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Research Article

Sequential vitamin D and parathyroid hormone measurement in patients with septic shock: Could they be prognostic marker in septic shock?

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ABSTRACT

Aim: Hypocalcemia is a common clinical problem in critically-ill patients and it is associated with increased morbidity and mortality. The aim of this study was to investigate serum calcium, vitamin D and parathyroid hormone (PTH) levels in surviving and non-surviving septic shock patients.

Method: Patients with septic shock criteria and who were older than 18 years of age were included, whereas patients with diseases influencing calcium homeostasis were excluded. Demographic and laboratory parameters were recorded prospectively.

Results: 41 patients, 20 of which were male were included in the study. The median (min-max) age of study population was 67 (19-88) years. Frequency of hypocalcemia in the study population was 29.2% and 68.2% according to corrected calcium and ionized calcium, respectively. On the day septic shock was diagnosed (day 1), median vitamin D levels of survivors and non-survivors were 8.7 ng/ml (4.3-30.4) and 5.3 ng/ml (1.0-21.7), respectively (p=0.05). On the same day, median PTH levels of survivors and non-survivors were 94 ng/L (16.9-1746) and 49 ng/L (6.6-339), respectively (p=0.042). Although vitamin D levels were suppressed and PTH levels were elevated in non-survivors at day 5, this change was not statistically significant (p=0.19 and p=0.187).

Conclusion: Hypocalcemia is frequent in septic shock patients, whereas vitamin D levels were low and PTH levels were high in the diagnosis day. These results suggest that vitamin D is suppressed by septic shock at non-surviving patients during course of septic shock. Parathyroid hormone may be a marker for worse outcome in critically ill patients.

Keywords: Septic shock; parathyroid hormone; vitamin D; hypocalcemia; prognostic markers.

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Introduction

Sepsis is a clinical entity which is characterized by infection and cardinal signs of inflammation such as vasodilation, leukocytosis and increased microvascular

permeability [1-3]. The spectrum of disease severity can range from sepsis to septic shock and multi organ dysfunction syndrome. The rate of sepsis vary widely in literature [1]. In the literature, incidence of sepsis reported ranging from 300 to 1301 cases per 100000 population [1, 4, 5]. Although sepsis mortality has declined from 40% to 20% over the last decades because of improved processes of care (e.g., earlier diagnosis, timely resuscitation with appropriate therapies), neuromuscular, metabolic, cardiovascular and renal complications persist and lead to impaired long-term worse outcomes and deteriorated quality of life among sepsis survivors [6-9].

Decreased concentration of ionized calcium in the circulation are common in critically ill patients, especially patients with sepsis, major burns and pancreatitis [10]. Studies showed that hypocalcemia is associated with longer intensive care unit (ICU) stay and increased ICU mortality [11]. Hypocalcemia has been shown to trigger cardiac dysfunction and hypotension which is reversible with calcium replacement [12-15]. More than 50% patients' etiology of hypocalcemia are unknown [16-18]. Vitamin D (25-OH-vitamin D3) deficiency, relative hypoparathyroidism, vitamin D resistance and 1-alpha hydroxylase deficiency are proposed mechanisms for hypocalcemia [10]. Animal studies showed that inflammatory cytokines such as interleukin-1 (IL-1) beta and interleukin-6 (IL-6) up-regulates calcium sensing receptors (CaSRs), decreases parathyroid hormone (PTH) and induces hypocalcemia [10]. Gram negative bacterial sepsis and toxic shock syndrome may have elevated tumor necrosing factor (TNF) alpha levels that have also been associated with hypocalcemia [15]. Current theories about sepsis and progression to septic shock focus on dysregulation of inflammatory response including uncontrolled release of proinflammatory cytokines and tissue damage [8]. Recent studies showed that vitamin D has a pivot role in innate and adaptive immunity besides effects on calcium homeostasis [19]. In contrast to its inhibitory role in adaptive immunity, vitamin D is a potent activator of innate immune system and a natural defense mechanism to microorganisms [20,21]. Evidences accumulated in literature in last five years suggest that significant proportion of critically ill patients have low vitamin D status [22,23] and this situation is associated with increased ICU mortality [24].

Our primary goal was to investigate the correlation between hypocalcemia and mortality, also, find out the response of vitamin D and PTH to dysregulated immune system during the course of septic shock.

Methods

Study population

The study was conducted in internal medicine intensive care unit at Hacettepe University, Ankara, Turkey, from September 2014 to January 2016. Included patients were older than 18 years old and diagnosed as septic shock according to Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. Patients were excluded if they had a disease affecting calcium, PTH and vitamin D metabolism such as malignancy, chronic kidney disease, parathyroid disorders, pancreatitis, tumor lysis syndrome, rhabdomyolysis, renal tubular disorders and pregnancy. 41 patients with septic shock were analyzed in the study.

Ethics statement

The cross-sectional study protocol conformed to ethical guidelines of the 1975 declaration of

Helsinki and all participants or their first degree relatives gave written informed consent and willingness to participate. The ethics committee of Hacettepe University Hospital approved the study protocol (Approval date: 23/07/2014, Project No:GO 14/400).

Clinical outcomes

Hospital electronic medical records system was used for baseline information such as sex, age, comorbidities, mechanic ventilation day and calculation of Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score and Charlson comorbidity index. The 28 days mortality rates and period of hospitalization in the ICU were determined for all patients. Also, fluid resuscitation, vasopressor treatment and calcium replacement and renal replacement treatment data collected during course of septic shock. The dose of vasopressor agents is expressed as the inotropic score and variables calculated as: (dopamine dose x 1) + (dobutamine dose x 1) + (adrenaline dose x 100) + (noradrenaline dose x 100). All doses are expressed as μg/kg/min. This score has also been referred to as the vasopressor score or catecholamine index [25, 26].

Laboratory measurements

Routine laboratory measurements and blood samples for biomarker (hemoglobin, white blood cell, platelet, creatinine, albumin, calcium, lactate, CRP, procalcitonin) analysis were obtained within the first hour of septic shock diagnosis. The serum for ionized calcium (reference range 1.15-1.3 mmol/L) was obtained from arterial blood gas analysis. Venous or arterial blood samples were collected directly into EDTA-containing tube (vitamin D) on first and fifth day of septic shock to measure vitamin D and PTH levels**.** The samples for vitamin D was immediately stored on ıce and then all samples were centrifuged within 30 minutes to separate out plasma. All samples centrifuged 5000 rpm for 5 minutes. Vitamin D and PTH were measured from the separated plasma at the same time. Serum level of PTH was estimated by Immuno Radio Metric Assay (IRMA) technique using Beckman Coulter (USA) and vitamin D was estimated by liquid chromatograph mass spectrometer (LC-MS) technique using Shımadzu LCMS-8040 (JAPAN).

Statistical analysis

Variables in the text and tables were shown as median (minimum- maximum). For data that were not normally distributed the Mann-Whitney U test was used if only two groups were compared. Wilcoxon test was used to more than one measurement in the same group. Receiver operating curve (ROC) analysis were plotted to illustrate day 1 vitamin D and PTH cutoff values. 28 days survival analysis was performed by means of Kaplan-Meier curves. P values less than 0.05 were considered to indicate statistical significance. Analyses were performed with SPSS 21.0.0.1 (SPSS, IBM, Armonk, NY) software for Windows.

Results

We evaluated 41 septic shock patients. Vitamin D and PTH data at day 5 were not available in 9 patients because of death before day 5. 28 days ICU mortality rate was 51.2% (21). Median age of study population was 67 (19-88) years and the median Apachee II score was 28 (11-45). There is no statistically differences according to gender, age, sofa score, Apachee II score, charlson comorbidity index and lenght of ICU stay between survivor and non-survivor groups. Table 1 shows

Table 1. Baseline characteristics of study population

Characteristics	Total patient (n=41)	Survivor (n=20)	Non-survivor (n=21)	p Value
Gender				
Male	20 (48.8%)	12 (60%)	9 (42.9%)	0.278
Age	67 (19-88)	67 (31-88)	69 (19-87)	0.784
APACHE II Score	28 (11-45)	27.5 (11-40)	30 (11-45)	0.130
SOFA Scores				
Day 1	11 (4-19)	11 (4-14)	11 (4-19)	0.132
Day 2	10 (3-18)	9.5 (3-15)	10.5 (7-18)	0.172
Day 3	8 (1-18)	7 (1-16)	9.5 (6-18)	0.168
Day 4	8 (1-20)	7 (1-17)	8 (4-20)	0.385
Day 5	8 (1-18)	7 (1-15)	9.5(4-18)	0.160
Comorbidities				
HT	15 (36.5%)	8 (40%)	7 (33.3%)	
CHF	8 (19.5%)	4 (20%)	4 (19%)	
CHD	13 (31.7%)	8 (40%)	5 (23.8%)	
DM	11 (26.8%)	7 (35%)	4 (19%)	
COPD	6 (14.6%)	1 (5%)	5 (23.8%)	
Charlson comorbidity score	6 (0-13)	6 (2-9)	6 (0-13)	0.823
Mec. Vent. (n)	32 (78%)	11 (55%)	21 (100%)	
Mec Vent., days	4 (0-34)	2 (0-34)	8 (1-21)	0.034
ICU stay, days	10 (0-86)	13.5 (1-86)	9 (1-27)	0.105
Hospital stay, days	27 (2-90)	38 (2-90)	22 (3-60)	0.004

APACHE II:Acute Physiology and Chronic Health Evaluation II, SOFA:Sequential Organ Failure Assessment score, HT:Hypertension, DM:Diabetes mellitus, CHF:Congestive heart failure, CHD:Coronary heart disease, COPD:Chronic obstructive pulmonary disease, Mec. Vent.: Mechanical ventilation

clinical characteristics of patients during the course of septic shock. Corrected calcium and ionized calcium deficiency rates in study population were 29.2% and 68.2% during the first day of septic shock. Statistically significance were determined between survivor and non-survivor groups neither corrected calcium nor ionized calcium during the course of septic shock**.** Baseline laboratory parameters of these groups are summarized in Table 2. The median lactate level, procalcitonin and C-reactive protein were 3.5 mmol/l (1.6-16), 3.04 ng/ml (0.1-283) and 14. mg/dl (1.64-42), respectively. These parameters were not significantly different between two groups. Although median fluid replacement during first 6 hours of septic shock was significantly high at survivors compared to non-survivors [1550 ml (510-2600) vs. 1200 ml (450-1728), p=0.01, respectively], this significance did not determined at the end of first day of septic shock [3102 ml (1720-6160) vs. 2500 ml (1197-6147), p=0.18]. Median inotrope score was not statistically significant between two groups [16 (3-100) vs. 30 (5-170), p=0.51]. Calcium replacement was needed 30% of survivors and 57% of non-survivors. Renal replacement treatment (RRT) was made 20% of survivors and 57% of non-survivors. Both calcium and renal replacement were not statistically significant between both groups (p=0.13 and p=0.13) (Table 3). Median day 1 vitamin D level was significantly higher in

Table 2. Laboratory values and treatment modalities of patients.

Parameters	Total patient (n=41)	Survivor (n=20)	Non-survivor (n=21)	p Value
ICU admission laboratory				
Hg (g/dl)	9.9 (6.2-14.6)	10 (7.7-14.6)	9.5 (6.2-14.2)	0.473
WBC (mm³)	12400 (300-25400)	9500 (2500-34100)	16600 (300-67700)	0.230
PLT(x10³ mm)	155 (5-567)	149.5 (16-567)	164 (5-508)	0.324
Crea. (mg/dl)	1.9 (0.38-8.9)	1.56 (0.38-8.9)	2.1 (0.46-4.58)	0.397
Alb. (g/dl)	2.48 (1.64-3.87)	2.6 (1.76-3.87)	2.31 (1.64-3.69)	0.167
cCa mg/dl	9.04 (4.7-11.5)	9.01 (8.3-10)	9.16 (4.7-11.5)	0.181
iCa (mmol/l)	1.09 (0.8-1.2)	1.07 (0.9-1.18)	1.1 (0.8-1.22)	0.374
Lactat (mmol/l)	3.5 (1.6-16)	3.65 (1.6-7.3)	3.5 (1.8-16)	0.784
CRP (mg/dl)				
0.Gün	14.8 (1.6-42)	13.7 (2.19-32)	14.8 (1.6-42)	0.68
3.Gün	7.97 (2.4-40)	7.97 (4.8-40)	6.37 (2.4-15)	0.35
Procalcitonin (ng/ml)				
0.Gün	3.04 (0.1-283)	5.94 (0.1-283)	2.83 (0.6-101)	0.75
3.Gün	0.1 (0.1-491)	0.1 (0.1-490)	0.1 (0.1-41)	0.19
Cause of sepsis				
RTI	25 (60.9%)	9 (45%)	16 (76.2%)	
UTI	4 (9.8%)	4 (20%)	0	
Wİ	1 (2.4%)	0	1(4.8%)	
Peritonitis	3 (7.3%)	2 (10%)	1(4.8%)	
Cellulitis	1 (2.4%)	0	1(4.8%)	
Other	7 (17.2%)	5 (25%)	2 (9.4%)	
Vitamin D (ng/ml)				
Day 1	6.8 (1-30.4)	8.7 (4.3-30.4)	5.3 (1-21.7)	0.05
Day 5*	5 (2-29)	12.3 (2-29)	5.7 (5-21.2)	0.19
PTH (ng/L)				
Day 1	54 (6.6-1746)	49 (6.6-339)	94 (16.9-1746)	0.042
Day 5*	92 (24-680)	66 (15-312)	112 (47.4-680)	0.187
Vitamin D/PTH				
Day 1	0.088 (0.004-2.37)	0.07 (0.006-0.56)	0.125 (0.004-2.37)	0.18
Day 5*	0.1025 (0.1-1.25)	0.157 (0.1-1.25)	0.054(0.1-0.17)	0.08

***n=** 20 for surviving patients, **n=** 12 for non-surviving patients. **ICU:**Intensive care unit, **Hg:**Hemoglobin, **WBC:**White blood cell, **PLT**:Platelet, **Crea:**Creatinin, **Alb:** albumin, **cCa:** Corrected calcium, **iCa:** Ionized calcium, **CRP:** C-reactive protein, **PCT:** procalcitonin, **RTI:** Respiratory tact infection, **UTI:** Uninary tract infection, **WI:**Wound infection.

survivor group compared to non-survivor group [8.7 ng/ml (4.3-30.4) vs. 5.3 ng/ml (1-21.7), p=0.05, respectively]. Median day 5 vitamin D level was not significantly different between two groups [12.3 ng/ml (2-29) vs. 5.7 ng/ml (5-21.2), p=0.19, respectively]. While vitamin D levels were high in survivor group, median PTH level was statistically significantly high in non-survivor group compare to survivors [94 ng/L (16.9-1746) vs. 49 ng/L (6.6-339), p=0.047]. Although higher median PTH level in non-survivors than the survivors at day 5, it failed to reach statistical significance [112 ng/L (47.4-680) vs. 66 ng/L (15-312), p=0.187, respectively] (Figure 1). In the subgroup analysis , vitamin D levels increased in the survivor group from 8.7 ng/ml in day 1 to 12.4 ng/ml in day 5 (p=0.17) and in the non-survivor group from 5.3 ng/ml to 5.7 ng/ml (p=0.89). Similar to vitamin D, PTH subgroup analysis was not statistically significant (p=0.07 and p=0.06) in subgroup analysis. Day 1 vitamin D/PTH ratio was similar between two groups (0.125 vs. 0.07, p=0.18). Day 5 vitamin D/PTH ratio of patients who was non-survivor, tended to fall compare to survivor (0.054 vs. 0.157, p=0.08) (Figure 2). The area under the curve for 25(OH) D levels in ROC analysis at day 1 in relation to mortality was 0.681 (95% Cl 0.52-0.85),

similar to those for day 1 PTH was 0.686 (95% Cl 0.51-0.84). The best cutoff values for vitamin D and PTH 6.4 ng/ml and 87 ng/L, with a sensitivity of 61.9% and 57.1%, specificity 65% and 80%. Kaplan Meier survival analysis revealed that patients with vitamin D levels ≥ 6.8 ng/ml (median) had increased 28 day survival as compared to patients with vitamin D levels ≤ 6.8 ng/ml (long rank test p=0.012) (Figure 3, Table 4).

Discussion

The main purpose of our study was to investigate hypocalcemia frequency, vitamin D and PTH levels and their response to hypocalcemia at septic shock patients. Day 1 median vitamin D was significantly higher at survivors compared to non-survivors. Although markedly elevation of vitamin D status at survivors during the course of septic shock, it was not statistically significant.

Table 3. Treatment modalities of patients.

Parameters	Total patient (n=41)	Survivor (n=20)	Non-survivor (n=21)	p Value
Fluid Replacement (ml)				
0-6 hour	1364 (450-2600)	1550 (510-2600)	1200 (450-1728)	0.01
0-24 hour	2850 (1197-6160)	3102 (1720-6160)	2500 (1197-6147)	0.18
24-48 hour	1831 (500-5143)	1831 (500-5000)	1950 (1100-5143)	0.82
48-72 hour	1610 (800-4100)	1692 (800-4100)	1600 (1100-3500)	0.92
Vazopressor Norepi. (mcg/kg/dk)				
Total	7.09 (0-132)	3.53 (0.35-74.7)	8.13 (0-132)	0.42
0-6 hour	0.58 (0.1-6)	0.43 (0.1-4.2)	0.6 (0.3-6)	0.13
0-24 hour	3.63 (0.35-27.4)	2.06 (0.35-17.2)	5.3 (0.65-27.4)	0.31
Inotrop score (First 24 hour)	25 (3-170)	16 (3-100)	30 (5-170)	0.51
Calcium Replacement				
No (n)	23 (56%)	14 (70%)	9 (42.8%)	0.13
Yes (n)	18 (44%)	6 (30%)	12 (57.2%)	
Total amount(gr)	10.89	3.78	7.11	
0-6 hour	1.44	0.18	1.26	
0-24 hour	4.86	0.72	4.14	
24-48 hour	2.52	0.81	1.71	
48-72 hour	1.89	1.17	0.72	
RRT				
No	25 (60.9%)	16 (80%)	9 (42.8%)	0.13
Yes	16 (39.1%)	4 (20%)	12 (57.2%)	
0-12 hour	7 (43.7%)	4 (100%)	3 (25%)	
12-24 hour	2 (12.5%)	0	2 (17%)	
24-48 hour	4 (25%)	0	4(33%)	
>48 hour	3 (18.8%)	0	3 (25%)	

Norepi: Norepinephrine, **RRT:**Renal replacement treatment.

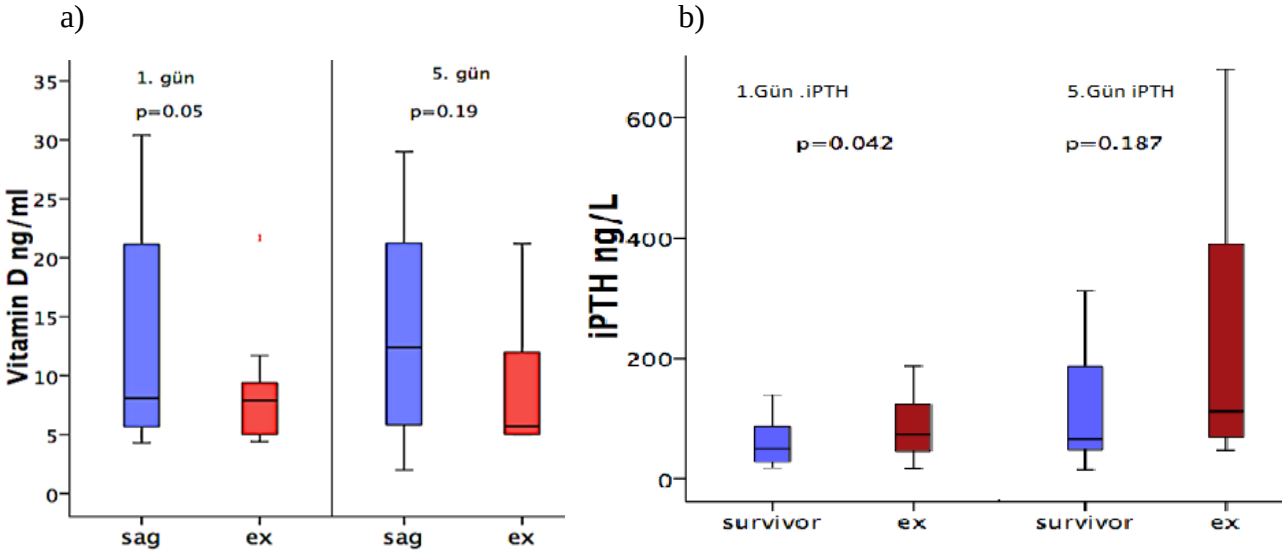

Figure 1. a) Vitamin D levels day 1 and day 5: Median day 1 vitamin D level was statistically significantly high at surviving group compare to non-surviving group. Median day 5 vitamin D level was not significantly different between both groups. **b) PTH levels day 1 and day 5:** Median day 1 PTH level was statistically significantly high at non-surviving group compare to surviving group. Median day 5 PTH levels was not statistically different between both groups

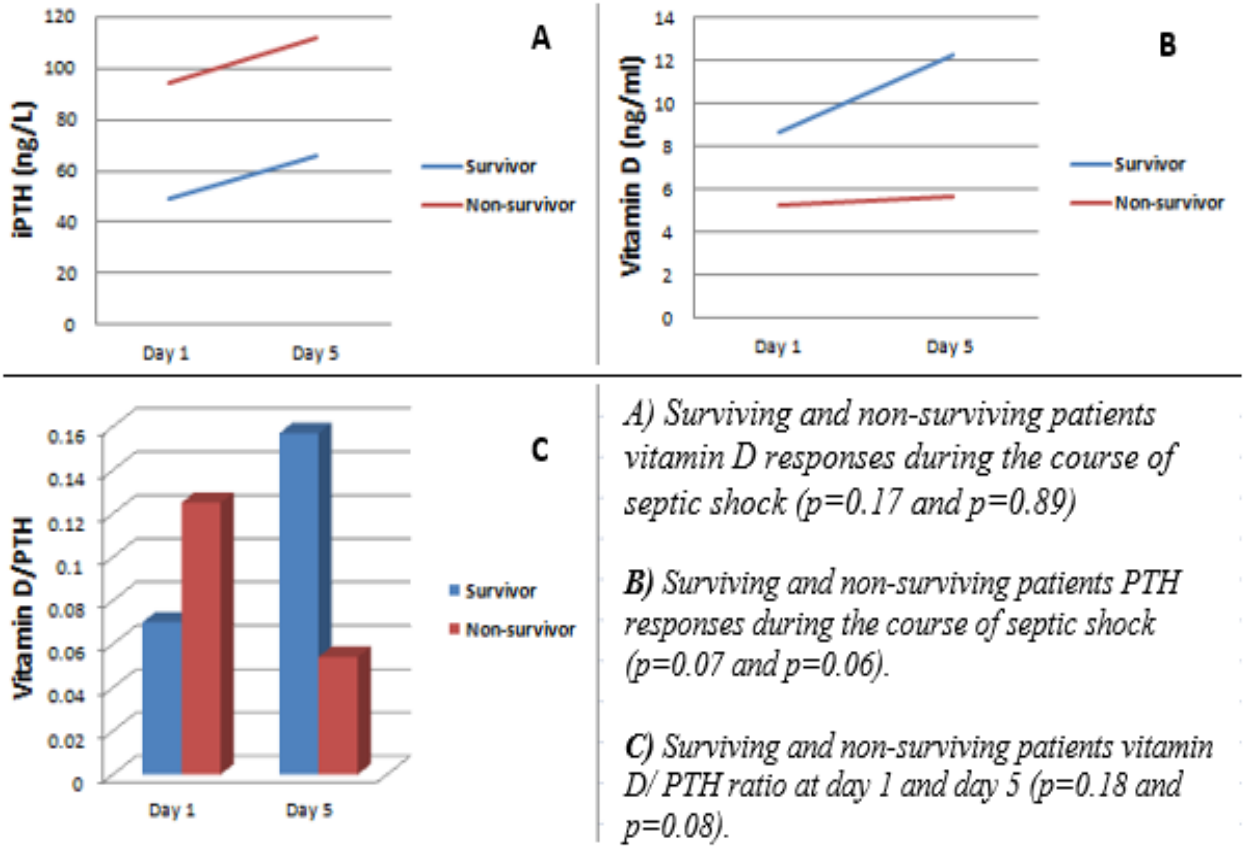

Figure 2. Vitamin D and PTH subgroup analysis.

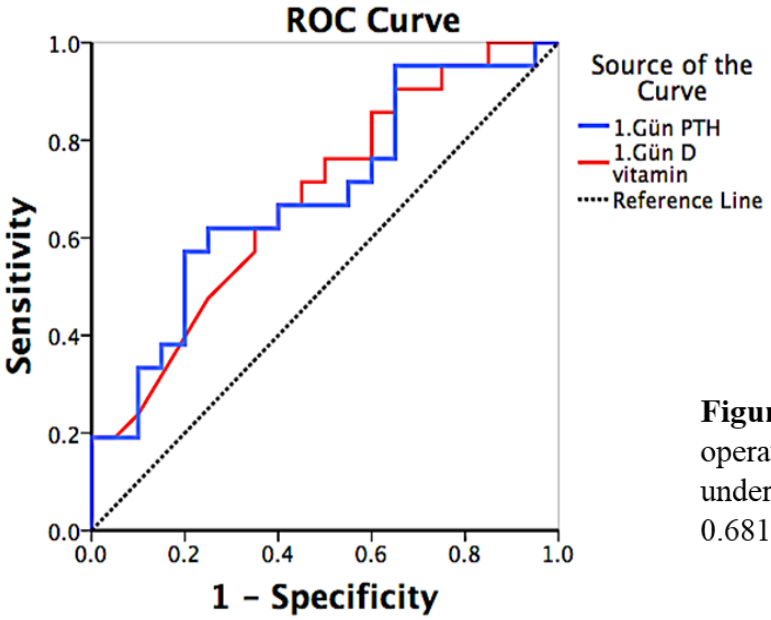

Figure 3. Day 1 vitamin D and PTH receiver operating curve: ROC revealing an area under the curve of 0.686 for PTH, 0.681 for vitamin D.

Parameters	P value	Cut-off value (ng/ml for Vitamin D; ng/L for PTH)	Sensitivity %	Specificity %	Youden index
Vitamin D	0.042	6.4	61.9	65	0.26
PTH	0.047	87	57.1	80	0.37

Table 4. Comparison of Vitamin D and PTH for cut-off value, sensitivity, specificity and Youden index.

Day 1 median PTH level of non-survivors was significantly higher than survivors. Day 5 median PTH elevated above the normal range at non survivors but it was not statistically significant.

Septic shock was diagnosed by using the 2012 surviving sepsis campaign guideline [2]. Although it was revised at 2015 [3], septic shock criterias did not change. Only septic shock patients were included in our study. As a result, this revision did not affect our assessment. Although fluid replacement treatment was significantly higher at survivors compared to non survivors at the first six hours of septic shock this difference was not statistically significant at the first day of septic shock. We used same septic shock treatment protocol to all patients and tried to keep central venous pressure (CVP) between 8-12 mm/hg as a recommendation of surviving sepsis campaign [2]. The present study showed a high incidence of total and ionized hypocalcemia in septic shock patients (29.2% and 68.2%) similarly to previous studies [16, 17]. Although we did not identify the association between hypocalcemia and mortality, this relation has been demonstrated in previous studies [16, 27, 28]. The cohort study at 2011 by Egi M. *et al.* demonstrated that lower than 0.8 mmol/l ionized calcium levels are independent risk factor for ICU mortality and stay of ICU length [29]. Our

study did not demonstrate this relation because it was not an intervention study so that calcium and albumin were replaced with the aim of keeping normal range during the hospital and ICU stay. Besides, small numbers of patients due to the exclusion of chronic kidney disease and malignancy may effect not to reach statistically significance.

It has been suggested that hypocalcemia in critically ill patients might be caused by the resistance to the action of PTH in the kidney and bone. There are many previous studies which are demonstrated elevation of PTH is associated with disease severity and mortality [23, 30-32]. Our results support previous studies. The median PTH concentration at day 1 was higher at non-survivors then survivors despite similar serum calcium levels and it was statistically significant. Although median PTH levels were higher at day five at non-survivors, it was not statistically significant. Despite raised PTH level was not statistically significant from day one to day five, survivor patients' median PTH levels elevated within normal range but non-survivor patients median PTH levels elevated above the normal range. Proposed mechanism of PTH elevation at non-survivors are cytokine dependent receptor resistance, hypocalcemia, low level of vitamin D levels at septic shock patients and end-organ in responsiveness [32-35]. İn addition to these mechanism, half-life of PTH at plasma is under 5 minutes and most of metabolites are removed by the kupffer cells and 20-30% of metabolites removed by renal tubules [36]. Multi organ failure during the course of septic shock may affect the PTH plasma levels.

Although PTH elevates in critically ill patients, hypocalcemia may be further deepens. It reminds other mechanisms than PTH have role at this pathology. In recent studies showed that vitamin D has an important role at innate and adaptive immunity, besides calcium metabolism [20, 21]. The results of our study showed that non-survivors had statistically significant low baseline vitamin D concentration than survivors. In our study, similar results were obtained with the prospective study of Lee P et al. [37], observational prospective study of Garcia-Soler P et al. [38] and meta-analysis of Zhang YP et al. [39]. In addition to these studies, we further evaluated the vitamin D status of patients during the course of septic shock. Although it was not statistically significant we showed that vitamin D levels were rised at survivors without any vitamin D supplementation. The fact that, statistical significance might not be achieved due to the small number of patients. Similar to our study, Alves FS et al. [24] reported that vitamin D level were rised at survivors during the course of septic shock in 51 ICU patients (26 of patients were septic shock and 25 of patients were without septic shock). But there were no data about mortality rates and subgroup analysis of survivors and non-survivors makes the study insufficient to determine to variation of vitamin D during the course of septic shock. In our study population vitamin D level of 6.8 ng/ml was the best cutoff for identification of septic shock patients at a higher risk of death. The relationship between mortality and serum vitamin D levels in critically ill patients is a topic of debate in the current literature [39-43]. Our study is in agreement with some of the retrospective and prospective studies in the literature. Moraes RB. et al. [42] suggested that vitamin D levels under 12 ng/ml remained an independent predictor of mortality at critically

ill patients in their cohort study. As Moraes RB. et al and our study, Venkatram S. et al. [44] suggested vitamin D levels under 10 ng/dl predicted hospital mortality in 83.6 % of their cohort.

Gruson D et al. suggested that 1,25 (OH)D and its ratio to PTH to be strongly and independently predict cardiovascular mortality in chronic heart failure [45]. On the basis of this study, we investigated the prognostic value of vitamin D/ PTH ratio at septic shock patients. We found neither day 1 nor day 5 vitamin D/ PTH value statistically significant. We might not achieve statistically significance because of low number of patients or not to use activated vitamin D as a parameter or dysregulation of inflammatory response including uncontrolled release of proinflammatory cytokines and tissue damage. Our study has several potential limitations. Firstly, we had low number of patients. But it was a single center study and on the contrary of other studies at the literature about this topic we excluded common diseases such as malignancies and chronic renal failure which effect calcium homeostasis. On the other hand, it was an advantage of our study about evaluation of vitamin D and PTH response during the course of septic shock. Secondly, we included only septic shock patients. This made difficult to evaluate the day 5 vitamin D and PTH status of patient because of high mortality rates. Although this limitations, this cross-sectional observational study is the largest study in the literature, which was evaluated vitamin D and PTH responses during the course of septic shock. Thirdly, the calcium replacement decision of the patients was left to the discretion of the clinician, for this reason we could not evaluate the association between hypocalcemia and mortality rate at septic shock patients. Finally, logistic regression analysis could not performed due to the low number of patients. A smaller sample size in the present study is not enough for the drawn conclusion.

Conclusion

Hypocalcemia is a common problem in septic shock patients. This could be associated with suppression of vitamin D as a result of cytokine storm during the course septic shock. PTH elevation at septic shock patients in contrast to physiological pathways could be a poor prognostic factor. At this point larger sample size and involvement of multicentric trials preferably involving wider spectrum of critically ill patients can probably widen our knowledge horizon regarding the crucial role of vitamin D and PTH.

Compliance with ethical standards

The authors declare that they have no conflicts of interest concerning for this article.

References

[1]Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis. 2015;15(5):581-14.

[2]Dellinger RP, Levy M, Rhodes A, Annane D, Gerlach H, Opal S, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. Intensive Care Med. 2013;39(2):165-28.

[3]Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801-10.

[4]Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the

United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546-54.

[5] Verstraete EH, De Coen K, Vogelaers D, Blot S. Risk factors for health care–associated sepsis in critically ill neonates stratified by birth weight. Pediatr Infect Dis J. 2015;34(11):1180-86.

[6] Linder A, Guh D, Boyd JH, Walley KR, Anis AH, Russell JA. Long-term (10-year) mortality of younger previously healthy patients with severe sepsis/septic shock is worse than that of patients with nonseptic critical illness and of the general population. Crit Care Med. 2014;42(10):2211-18.

[7] Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med. 2014;189(9):1075-81.

[8] Esper AM, Martin GS. Extending international sepsis epidemiology: the impact of organ dysfunction. Critical Care. 2009;13(1):120.

[9] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303-10.

[10] Klein GL, Castro SM, Garofalo RP. The calcium-sensing receptor as a mediator of inflammation. Semin Cell Dev Biol. 2016;49:52-6..

[11] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.

[12] Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117(4):503-11.

[13] Fallah-Rad N, Morton AR. Managing hypercalcaemia and hypocalcaemia in cancer patients. Curr Opin Support Palliat Care. 2013;7(3):265-71.

[14] Wheeler AL, Shoback DM. Clinical presentation of hypoparathyroidism. Hypoparathyroidism: Springer; 2015. p. 155-65.

[15] Kelly A, Levine MA. Hypocalcemia in the critically ill patient. J Intensive Care Med. 2013;28(3):166-77.

[16] Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: a pervasive metabolic abnormality in the critically ill. Am J Kidney Dis. 2001;37(4):689-98.

[17] Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. The Am J Med. 1988;84(2):209-14.

[18] Hästbacka J, Pettilä V. Prevalence and predictive value of ionized hypocalcemia among critically ill patients. Acta Anaesthesiol Scand. 2003;47(10):1264-69.

[19] Rodríguez-Ortiz ME, Canalejo A, Herencia C, Martínez-Moreno JM, Peralta-Ramírez A, Perez-Martinez P, Navarro-González JF, et al. Magnesium modulates parathyroid hormone secretion and upregulates parathyroid receptor expression at moderately low calcium concentration. Nephrol Dial Transplant. 2014 ;29(2):282-89.

[20] Fabri M, Stenger S, Shin D-M, Yuk J-M, Liu PT, Realegeno S, et al. Vitamin D is required for IFN-γ–mediated antimicrobial activity of human macrophages. Sci Trans Med. 2011;3(104):104ra102.

[21] Kankova M, Luini W, Pedrazzoni M, Riganti F, Sironi M, Bottazzi B, et al. Impairment of cytokine production in mice fed a vitamin D3-deficient diet. Immunology. 1991;73(4):466.

[22] Holick MF. Vitamin D deficiency. N Eng J Med. 2007;357(3):266-81.

[23] Carlstedt F, Lind L, Rastad J, Stjernström H, Wide L, Ljunghall S. Parathyroid hormone and ionized calcium levels are related to the severity of illness and survival in critically ill patients. Eur J Clin Invest. 1998;28(11):898-903.

[24] Alves FS, Freitas FGR, Bafi AT, Azevedo LCP, Machado FR. Serum concentrations of vitamin D and organ dysfunction in patients with severe sepsis and septic shock. Rev Bras Ter Intensiva. 2015;27(4):376-82.

[25] Zuppa AF, Nadkarni V, Davis L, Adamson PC, Helfaer MA, Elliott MR, et al. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. Crit Care Med. 2004;32(11):2318-22.

[26] Tsujimoto H, Ono S, Hiraki S, Majima T, Kawarabayashi N, Sugasawa H, et al. Hemoperfusion with polymyxin B-immobilized fibers reduced the number of CD16+ CD14+ monocytes in patients with septic shock. J Endotoxin Res. 2004;10(4):229-37.

[27] Saleh MT, Sherif LS, Mourice W, Fakhry D, El Khayat Z, Awadalla R. Assessment of serum calcium, calcitonin and parathormone levels in critically ill children. J Applied Sci Res. 2008;4(4):360-6.

[28] Iqbal M, Rehmani R, Hijazi M, Abdulaziz A, Kashif S. Hypocalcemia in a Saudi intensive care unit. Ann Thorac Med. 2008;3(2):57-9.

[29] Egi M, Kim I, Nichol A, Stachowski E, French CJ, Hart GK, et al. Ionized calcium concentration and outcome in critical illness. Crit Care Med. 2011;39(2):314-21.

[30] Burchard KW, Gann DS, Colliton J, Forster J. Ionized calcium, parathormone, and mortality in critically ill surgical patients. Ann Surg. 1990;212(4):543-49.

[31] Carlstedt F, Lind L, Wide L, Lindahl B, Hänni A, Rastad J, et al. Serum levels of parathyroid hormone are related to the mortality and severity of illness in patients in the emergency department. Eur J Clin Invest. 1997;27(12):977-81.

[32] Haghbin S, Serati Z, Sheibani N, Haghbin H, Karamifar H. Correlation of hypocalcemia with serum parathyroid hormone and calcitonin levels in pediatric intensive care unit. Indian J Pediatr. 2015;82(3):217-20.

[33] Lind L, Carlstedt F, Rastad J, Stiernström H, Stridsberg M, Ljunggren Ö, et al. Hypocalcemia and parathyroid hormone secretion in critically ill patients. Crit Care Med. 2000;28(1):93-9.

[34] Hendy GN, Canaff L. Calcium-sensing receptor, proinflammatory cytokines and calcium homeostasis. Semin Cell Dev Biol. 2016;49:37-43.

[35] Muller B, Becker K, Kranzlin M, Schachinger H, Huber P, Nylen E, et al. Disordered calcium homeostasis of sepsis: association with calcitonin precursors. Eur J Clin Invest. 2000;30(9):823-31.

[36] Tekce BK. The factors affectiing parathyroid hormone measurement resullts in chronic kidney disease. Medical Journal of Kocaeli. 2015; 4(1): 5-12.

[37] Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Eng J Med. 2009;360(18):1912-14.

[38] García-Soler P, Morales-Martínez A, Rosa-Camacho V, Lillo-Muñoz JA, Milano-Manso G. Vitamin D deficiency and morbimortality in critically ill paediatric patients]. An Pediatr (Barc). 2017;87(2):95-103.

[39] Zhang YP, Wan YD, Sun TW, Kan QC, Wang LX. Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies. Crit Care. 2014;18(6):684.

[40] Ala-Kokko TI, Mutt SJ, Nisula S, Koskenkari J, Liisanantti J, Ohtonen P, et al. Vitamin D deficiency at admission is not associated with 90-day mortality in patients with severe sepsis or septic shock: Observational FINNAKI cohort study. Ann Med. 2016;48(1-2):67-75.

[41] Upala S, Sanguankeo A, Permpalung N. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. BMC Anesthesiol. 2015;15:84.

[42] Moraes RB, Friedman G, Wawrzeniak IC, Marques LS, Nagel FM, Lisboa TC, et al. Vitamin D deficiency is independently associated with mortality among critically ill patients. Clinics. 2015;70(5):326-32.

[43] Lee P, Nair P, Eisman JA, Center JR. Vitamin D deficiency in the intensive care unit: an invisible accomplice to morbidity and mortality? Intensive Care Med. 2009;35(12):2028-32.

[44] Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G. Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crit Care. 2011;15(6):R292.

[45] Gruson D, Ferracin B, Ahn SA, Zierold C, Blocki F, Hawkins DM, et al. 1, 25-Dihydroxyvitamin D to PTH (1–84) ratios strongly predict cardiovascular death in heart failure. PloS one. 2015;10(8):e0135427.