

## Serum vitamin D level variation in SIRS, sepsis and septic shock

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### ABSTRACT

**Objectives:** Vitamin D has potent immunomodulatory effects with the capability of acting as an autocrine and paracrine agent, and inhibits inflammatory signaling. In this study, our aim was to evaluate the relationship between vitamin D levels in systemic inflammatory response syndrome (SIRS), sepsis and, septic shock patients and outcomes.

**Patients and Methods:** A total of 45 patients whose vitamin D levels were measured within the first 48 hours of Intensive Care Unit (ICU) admission and 20 healthy controls were studied prospectively. The patients were grouped as, SIRS (Group-I,n=10), sepsis (Group-II,n=25), septic shock (Group-III,n=10) and healthy subjects (Group-IV,n=20). Serum vitamin D levels were categorized as a deficiency ( $\leq 15$ ng/mL), insufficiency (16-29ng/mL) and sufficiency ( $\geq 30$ ng/mL). Demographic characteristics, Acute Physiology and Chronic Health Assessment II (APACHE-II) scores, and biochemical parameters were noted.

**Results:** Vitamin D levels were significantly lower in all study groups compared to the control group ( $p < 0.01$ ), but were similar among the study groups. The hospital and ICU length of stay (LOS), and biochemical parameters were similar among the study groups. The mortality rates were 40% in Group I, 57 % in Group II, and 80 % in Group III.

**Conclusion:** In our study patients with SIRS, sepsis and septic shock had lower serum 25-OH vitamin D levels compared to the control group. Our results are in line with the literature that supports a relationship between vitamin D deficiency and inflammation.

**Keywords:** Critically ill patients, Vitamin D, Sepsis, SIRS

## 1. INTRODUCTION

Sepsis was defined as a clinical syndrome by the presence or suspected of both infection and systemic inflammatory response combined with organ injury in the 2001 by International Sepsis Definitions Conference [1]. The incidence of sepsis, which is one of the most important reasons for admission to the intensive care unit (ICU), has increased significantly in the last 20 years. However; although the positive effects of advances and awareness campaigns in the management of sepsis provide an increase in survival, sepsis is still the most important cause of mortality and morbidity in ICU [2].

A large amount of vitamin D, which is fat-soluble, is produced on the skin by sunlight and a limited amount is obtained from the diet. It plays an important role in the regulation of bone and calcium metabolism. Vitamin D is stored in fat cells and is converted to hydroxyvitamin D<sub>3</sub>, the so-called circulating form in the liver. Hydroxyvitamin D<sub>3</sub> is mainly converted to calcitriol, the active metabolite in the kidneys [3,4].

Vitamin D metabolites have significant pleiotropic effects on innate and adaptive immune system cells. The calcitriol, biologically active metabolite of vitamin D, increases the production of cathelicidin and defensin and thus plays a role in the innate immune system. In addition, it exerts its effects on the adaptive immune system via vitamin D receptors on monocytes, T, and B cells. Vitamin D also affects the proliferation and differentiation of T and B cells and modulates immunoglobulin production [5-7].

It is assumed that more than 1 billion people worldwide have vitamin D deficiency. It was well-established that vitamin D deficiency is a well-known cause of musculoskeletal disorders. Recent studies have shown that vitamin D deficiency may play a role in the pathogenesis of infection, immunological, neurological, cardiovascular and respiratory diseases [4,6-8].

Its deficiency is frequently observed in critically ill patients and has been shown to be associated with increased mortality and prolonged hospital stay. Similarly, the deficiency was reported to

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be a risk factor for mortality in critically ill patients with sepsis [6,8-11].

In this study, we aimed to evaluate the relationship between the severity of sepsis and serum 25-OH vitamin D levels and its effect on survival in critically ill patients.

## 2. PATIENTS and METHODS

### Study Design

A prospective cohort study was performed between January 2015 and July 2015 in the ICU of the Marmara University Training and Research Hospital. A total of 45 critically ill patients and 20 voluntary healthy volunteers were included in the study. The study protocol was approved by the Institutional Ethics Committee and was in compliance with the principles of the Declaration of Helsinki. The informed written consent form was obtained from patients and healthy volunteers.

Demographic data of the patients, Acute Physiology and Chronic Health Assessment II (APACHE II) scores, length of intensive care and hospital stay, serum 25-OH vitamin D, C-reactive protein (CRP), procalcitonin, parathyroid hormone (PTH) levels, hemogram, and biochemical parameters were recorded.

The patients were divided into groups as, systemic inflammatory response syndrome (SIRS) (Group I, n=10), sepsis (Group II, n=25), septic shock (Group III, n=10) and voluntary healthy subjects (Group IV, n=20) for the control group.

### Definitions

The serum 25-OH vitamin D levels were categorized as deficiency ( $\leq 20$  ng/mL), insufficiency (20-29 ng/mL) and sufficiency ( $\geq 30$  ng/mL) in accordance with the guidelines of the Endocrine Society. Also, the serum 25-OH vitamin D level  $\leq 10$  ng/mL were defined as very severe vitamin D deficiency [12].

Systemic inflammatory response syndrome; is a systemic inflammatory response to various clinical conditions. Body temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , heart rate  $> 90/\text{min}$ , respiratory rate  $>20/\text{min}$  or  $\text{PaCO}_2 <32$  mmHg, with the presence of at least two of the followings; leukocyte count  $>12000/\text{mm}^3$  or  $<4000/\text{mm}^3$  or  $> 10\%$  of the young neutrophil [1].

According to the 2001 International Sepsis Definitions Conference, sepsis patients were defined as a clinical syndrome of systemic inflammatory response together with infection. Septic shock patients were defined as persistent arterial hypotension (systolic arterial pressure  $<90$  mmHg, mean arterial pressure  $<60$  mmHg, or blood pressure decreased to 40 mmHg from normal baseline value) which cannot be explained for other reasons and is unresponsive to fluid resuscitation [1].

### Clinical Data

25-OH vitamin D levels and other biochemical parameters of the patients were measured within 48 hours after they were admitted to the ICU. Serum 25-OH vitamin D levels were determined by

high – performance liquid chromatography method (HPLC; Recipe Chemicals, Munich, Germany), serum CRP level by BN II nephelometer method (Siemens, Erlangen, Germany), serum procalcitonin levels by electrochemiluminescence immunoassay method (Roche Cobas e411; Roche Diagnostics, Indianapolis, USA), serum PTH level was measured by chemiluminescence immunoassay method (Modular Analytics E170; Roche Diagnostics, Mannheim, Germany) and other biochemical values were measured by enzymatic colorimetric method (Roche Diagnostics, Indianapolis, USA). The complete blood count parameters were measured by Coulter STKS hematological analyzer method (Beckman Coulter Cooperation, Miami, FL, USA).

### Statistical Analysis

In this study, data showing normal distribution were given as mean  $\pm$  standard deviation, data not showing normal distribution were given as median (min-max) values as numbers. The One-Way Anova test was used for the analysis of distributed data. The results were evaluated with a 95% confidence interval, and  $p < 0.05$  was considered as the level of statistical significance. Statistical Package for Social Sciences (SPSS) for Windows 21.0 was used for statistical analysis.

## 3. RESULTS

Sixty-five patients were enrolled into the study. The patients were grouped as, SIRS (Group I, n=10), sepsis (Group II, n=25), septic shock (Group III, n=10) and healthy volunteers (Group IV, n=20) for the control group. Patients with SIRS, sepsis, and the septic shock had significantly lower 25-OH vitamin D levels than healthy volunteers ( $p=0.001$ )(Figure 1). The baseline demographic characteristics, 25-OHD levels, and other clinical parameters of patients and healthy volunteers are given in Table I. The clinical and laboratory findings of patients are presented in Table II.

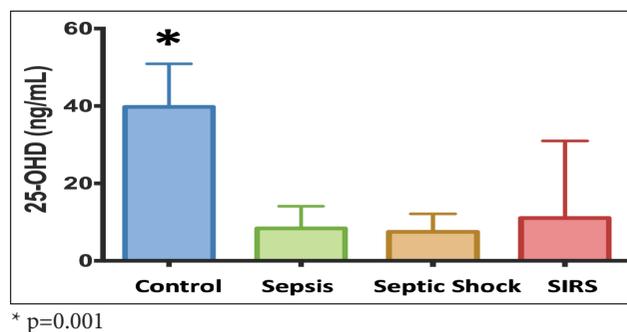


Figure 1. Serum 25-OH vitamin D levels in patients and healthy volunteers.

**Table I.** The baseline demographic characteristics, 25-OHD levels and other clinical parameters of patients and healthy volunteers

	SIRS	Sepsis	Septic Shock	Healy Control	p value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	62.38 ± 16.69	55.74 ± 17.81	60.70 ± 11.56	44.81 ± 15.03	<b>0.016</b>
APACHE-II score	14.90 ± 5.15	22.21 ± 8.54	22.40 ± 5.04	N/A	<b>0.03</b>
ICU LOS (days)	13.80 ± 19.26	26.52 ± 54.46	16.90 ± 22.90	N/A	0.69
Hospital LOS (days)	18.50 ± 18.77	31.39 ± 60.60	18.60 ± 22.40	N/A	0.67
25-OHD (ng/mL)	8.39 ± 5.70	7.49 ± 4.64	5.16 ± 3.97	39.77 ± 11.13	<b>0.001</b>

25-OHD: 25-hydroxy vitamin D, ICU LOS: Intensive care unit length of stay, LOS: length of stay, APACHE II: Acute Physiology and Chronic Health Evaluation II, N/A: Not Applicable, SD: Standard Deviation

**Table II.** The clinical and laboratory findings of the patients

	SIRS	Sepsis	Septic Shock	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
WBC (/mm <sup>3</sup> )	14229 ± 7013	14434 ± 7201	13127 ± 7073	0.09
25-OHD (ng/mL)	8.39 ± 5.70	7.49 ± 4.64	5.16 ± 3.97	0.19
Albumin (g/dL)	2.57 ± 0.81	3.42 ± 3.65	2.22 ± 0.60	0.66
BUN (mg/dL)	30.30 ± 28.22	28.57 ± 16.83	42.55 ± 29.10	0.44
Creatinine (mg/dL)	1.22 ± 1.24	1.02 ± 0.65	1.62 ± 1.23	0.25
Glucose (mg/dL)	143.50 ± 55.08	125.61 ± 26.32	166.73 ± 60.51	0.05
Calcium (mg/dL)	7.66 ± 1.32	8.13 ± 0.95	7.68 ± 1.18	0.40
Parathormone (pg/mL)	78.45 ± 66.36	110.44 ± 123.20	78.33 ± 108.84	0.63
CRP (mg/L)	126.72 ± 66.88	156.27 ± 106.39	184.79 ± 119.07	0.44
Procalcitonin (ng/mL)	1.96 ± 2.39	12.51 ± 27.44	5.09 ± 9.54	0.35
Phosphorus (mg/dL)	2.82 ± 0.97	3.07 ± 1.31	3.52 ± 1.50	0.45

25-OHD: 25-hydroxy vitamin D, WBC: White Blood Cells, BUN: Blood Urea Nitrogen, CRP: C-reactive Protein, SD: Standard Deviation

Patient's baseline laboratory parameters at ICU admission, ICU length of stay (LOS), and hospital LOS were similar in patients' groups. We found lower serum 25-OH vitamin D levels in sepsis and septic shock patients compared to patients who had SIRS but without a statistical significance (p=0.19). The mortality rates were 40% in Group I, 57% in Group II, and 80% in Group III. In addition to this, serum 25-OH vitamin D levels were lower in

non-survivor patients compared with the survivors (6.9 ± 5.3 vs. 7.4 ± 3.6), but without a statistical significance (p=0.71).

#### 4. DISCUSSION

In the present study, we evaluated the relationship between vitamin D levels in SIRS, sepsis, and septic shock patients and outcomes. The main finding of this study showed that the serum 25-OH vitamin D levels were significantly lower in all study groups compared to the control group. In addition, vitamin D levels were found lower in non-survivor patients, even if it was not statistically significant. The hospital and ICU LOS, biochemical parameters were similar among the study groups.

Vitamin D is a fat-soluble steroid hormone, and it has a very important role in bone health, calcium homeostasis and also maintaining the optimal function of many organ systems [7,8]. Various clinical studies emphasize deficiency is a major healthcare problem worldwide and has a crucial role in some disease pathogenesis such as musculoskeletal diseases. Also, recent studies have shown that vitamin D deficiency is associated with systemic inflammation, infection, cancer, immunological, neurological, cardiovascular, and respiratory diseases [8,13]. Furthermore, the correlation between vitamin D deficiency and increased mortality has been shown in the general population [14,15]. Melamed et al., showed that lower serum vitamin D levels were associated with higher mortality in the general population [14]. Also, clinical studies and meta-analysis on patients with chronic kidney diseases have shown that higher serum vitamin D levels and also vitamin D supplementation were associated with improved survival [15,16].

Vitamin D deficiency in critically ill patients has been well established [7]. The prevalence of low vitamin D concentrations was more than 90% among critically ill patients and higher than in patients who were hospitalized in non-critical units [17]. Recently, published studies and meta-analysis emphasized the association between vitamin D deficiency and mortality in critically ill patients [17-20]. There was a 1.81-fold higher risk of death in critically ill patients with vitamin D deficiency [21]. Furthermore, vitamin D deficiency has been associated with longer hospital stay and ICU LOS, increased risk of ICU-acquired infections, and sepsis [7,17-19,21,22]. In our study, we found that 95.5% of patients had vitamin D deficiency (≤ 20 ng/mL) on admission to the ICU. We found that vitamin D levels were lower in non-survivor patients compared with the survivors, but it was not statistically significant.

Vitamin D deficiency is associated with an increased risk of infectious diseases and sepsis. It was considered a significant prognostic factor for mortality in patients with sepsis [6,7,11,17,20,23,24]. Its deficiency affects the development of sepsis with several mechanisms that includes adaptive and innate immune modulation, suppression of the inflammatory response, enhanced phagocytosis and chemotaxis, and increased production of antimicrobial peptide β-defensins and cathelicidins [17,25-28]. It was shown that high levels of serum 25-OH vitamin D (38 ng/mL or greater) decreased the incidences of urinary tract infections [25]. However, the association

between respiratory tract infections (RTI) and serum vitamin D levels is controversial. Some observational and case-control studies revealed that hospital admission due to RTI is associated with lower vitamin D serum levels [26,27]. In contrast to this, some studies claimed that there was no relationship between vitamin D status and RTI [28,29]. In a prospective cohort study, including 461 patients with suspected sepsis, no statistically significant difference was found in 1,25(OH) D levels between those with or without infections [30].

Also, there is a correlation between serum levels of vitamin D and the severity of sepsis and still a contributing factor of organ dysfunction. Patients with septic shock had a lower serum level of vitamin D compared with septic patients without organ dysfunction [29,30]. Jeng et al., found that there were no significant differences in serum levels of vitamin D between patients with sepsis and critically ill patients [31]. In the present study, we found that critically ill subjects had significantly lower plasma serum levels of vitamin D compared with healthy controls even if low serum levels of vitamin D seen in septic shock, sepsis and SIRS patients but the levels were comparable among the study groups.

### Limitations

The mean 25-OH vitamin D proportion of deficiency does not vary across different ages. Therefore, we did not take the age difference between the groups into account. We also did not pay attention to the comorbidities and malnutrition, which are important causes of vitamin D deficiency. In addition to this, pre-illness vitamin D levels were unknown in study groups.

### Conclusion

Vitamin D deficiency is commonly seen in critically ill patients. Although, it is not an independent factor for mortality, it might be related to worse clinical status during ICU stay. In our study, we found that the serum 25-OH vitamin D level in ICU patients with SIRS, sepsis and septic shock were lower than healthy individuals, but the levels of serum vitamin D were similar among the study groups. Our results showed that the severity of the disease had no effect on the serum levels of vitamin D. Thus, inflammation mainly may cause alterations in vitamin D metabolisms. The new trials are needed to determine the role of vitamin D before or during critical illnesses, and to investigate whether it can improve clinical outcomes.

**Disclosure:** The authors declare that there is no conflict of interest regarding the publication of this article.

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