Journal of Critical Care 43 (2018) 294–299

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Vitamin D kinetics in the acute phase of critical illness: A prospective observational study ☆

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ARTICLE INFO

Available online xxxx

Keywords:
Vitamin D
Pleiotropy
Intensive care
Mortality
Kinetics
Critical illness

ABSTRACT

Purpose: The objective of this study was to assess the vitamin D kinetics in critically ill patients by performing periodic serum vitamin D measurements in short time intervals in the initial phase of a critical illness.
Materials and methods: We performed vitamin D serum measurements: at admission and then in 12-hour time intervals. The minimum number of vitamin D measurements was 4, and the maximum was 8 per patient.
Results: A total of 363 patients were evaluated for participation, and 20 met the inclusion criteria. All patients had an initial serum vitamin D level between 10.6 and 39 ng/mL. Nineteen patients had vitamin D levels between 10 and 30 ng/mL, which means that they had vitamin D insufficiency or deficiency, and only one patient had a normal vitamin D serum plasma level. We observed that the median of the vitamin D level decreases until the fourth measurement then stabilizes around the 4th and 5th measurement and then appears to increase unevenly. The highest drop is at the very beginning.
Conclusions: The vitamin D serum level is changeable in the initial phase of a critical illness. We hypothesize that the serum vitamin D concentration can mirror the severity of illness.

1. Introduction

The widely recognized role of vitamin D (25-hydroxyvitamin D; 25(OH)D3) in the human body is usually linked to extracellular calcium metabolism by intestinal absorption regulation and skeletal mineralization [1-3]. However, its function is much more complex. The non-classic (pleiotropic) vitamin D mechanisms of action rely on its binding to the nuclear receptor (VDR) and the formation of a heterodimer with the retinoid X receptor. The abovementioned interaction regulates the transcription of DNA into RNA by binding to genomic sequences called vitamin D response elements (VDREs) in many tissues and subsequently mediates the regulation of cell proliferation, differentiation, apoptosis, angiogenesis, hormone secretion, membrane stabilization, anti-inflammatory action, blood pressure regulation, blood sugar control and, finally, regulation of innate and adaptive immunity [1,3-8].

Dysregulated vitamin D pleiotropy caused by vitamin D deficiency, which is currently linked with cancer, autoimmune, infectious and cardiovascular diseases, is well recognized in intensive care patients [1]. Vitamin D deficiency is linked to morbidity and life-threatening organ dysfunction due to a dysregulated host response to infection (sepsis) in the intensive care unit (ICU) [9-15]. However, a few studies did not confirm such dependencies, and it seems that this is still an area of uncertainty [16,17]. Several studies performed in ICUs report a relationship between an extremely low serum vitamin D concentration (severe deficiency) and mortality in intensive care patients [11,18-28]. However, most of those trials were retrospective, and the vitamin D concentration was measured only once (at a certain point of time, usually at admission). We still do not know if vitamin D is a modifiable factor, which, if properly corrected, could substantially influence the patient outcome or another simple marker of the poor condition of the patient. Typically, the course of the early resuscitation phase of a critical illness is dynamic, potentially influencing vitamin D kinetics (serum level changes in time). There are only a few prospective observational or interventional clinical trials studying vitamin D kinetics in critically ill patients [26,29-34]. The methodology of these trials is

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http://dx.doi.org/10.1016/j.jcrc.2017.09.179
0883-9441/

heterogeneous, which makes any comparisons or generalizations very difficult or even impossible to perform.

The main objective of this study was to assess the vitamin D kinetics in critically ill patients by performing periodic serum vitamin D measurements in short time intervals (every 12 h) in the initial phase of a critical illness. Defining the typical vitamin D kinetic profile could potentially be helpful for planning supplementation regimens and future randomized prospective trial designs to adequately study the relationship between vitamin D deficiency correction and mortality rate reduction in critically ill patients. We hypothesized that the serum vitamin D levels are unstable in the initial, acute phase of a critical illness.

2. Materials and methods

This was a prospective observational study conducted from September 2015 to September 2016 in a single, eleven-bed, medical/surgical ICU. Written informed consent was obtained from the patients' relatives. The study was approved by the Regional Ethics Committee in Opole, Poland (protocol number: 214/2015; the date of approval: 25/03/2015), it was registered before the recruitment of participants (clinicaltrials.gov NCT02414386) and was carried out according to the principles of the Declaration of Helsinki. The current presentation should be treated as a preliminary report for a larger study on serum vitamin D level measurements in critically ill patients undergoing continuous renal replacement therapy with regional citrate anticoagulation. Our aim was to study the vitamin D serum levels and kinetics in a homogenous intensive care population, which should be treated as a representative control cohort in the ICU.

We included in the study consecutive critically ill patients with vitamin D levels above 10 ng/mL at admission and the coexistence of respiratory and circulatory failure. We defined respiratory failure as a need for invasive mechanical ventilation and circulatory failure as a need for inotrope and/or vasopressor administration. Patients who met any of the following criteria were excluded: acute liver failure, acute kidney injury treated with renal replacement therapy, hypercalcemia at admission (total calcium plasma level > 10.6 mg/dL; total ionized calcium plasma level > 1.35 mmol/L), parathyroid gland disease at admission, serum vitamin D level < 10 ng/mL at admission, end-stage renal disease, admission from another ICU or readmission, age younger than 18 years, or lack of consent from relatives.

The vitamin D serum measurement procedure strictly adhered to the standard defined by the Central Hospital Laboratory of PS ZOZ Wojewodzkie Centrum Medyczne w Opolu. Blood samples were taken from an arterial line, central venous line or by direct peripheral venous puncture and were collected in ethylenediamine tetraacetic acid (EDTA) tubes. Blood samples were protected from light exposure, transported to the hospital laboratory within 30 min, then centrifuged at 3500 rpm for 10 min and processed by laboratory technicians. The vitamin D serum level was measured using an electrochemiluminescence binding assay on Cobas e411 or Cobas 6000 immunoassay analyzers (Roche Diagnostics GmbH, Mannheim, Germany). The coefficient of variation (the amount of variability relative to the mean) of that method is estimated to be 0.8%–5.8% [35].

Consecutive patients admitted to the ICU were assessed in terms of the study participation (inclusion and exclusion criteria). In every patient included in the study group, blood samples were collected within 12 h of admission. In the majority of patients, the first vitamin D serum level was measured with the first laboratory diagnostic tests performed at the time of admission to the ICU. If the first vitamin D serum level was <10 ng/mL (severe vitamin D deficiency), the patient was excluded from the study. The next vitamin D serum levels were taken in 12-hour time intervals (twice daily, at 6 am and 6 pm). The minimum acceptable number of vitamin D measurements was 4, and the maximum was 8 per patient. All demographic data (date, name, hospital documentation number, sex, age, diagnosis at admission, comorbidities, Therapeutic Intervention Scoring System (TISS-28), Sequential Organ Failure Assessment Score (SOFA), additional laboratory tests) were recorded into the hospital's electronic database and stored in the electronic form. After the recruitment process, patient data were extracted from the electronic database, the patient identification was blinded, and the data were transferred to the statistician for statistical analysis.

We summarized the patients' descriptive statistics, including the mean, median, interquartile range (25th to 75th percentile), and ranges. Some of these measures were illustrated on a box-plot. Linear and nonlinear mixed effect models were used to investigate (a) the pattern of changes in the levels of vitamin D over time, (b) how baseline covariates, such as age, TISS-28, and SOFA, affect the average response, and (c) patient specific-effects. All computations were performed in R ver. 3.3.2 (R Core Team, 2016) using the lmr4 package (Bates et al., 2015) and ggplot2 package (Wickham, 2016) [36-38].

3. Results

A total of 363 patients were evaluated for participation in the trial. After the initial evaluation, 343 patients were excluded from the study. Exclusion reasons were the following: no circulatory failure, no respiratory failure, vitamin D measurement was not performed, end-stage renal disease, acute kidney injury treated with renal replacement therapy, admission from another ICU or readmission, acute liver failure, age <18. The study flow chart is depicted in Fig. 1. In 127 (35%) patients with coexisting respiratory and circulatory failure, vitamin D serum levels were measured. In 95 patients, vitamin D serum plasma level was <10 ng/mL in the first measurement and, in 44 patients, it was <3 ng/mL in the first measurement, which is an undetectable serum concentration. In 32 patients, the vitamin D serum plasma level was >10 ng/mL (20 patients in the range of 10–20 ng/mL, 11 patients in the range of 20–30 ng/mL, and 1 patient with >30 ng/mL). In 7 patients initially included in the trial, the minimum number of 4 vitamin D measurements was not reached. In 5 patients with vitamin D serum plasma levels of >10 ng/mL who were initially included in the trial, acute kidney injury was subsequently diagnosed, and they underwent continuous renal replacement therapy with regional citrate anticoagulation; these patients were also excluded.

Finally, 20 patients met the inclusion criteria and were included in the study for a vitamin D kinetics evaluation. The baseline demographics of the study group are depicted in Table 1. All patients in the study group had an initial serum vitamin D level between 10.6 and 39 ng/mL. Nineteen patients in the study group had serum plasma vitamin D levels between 10 and 30 ng/mL, which means that they had vitamin D insufficiency or deficiency, and only one patient in the study group had a normal vitamin D serum plasma level. Absolute numbers for vitamin D serum levels are depicted in Table 2. None of patients in the study group received potential vitamin D metabolism modifiers. The only exception was the patient with septic shock received supplemental dose of steroids but the risk of vitamin D metabolism modification was assessed as low.

Fig. 2 summarizes the observations at each time of measurement using summary statistics. The median of the vitamin D level decreases until the fourth measurement. It stabilizes around the 4th and 5th measurement and then appears to increase unevenly. In the large majority of the time points, the distributions are skewed. The variability (according to the interquartile range) of the observations is not constant over time, but there is no apparent trend. One patient always had relatively high levels of vitamin D, which are depicted as outliers.

Based on the evidence presented so far, we start by fitting a model with three random effects: intercept, slope, and a quadratic term, obtaining LL = −347.96 (log likelihood), AIC = 715.91 and df = 10 (degrees of freedom). We compare this model with a model based on a linear trend (LL = −365.36, AIC = 742.72, df = 6), a model based on an inverse relationship (LL = −357.69, AIC = 727.39, df = 6) and a flexible semiparametric model, i.e., a restricted cubic spline (LL = −348.23, AIC = 716.47, df = 10). Likelihood ratio tests (LRTs)