The Effect of Vitamin D Supplementation in Patients with Acute Traumatic Brain Injury

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OBJECTIVE: **To investigate the acute and long-term effects of vitamin D supplementation on the recovery of patients with traumatic brain injury (TBI).**

METHODS: **A retrospective study was conducted involving 345 patients with TBI who visited a single trauma center. Vitamin D serum levels were measured without supplementation at admission, 1 month, and 3 months post-TBI (control group) from August to December 2016. From January 2017, vitamin D supplementation was provided to patients with TBI with low vitamin D serum levels at admission (supplement group). The outcomes were investigated by assessing performance function (Extended Glasgow Outcome Scale) and cognitive function (Mini-Mental Status Examination, and Clinical Dementia Rating) at 1 week and 3 months post-TBI.**

RESULTS: **The mean vitamin D serum level in patients with TBI at admission was 13.62 ± 9.01 ng/mL. The level significantly increased from 14.03 ± 8.68 ng/mL at admission to 37.42 ± 12.57 ng/mL at 3 months post TBI in the supplement group ($P < 0.001$). The cognitive outcomes (Mini-Mental Status Examination/Clinical Dementia Rating, $P = 0.042$/$P = 0.044$) and GOS-E score (total TBI, $P = 0.003$; mild-to-moderate TBI, $P = 0.002$) significantly improved from the first week to 3 months post TBI in the patients with vitamin D supplementation.**

CONCLUSIONS: **Administration of vitamin D supplements in mild-to-moderate TBI patients with significant vitamin D deficiency during the acute phase of the injury may improve long-term performance and cognitive outcomes. Therefore, the treatment strategies should be individually planned for the patients with TBI based on their baseline vitamin D level.**

INTRODUCTION

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, as well as for multiple other biological effects.[1] For humans, the most important compounds of this group are vitamins D3 and D2, also referred to as cholecalciferol and ergocalciferol, respectively.[2,3] Both compounds can be obtained from a healthy diet and supplements.[2,4] Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol). The metabolite from this reaction, 25-hydroxyvitamin D3 (25-OH vitamin D3), is measured in the serum to determine an individual's vitamin D status.[5,6] Vitamin D regulates the proliferation and function of immune cells, such as dendritic cells, macrophages, and lymphocytes, and has been actively studied in the fields of cardiology and oncology.[6-8] When administered to patients with osteoporosis, vitamin D supplements reportedly increase bone formation, thereby inducing calcium regulation and hormonal changes and consequently reducing the risk of facture.[9-11] Neurobiological research has further revealed an association between vitamin D and schizophrenia by means of the metabolism of a substance similar to proline as well as an association between vitamin D and the neuroprotective effect against cognitive decline and dementia.[12-15]

Head trauma is divided into primary and secondary injuries according to the time of injury; the former is caused by the insult

Key words
- Brain injuries
- Cognition
- Glasgow outcome scale
- Traumatic
- Vitamin D

Abbreviations and Acronyms
25-OH vitamin D3: 25-Hydroxyvitamin D3
CDR: Clinical Dementia Rating
GOS-E: Extended Glasgow Outcome Scale
MMSE: Mini-Mental Status Examination
TA: Traffic accident
TBI: Traumatic brain injury

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Citation: World Neurosurg. (2019). https://doi.org/10.1016/j.wneu.2019.02.244

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

from the initial injury, whereas the latter corresponds to any additional injuries that occur after and as a consequence of the primary injury.[16,17] Secondary injury is primarily accounted for by edema induced by the immune response and free-radical damage to neural cells, which is associated with the release of calcium ions.[18,19] As vitamin D is involved in the regulation of calcium ions, the immune response, and the generation of oxygen free-radicals,[6,8] vitamin D supplements administered in the acute phase of the injury may attenuate the secondary injury. Testing this hypothesis, some studies in animals have demonstrated that vitamin D is effective in improving recovery from traumatic brain injury (TBI).[20] This study was therefore conducted to investigate the effects of vitamin D supplementation on the patients who were admitted during the acute phase of a TBI.

MATERIALS AND METHODS

This study was approved by the institutional review board, and the need for informed consent was waived.

Study Design

The present retrospective study included 476 patients who were treated for TBI at a single regional trauma center between August 2016 and December 2017. The inclusion criteria were as follows: patients who visited the emergency department with TBI, patients who were admitted to the neurosurgery department with the largest injury-severity score for the head, and patients whose serum level of vitamin D was assessed immediately after arrival to the emergency department.[21] Among the 476 patients with TBI, 73 were excluded due to poly-trauma with TBI, 20 on account of death in the emergency department, and 38 due to their vitamin D serum level not having been checked immediately after arrival to the emergency department. Finally, 345 patients were enrolled in this study.

Serum Level of Vitamin D

The serum levels of vitamin D were obtained by measuring 25-OH vitamin D3.[3] The reference range for serum 25-OH vitamin D3 was 30–50 ng/mL, whereas vitamin D deficiency was defined as a serum level of less than 30 ng/mL.[22-24] Control data were collected from August to December 2016, which corresponded to serum level of vitamin D checked immediately after a patient's arrival to the emergency department. No supplements were administered to these patients, even if the recorded serum level was outside the reference range. Supplementation data were collected from January 2017 to December 2017. If a patient exhibited a vitamin D deficiency, cholecalciferol was immediately injected at 100,000 IU intramuscularly; if oral medication was possible on the day following intramuscular injection, 0.5 μg/day of alfacalcidol was also administered.[25] Each patient's serum level of vitamin D was checked at 1 and 3 months after TBI. It was adjusted by administering alfacalcidol in cases in which it was outside the reference range. However, vitamin D supplementation was not performed when the patient exhibited a renal disease or hypercalcemia owing to the risk of hypercalcemia associated with vitamin D supplementation.

Clinical Data Collection

The patients' clinical information was obtained via retrospective chart reviews. The data included sex, age, trauma mechanism, history of diabetes, hypertension, dyslipidemia, end-stage renal disease, smoking, alcoholism, education level, patient's job, and initial score on the Glasgow Coma Scale. The trauma mechanism was classified as one of the following depending on the cause of the traumatic incident: a car traffic accident (TA; driver or passenger), motorcycle TA, bicycle TA, pedestrian TA, cultivator accident, fall, slip, head collision, or an assault. Consumption of more than 14 standard drinks per week or 4 drinks per day was set as a criterion to determine alcoholism.[26] Education level was classified based on the degree of education attained: none, elementary, middle, high school, or college and greater. The patient's job was classified as none, production worker, office worker, service industry, or student. Initial Glasgow Coma Scale score was defined as the score obtained at the time of patients' arrival to the emergency department after their accident.

Outcomes and Follow-Up

Outcomes were divided into performance and cognitive functions. The former was based on the Extended Glasgow Outcome Scale (GOS-E) classification and was assessed at 1 week and 3 months after TBI.[27] Data were reviewed by 3 neurosurgeons for accurate GOS-E classification and discussed in case of conflicting opinions. Cognitive function was classified on the basis of Mini-Mental Status Examination (MMSE) and Clinical Dementia Rating (CDR) at 1 week and 3 months after TBI.[28,29] However, because we were unable to measure cognitive function for the patients with the most severe TBI, cognitive function was measured only in patients with mild-to-moderate TBI.

Statistical Analyses

Statistical analyses were performed using SPSS, Version 21.0 (IBM Corp., Armonk, New York, USA). The relationship between the serum level of vitamin D and GOS-E score at 1 week after TBI was analyzed by the Pearson correlation analysis or the Spearman analysis depending on the distribution of the data. In addition, the Student t test was applied to the relationship between the serum level of vitamin D and mortality. In the subgroup analysis of patients who underwent a 3-month follow-up, baseline characteristics were assessed and compared between the 2 groups (supplement vs. control) by using the χ^2 test, Fisher's exact test, linear by linear test, Student t-test, or Mann–Whitney U test. The paired t test was used to analyze the change in serum level of vitamin D across the 3 months. For the analysis of the serum level of vitamin D and the comparison of the change in performance and cognitive functions between the 2 groups, the repeated measured analysis of variance test was used. For all analyses, P values of $\leq$0.05 were considered statistically significant.

RESULTS

The mean value of serum levels of vitamin D in the 345 patients with TBI at admission was 13.62 ± 9.01 ng/mL. Most patients had vitamin D deficiency, and only 18 patients (5.2%) had a serum level of vitamin D within the reference range. The mean GOS-E score at the first week post-TBI was 5.87 ± 2.30. There was no

significant correlation between the serum level of vitamin D and GOS-E score ($P = 0.080$).

The initial serum level of vitamin D and first week post-TBI GOS-E score in the severe TBI group ($n = 66$) were 10.38 ± 7.61 ng/mL and 3.25 ± 2.31, respectively; these values for the mild-to-moderate TBI group ($n = 279$) were 14.38 ± 9.15 ng/mL and 6.49 ± 1.80, respectively. There were no significant correlations between the initial serum levels of vitamin D and GOS-E score in the 2 groups (severe group, $P = 0.980$; mild-to-moderate group, $P = 0.923$), nor was there a significant correlation between the initial serum level of vitamin D and MMSE score (20.71 ± 7.86, $P = 0.994$) or CDR (0.98 ± 1.11, $P = 0.974$) in the mild-to-moderate TBI group.

Mortality occurred in 25 (7.2%) cases. The initial serum levels of vitamin D in the deceased and surviving patients were 13.81 ± 8.77 ng/mL and 11.52 ± 11.60 ng/mL, respectively; the difference between these 2 values was not statistically significant.

In the analysis of the 244 patients who underwent the 3 months of follow-up, 180 patients received supplementation with vitamin D, whereas 64 were classified as controls without supplementation. Serum levels of vitamin D significantly increased from 14.03 ± 8.68 ng/mL at admission to 37.42 ± 12.57 ng/mL at 3 months post-TBI in the supplement group ($P < 0.001$) and from 13.57 ± 9.12 ng/mL at admission to 16.77 ± 1.52 ng/mL at 3 months post-TBI ($P = 0.021$) in the control group. Thus, the increase in the serum level of vitamin D was greater in the supplement group than in the control group ($P < 0.001$) (Table 1). There was no significant difference between the 2 groups in any of the baseline characteristics (Table 2).

Concerning the performance outcome of all the patients who attended the 3-month follow-up, there was no significant difference between the GOS-E score of the supplement (6.35 ± 1.75) and control groups (6.53 ± 1.78) at the first week post TBI ($P = 0.471$). In addition, there was no significant difference between the GOS-E score of the supplement (4.65 ± 2.03) and control groups (4.64 ± 2.02) at the first week post TBI among patients with severe TBI who attended the 3-month follow-up ($P = 0.992$), nor was there a significant difference between the GOS-E score of the supplement (6.90 ± 1.41) and control groups (6.75 ± 1.40) at first week post TBI among patients with mild-to-moderate TBI with 3 months of follow-up ($P = 0.503$). The supplement group attained a greater GOS-E score at 3 months post-TBI than did the control group; however, there was no statistically significant difference between the 2 groups across all TBI conditions (total TBI, $P = 0.471$; severe TBI, $P = 0.286$; mild-to-moderate TBI, $P = 0.191$; Table 3). The patients who received supplementation in the total TBI ($P = 0.003$) and mild-to-moderate TBI ($P = 0.020$) groups showed a significant improvement in the recovery rate of GOS-E

Table 1. Comparison of the Serum Levels of Vitamin D at the Time of Admission and 3 Months Post-TBI in the Supplement and Control Groups

Vitamin D Level, ng/mL	Admission	3 Months Post-TBI	*P* Value
Control group ($n = 64$)	13.57 ± 9.12	16.77 ± 1.52	0.021
Supplement group ($n = 180$)	14.03 ± 8.68	37.42 ± 12.57	<0.001

TBI, traumatic brain injury.

Table 2. Comparison of Baseline Characteristics Between the Vitamin D Supplement and Control Groups

	Control Group ($n = 64$)	Supplement Group ($n = 180$)	*P* Value
Sex (male)	53 (82.8%)	132 (73.3%)	0.173
Age, years	55.91 ± 17.81	56.76 ± 16.16	0.724
Trauma mechanism			0.377
Traffic accident			
Driver	8 (12.5%)	10 (5.6%)	
Passenger	2 (3.1%)	12 (6.7%)	
Pedestrian	8 (12.5%)	24 (13.3%)	
Bicycle	5 (7.6%)	10 (5.6%)	
Motorcycle	8 (12.5%)	25 (13.9%)	
Fall	8 (12.5%)	24 (13.3%)	
Slip	21 (32.8%)	55 (30.6%)	
Head collision	3 (4.7%)	18 (10.0%)	
Assault	1 (1.6%)	2 (1.1%)	
Diabetes	9 (14.1%)	37 (20.6%)	0.273
Hypertension	24 (37.5%)	68 (37.8%)	1.000
Dyslipidemia	8 (12.5%)	26 (14.4%)	0.835
ESRD	0	1 (0.6%)	1.000
Smoking	28 (43.8%)	59 (32.8%)	0.130
Alcohol abuse	13 (20.3%)	47 (24.6%)	0.401
Education level			1.000
No	0	4 (2.2%)	
Elementary school	14 (21.9%)	36 (20.0%)	
Middle school	9 (14.1%)	35 (19.4%)	
High school	33 (51.6%)	67 (37.2%)	
Above college	8 (12.5%)	38 (21.1%)	
Job			0.155
No	19 (29.7%)	64 (35.6%)	
Production worker	24 (37.5%)	70 (38.9%)	
Office worker	7 (10.9%)	19 (10.6%)	
Service occupations	10 (15.6%)	23 (12.8%)	
Student	4 (6.3%)	4 (2.2%)	
Serum level of vitamin D at admission, ng/mL	13.57 ± 9.12	14.03 ± 8.68	0.720
Initial GCS[1]	12.36 ± 3.11	13.14 ± 2.89	0.070

ESRD, end-stage rental disease; GCS, Glasgow Coma Scale.

Table 3. Comparison of Performance Outcome Between the Vitamin D Supplement and Control Groups at Different Severity Levels of TBI

	Control Group (n = 64)	Supplement Group (n = 180)	P Value
Total TBI			
1 week	6.53 ± 1.78	6.35 ± 1.75	0.471
3 months	6.81 ± 1.70	7.16 ± 1.40	0.113
Severe TBI			
1 week	4.64 ± 2.02	4.65 ± 2.03	0.992
3 months	5.29 ± 2.23	6.13 ± 1.96	0.286
Mild or moderate TBI			
1 week	6.90 ± 1.41	6.75 ± 1.40	0.503
3 months	7.20 ± 1.23	7.43 ± 1.09	0.191

TBI, traumatic brain injury.

score from the first week to 3 months post-TBI. However, patients with severe TBI (P = 0.321) demonstrated no significant improvement in the GOS-E score.

With respect to cognitive outcome, there was no significant difference in the MMSE score between the supplement and control groups at first week post TBI (P = 0.981). However, MMSE score of the supplement group at 3 months post TBI (24.1 ± 7.3) was significantly greater than that of the control group (21.6 ± 8.3; P = 0.045; Table 4). In addition, the recovery rate of MMSE score from first week to 3 months was significantly greater in the supplement group than in the control group (P = 0.042). In the analysis of CDR, there was no significant difference between the supplementary and control groups at both the first week (P = 0.059) and 3 months post-TBI (P = 0.781) (Table 4). However, the recovery rate of CDR was significantly greater in the supplement group than in the control group (P = 0.044).

Table 4. Comparison of Cognitive Outcome Between the Vitamin D Supplement and Control Groups in Patients with Mild-to-Moderate TBI

	Control Group (n = 64)	Supplement Group (n = 180)	P Value
MMSE			
1 week	19.7 ± 7.5	20.6 ± 8.5	0.981
3 months	21.6 ± 8.3	24.1 ± 7.3	0.045
CDR			
1 week	0.94 ± 1.10	1.10 ± 1.13	0.059
3 months	0.90 ± 1.23	0.82 ± 1.01	0.781

TBI, traumatic brain injury; MMSE, mini-mental status examination; CDR, clinical dementia rating.

DISCUSSION

Several Korean studies have reported that only 13.2% and 6.7% of Korean men and women, respectively, have a sufficiently high serum level of vitamin D, and that the widespread vitamin D deficiency is more severe among younger populations due to their indoor lifestyle. Consequently, researchers recommended that policies concerning food fortification and vitamin D supplementation should be made more aggressive.[30] At first, the patients in the present study were observed to have vitamin D deficiency but recovered with vitamin D supplementation. Although the serum levels of vitamin D also increased in patients who did not receive supplements, they were still below the recommended range. Such an increase may be attributed to the patients having spent more time outdoors after discharge.

In addition, we found no association between the initial serum level of vitamin D and the first-week performance or cognitive outcome of the 345 patients with TBI who participated in the overall study. These results suggest that the initial serum level of vitamin D is not associated with the recovery in the acute phase. It might also not be significantly related with the performance or cognition before the accident. Therefore, the hypothesis that a patient with a low serum level of vitamin D before an accident will also exhibit bad performance and cognition before the accident can be ruled out.

The analysis of the patients who underwent the 3-month follow-up revealed no statistical difference in any of the baseline characteristics between the supplement and control groups. The data on the comparison between the 2 groups is therefore reliable.

In our analysis of the performance outcome, we found no differences among total, severe, and mild-to-moderate TBI patients in the initial serum level of vitamin D and GOS-E score at the first week post TBI. However, although not statistically significant, the GOS-E at 3 months post-TBI was greater in the supplement group than in the control group. Regarding the recovery rate of GOS-E score, the total TBI and mild-to-moderate TBI patients who received supplements featured a greater degree of recovery at 3 months than did the control group. However, supplementation did not influence the recovery rate of GOS-E score for the patients with severe TBI. These results suggest that the administration of vitamin D supplements to patients with mild-to-moderate TBI does not improve recovery in the short term but does in the long term. In addition, the fact that the majority of the subjects belonged to the mild-to-moderate TBI group may account for the recovery observed in the total TBI group.

The neurologic outcome of patients is reportedly affected by the levels of excitatory amino acids, an increase in intracellular levels of calcium and free radicals that induce apoptosis, or necrosis of nerve cells several days or weeks after the primary injury.[18,19] Vitamin D supplementation already has been incorporated into a variety of treatments, such as chemotherapy and immunotherapy, as it has a positive effect on calcium-ion regulation, immune response, and regulation of the free radical production.[6,8] However, it seems to be ineffective in helping patients to recover from the immense injury-induced destruction of neuronal cells and the vast release of related metabolites, as vitamin D supplementation did not improve the outcomes of patients with severe TBI.

Concerning the analysis of the cognitive function in patients with mild-to-moderate TBI, supplementation did not influence the

MMSE score and CDR from the first week post-TBI; however, the MMSE of the supplement group improved significantly by 3 months post-TBI. In addition, we confirmed that the recovery rates of MMSE score and CDR were greater in the supplement group.

Pathologic research has revealed that post-traumatic dementia is caused by the deposition of amyloid precursor proteins, tau proteins, and neurofibrillary tangles in the cortex.[31,32] A recent study reported that vitamin D affects the production and inhibition of some metabolites related to the occurrence of mood disorder or schizophrenia.[15] Although the mechanism by which vitamin D supplementation affects cognitive dysfunction remains unknown, it may be possible to reduce the incidence of cognitive impairment by attenuating the protein synthesis or deposition that underlies the post-traumatic dementia.[33,34] To completely elucidate the mechanism of post-traumatic dementia and thereby inform such therapeutic strategies, additional research on the correlation of the condition with vitamin D supplementation and the synthesis or deposition of proteins that induce dementia is required.

Limitations

This study is subject to several limitations. Our investigation features the drawbacks of selective bias and compound effect inherent to retrospective analyses. However, as there was no significant difference in baseline characteristics between the supplement and control groups, the potential bias of the results is likely minimal. Second, the number of patients in the supplement group was about 3 times than that of the control group, which may have affected the results. However, there was no statistically significant difference in the baseline characteristics between the 2 groups. Thus, the effect on the outcome is expected to be small. Third, the number of patients in the control group who were involved in a car accident as a driver was twice that in the supplement group. The TBI following a car accident is diffuse and may negatively affect the functional outcome and, hence, the GOS score. However, there was no statistical difference between the 2 groups with respect to the trauma mechanism. Moreover, the number of driver TAs was greater in the control group, whereas that of the passenger TAs was greater in the supplement group. With car TA as the cause of TBI, the number of cases was similar between the 2 groups. Therefore, we believe that the effect of a greater number of driver TA in the control group on our result was small. In addition, the educational levels of the 2 groups varied, that may have affected the cognitive outcome. Thus, a subgroup analysis was performed between the patients who were classified as above-college and high-school groups. The results indicated that the MMSE score was significantly greater in the above-college group at the first week post-TBI (high school vs. above college, 20.86 ± 8.06 vs. 23.96 ± 6.31, $P = 0.007$), and at 3 months post-TBI (23.63 ± 7.75 vs. 27.12 ± 5.29, $P = 0.003$); however, CDR was greater in the high-school group at the first week post-TBI (0.996 ± 1.200 vs. 0.736 ± 1.022, $P = 0.171$), and at 3 months post-TBI (0.798 ± 1.092 vs. 0.464 ± 0.893, $P = 0.087$). However, there was no significant difference in the recovery rates of the MMSE score (2.83 ± 5.88 vs. 3.29 ± 4.72, $P = 0.659$) and CDR (0.230 ± 0.792 vs. 0.298 ± 0.741, $P = 0.643$) between the 2 groups. Moreover, the difference in level of education was not statistically significant between the supplement and control groups. Therefore, we believe that it may have had only a small effect on the results of cognitive recovery.

Fourth, although GOS-E score at 3 months post-TBI was greater in the supplement group than in the control group, there was no statistically significant difference in GOS-E score between the 2 groups at 1 week or 3 months post-TBI. However, the recovery rates of MMSE score and CDR of patients with mild-to-moderate TBI were greater in the supplement group. Since the performance and the cognitive outcomes affect one another, the recovery rate of the GOS-E score may have actually increased. Fifth, mortality cases, which accounted for 40% of patients with severe TBI, that had included a 3-month follow-up were excluded from the patient data. This may have affected the outcomes of severe TBI and total TBI groups. Therefore, a subgroup analysis of mortality cases was performed. Mortality was not correlated with the initial serum levels of vitamin D, and there was no significant difference in the numbers of mortality cases between the supplement ($n = 19$, 7.4%) and control groups ($n = 7$, 7.9%; $P = 1.000$). A randomized controlled trial involving a large-scale multicenter study should be conducted in the future to collect data concerning the long-term effects of vitamin D supplementation in cases of severe TBI.

CONCLUSIONS

Administration of vitamin D supplements to patients with mild-to-moderate TBI with significant vitamin D deficiency during the acute phase of the injury may improve the long-term performance and cognitive outcomes. Therefore, treatment strategy should be individually planned for the patients with TBI based on their baseline vitamin D level.

REFERENCES

1. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004;80:1678S-1688S.
2. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*. 2006;81:353-373.
3. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab*. 2004;89:5387-5391.
4. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr*. 2005;135:310-316.
5. Hollis BW. Assessment of vitamin D nutritional and hormonal status: what to measure and how to do it. *Calcif Tissue Int*. 1996;58:4-5.
6. Bikle DD. Vitamin D: newly discovered actions require reconsideration of physiologic requirements. *Trends Endocrinol Metab*. 2010;21:375-384.
7. Wong MS, Leisegang MS, Kruse C, et al. Vitamin D promotes vascular regeneration. *Circulation*. 2014;130:976-986.
8. Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med (Berl)*. 2010;88:441-450.
9. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr*. 2008;88:491S-499S.

10. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669-683.

11. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365:1621-1628.

12. Miller JW, Harvey DJ, Beckett LA, et al. Vitamin D status and rates of cognitive decline in a multiethnic cohort of older adults. *JAMA Neurol*. 2015;72:1295-1303.

13. Annweiler C, Milea D, Whitson HE, et al. Vitamin D insufficiency and cognitive impairment in Asians: a multi-ethnic population-based study and meta-analysis. *J Intern Med*. 2016;280:300-311.

14. Toffanello ED, Coin A, Perissinotto E, et al. Vitamin D deficiency predicts cognitive decline in older men and women: the Pro.V.A. study. *Neurology*. 2014;83:2292-2298.

15. Clelland JD, Read LL, Drouet V, et al. Vitamin D insufficiency and schizophrenia risk: evaluation of hyperprolinemia as a mediator of association. *Schizophr Res*. 2014;156:15-22.

16. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth*. 2007;99:4-9.

17. Park E, Bell JD, Baker AJ. Traumatic brain injury: Can the consequences be stopped? *CMAJ*. 2008;178:1163-1170.

18. Beauchamp K, Mutlak H, Smith WR, Shohami E, Stahel PF. Pharmacology of traumatic brain injury: where is the "golden bullet"? *Mol Med*. 2008;14:731-740.

19. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. *Dis Model Mech*. 2013;6:1307-1315.

20. Cekic M, Cutler SM, VanLandingham JW, Stein DG. Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats. *Neurobiol Aging*. 2011;32:864-874.

21. Baker SP, O'Neill B. The injury severity score: an update. *J Trauma*. 1976;16:882-885.

22. Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Adv Exp Med Biol*. 2014;810:500-525.

23. Dahlquist DT, Dieter BP, Koehle MS. Plausible ergogenic effects of vitamin D on athletic performance and recovery. *J Int Soc Sports Nutr*. 2015;12:33.

24. Ross AC. The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr*. 2011;14:938-939.

25. Zold E, Szodoray P, Nakken B, et al. Alfacalcidol treatment restores derailed immune-regulation in patients with undifferentiated connective tissue disease. *Autoimmun Rev*. 2011;10:155-162.

26. Fogli-Cawley JJ, Dwyer JT, Saltzman E, McCullough ML, Troy LM, Jacques PF. The 2005 dietary guidelines for Americans adherence index: development and application. *J Nutr*. 2006;136:2908-2915.

27. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15:573-585.

28. Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. *Appl Nurs Res*. 2000;13:209-213.

29. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.

30. Choi HS. Vitamin d status in Korea. *Endocrinol Metab (Seoul)*. 2013;28:12-16.

31. Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: What is the pathology? *Arch Neurol*. 2012;69:1245-1251.

32. Sayed N, Culver C, Dams-O'Connor K, Hammond F, Diaz-Arrastia R. Clinical phenotype of dementia after traumatic brain injury. *J Neurotrauma*. 2013;30:1117-1122.

33. Landel V, Annweiler C, Millet P, Morello M, Feron F. Vitamin D, cognition and Alzheimer's disease: the therapeutic benefit is in the D-tails. *J Alzheimers Dis*. 2016;53:419-444.

34. Banerjee A, Khemka VK, Ganguly A, Roy D, Ganguly U, Chakrabarti S. Vitamin D and Alzheimer's disease: neurocognition to therapeutics. *Int J Alzheimers Dis*. 2015;2015:192747.

Conflict of interest statement: This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (grant number: 2017R1C1B5018173).

Received 13 November 2018; accepted 27 February 2019

Citation: World Neurosurg. (2019). https://doi.org/10.1016/j.wneu.2019.02.244

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

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