-hazard ratio [HR]=0.66 (0.44–0.98)). In the subgroup of patients admitted to the ICU, severe vitamin D deficiency was associated with an increased 28-day adjusted mortality (HR=3.06 (1.05–8.94), p=0.04) and lower chances of discharge (sub-HR=0.51 (0.32–0.81)).

Conclusions

Severe vitamin D deficiency at emergency department admission is associated with higher mortality and longer hospital stay in patients with severe sepsis.

What is already known

Vitamin D has been repetitively associated with worse outcomes in critical care patients. Randomized controlled trials of Vitamin D supplementation in critical patients could only suggest a benefit in the subset of severely deficient patients and some recent supplementation trials could not observe any benefit in supplemented patients.

What this paper adds

Vitamin D sampling and supplementation in this study has been realized at hospital admission, before any dilution or interference associated to treatment. This allows to appreciate the impact of vitamin D severe deficiency, adjusted for co-pathologies and severity of illness, on sepsis outcomes, irrespective from any dilution or interference associated with early treatment.

Keywords

Sepsis, Septic shock, Vitamin D, Resuscitation

Introduction

Vitamin D deficiency is highly prevalent in both critically ill patients and the general population.[1] Its severity is defined as moderate when serum 25-hydroxycholecalciferol [25(OH)D] concentration is between 12 ng/mL and 20 ng/mL and severe when it is < 12 ng/mL.

Since the discovery of the pleiotropic effects of vitamin D, and the presence of the receptors of its active form (1,25-dihydroxycholecalciferol [1,25(OH)2D] or calcitriol) in nearly every tissue, research has been dedicated to identifying its potential role in the care of critically ill patients. Vitamin D plays an immunomodulating role,[2] influencing both innate and adaptive immunity.[3] It is also involved in inflammatory mediator regulation and chemoattraction of immune cells to the site of infection.[4]

Several observational studies have shown that vitamin D deficiency is a potentially modifiable risk factor, that increases susceptibility to infections and complications reflected by longer hospital and intensive care unit (ICU) stays, organ injury, prolonged mechanical ventilation, and death.[5,6] However, these associations can be confounded by a chronically poor health status related to limited physical activity, sunlight exposure, obesity, advanced age, and a low-quality diet. Randomized controlled trials assessing the impact of vitamin D deficiency and 1,25(OH)2D supplementation in the management of critically ill patients have yielded mixed results. These differences could be due to the degree of deficiency at trial inclusion, the timing, dose of supplementation, and the extent of monitoring of achieved vitamin D status after repletion.[7–9] In contrast to previous studies, vitamin D status was assessed as early as possible after admission, to avoid confounding factors associated with fluid and drug administration.[10] Indeed, previous interventional and observational studies included ICU patients enrolled 12 to 72 hours after admission. Therefore, study inclusion occurred relatively late in the course of illness and after administration of fluids and medications that may have yielded a falsely low 25(OH)D plasma concentration.[11] This study aimed to determine whether severe vitamin D deficiency, measured at admission in patients with severe sepsis/septic shock presenting to the emergency department (ED), is associated with increased 90-day mortality and longer hospital stays, after adjustment for potential confounders.

Methods

Study design and setting

This was a prospective single-center study designed to assess the association between vitamin D deficiency at admission and the outcome of patients presenting to the ED with severe sepsis from April 1, 2014, to December 31, 2017. The study was approved by the Institutional Ethical Committee of the University Hospital of Saint Pierre (B076201215481). Following the national and the European Union requirements, as well as the principles of the Declaration of Helsinki, verbal consent was obtained directly from the patient, if possible, or from the legal surrogate.

Selection of participants

Adult patients (≥ 18 years) admitted to the ED of the University Hospital of Saint Pierre with suspicion of severe sepsis were eligible for inclusion in this study. Severe sepsis was defined as a suspected source of clinical infection with two or more manifestations of the Systemic Inflammatory Response Syndrome criteria and the presence of sepsis-induced organ dysfunction.[12] Patients without sepsis after ED workout, with a non-severe form of sepsis, or with therapeutic limitations, considered as any form of treatment withholding, were excluded from the analysis (Figure 1). Pregnant women and moribund patients, whose survival at study enrollment was expected to be less than 12 hours, were also excluded.

Measurements

Data were collected from patients' medical records through the computerized hospital database. Collected variables included demographics (age, sex), body mass index (BMI), age-adjusted Charlson Comorbidity Index (ACCI),[13] use of immunosuppressant drugs, identified infection site, causative microorganisms, presence of shock, APACHE II and SOFA scores. Data on the presence of acute respiratory distress syndrome (ARDS), requirements for mechanical ventilation, serum albumin, lactate, and ionized calcium levels at admission were also collected. At least two sets of blood cultures were taken during the ED stay for each patient.

A venous blood sample for serum 25(OH)D measurement was taken at admission, synchronously with routine blood samples in most of the cases, or within 24 hours of admission only if < 1 L of crystalloid fluid was infused before sampling. Patients were followed up for 90 days or until death. Blood samples were collected in 3.5 mL serum-separating tubes and analyzed using the Elecsys® Vitamin D total electro-chemiluminescence binding assay (Roche) on a Cobas E 601 analyzer.

Data and outcomes definition

Definition of Vitamin D Deficiency

The severity of vitamin D deficiency was categorized as moderate when 25(OH)D was between 12ng/mL and 20 ng/mL, as per the recommendations of the Endocrine Society,[14] and severe when 25(OH)D was < 12 ng/mL, based on previous studies showing this value as the hallmark of higher mortality rates and worse outcomes in septic patients.[9] A predefined analysis of patients with severe vitamin D deficiency was specified and analyzed as an exposure variable.

Outcomes and variables definition

Study populations were categorized according to the presence of severe vitamin D deficiency. The primary outcome was all-cause 90-day mortality. Outcome data were ascertained using clinical records and a database crossed-linked with the national demographic archives. Secondary outcomes were hospital length of stay and ICU-associated outcomes such as ventilator-free days, vasopressor-free days, renal replacement therapy-free days, 28-day mortality, and length of stay. Ventilator-free days, renal replacement therapy-free days, and vasopressor-free days were defined as days free from the respective organ support therapy within the observation period of 28 days from ICU admission. Severe sepsis was defined as a suspected source of clinical infection with two or more manifestations of systemic infection fulfilling systemic inflammatory response syndrome criteria and the presence of sepsis-induced organ dysfunction[12]; septic shock was defined as sepsis and

arterial hypotension despite adequate fluid resuscitation requiring vasopressors. Acute respiratory distress syndrome was defined according to the Berlin Definition. Concomitant bacteremia was defined as the presence of a positive hemoculture. Adjudication of infectious site was done on the basis of radiological, clinical and microbiological data. Causative microorganism were any non-contaminant pathogen isolated from a hemoculture or at the infection site.

Statistical analysis

The distribution of variables was assessed using the Shapiro-Wilk test. Variables with a non-normal distribution were assessed using the Wilcoxon rank-sum test, and the results were presented as median and interquartile range (IQR) showing selected percentiles (25th to 75th). Variables with a normal distribution were assessed using Student's t-test and were presented as mean and standard deviation (SD). Categorical variables were presented as proportions and were analyzed using the chi-squared test. Given the binary primary outcome a logistic multivariable regression was used as the modelling approach to study 90-days mortality. Hypoalbuminemia was not included in the multivariable analysis as it was considered a mediator for cirrhosis; hypocalcemia was not included neither as it was as it was considered as a collider bias. Collinearity among confounding variables was assessed using the variance inflation factors. Variables with variance inflation factors >6 were removed from the multivariable analysis. History of cancer, diabetes, immunosuppression, age, vasopressor support, SOFA score and mechanical ventilation were removed from the multivariable regression due to high multicollinearity with the APACHE II and ACCI, a predictable result as these variables are used for the calculation of the two abovementioned scores. For survival analysis, Kaplan-Meier estimates of survival functions were used together with the log-rank test. Hazard ratios (HRs) and corresponding 2-sided 95% confidence intervals (CIs) were estimated using a Cox regression model adjusting for selected variables. The length of hospital and ICU stay analysis considered time to hospital discharge as the survival endpoint with death as a competing event. A sample size of 162 was calculated to have an 80% power with a two-sided type I error of 0.05, in order to detect a difference of 50% of the primary outcome (90-day mortality), assuming a risk factor prevalence of 50% in the study cohort and a baseline mortality risk of 20%. Exploratory subgroup analysis according to ACCI, BMI, age, diabetes, sex, chronic kidney disease, and presence of a gram-positive isolate were carried out to assess between-group heterogeneity in the adjusted effect of severe vitamin D deficiency on 90-day mortality. Only available data were analyzed and missing data were treated as missing without any imputation except for arterial lactate, were random normal values were imputated in missing cases if pH and bicarbonate were normal. Statistical analyses were performed using Stata software (version 14.0; Stata Corp., College Station, Texas, USA).

Patient and public involvement

Patients and the public had no input into decisions regarding the research question, outcome measures, study design or recruitment to the study. Patients and the public were not asked to assess the burden of the vitamin D sampling. Patients and the public were not involved in our plans to disseminate the study results to participants and relevant patient communities. However, the dataset supporting our conclusions, is available in a public repository to facilitate the dissemination of science.

Results

During the 45-month study period, 164 patients were included in this study (Figure 1). Vitamin D deficiency was present in 62.8% (n=103), 73.8% of whom (n=76) had severe deficiency. A total of 121 patients required ICU admission. Patient characteristics at ED admission are shown in Table 1. Patients with severe vitamin D deficiency were more likely to be younger, male, have a lower ACCI, lower ionized calcium levels, and higher rates of concomitant bacteremia than patients without severe vitamin D deficiency. There were no significant differences between the two patient groups in terms of comorbidities, identified infection sites, the severity of sepsis, septic shock prevalence, ARDS, and distribution of causal microorganisms. (Table 1)

Main results

The overall 90-day mortality was 26.4% and the median hospital length of stay was 14 days (7–24 days). During the 90-day observation period, 32.9% (n=25) of the patients in the severe vitamin D deficiency group had died, compared to 20.5% (n=18) of the patients in the non-severely deficient group. The multivariable analysis, adjusted for severity, sex and comorbidities showed that severe vitamin D deficiency, was independently associated with 90-day mortality (OR=2.69 (1.03–7.00), p=0.043). (Table 2)

Cox analysis adjusted for APACHE II, ACCI, sex, arterial lactate and presence of cirrhosis showed an increased mortality hazard associated with severe vitamin D deficiency (HR=2.80 (1.43–5.49), p=0.003) (Table 3) with survival curves that diverged from the time of admission (Figure 2). Length of hospital stay analysis, adjusted for the same confounders, showed that severe vitamin D deficiency was associated with decreased chances of hospital discharge (sub-HR=0.66 (0.44–0.98)) (Table 4).

Among patients admitted to the ICU, subjects with severe vitamin D deficiency had an increased 28-day adjusted mortality (HR=3.06 (1.05–8.94), p=0.04) and decreased chances of discharge (sub-HR=0.51 (0.32–0.81)). Patients with severe vitamin D deficiency admitted to the ICU had fewer vasopressor-free days than patients without severe deficiency (25 days [0–28 days] vs. 28 days [24.5–28 days], p=0.04), while ventilator-free days (23 days [0–28 days] vs. 26 days [22–28 days], p=0.12) and renal replacement-free days (28 days [0–28 days] vs. 28 days [28–28 days], p=0.09) were similar between the two groups (Supplementary Table 1). Patients with severe vitamin D deficiency had higher rates of concomitant bacteremia (44.8% vs. 28.4%, p=0.03).

Exploratory subgroup analysis is shown in Supplementary Figure 1. It revealed substantial between-group heterogeneity regarding the effect of vitamin D status on 90-day mortality. Higher 90-day mortality was observed in severely vitamin D-deficient patients with an age below the median (66.7 years), ACCI below the median (5), diabetes, female sex, and presence of a causal gram-positive isolate. Sensitivity analysis of vitamin D association with study outcomes recalculated by classifying vitamin D status as severely deficient (< 12 ng/mL), moderately deficient (12-20 ng/mL), and nondeficient (> 20 ng/mL) are shown in Supplementary Tables 2A, 3A, 4A, and Figure 2A.

Discussion

In this prospective single-center study, severe vitamin D deficiency was independently associated with increased 90-day mortality and longer hospital stay, regardless of sepsis severity and

comorbidities. Likewise, the adjusted-hospital stay was longer in the severely vitamin D-deficient group. Severe vitamin D deficiency was also associated with increased duration of ICU stay, ICU 28-day mortality, vasopressor treatment, and a higher rate of bacteriemia as reported by others.[6]
The vitamin D status of patients included in our study was evaluated based on the serum level of 25(OH)D, the precursor of the active vitamin D metabolite 1,25(OH)2D. To date, 25(OH)D is considered the best marker of a patient's vitamin D status.[15,16]
The observed prevalence of vitamin D deficiency (62.6%) in our study was in line with previously reported rates in northwestern Europe.[17,18] The findings of our study are consistent with a meta-analysis of eight studies of almost 2,000 patients published between 2014 and 2017. It showed that severe, but not moderate, vitamin D deficiency in septic patients was independently associated with an increased risk of mortality.[19] However, in contrast with the studies assessed in this meta-analysis, the samples used for 25(OH)D measurements in our study were drawn at the time of ED admission, before any treatment-related dilutional effects,[10] as suggested by the high values of plasma albumin level.[20] Our study is representative of an urban center caring for a heterogeneous population with a high incidence of chronic diseases. The increasing vitamin D levels with increasing age and comorbidities can be explained by the more frequent vitamin D supplementation in older patients with poorer chronic health conditions.
Cardiovascular mechanic conclusions are difficult to deduce, however, the increased vasopressor requirements for severely vitamin D deficient ICU patients of our study have been reported before.[6] This could be explained by the cardiotropic effects of vitamin D,[21] or its modulating effect on angiotensin II.[22] Moreover, the increased duration of ICU stay, increased ICU 28-day mortality and the higher rate of concomitant bacteriemia found in our study have also been reported before.[6]
The early divergence between the survival curves of our study suggests the presence of vitamin D deficiency-related alterations in the initial response to infection. Possible mechanisms could be related to the increased production of inflammatory cytokines such as TNF alpha, IL-1, IL-6, and IL-8,[23] the reduction in circulating anti-microbial peptides (cathelicidin (LL-37) and β-defensin 2) involved in the phagocytosis and chemoattraction of immune cells at the site of infection[24], or alterations in the regulation of the balance between innate and acquired immunity.[4,25] The effect of severe vitamin D deficiency according to the presence of gram-positive isolates may be explained by the known immunomodulating effect of vitamin D on Toll-like receptor 2, CD14 co-receptor for peptidoglycan, a component of the outer cell wall of gram-positive bacteria.[26]
Our results support the hypothesis that vitamin D severe deficiency at ED admission in septic patients is associated with mortality. However, randomized controlled trials on vitamin D supplementation in critical patients have reported mixed results. The VITDAL-ICU study (Correction of Vitamin D Deficiency in Critically Ill Patients) showed a beneficial effect of vitamin D supplementation only in the severely deficient subgroup (< 12 ng/mL) and no effect on mortality or length of stay in non-severely deficiency groups.[9] The VIOLET study (Vitamin D to Improve Outcomes by Leveraging Early Treatment), a subsequent interventional randomized controlled trial, reported no effect of supplementation on 90-day mortality or other nonfatal outcomes among critically ill, vitamin D-deficient patients.[27] Differences in reported results may be related to the degree of vitamin D deficiency at study inclusion, the doses, and the timing of supplementation.[7] Currently, the VITDALIZE study, a phase three randomized controlled trial including severely vitamin D-deficient patients is being conducted. These critically ill patients are being supplemented

with high-dose vitamin D3.[28] The results of this study may help to clarify the role of vitamin D supplementation in the critical setting.

One could speculate that given the available results from randomized controlled trials showing little or no effect of vitamin D supplementation that the observed association is likely a marker of poor prognosis and not causal. Nevertheless, another plausible interpretation of current data would be that while severe vitamin D deficient is a causal determinant of sepsis outcomes but therapeutical interventions aimed at restoring optimal vitamin D status once the septic process is installed are futile because intervening too late in the disease process.

The single-center design of this study limits the generalizability of the results to different settings. Moreover, due to their small recruitment basin, single-center studies are more prone to type II error, given the low number of included patients. Nonetheless, the predefined recruitment goal was reached, minimizing the risk of this error. Despite being a limitation, single-center studies offer some advantages, in the homogeneity of the sampling and analysis techniques, adding to the consistency of the results.

Moreover, information on chronic medications, including vitamin D supplementation, were not included in this study. The definition of severe sepsis used was that applicable during the study period (2014–2017). It is important to note that a new definition of sepsis was introduced in 2016.[29] Despite using an older definition, all patients in the study, had sepsis according to the current definition.

Another limitation is the absence of collected data on ethnic origin which might be a potential confounding factor as both associated to vitamin D deficiency and sepsis outcomes. While being unaccounted for in the multivariable regression, ethnic origin is heterogenous at our site with a substantial representation of north-African and sub-tropical African patients favoring the generalization of our results. Finally we have not measured VDBP levels, a promising element in the search for the influence of vitamin D in sepsis[30]

Conclusion

This study suggests a higher mortality rate at 3 months and a longer duration of hospitalization in severely vitamin D-deficient septic patients, with vitamin D levels measured at the time of presentation in the Emergency Department, before any resuscitation measures were initiated.

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Conflict of interest statement

Stefano Malinverni has no conflicts of interest to report
Queitan Ochogavia has no conflicts of interest to report
Sarah Lecrenier has no conflicts of interest to report
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Pierre Mols has no conflicts of interest to report
Magali Bartiaux has no conflicts of interest to report

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Authorship statement

Stefano Malinverni substantially contributed to the conception and design of the study, the acquisition and both the analysis and interpretation of the data. SM drafted the article and provided final approval of the version submitted for publication.
Queitan Ochogavia substantially contributed to the conception and design of the study as well as the acquisition of the data. QO provided critical revision to the article and approved the final version of the manuscript submitted for publication.
Sarah Lecrenier substantially contributed to the analysis and interpretation of the data. SL provided critical revision to the article and approved the final version of the manuscript submitted for publication.
Margherita Scorpiniti substantially contributed to the acquisition of the data. MS provided critical revision to the article and approved the final version of the manuscript submitted for publication.
Frédéric Cotton substantially contributed to the acquisition and interpretation of the data. FC provided critical revision to the article and approved the final version of the manuscript submitted for publication.
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Pierre Mols substantially contributed to the interpretation of the data. PM provided critical revision to the article and approved the final version of the manuscript submitted for publication.
Magali Bartiaux substantially contributed to the interpretation of the data. MB provided critical revision to the article and approved the final version of the manuscript submitted for publication.

Datasharing

Data are available at the following DOI:10.6084/m9.figshare.13573502