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Original Article / Özgün Araştırma

Serum Vitamin D Level at ICU Admission and Mortality

Yoğun Bakım Girişinde Serum D Vitamini Düzeyi ve Mortalite

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Abstract / Öz

Objective: Vitamin D is a fat-soluble vitamin that plays a major role in the regulation of bone and calcium metabolism and has effects on the immune and cardiovascular systems. Vitamin D deficiency is commonly seen in the general population as well as in critically ill patients and is reported to be associated with increased mortality and morbidity. Our aim was to determine the relationship between vitamin D level at ICU admission and mortality.

Methods: A total of 491 patients admitted to the ICU between January 2014 and January 2015 were evaluated retrospectively. The patients who were under 18 years old, had elective surgery, or whose serum vitamin D levels and outcomes were unknown were excluded. The patient's age, gender, APACHE II score, number of organ dysfunction, serum vitamin D level at ICU admission and outcomes were recorded.

Results: Vitamin D level was low (<25 ng dL^{-1}) in 166 (77.1%) of the patients. In non-survivor patients, APACHE II score and the number of organ dysfunction were significantly higher than the survivor patients (p<0.001 and p<0.001). There was a negative correlation between vitamin D level and APACHE II score (r^2=0.04, p=0.006). In multivariate analyses, the likelihood of mortality was increased 9.8-fold (range 4.2–17.6) and 8.9-fold (range 3.9–14.1) with an APACHE II score ≥24 and the number of organ dysfunction ≥2, respectively (p<0.001 and p<0.001).

Conclusion: Vitamin D deficiency is commonly seen in intensive care patients. Although it is not an independently decisive factor for mortality, it might be related with poor clinical status at ICU admission. The APACHE II score and number of organ dysfunction are still important parameters for increased mortality.

Keywords: Vitamin D, APACHE II score, number of organ dysfunction, mortality

Amaç: Yağda çözünen bir vitamin olan D vitamini kemik ve kalsiyum metabolizmasının düzenlenmesinde majör bir rol oynar ve immün ve kardiovasküler sistem üzerinde etkilere sahiptir. D vitamini eksikliği genel populasyonun yanı sıra kritik hastalarda da sık görülür ve morbidite ve mortaliteyi arttırdığı bildirilmiştir. Bizim amacımız yoğun bakım girişindeki D vitamini düzeyi ile mortalite ilişkisini araştırmaktı.

Yöntemler: Ocak 2014 ile Ocak 2015 arasında yoğun bakıma alınmış toplam 491 hasta retrospektif olarak değerlendirildi. 18 yaşın altında, elektif cerrahi hastaları ve serum D vitamini düzeyleri ve hastane çıkış statüleri bilinmeyen hastalar çalışma dışı bırakıldı. Hastaların yaş, cinsiyet, APACHE II skoru, yetersiz organ sayısı, yoğun bakım girişindeki D vitamini düzeyi ve mortalite kaydedildi.

Bulgular: 166 (%77,1) hastanın yoğun bakım girişindeki serum D vitamini düzeyi düşüktü (<25 ng dL^{-1}). Ölen hastalarda APACHE II skoru ve yetersiz organ sayısı yaşayan hastalardan anlamlı yüksekti (p<0,001; p<0,001). Yoğun bakım girişindeki D vitamin düzeyi ile APACHE II skoru arasında negatif korelasyon tespit edildi (r^2=0,04 p=0,006). Multivariate analizde, APACHE II skorunun 24'e eşit ve üstünde olması ve organ yetersizliği sayısının 2'ye eşit ve üstünde olması mortalite ihtimalini sırasıyla 9,8 kat (4,2-17,6) ve 8,9 kat (3,9-14,1) arttırmaktaydı (p<0,001 p<0,001).

Sonuç: D vitamin eksikliği yoğun bakım hastalarında sıklıkla görülmektedir. D vitamini düzeyi mortalite için bağımsız belirleyici bir faktör olmamasına rağmen yoğun bakım girişindeki kötü klinik durum ile ilişkili olabilir. APACHE II skoru ve organ yetersizliği ise artmış mortalite için hala önemli parametrelerdir.

Anahtar Sözcükler: D vitamini, APACHE II skoru, yetersiz organ sayısı, mortalite

Introduction

Vitamin D is a fat-soluble vitamin consisting of two bio-equivalent forms, vitamin D_2 and Vitamin D_3. Vitamin D_2 is obtained from vegetables and oral supplements. Vitamin D_3 is obtained primarily through skin exposure to ultraviolet B radiation from sunlight, oily fishes and oral supplements. They are metabolised into 25(OH) vitamin D (calcidiol) in the liver and subsequently to 1,25(OH) vitamin D (calcitriol) in the kidneys. Calcitriol activates the vitamin D receptors in the cells, and this triggers the endocrine and autocrine effects of vitamin D. Vitamin D plays a major role in calcium homeostasis and bone metabolism, as well as in the immunoregulatory system (1). Vitamin D deficiency is defined as serum calcidiol levels below 25 ng mL^{-1}, and the incidence in intensive care patients varies between 17% and 82% (1-3). Reduced formation of calcitriol in the tissues might lead to impaired immune responses, mucosal barriers and endothelial

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functions (4-6). It is known that vitamin D deficiency is associated with diabetes mellitus, chronic obstructive pulmonary diseases and autoimmune diseases (7, 8). Moreover, it is known to be related with disease severity, increased systemic inflammatory markers, increased infection and mortality (9-11). The aim of this study was to investigate the relationship between vitamin D level at ICU admission and mortality.

Methods

Study design

A total of 491 patients admitted to the ICU of Atasehir Memorial Hospital between January 2014 and January 2015 were evaluated retrospectively. The study protocol was approved by the Acibadem University Ethics Committee. Informed consent was not required because of the retrospective nature of the study. The patients who were under 18 years old, readmitted, had elective surgery, or had undocumented serum vitamin D levels and outcomes were excluded from the study (Figure 1). Vitamin D level <25 ng mL^{-1} was accepted as vitamin D deficiency. The patient's age, gender, APACHE II score, logistic organ dysfunction system (LODS) score, serum vitamin D (ng mL^{-1}) and calcium levels (mg dL^{-1}), length of ICU stay and mortality were recorded. The number of organ dysfunction was defined as each organ that was given a point in accordance with the LODS score.

Vitamin D measurement

In our clinic, calcidiol is measured with the COBAS 6000 Entegre device using the ECLIA (electrochemiluminescent immunoassay) method. The normal serum vitamin D level is between 25 and 80 ng mL^{-1} in accordance with Mayo Medical Laboratories (Table 1).

Statistical analysis

The statistical analysis was performed using Wizard Pro Version 1.7.20. All variables in the database were summarised using descriptive statistics. Categorical data were described as number (percentage) and analysed with the chi-square test. Survivor and non-survivor groups were compared with the Mann-Whitney U test. Results were given as the percentage and median (interquartile). Pearson's correlation test was used for correlation between parameters and was given as the r^2 value. Multivariate logistic regression analysis included age, diagnosis (sepsis), number of organ dysfunction, APACHE II score and vitamin D level at ICU admission. The type 1 error level was set as 0.05.

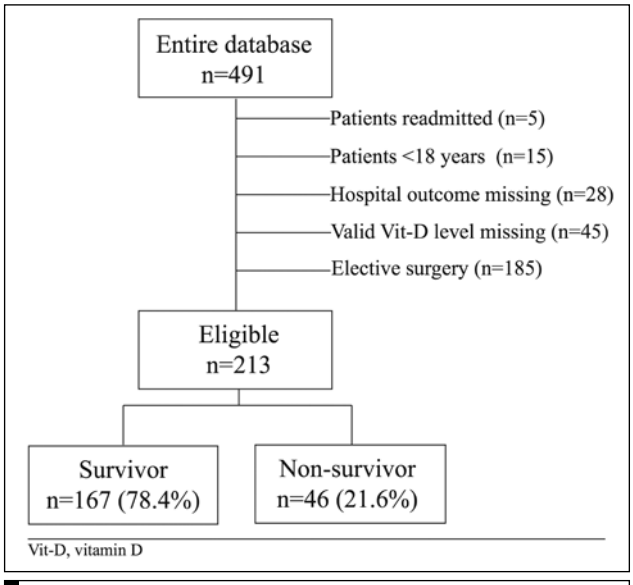

Figure 1. Study flowchart

Results

Vitamin D level at ICU admission was low in 166 (77.9%) patients. The mortality rate was 21.6% (Figure 1). While age, gender, diagnosis (septic patients), vitamin D level at ICU admission and length of ICU stay were similar in both groups, the APACHE II score and the number of organ dysfunction were significantly higher in non-survivor patients (p<0.001 for both) (Table 2). There was a poor negative correlation between vitamin D level at ICU admission and APACHE II score (r^2=0.05 p=0.006) (Figure 2). The mortality rate was similar between patients with normal (47 patients) and low (166 patients) vitamin D levels at the ICU admission (p=0.388). Also, there was no significant difference between mortality rates of septic patients with normal (19 patients) and low (74 patients) vitamin D levels (p=0.071). In the multivariate logistic regression model, the likelihood of mortality was increased 9.8-fold (range 4.2–17.6) and 8.9-fold (range 3.9–14.1) for an APACHE II score ≥24 and for the number

Table 1. Serum vitamin D levels

Severe deficiency	<10 ng mL^{-1}
Mild to moderate deficiency	10–24 ng mL^{-1}
Optimal	25–80 ng mL^{-1}
Possible toxicity	>80 ng mL^{-1}

Table 2. Comparisons of survivor and non-survivor patients

	Survivors (n=167)	Non-survivors (n=46)	p
Age, (years)	63 (53–71)	62.5 (53–71)	0.915
Male, n (%)	109 (67.4)	31 (65.3)	0.788
APACHE II	19 (16–22)	28 (25–29)	<0.001
Number of organ dysfunction	1 (0–2)	2 (2–3)	<0.001
Sepsis, n (%)	68 (40.7)	21 (54.3)	0.099
Vitamin D level at ICU admission (ng mL^{-1})	8.2 (3.0–18.8)	7.5 (3.0–16.4)	0.229
Length of ICU stay (days)	12 (8–17)	15 (4–18)	0.712

Results are given as median (interquartile range). P<0.05 is accepted as statistically significant. APACHE II: Acute Physiology and Chronic Health Evaluation.

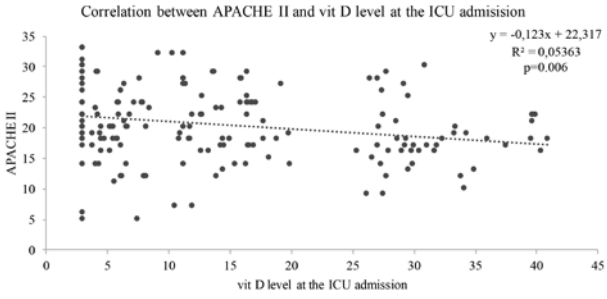

Figure 2. Correlation between vitamin D level and APACHE II score

Table 3. Multivariate logistic regression model for mortality

	OR (95% CI)	p
Vitamin D level at ICU admission <8 ng dL^{-1}	0.5 (0.2–1.4)	0.206
Age ≥63	0.6 (0.2–1.6)	0.277
Sepsis	1.1 (0.4–3.2)	0.819
APACHE II ≥24	9.8 (4.2–17.6)	<0.001
Number of organ dysfunction ≥2	8.9 (3.9–14.1)	<0.001

95% CI. OR: odds ratio; CI: confidence interval

of organ dysfunction ≥2, respectively (p<0.001 for both) (Table 3).

Discussion

The present study showed that vitamin D deficiency was commonly observed in critically ill patients at ICU admission. Moreover, serum vitamin D level was poorly and negatively correlated with APACHE II score. However, mortality was associated only with APACHE II score and number of organ dysfunction.

It has been argued that vitamin D has antimicrobial and immunomodulatory effects (1, 12, 13). Recent studies have reported the incidence of vitamin D deficiency in intensive care patients to be 17%–82% (2, 3). This is quite a wide range, and in this study we observed vitamin D deficiency in 77.9% of all patients. According to this result, most of the critically ill patients might be at risk of immune dysregulation because of vitamin D deficiency. Therefore, we strongly believe that it is important to measure and analyse the serum vitamin D level in critically ill patients at the time of ICU admission.

Several studies report that vitamin D deficiency in critically ill patients is associated with infection, the development of sepsis and acute respiratory distress syndrome (ARDS) and increased mortality rates (9, 11, 14-20). Moromizato et al. (21) found that serum vitamin D level below 16 ng mL^{-1} is associated with sepsis. Van de Berghe et al. (22) showed significantly lower serum vitamin D levels in non-survivor critically ill patients. In a CopD study, a range of 20–24 ng mL^{-1} was found to be related to decreased mortality (23). In contrast to the above studies, Cecchi et al. (24) concluded that serum vitamin D levels do not have any significant effects on the outcome in septic patients. In the present study, the median vitamin D levels in septic and non-septic patients were 7.9 ng mL^{-1} and 8.2 ng mL^{-1}, respectively. Furthermore, we did not find any relationship between vitamin D level at ICU admission and outcomes. However, we knew that all patients with low vitamin D level had received vitamin D as a single loading dose of 600,000 IU in this study. It has been demonstrated that vitamin D deficiency can be corrected with the same dose of enteral vitamin D replacement in critically ill patients (25, 26). In our study, patients with vitamin D level <25 ng mL^{-1} at ICU admission had a median vitamin D level after vitamin D replacement of 31.6 ng mL^{-1}. Therefore, we believe that a single high dose of enteral vitamin D replacement is sufficient to correct vitamin D deficiency. In support of this, many studies report that vitamin D supplementation in critically ill patients is associated with decreased mortality (27, 28). Conversely, in the VITdAL-ICU study, administration of high dose vitamin D compared with placebo did not reduce hospital length of stay, hospital mortality, or 6-month mortality (29). We found that the median APACHE II score and number of organ dysfunction were 28 and 2, respectively, in 38 non-survivor patients with low vitamin D level even though vitamin D had been administered to them, and they were 27.5 and 3 in 8 non-survivor patients with normal vitamin D level. As a result of this work, we can only conclude that increased mortality is related to increased APACHE II score and increased number of organ dysfunction. The low serum vitamin D levels might only be related to increased APACHE II score, and they might be solely responsible from the worse clinical status at ICU admission. Thus, if there is low vitamin D level in patients with high APACHE II score at ICU admission, it is recommended to treat the vitamin D deficiency.

Conclusion

Vitamin D deficiency is commonly seen in intensive care patients. Although it is not an independently decisive factor for mortality, it might be related to worse clinical status at ICU admission. The effect of vitamin D replacement on mortality is controversial, but the APACHE II score and number of organ dysfunction are still important parameters for increased mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Acıbadem University School of Medicine.

Informed Consent: Informed consent was not required because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.K.A.; Design – H.K.A., B.G.; Supervision – B.G.; Resources – H.K.A.; Materials – H.K.A.; Data Collection and/or Processing – H.K.A.; Analysis and/or Interpretation – B.G.; Literature Search – H.K.A., B.G.; Writing Manuscript – H.K.A., B.G.; Critical Review – H.K.A., B.G.; Other – H.K.A., B.G.

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