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Research Article

The relationship between vitamin D and prognosis in neurology intensive care patients

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Abstract

Objectives: Vitamin D level has been associated with mortality and length of hospitalization (LOH) in critically ill patients in the intensive care unit (ICU). This study is an investigation of the vitamin D level of patients in a neurology ICU, the LOH in the ICU, bacterial growth observed in a hemoculture, and mortality.

Methods: Eighty-four patients whose vitamin D level was measured at the time of admission to the ICU and 85 controls were enrolled in the study. Details of the reason for hospitalization, additional diseases, LOH, the presence of bacterial development in a hemoculture during hospitalization, and 30-day and 90-day mortality after diagnosis were recorded and analyzed.

Results: The mean vitamin D value was 20.29±12.82 ng/mL in the control group, while it was 12.72±9.48 ng/mL in the patient group, which was significantly lower ($p<0.001$). The mean vitamin D level (12.36±8.85 ng/mL) in hospitalized patients with an ischemic cardiovascular event (CVE) was lower than that of the hemorrhagic CVE group (16.69±12.75 ng/mL). There was no statistically significant difference between 30-day and 90-day mortality according to the vitamin D group ($p\geq0.05$); however, those with an adequate vitamin D level had a lower 90-day mortality. The vitamin D level of patients who died in the non-CVE group was significantly lower at 90 days compared with that of survivors ($p<0.024$).

Conclusion: The results indicated that vitamin D may be associated with etiology in ischemic CVEs and may have a relationship to prognosis in cases of infection or immunological events. A sufficient level of vitamin D may reduce the risk of ischemic CVE in older age and contribute to a life with fewer comorbidities.

Keywords: Intensive care, neurology, prognosis, vitamin D

Vitamin D, or 25-hydroxyvitamin D (25[OH]D), is primarily a product of ultraviolet light conversion of 7-dehydrocholesterol in the skin. Consumption of items such as eggs, fish, butter, dairy products, and supplements also provides vitamin D. Although the primary role of vitamin D is to increase calcium absorption from the small intestine [1], vitamin D can affect hypertension, diabetes, cardiovascular disease, cancer, autoimmune diseases, and mortality [2-6].

Vitamin D has a role in immune system regulation, and infection has been associated with vitamin D deficiency. Studies conducted over the last 20 years have found a strong relationship between a low serum 25(OH)D level and susceptibility to tuberculosis infection as well as the severity of infection [7, 8]. A relationship between a low or insufficient serum vitamin D concentration and respiratory tract infections has been reported in studies of children [9, 10]. In cases of vitamin D deficiency, signs or symptoms of infection occur before skeletal system abnormalities (richets, osteomalacia etc.).

During sepsis, the active vitamin D level decreases, which contributes to systemic inflammatory response syndrome, especially in patients in an intensive care unit (ICU) [11]. Although vitamin D deficiency is prevalent in the general population, the rate is higher in ICU patients (more than 90%) [12].

The hypothesis of this study proposed that the data would reveal that the vitamin D level in neurologic intensive care pa-

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tients was low at the time of admission, and that vitamin D deficiency was associated with an increased risk of mortality, longer hospitalization in the ICU, and greater risk of infection.

An investigation of the difference in the vitamin D level of patients who were followed up in the neurology ICU between April 2016 and November 2018 and a control group was performed. The level of vitamin D is generally lower in Turkish population than the established standard. The patient group and the control group consisted of participants of similar age, gender, and comorbidities in order to ensure an objective evaluation of the relationship between neurological disease and vitamin D. The relationship between the vitamin D level of the patients and the length of hospitalization (LOH), mortality, and bacterial growth observed in a hemoculture was also examined.

The relationship between vitamin D, mortality, and infection in patients hospitalized in the ICU for a cerebrovascular event (CVE) (ischemic or hemorrhagic) was evaluated in order to perform a subgroup analysis in a specific homogeneous group.

Materials and Methods

Study subjects and laboratory analyses

Eighty-four patients whose 25(OH)D level was measured at the time of admission to the neurology ICU and 85 age- and gender-matched controls were enrolled in this prospective study. The control group consisted of patients who were not hospitalized in the ICU, but had similar comorbidities (diabetes, hypertension, coronary arterial disease, etc.). The study protocol was approved by the local ethical committee of our hospital (IRB number: 2016/178). Data of the reason for hospitalization, additional diseases, LOH, the presence of bacterial development in a hemoculture during hospitalization, the use of antibiotics, and 30-day and 90-day mortality after diagnosis were recorded.

Four groups were evaluated according to vitamin D level: Group 1: vitamin D level was too low to be measured (25[OH]D <3 ng/mL), Group 2: vitamin D deficiency (25[OH]D ≤15 ng/mL), Group 3: vitamin D insufficiency (25[OH]D 16-29 ng/mL), and Group 4: adequate vitamin D level (25[OH]D ≥30 ng/mL). The patient group was also divided based on an ischemic cerebrovascular event (CVEi), a hemorrhagic cerebrovascular event (CVEh), and other non-CVE (meningitis, encephalitis, myasthenia gravis).

Venous blood samples were centrifuged for 10 minutes at 2500 rpm. The serum was collected and stored at -80°C until further analysis. The vitamin D level was measured in samples taken during hospitalization in the ICU using a UniCel DXL 800 (Beckman Coulter Inc., Brea, CA, USA) and the chemiluminescence method. The coefficient of variation (CV) and SD were calculated using the manufacturer's external quality control materials. The results obtained were a CV of 11.3% and a SD of -0.25. Hemocultures were performed with regularly calibrated BacT-Alert 3D microbial detection system (BioMerieux SA, Marcy-l'Étoile, France). The instruments measure color changes every 10 minutes and analyze the changes.

Statistical analysis

Statistical analyses were performed with NCSS 11 software (NCSS, LLC, Kaysville, UT, USA) and MedCalc Statistical Software version 18 (MedCalc Software bv, Ostend, Belgium). For relationships between categorical variables, a chi-square analysis was used. Where appropriate, categorical variables were evaluated using the Fisher exact test and the Fisher-Freeman-Halton test. An independent sample t-test was used to compare 2 groups of continuous independent variables showing normal distribution, and one-way analysis of variance was performed for comparisons of more than 2 groups. The Mann-Whitney U test was used for comparisons of 2 independent groups and the Kruskall-Wallis H test was used for comparisons of more than 2 groups. The Kaplan-Meier estimator (log rank) was used to evaluate survival time. $P<0.05$ was considered statistically significant.

Results

Of the participants in our study, 45.56% (n=77) were women and 54.44% (n=92) were men. There was no significant difference in gender distribution. The mean age was 66.91±16.49 years (median: 68 years). Of the 84 patients hospitalized in the ICU, 76 were followed for CVE (ischemic: n=65, 85.5%; hemorrhagic: n=11, 14.5%).

When the participants were classified according to vitamin D level, it was observed that 7.69% had a very low value (n=13), 37.8% had vitamin D deficiency (n=64), 45.5% had vitamin D insufficiency (n=77), and only 8.87% (n=15) had an adequate vitamin D level (Table 1). The mean vitamin D value was 20.29±12.82 ng/mL in the control group, while it was 12.72±9.48 ng/mL in the patient group, which was significantly lower ($p<0.001$) (Table 2). The results of the patient group revealed that the mean vitamin D level (12.36±8.85 ng/mL) in CVEi patients was lower than that of the CVEh group (16.69±12.75 ng/mL) (Table 2).

There was no significant difference seen when age and vitamin D group was compared, but 92.31% of Group 1 patients, a vitamin D level too low to measure, were aged 65 years or more (Table 1). In the patient group, the mean age of the non-CVE group (52.88±25.64 years) was lower than that of the CVEi group (69.09±15.13 years) and the CVEh group (63.55±14.45 years) ($p<0.026$) (Table 3).

There was no significant difference between the CVEi, CVEh, and non-CVE groups in the mean LOH (20.98±16.8, 19.55±13.82, 26.5±16.46 days, respectively) (Table 3).

Of the 84 patients who were followed up in the ICU, 14 patients (16.66%) died within 30 days and 32 patients (38.09%) died within 90 days.

Although the patients who died generally had a very low vitamin D level at admission, they were not included in the Lenght of hospitalization (LOH) analysis because they would affect the duration of hospitalization statistics. When the extreme values were eliminated, it was found that vitamin D level was

Table 1. Age, mortality, and hemoculture status according to vitamin D group

	Vitamin D groups								p
	1 (<3ng/mL)		2 (≤15ng/mL)		3 (16-29ng/mL)		4 (≥30ng/mL)		
	n	(%)	n	(%)	n	(%)	n	(%)	
Total	13	(7.7)	64	(37.8)	77	(45.5)	15	(8.9)	
Age (years)									
Young	1	(7.69)	5	(11.63)	5	(20.83)	0	(0.00)	0.062
Middle-aged	0	(0.00)	16	(37.21)	7	(29.17)	2	(50.00)	
Elderly	12	(92.31)	22	(51.16)	12	(50.00)	2	(50.00)	
30-day status									
Alive	9	(69.23)	39	(90.70)	19	(79.17)	3	(75.00)	0.160
Dead	4	(30.77)	4	(9.30)	5	(20.83)	1	(25.00)	
90-day status									
Alive	5	(38.46)	29	(67.44)	15	(62.50)	3	(75.00)	0.291
Dead	8	(61.54)	14	(32.56)	9	(37.50)	1	(25.00)	
Hemoculture									
Positive	11	(84.62)	35	(81.40)	20	(83.33)	4	(100.00)	1.000
Negative	2	(15.38)	8	(18.60)	4	(16.67)	0	(0.00)	
		Mean±SD Median (min-max)		Mean±SD Median (min-max)		Mean±SD Median (min-max)			
*Length of Stay (days)	7	34.43±13.2 28 (25-63)	39	22.79±17.07 16 (3-70)	20	16.55±13.02 14.5 (2-42)		-	0.031

Fisher- Freeman-Halton test. *Kruskall-Wallis H test. Vitamin D Group 1: Too low to measure, 2: Deficiency, 3: Insufficiency, 4: Adequate. Young: Under 45 years, Middle-aged: 45-64 years, Elderly: 65 years and older. Total: Patient and control

a statistically significant factor in the LOH (p=0.031) (Table 1). Group 4 was also not included in the hospitalization time statistical analysis because of the small number of patients (n=4). A Bonferroni-corrected Dunn multiple comparison test indicated that the mean LOH was significantly higher in Group 1 (34.43±13.2 days) than in Group 3 (16.55±13.02 days), which had an insufficient vitamin D level (p=0.031).

There was no statistically significant difference between 30-day and 90-day mortality data according to vitamin D level classification (p≥0.05); however, those with an adequate vitamin D level had a lower 90-day mortality rate (Table 1). A 90-day mortality evaluation revealed that the vitamin D level of subjects who died was significantly lower in the non-CVE group compared with the survivors (p=0.024) (Table 4). Although no significant difference in survival was observed between the CVE groups, the effects of vitamin D on the prognosis and survival of the non-CVE group (consisting of patients with immunological and infectious diseases like meningitis, encephalitis, and myasthenia gravis) were significant (Table 5). When the Group 1 vitamin D level was compared with that of Group 2 and Group 3, the 90-day survival rate was lowest in Group 1; i.e., the group with the lowest vitamin level (log rank=0.0177, log rank=0.0389) (Table 5).

Another factor affecting the LOH was the presence or absence of bacterial growth in a hemoculture. Bacterial growth was observed in 14 patients. Although there was no statistically significant difference between the presence or absence of bacterial growth and vitamin D level (p≥0.05), there was no bacterial growth recorded in the group with an adequate vitamin D level (Table 2, 4).

Discussion

Studies conducted since the 1980s have revealed that vitamin D has very important biological effects, including cell differentiation, proliferation, inhibition, and immunomodulation, in addition to a role in maintaining calcium homeostasis and bone metabolism [13]. Evidence has demonstrated that vitamin D receptors and vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) are expressed in several cells outside the bones and kidneys, such as in the intestines, platelets, pancreas, and prostate [14].

Vitamin D can also improve the microbicidal ability of monocytes/macrophages and reduce inflammatory cytokines produced by T lymphocytes [15]. Vitamin D can regulate the innate immune system, as well as enhance the physical barrier function of epithelial cells and increase phagocytic ability on

Table 2. Comparison of vitamin D level in control and patient groups

	Vitamin D (ng/mL)	
	(n) Mean±SD Median (min-max)	p*
Control group	(n=85) 20.29±12.82 19 (4-88)	
*Patient group	(n=84) 12.72±9.48 10.8 (1-48.6)	<0.001
CVEi	(n=65) 12.36±8.85 10.7 (1-48.6)	
CVEh	(n=11) 16.69±12.75 15.6 (1-39.7)	<0.001
Non-CVE	(n=8) 10.19±9.13 7.55 (1-26.5)	

Kruskall-Wallis H test comparision of patient subgroups and controls, *Mann-Whitney U test comparision of patients and controls. CVEh: Hemorrhagic cerebrovascular event, CVEi: Ischemic cerebrovascular event, Non-CVE: Other causes of cerebrovascular event

immune cells [5, 16]. In particular, 1,25(OH)2D3 may enhance the epithelial barrier function in the cornea [17] and intestines [18]. In our study, the lack of bacterial growth in the group with adequate vitamin D (Group 4) suggests that vitamin D may also contribute to clinical status by supporting the immunity of neurology intensive care patients. When these data are examined together, the importance of vitamin D in the defense of the organism against pathogens is clear and may support supplementation of vitamin D for in patients with acute or chronic infection. However, no evaluation of supplementation was performed in this study. During sepsis, the level of active vitamin D decreases, thus worsening the stages of systemic inflammatory response syndrome, especially in patients in an ICU [11]. Although there was no sepsis in our patients, our findings also suggest that clinical prognosis is tend to be much worse in ICU patients with inadequate vitamin D level. The non-CVE group in this study consisted of meningitis, encephalitis, and myasthenia gravis patients. These diseases are generally related to an insufficient or malfunctioning immune system and the presence of an infectious agent. The vitamin D level in this patient group was lower than that of the CVE patients.

Infections will likely be more severe in patients with vitamin D deficiency/insufficiency. The LOH was longer in the group with a very low level of vitamin D and the 90-day mortality rate was greater in the group with a low vitamin D level. In our study, the level of vitamin D in ICU patients who had bacteremia with bacteria observed in a hemoculture was lower than other patients, but it was not a statistically significant difference. There was no bacterial growth in the blood of patients with adequate vitamin D levels (Table 4).

Many clinical studies have shown a relationship between vitamin D deficiency and cardiovascular disease, and vitamin D deficiency has also been associated with obesity, insulin resistance, and systemic inflammation. The results of a large series indicated that there was no increase in the risk of cardio and cerebrovascular disease in patients taking 400U vitamin D with 1g calcium for 7 years [2, 19, 20]. Vitamin D increases anticoagulants and decreases procoagulants. A study published in 2008 also supported this thesis. Increased platelet aggregation and thrombosis risk have been demonstrated in Vitamin D receptor null mice. Active vitamin D has been shown to reduce thrombosis in disseminated intravascular coagulation mice [21]. Our research yielded similar findings. The vitamin D level in ischemic CVE patients was lower than that seen in hemorrhagic CVE patients. This supports an association between vitamin D deficiency and thromboembolic events. Our

Table 3. Age, length of stay and vitamin D distribution of according to patient subgroups

	CVEi	CVEh	nonCVE	
	(n) Mean±SD Median (min-max)	(n) Mean±SD Median (min-max)	(n) Mean±SD Median (min-max)	p*
Age (year)	(n=65) 69.09±15.13 70 (38-98)	(n=11) 63.55±14.45 61 (40-83)	(n=8) 52.88±25.64 66 (22-79)	0.026
Length of stay (day)	20.98±16.8 15 (2-70)	19.55±13.82 13 (3-42)	26.5±16.46 22.5 (8-50)	0.470[a]
Vitamin D (ng/mL)	12.36±8.85 10.7 (1-48.6)	16.69±12.75 15.6 (1-39.7)	10.19±9.13 7.55 (1-26.5)	0.351[a]

One way analysis of varianc, [a]Kruskall Wallis H test. CVEh: Hemorrhagic cerebrovascular event, CVEi: Ischemic cerebrovascular event, non-CVE: Other causes of cerebrovascular event

Table 4. 30-day survival, 90-day survival and hemoculture status comparisons in cerebrovascular disease status according to vitamin D

	CVEi	CVEh	Non-CVE
	(n) Mean±SD Median (min-max)	(n) Mean±SD Median (min-max)	(n) Mean±SD Median (min-max)
30-day status			
Alive	(n=54)	(n=9)	(n=7)
	12.12±8.23	17.44±14.02	11.5±9.01
	10.65 (1-48.6)	15.6 (1-39.7)	7.9 (1-26.5)
Dead	(n=11)	(n=2)	(n=1)
	13.54±11.88	13.3±5.09	1±0.001
	14.1 (1-40.1)	13.3 (9.7-16.9)	1 (1-1)
	0.793	0.813	0.188
90-day status			
Alive	(n=40)	(n=7)	(n=5)
	12.24±8.46	18.4±14.15	14.7±8.6
	10.8 (1-48.6)	15.6 (1-39.7)	10.9 (7.2-26.5)
Dead	(n=25)	(n=4)	(n=3)
	12.56±9.63	13.7±11.1	2.67±2.89
	10.7 (1-40.1)	13.3 (1-27.2)	1 (1-6)
	0.850	0.636	0.024
Hemoculture			
Negative	(n=56)	(n=8)	(n=6)
	12.37±9.16	17.48±13.44	12.42±9.51
	11.3 (1-48.6)	14.75 (1-39.7)	9.4 (1-26.5)
Positive	(n=9)	(n=3)	(n=2)
	12.31±7.08	14.6±13.13	3.5±3.54
	9.7 (4.4-26.8)	15.6 (1-27.2)	3.5 (1-6)
p*	0.902	0.759	0.131

p*Fisher's exact test. CVEh: Hemorrhagic cerebrovascular event, CVEi: Ischemic cerebrovascular event, non-CVE: Other causes of cerebrovascular event

Table 5. 90-day survival analysis of vitamin D levels in non-CVE patients

Vitamin D Groups	Mean survival (days)	SEM	95% CI	Median survival (days)	95% CI	p
1	33.000	7.000	19.280–46.720	26.000	26.000–40.000	0.0141
2	81.750	7.145	67.746–95.754			
3	90.000	0.000	90.000–90.000			
1	33.000	7.000	19.280–46.720	26.000	26.000–40.000	0.0177
2	81.750	7.145	67.746–95.754			
1	33.000	7.000	19.280–46.720	26.000	26.000–40.000	0.0389
3	90.000	0.000	90.000–90.000			

CI: Confidence interval, CVE: Cerebrovascular event, Non-CVE: Other causes of cerebrovascular event, SEM: Standard error of mean. Vitamin D Group 1: Too low to measure, 2: Deficiency, 3: Insufficiency

results provide important information about the effect of vitamin D level on the etiology and prognosis of cerebrovascular diseases (especially ischemic and hemorrhagic events). Particular attention was paid to a balanced distribution of comorbid diseases between the patient and control groups.

Although we did not find any significant difference in the survival of the CVE groups, the effect of vitamin D on survival in the non-CVE group was quite significant. The non-CVE group consisted mostly of infections and diseases related to the immune system. The limited number of patients may have con-

tributed to these results. There is a need for additional studies with a larger patient group. The data indicate that as the vitamin D level increases, the survival rate increases. These findings are consistent with previous studies on the role of vitamin D in immune and sepsis.

In our study, the LOH was higher in patients with vitamin D deficiency (Group 2) than in the group of those with vitamin D insufficiency (Group 3) ($p<0.001$). In other words, the LOH was prolonged as the vitamin D level decreased. Our results were similar to those of Matthews et al. [15], who studied 258 patients hospitalized in a surgical intensive care unit in the USA. In the group with severe vitamin D deficiency, the mean length of stay (13.33±9.5 days) was longer than that of the moderate and mild vitamin D deficiency groups (7.29±15.3 days and 5.17±6.5 days, respectively) ($p<0.002$).

The vitamin D level is often low in the elderly population [22]. In our patient group, 92.31% of the group with a very low vitamin D level were patients over 65 years of age.

Although the data suggest that the vitamin D level may affect various outcomes, such as length of stay in intensive care, rehospitalization, general costs, and mortality, the role of vitamin D in the maintenance of functional status in intensive care patients has not been widely investigated [19, 23-28].

The principal limitations of our study are the small number of patients and the fact that vitamin D levels were measured only in the ICU and not measured again during hospitalization.

Conclusion

According to the results of our study, it would appear that vitamin D may be associated with etiology in ischemic CVE. In addition, vitamin D may have an effect on the prognosis of diseases associated with infection or immune system dysregulation. Vitamin D will continue to be the focus of subsequent research in the future. Vitamin D deficiency and supplementation are likely to be important concerns for public health organizations and health policy, especially for the growing advanced age group with greater frequency and severity of disease. Maintenance of a normal vitamin D level might reduce the risk of ischemic CVE and contribute to fewer comorbidities in old age.

Conflict of Interest: The authors report that there is no potential conflict of interest relevant to this article.

Ethics Committee Approval: This study was approved by the clinical ethics board of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Date: 15.06.2016/Number: 2016-178).

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