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Relationship between vitamin D levels and mortality rates of critically ill patients in intensive care unit

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ABSTRACT

Introduction: Vitamin D has a pivotal role in bone metabolism. It regulates immunity and inflammation. In this current research, it was aimed to determine whether there is an association between the mortality rate and the vitamin D level of critically ill patients who were followed in intensive care unit (ICU).

Material and Method: Fifty two patients (30 (58%) female and 22 (42%) male) admitted to ICU with the diagnosis of respiratory failure, sepsis, acute renal failure, multiple organ failure, GIS bleeding were included in the study. During the admission to the ICU, all of the patients' complete blood count, C-reactive protein, serum calcium, albumin, urea, creatinine, 25-OH vitamin D, potassium, and arterial/venous blood gas levels were measured. Their acceptable mortality risk was calculated according to the APACHE II scoring system.

Results: The level of vitamin D was found at least 1 up to 78.6 range, and the average was 19.61 ng/dl. Eighteen (35%) patients were discharged and 34 (65%) of the ICU patients were died. Vitamin D deficiency was observed to be a very common issue in our critically ill patients (65.4%). The difference between the two groups of age, accepted mortality and urea levels were found to be statistically significant ($p<0.05$). According to the terms of the patient's vitamin D status, differences were not significant ($p=0.269$). Vitamin D deficiency in the multivariate analysis was not an independent risk factor for mortality.

Discussion: Vitamin D deficiency occurs quite often in patients with chronic, severe disease. These patients are admitted to the ICU with more serious acute problems. They have high Apache II scores as well as poor prognosis and high mortality rates during ICU. Our results suggest that although vitamin D deficiency is not a real risk factor, it is a supporting factor in explaining increased mortality rates.

Keywords: Vitamin D deficiency, critically ill, intensive care unit

INTRODUCTION

Critical illnesses are important public health problems due to high mortality rates, the growing use of the intensive care units (ICU), and high health expenditures. The patients admitted to ICU have low quality of life and high mortality risk. The nutritional needs of critical patients are not fully understood and differ in each stage of the disease. The primary goal of nutritional support is to change the course and consequence of the critical illness, even though the results have not been obtained adequately by randomized trials (1-3).

Vitamin D is a member of vitamins that melt in the oil. It is a sterol with hormone and hormone precursors which can be synthesized endogenously in suitable biological medium. Many foods naturally contain vitamin D, but it is mainly synthesized through the skin. If vitamin D level is below 20 ng/ml, it is called vitamin D deficiency. On the other hand, the level above 150 ng/ml is defined as intoxication (4). The most important effects of vitamin D are related with calcium and phosphorus metabolism, and bone mineralization. Recently, it has been shown that deficiency of vitamin D affects many kinds of cancers, cardiovascular diseases, metabolic diseases, infectious and autoimmune diseases in a negative way (3-5). However, the relationship between deficiency of vitamin D and risk of mortality in critical illnesses is unclear.

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In this study, it was aimed to determine whether there is a relationship between the mortality rate and the vitamin D level of critically ill patients in ICU.

MATERIAL AND METHOD

Fifty two patients admitted to GATA Haydarpaşa Training Hospital Internal Diseases ICU with the diagnosis of respiratory failure, sepsis, acute renal failure, multiple organ failure, GIS bleeding were included in the study. The study was completed between October 2015 and May 2016. The written consents of the patients were obtained after informing them about the study. Ethics committee approval for the study was received from GATA Haydarpaşa Training Hospital Ethics Committee meeting held on 05.11.2015 (2015/41). The trial was conducted in accordance with the Helsinki Declaration principles.

Cases that received vitamin D vitamin replacement in the last year and patients with primary bone metabolism disorders were not included in the study. During the admission to the ICU, all of the patients' complete blood count (CBC), C-reactive protein (CRP), serum calcium, albumin, urea, creatinine, 25-OH vitamin D, potassium, and arterial/ venous blood gas levels were measured and recorded. Quantitative determination of serum 25-OH vitamin D level was performed with chemiluminescent microparticle immunoassay (CMIA) method by using 3L52 artcihet reagent 25-OH vitamin D reagent kit. Also, acceptable mortality risk was calculated according to the APACHE II scoring system, which is one of the common intensive care predictive scoring systems, by detecting patients' vital signs, disease history, and Glasgow coma scores (4).

Statistical Analysis

The study was done using the SPSS version 15.0 program. Continuous variables, arithmetic mean±standard deviation; categorical variables were expressed as number and %. The distribution of continuous variables was examined by Kolmogorov-Simirnov test. While the comparison of normal distributed parameters according to D-vitamin groups was performed with the T-group comparison test, non-normal distributed parameters were compared with Mann Whitney U test. Pearson's correlation coefficient test as used to analyze correlations between variables.

RESULTS

The age distribution of the patients was found between 49 and 93 years with a mean and standard deviation as 77.94±10.2 years. Of the 52 participants included in the study, 30 (58%) were female and 22 (42%) were male. The Apache Score of the patients was found between 5 and 35 values with a mean and standard deviation as 17.73±6.09. The distribution of mortality risk of the patients according to Apache ll Score was found between 5.8 and 83 values with a mean and standard deviation as 30.63±16.47. The vitamin D distribution of the patients was found between 1 and 78.6 values with a mean and standard deviation as 19.61±15.89. The frequency of vitamin D deficiency in ICU was found 65.4%. lt was observed that this rate increased up to 84% when the vitamin D values between 20-30 ng/dl were also defined as vitamin D deficiency. This rate was 70% in females and 68% in males respectively.

The duration of hospitalization was found in the range of at least 2 and at most 57 days. Of the 52 participants who were included in the study 18 (35%) were discharged and 34 (65%) died. The distribution of biochemical and important disease variables according to hospital status (exitus/discharge) of 52 participants were examined. There were statistically significant difference between exitus and discharge groups according to age, Apache II score, mortality risk and urea values ($p<0.05$). The distribution of age of the patients in exitus and discharged groups was found to be 80.44±8.88 and 73.22±11.09 respectively. It was statistically significant that the patients in exitus group had older ages ($p=0.014$). The distribution of mortality risk according to the Apache II score was found to be 35.42±16.08 and 21.57±13.39 for the patients in exitus group and discharge group respectively. It was statistically significant that the exitus group had the higher distribution of mortality risk according to Apache II score ($p=0.004$). The distribution of urea was found to be 120.59±66.03 and 78.61±45.49 for patients in exitus and discharge group respectively. It was statistically significant that the urea distribution was higher in exitus group ($p=0.024$). There was no significant difference between exitus and discharge groups in terms of vitamin D distribution ($p=0.269$) (**Table 1**).

Table 1. Exitus/discharge distribution of the patients

	Exitus	Discharge	P value
Age (year)	80.44±8.88	73.22±11.09	0.014**
Apache score	19.74±5.25	13.94±5.88	0.003
Mortality risk according to Apache II score	35.42±16.08	21.57±13.39	0.004**
Vitamin D (mg/dl)	17.28±12.44	24±20.63	0.269
Calcium (mg/dl)	10.02±12.39	7.91±0.96	0.736
Albumin (mg/dl)	2.96±0.59	3.06±0.73	0.736
Urea (mg/dl)	120.59±66.03	78.61±45.49	0.024**
Creatinine (U/L)	2.35±1.49	1.79±1.18	0.229
CRP (mg/L)	112.12±103.76	136.78±140.33	0.788
Hemoglobin (g/dl)	10.63±2.09	10.65±2	0.847
Leukocyte ($\times10^3$/u)	15.24±6.95	12.73±4.24	0.308
Thrombocyte ($\times10^3$/u)	224.21±117.57	238.61±129.84	0.832
Duration of stay (day)	37.88±79.94	13.22±9.93	0.098

*:Mann Whitney U test; **: Statistically significant.

When 52 participants were considered in terms of Apache II score, statistically significant positive correlation was found between the mortality risk and Apache score (r= 0.98, p=0.0001), between urea and Apache score (r=0.613; p=0.0001) and between creatinine and Apache score (r=0.567; p=0.0001); but a negative correlation was found between albumin and Apache score (r=-292; p=0.036). There was a statistically significant positive correlation between vitamin D and platelet count (r=0.304; p=0.028), between hemoglobin and albumin (r=0.613; p=0.001), between urea and creatinine (r=0.739; p=0.0001) and between leucocyte count and platelet count (r=0.319; p=0.021). However there was a significant negative correlation between CRP and albumin (r=-275; p=0.049 (**Table 2**).

The effects of all variables that may affect the discharge status of patients were analysed by logistic regression analysis. The Bacwald (Wald) method was used to select the best model equation. In the last 10th step, the best model equation was attained. According to the statistical analysis of the last equation; the result of the model equation in step 10 is statistically significant (Hosmerand Lemeshow Test p=0.207). This model represented the recovery as 88.5%. According to this model, Apache score and Vitamin D level are statistically significant risk factors. Although CRP and duration of hospitalization are not statistically significant but they need to be regarded as important risk factors (**Table 3**).

According to the hospital status of 52 participants (exitus/discharge), the accepted mortality value affects the average duration of stay in hospital 1.026 times as statistically significant. The effects of all variables of this thesis study that may affect the duration of stay in hospital according to the hospitalization time were analyzed by Cox regression analysis. The Backward (Wald) method was used to select the best model equation. In the last 11th step, the best model equation was attained. Apache Score and calcium level are statistically significant factors according to the statistical analysis of the last equation; (**Table 4**).

Table 3. Regression analysis of C-reactive protein, duration of hospital stay, Apache II score and vitamin D levels

	B	S.E.	Wald	Sig.	Exp(B)	95% CI for Exp (B)	
						Lower	Upper
Apache score	-.275	.092	8.895	.003	.760	.634	.910
Vitamin D	.064	.026	5.941	.015	1.066	1.013	1.123
CRP	.007	.004	3.417	.065	1.007	1.000	1.015
Duration of hospital stay	-.065	.035	3.409	.065	.937	.875	1.004

Table 2. Pearson correlation analysis table

		Day of stay	Apache score	Acceptance mortality	Vitamin D	Calcium	Albumin	Urea	Creatinine	Crp	Hemoglobin	Leucocyte	Trombocyte
Day of stay	r*	1	.022	-.005	-.064	-.037	-.071	-.018	-.142	.049	-.010	.176	.237
	p		.875	.973	.653	.792	.617	.899	.317	.728	.942	.213	.090
Apache score	r*	.022	1	.979**	.086	-.050	-.292**	.613**	.567**	.108	-.209	.148	-.108
	p	.875		.000	.546	.726	.036	.000	.000	.447	.137	.295	.447
Acceptance mortality	r*	-.005	.979**	1	.073	-.099	-.263	.646**	.581**	.138	-.223	.137	-.117
	p	.973	.000		.609	.486	.060	.000	.000	.329	.112	.332	.410
Vitamin D	r*	-.064	.086	.073	1	-.017	.039	-.014	.039	-.161	-.162	.130	.304**
	p	.653	.546	.609		.906	.782	.919	.784	.255	.252	.359	.028
Calcium	r*	-.037	-.050	-.099	-.017	1	-.130	-.149	-.138	-.043	.057	.054	-.173
	p	.792	.726	.486	.906		.359	.292	.330	.761	.690	.704	.219
Albumin	r*	-.071	-.292*	-.263	.039	-.130	1	-.262	-.259	-.275**	.448**	-.155	-.044
	p	,617	,036	,060	,782	,359		,061	.063	.049	.001	.272	.758
Urea	r*	-.018	.613**	.646**	-.014	-.149	-.262	1	.739**	.242	-.139	.133	-.199
	p	.899	.000	.000	.919	.292	.061		.000	.084	.327	.346	.158
Creatinine	r*	-.142	.567**	.581**	.039	-.138	-.259	.739**	1	.177	-.192	.072	-.094
	p	.317	.000	.000	.784	.330	.063	.000		.209	.173	.610	.506
Crp	r*	.049	.108	.138	-.161	-.043	-.275**	.242	.177	1	-.060	.098	-.070
	p	.728	.447	.329	.255	.761	.049	.084	.209		.672	.491	.624
Hemoglobin	r*	-.010	-.209	-.223	-.162	.057	.448**	-.139	-.192	-.060	1	-.185	-.043
	p	.942	.137	.112	.252	.690	.001	.327	.173	.672		.190	.760
Leucocyte	r*	.176	.148	.137	.130	.054	-.155	.133	.072	.098	-.185	1	,319*
	p	.213	.295	.332	.359	.704	.272	.346	.610	.491	.190		.021
Trombocyte	r*	.237	-.108	-.117	.304**	-.173	-.044	-.199	-.094	-.070	-.043	.319*	1
	p	.090	.447	.410	.028	.219	.758	.158	.506	.624	.760	.021	

**: Statistically significant.

Table 4. Regression Analysis of Apache II score and calcium values

	B	SE	Wald	Sıg.	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Apache score	.087	.039	5.018	.025	1.091	1.011	1.177
Calcium	.034	.016	4.369	.037	1.034	1.002	1.067

DISCUSSION

Vitamin D deficiency has been charged with many kind of disorders such as infections, cardiac problems, autoimmune diseases, various pulmonary diseases and tuberculosis (5,6). Also vitamin D deficiency may cause negative consequences like increased infection rates, prolonged hospitalization in intensive care units, increased hospital mortality and increased health care expenses. Many recent papers showed a close association between vitamin D deficiency and some systemic diseases that have significant morbidity and mortality rates (5,6). However, Ralph et al. found no relationship between vitamin D and mortality risk in critically ill patients as in our study (7). For this reason, currently the consequences of vitamin D deficiency on mortality and morbidity in critically ill patients is still unclear.

In this current study, vitamin D deficiency was found as 70% in females and 68% in males. This high rate primarily may be related to the high age distribution of patients. The average age was 77.9 (min 49 and max 93). Another reason may be the study time that included the interval between September and May. One of the important factors for the synthesis of vitamin D3 in the skin is the zenith angle of the sunlight (8). The increase in this angle causes UVB photons to travel longer (more oblique). In this study, we used <20 ng/dL 25-OH D level as a threshold value to define vitamin D deficiency. And by using this threshold value vitamin D deficiency of patients in ICU was found with a frequency of 65.4%. It was seen that this ratio increased up to 84% when the vitamin D values between 20 to 30 ng/dl were accepted as inadequate. The vitamin D levels of the patients included in our study were examined in detail. It was seen that the lowest level was 1 ng/ml, the highest level was 78.6 ng/ml and the mean serum level was 19.6 ng/ml. Also, the mean serum vitamin D level was found as 17.28 ng/mL in patients resulted in death and 24.20 ng/mL in discharged patients respectively, but no statistically significant difference was found.

Most of the published studies have reported that vitamin D deficiency has a higher prevalence in women and in the elderly in the general population (8). Similarly, in our study, the mean age was 77.9 years and female gender was more dominant in the patient sampling used. The vitamin D replacement therapy was not routinely included in the intensive care treatment protocol. That is why in this study no vitamin D measurements were routinely performed and the decrease in vitamin D levels of patients in ICU was not showed in a comprehensive manner.

Standard vitamin D supplements included in nutritional support may be inadequate for the patients in ICU. Various studies prove that daily enteral and parenteral nutritional support is still insufficient. High doses of vitamin D supplements may be more effective in ICU patients. A number of recent studies in ICU have shown that high doses of vitamin D can be given to critical patients within a short time (few days) without complications (9). The replacement of vitamin D was not included in our treatment protocol, that's why the benefit of high doses of vitamin D supplements in critically ill patients could not be evaluated. More studies are needed to determine the effectiveness of vitamin D supplements in critically ill patients (9).

Vitamin D deficiency may increase hospital mortality rates in critically ill adult patients. Although the factors that cause this situation are still unclear today, various mechanisms are speculated. For example, many kind of biological responses involving the immune system, cell growth and proliferation can be affected by vitamin D (10,11). On the other hand, vitamin D affects the production of antimicrobial proteins such as cathelicidin (IL-37) and β-defensin which have important roles in the immune system (12-15). The close association between vitamin D deficiency and human infections has been exhibited in some previous papers (16,17). Liu et al. have showed the dose dependent katelicidin production in response to 1-25-dihydroxyvitamin D (18). Moreover, it is suggested that vitamin D is related with Toll-like receptor (TLR) activation (18-20). Therefore, vitamin D deficiency may suppress the body immunity and may expand the risk of sepsis in ICU patients (21,22).

Also, vitamin D provides the up-regulation of anti-inflammatory cytokines such as IL-4, IL-5 and IL-10 (23). For this reason, vitamin D deficiency may increase mortality by suppressing immunity in ICU patients. In addition, in critically ill patients the tissues may require more vitamin D and vitamin D deficiency may cause widespread tissue dysfunction (22,23). These effects may explain why systemic inflammatory response syndrome, organ failure and mortality rates due to metabolic dysfunction increase in critically ill patients. In our current study, there was a correlation between mortality and vitamin D deficiency in univariate analysis. However, vitamin D deficiency was not found as a solely mortality risk factor in multivariate analysis. Our results suggest that vitamin D deficiency is a consequence of chronic, severe diseases or comorbid conditions of the patients. Our results suggest that although vitamin D deficiency is not a real risk factor, it is a helpful factor in explaining increased mortality rates.

Our research has some potential limitations. First, it was originally designed as a single-center study with a relatively small sample size. Thus, the results of our research cannot be generalized. The 25 (OH) D levels obtained in patient admission are probably a reflection of preliminary insufficiency. No samples were taken for 25 (OH) D levels during clinical follow-up. Therefore, replacement was not made by following vitamin D levels during stay in ICU.

CONCLUSION

Consequences of vitamin D deficiency on mortality and morbidity in ICU patients, is still remains unclear. Our current study was carried out in an internal medicine ICU. Thus, there is a need for studies including cardiac, anesthesia, surgery and other ICUs in terms of the relationship between vitamin D levels and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of GATA Haydarpaşa Training Hospital Ethics Committee (meeting held on 05.11.2015, decision number: 2015/41)

Informed Consent: Written informed consent was obtained from all participants or their relatives who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Moniz P, Coelho L, Póvoa P. Antimicrobial stewardship in the intensive care unit: the role of biomarkers, pharmacokinetics, and pharmacodynamics. Adv Ther 2021; 38: 164-79.
2. Kaplan M, Duzenli T, Tanoglu A, Cakir Guney B, Onal Tastan Y, Bicer HS. Presepsin: albumin ratio and C-reactive protein: albumin ratio as novel sepsis-based prognostic scores: a retrospective study. Wien Klin Wochenschr 2020; 132: 182-7.
3. Karagöz E, Tanoglu A. Mean platelet volume: a novel predictive marker for mortality in intensive care unit (ICU) patients? Clin Respir J 2016; 10: 535-6.
4. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev 2005; 10: 94-111.
5. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 2005; 98: 1024-7.
6. Beyazit Y, Kocak E, Tanoglu A, Kekilli M. Oxidative stress might play a role in low serum vitamin D associated liver fibrosis among patients with autoimmune hepatitis. Dig Dis Sci 2015; 60: 1106-8.
7. Ralph R, Peter JV, Chrispal A, et al. Supraphysiological 25-hydroxy vitamin D3 level at admission is associated with illness severity and mortality in critically ill patients. J Bone Miner Metab 2014; 33: 239-43.
8. Henry HL, Bouillon R, Norman AW, et al. 14th Vitamin D Workshop consensus on vitamin D nutritional guidelines, J Steroid Biochem Mol Biol 2010; 121: 4-6.
9. Amrein K, Sourij H, G. Wagner G, et al. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study. Crit Care 2011; 15: R104.
10. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266–81.
11. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis 2007; 66: 1137–42.
12. Durr UH, Sudheendra US, Ramamoorthy A. LL-37, the only human member of the cathelicidin family of antimicrobial peptides. Biochim Biophys Acta 2006; 1758: 1408–25.
13. Wang TT, Nestel FP, Bourdeau V, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004; 173: 2909–12.
14. Aygencel G, Turkoglu M, Tuncel AF, et al. Is vitamin D insufficiency associated with mortality of critically ill patients? Crit Care Res Pract 2013; 2013: 856747.
15. Nair P, Lee P, Reynolds C, et al. Significant perturbation of vitamin D–parathyroid–calcium axis and adverse clinical outcomes in critically ill patients. Intensive Care Med 2013; 39: 267-74.
16. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020; 32: 1195-8.
17. Zisi D, Challa A, Makis A. The association between vitamin D status and infectious diseases of the respiratory system in infancy and childhood. Hormones (Athens) 2019; 18: 353-63.
18. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 2007; 179: 2060–3.
19. Heine G, Anton K, Henz BM, Worm M. 1alpha,25-dihydroxyvitamin D3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro. Eur J Immunol 2002; 32: 3395–404.
20. Adorini L, Penna G, Giarratana N, et al. Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands. J Steroid Biochem Mol Biol 2004, 89–90: 437–41.
21. Baeke F, Takiishi T, Korf H, et al. Vitamin D: modulator of the immune system. Curr Opin Pharmacol 2010; 10: 482–96.
22. Baeke F, Gysemans C, Korf H, Mathieu C. Vitamin D insufficiency: implications for the immune system. Pediatr Nephrol 2010; 25: 1597–606.
23. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 2010; 39: 365–79.