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The association between the serum vitamin D levels and the stroke lesion size, functional ability, and cognition in elderly Korean ischemic stroke patients

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Abstract

The purpose of this study was to confirm the association between the serum vitamin D levels and ischemic stroke lesion size, functional ability, and cognitive function in elderly ischemic stroke patients. This study included Korean ischemic stroke patients aged 65 to 85 years. The size of the lesion was measured in brain images taken within 24 hours of hospitalization. The level of 25-(OH) Vitamin D (ng/mL), a metabolite of vitamin D, in the serum collected within 48 hours of hospitalization, and the modified Barthel index (MBI), gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and mini-mental status examination (MMSE) were recorded within 1 week of the onset of the disease. Each factor was compared through correlation analysis, and the significance was confirmed using the Spearman correlation coefficient method. The association between the serum vitamin D levels and the size of the ischemic stroke lesion, the MBI, gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and the MMSE were analyzed. It was confirmed that there was a significant correlation between all the factors ($P < .005$). In patients with serum vitamin D levels of ≥ 30 ng/mL, both the functional ability and cognitive functions were better than in patients lower than 30 ng/mL. We confirmed the lower the level of serum vitamin D levels, the larger the size of the ischemic stroke lesion when it occurred in elderly Koreans. And we confirmed that serum vitamin D levels affected the functional ability and cognitive function. And we recommend that elderly Koreans should maintain their blood vitamin D level above 30 ng/mL. We believe that this will help preserve the functional ability and cognitive function when ischemic stroke occurred.

Abbreviations: FIM = functional independence measure, MBI = modified Barthel index, MMSE = mini-mental status examination, MRI = magnetic resonance imaging, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale.

Keywords: cognition, functional status, stroke volume, vitamin D

1. Introduction

Vitamin D is a secosteroid hormone that plays important roles in several physiological processes such as mineral metabolism, bone metabolism, blood pressure regulation, muscle metabolism, immune response regulation, and cell proliferation.[1] Recently, there has been an increase in vitamin D deficiency cases among Koreans which has been attributed to a wide range of factors including old age, inadequate vitamin D intake, and inadequate exposure to sunlight due to increased indoor activities during the day.[2] Vitamin D deficiency has been reported as one of the risk factors for ischemic stroke,[3,4] and several studies have reported decreased serum vitamin D levels in ischemic stroke patients.[5–9] In addition, there are higher incidences of fractures or falls and prevalence of other cardiovascular diseases, malignancies, type 2 diabetes, and Alzheimer disease, in ischemic stroke patients with vitamin D deficiency, than in those without vitamin D deficiency.[5,10–13] Previous studies have examined the association between blood vitamin D levels and size of ischemic stroke lesion and mortality rate.[14–16] Some studies have also analyzed the results of functional recovery through the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS).[15,17,18] However, there are no studies on the association between serum vitamin D levels and ischemic stroke severity assessed by factors such as lesion size, functional ability, gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and cognitive function, in Korean ischemic stroke patients aged 65 to 85 years. The aim of this retrospective study was to investigate the association between serum vitamin D levels, and size of ischemic stroke lesion, functional ability, gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and cognitive function, in Korean ischemic stroke patients aged 65 to 85.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

This study included 82 patients aged 65 to 85 years, who were hospitalized with ischemic stroke from July 2013 to June 2021. Ischemic stroke was confirmed within 24 hours of hospitalization through a brain computed tomography or magnetic resonance imaging (MRI). The inclusion criteria were: patients diagnosed with ischemic stroke and measured serum vitamin D levels within 48 hours after hospitalization. The exclusion criteria were: patients with a history of stroke treatment before hospitalization, patients diagnosed with transient ischemic attacks, patients with a history of central nervous system disorders, such as brain trauma, cerebral hemorrhage, hydrocephalus, and Parkinson disease, patients with a history or undergoing treatment of diabetes, hypertension, hyperlipidemia, and heart disease, and patients with insufficient medical records. This study was approved by the Institutional Review Boards (IRB No. 2020-04-026).

The level of 25-(OH) Vitamin D (ng/mL), a metabolite of vitamin D, was measured using SIEMENS ADVIA Centaur XPT immunoassay system within 48 hours of hospitalization. We defined vitamin D deficiency as a level of 25-(OH) vitamin D below 20 ng/mL as defined by the World Health Organization and the American Medical Association.[19,20] We measured the size of the ischemic stroke lesion using the Image J (1.53e version, Fiji) program at the location where the ischemic stroke area was the largest on the axial view image of diffusion-weighted imaging in the brain MRI. We assessed the modified Barthel index (MBI) and gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and the mini-mental state examination (MMSE) within one week of ischemic stroke. The gait performance was divided into 4 categories: when gait was impossible, when gait was possible with assistance, when indoor gait was possible without assistance, and when outdoor gait was possible without assistance. The muscle power of hip and knee extensors on the hemiplegic side was measured using a manual muscle test, as 0 (muscle contraction is not felt), 1 (muscle contraction is visible or felt, but no movement), 2 (the full range of motion can be achieved after removal of gravity), 3 (the full range of motion can be achieved by resisting gravity), 4 (the full range of motion can be achieved by resistance to some pressure), 5 (the full range of motion can be achieved by resistance to strong pressure). The MMSE was determined using the Korean mini-mental status examination. All the tests were performed directly by an experienced rehabilitation physician. In addition, the onset period was analyzed by dividing the occurrence period into spring in March-May, summer in June-August, autumn in September-November, and winter in December-February to find out the differences in serum vitamin D levels and disease incidence between seasons.

The correlation between the serum 25-(OH)Vitamin D (ng/mL) level and the size of the lesion, MBI, the gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and the MMSE score were compared through correlation analysis and, the Spearman Correlation coefficient was calculated to confirm the association. One-way analysis of variance was used to compare demographic data, size of stroke lesion, functional abilities, and cognitive function within the groups divided by season. Mann–Whitney *U* test was used for the groups divided by sex and the groups divided based on the serum vitamin D level of 20 ng/mL. All statistical analysis was performed with SPSS for the Windows version, and statistical significance was defined as having a *P* value of < .005.

3. Results

1. Characteristics of the test subject: The present study included 82 ischemic stroke Korean patients aged between 65- and 85-year-old who were hospitalized from July 2013 to June 2021; 44 males (53.7%) and 38 females (46.3%). The mean age was 74.6 ± 6.1 years. Their demographic characteristics and stroke lesion sizes are presented in Table 1. There were no significant differences between the groups divided by seasons and sex. However, a significant difference was found between the vitamin D deficient group with serum vitamin D levels of < 20 ng/mL and a normal group with serum vitamin D levels of ≥ 20 ng/mL ($P < .005$).
2. The association between the serum vitamin D levels and size of stroke lesion in elderly ischemic stroke patients: The correlation coefficient between the serum vitamin D levels and size of ischemic stroke lesion which was calculated using the Spearman correlation coefficient method was, –0.604 for men, –0.628 for women, and –0.620 for men and women together (Table 2). All the *P* values were < .005, (significant negative correlation) (Table 2). When a linear graph was plotted through a scatterplot, the horizontal axis was the serum vitamin D levels and the vertical axis was the size of the stroke lesion, the graphs show a significant negative correlation with an explanatory power of 28.8% ($R^2 = 0.288$) for men, 21.0% ($R^2 = 0.210$) for women, and 19.2% ($R^2 = 0.192$) for men and women together (Fig. 1).
3. The association between the serum vitamin D levels and MBI in elderly ischemic stroke patients: The correlation coefficient between serum vitamin D level and MBI which was calculated using the Spearman correlation coefficient method, was 0.777 for men, 0.680 for women, and 0.742

Table 1

Patient characteristics.

Characteristics	N
Sex	
Male	44 (53.7%)
Female	38 (46.3%)
Age (yr)	
Total	74.6 ± 6.1
Male	73.4 ± 6.3
Female	76.0 ± 5.7
Cerebral infarction territory	
Middle cerebral artery	24 (29.3%)
Anterior cerebral artery	2 (2.4%)
Posterior cerebral artery	2 (2.4%)
Corona radiata	10 (12.2%)
Basal ganglia	10 (12.2%)
Pontine	10 (12.2%)
Thalamus	7 (8.5%)
Cerebellar	3 (3.7%)
Medulla	5 (6.1%)
Multifocal	9 (11.0%)
Involved cerebral infarction hemisphere of	
Right	28 (34.1%)
Left	46 (56.1%)
Both	8 (9.8%)
Seasons	
Spring (March, April, May)	31 (37.8%)
Summer (June, July, August)	8 (9.8%)
Fall (September,October, November)	19 (23.2%)
Winter (December, January, February)	24 (29.2%)

Values are mean ± standard deviation or number.

Table 2

Spearman correlation analysis between the serum 25(OH) vitamin D and size of stroke lesion, functional ability, and cognitive function.

		Size of stroke lesion	MBI score	Gait performance	Muscle power of hip and knee extensors (hemiplegic side)	MMSE
Total	R	–0.620*	0.742*	0.718*	0.735*	0.692*
	P value	<.005	<.005	<.005	<.005	<.005
Male	R	–0.604*	0.777*	0.823*	0.812*	0.574*
	P value	<.005	<.005	<.005	<.005	<.005
Female	R	–0.628*	0.680*	0.595*	0.652*	0.827*
	P value	<.005	<.005	<.005	<.005	<.005

MBI = modified Barthel index, MMSE = mini-mental state examination, R = Spearman rho.
*Correlation is significant at the 0.01 level (2-tailed).

for men and women together (Table 2). All the *P* values were < .005 (a significant positive correlation) (Table 2). When a linear graph was plotted through a scatterplot, the horizontal axis was the serum vitamin D level and the vertical axis was the MBI score, the graphs show a significant positive correlation with an explanatory power of 43.1% ($R^2 = 0.431$) for men, 33.6% ($R^2 = 0.336$) for women, and 37.2% ($R^2 = 0.372$) for men and women together (Fig. 2). In all the patients with serum vitamin D level of 30 ng/mL or higher, the MBI score was 75 or higher, which was classified as mild or minimal dependence (Fig. 2).

4. The association between the serum vitamin D levels and gait performance in the elderly ischemic stroke patients: The correlation coefficient between the serum vitamin D level and gait performance which was calculated using the Spearman correlation coefficient method, was 0.823 for men, 0.595 for women, and 0.718 for men and women together (Table 2). All the *P* values were < .005 (a significant positive correlation) (Table 2). The Spearman correlation coefficient showed a stronger positive correlation in men (0.823) than in women (0.595). When a box and whisker plot was drawn with the horizontal axis as gait performance and the vertical axis as serum vitamin D level, positive correlations were observed for all regardless of gender (Fig. 3). In all the patients with serum vitamin D levels of 30 ng/mL or higher, gait was possible with or without assistance (Fig. 3).
5. The association between the serum vitamin D levels and the muscle power of hip and knee extensors on the hemiplegic side in elderly ischemic stroke patients: The correlation coefficient between serum vitamin D level and the muscle power of hip and knee extensors on the hemiplegic side which was calculated using the Spearman correlation coefficient method, was 0.812 for men, 0.652 for women, and 0.735 for men and women as a whole (Table 2). All the *P* values were < .005, (a significant positive correlation) (Table 2). Spearman correlation coefficient showed a stronger positive correlation in men (0.812) than in women (0.652). Using the SPSS program, when a box and whisker plot were drawn with the horizontal axis as the muscle power of hip and knee extensors on the hemiplegic side and the vertical axis as serum vitamin D level, positive correlations were observed for all regardless of gender (Fig. 4). In all patients with serum vitamin D levels of 30 ng/mL or higher, the muscle power of hip and knee extensors was grade 4 (Fig. 4).
6. Association between the serum vitamin D levels and cognitive function in elderly ischemic stroke patients: The correlation coefficient between the serum vitamin D levels and cognitive function which was calculated using the Spearman correlation coefficient method, was 0.574 for men, 0.827 for women, and 0.692 for men and women together (Table 2). All the *P* values were < .005 (a significant positive correlation) (Table 2). The Spearman correlation coefficient showed a stronger positive correlation in women (0.827) than in men (0.574). When a linear graph was plotted through a scatterplot, the horizontal axis was the serum vitamin D level and the vertical axis is MMSE score, the graphs showed a significant positive correlation with an explanatory power of 28.6% ($R^2 = 0.286$) for men, 44.5% ($R^2 = 0.445$) for women, and 35.2% ($R^2 = 0.352$) for men and women together (Fig. 5). In the patients with serum vitamin D levels of 30 ng/mL or higher, the MMSE score was ≥ 24, which is diagnostic score for mild cognitive impairment (Fig. 5).

4. Discussion

Vitamin D, which plays important role in a wide range of physiological processes, is absorbed through the intestine or synthesized through photolysis of provitamin D by ultraviolet B in the skin.[21] Vitamin D is stored in the body in the form of vitamin D3 (cholecalciferol), converted to 25-hydroxyvitamin D (25-(OH) vitamin D) in the liver, and converted to 1,25-dihydroxyvitamin D, which is the active form of vitamin D, in the kidneys.[1] The active form of vitamin D enhances the absorption of calcium and phosphorus in the intestine and improves neuromuscular function by increasing protein synthesis in the muscles.[1] In addition, it plays a neuroprotective role by promoting the production of specific neuroprotective growth factors, reducing arterial pressure through vasodilation, and inhibiting free radicals.[8,16,22,23] Serum vitamin D levels decrease as the conversion of vitamin D into the active form in the skin or kidneys decreases due to poor intake or a decrease in exposure to sunlight due to an increase in time spent indoor living for example in the aged.[24] According to data from the Health Insurance Review and Assessment Service of Korea, from 2013 to 2017, the number of vitamin D deficiency patients increased from 18,700 to 90,000 which is an annual average of 48.1%. In addition, in a study by Kim et al, vitamin D deficiency was confirmed in 62.1% of the elderly Korean (65 years or older).[2]

To determine the level of serum vitamin D in ischemic stroke patients aged 65 to 85, we measure and analyzed the levels of 25-(OH) Vitamin D(ng/mL) because it is the most stable and abundant vitamin D in human serum and a metabolite that is an indicator of the supply rather than the function of vitamin D.[3,25]

First, considering the antecedent relationship of vitamin D deficiency observed in ischemic stroke patients in this study, the biological half-life of 25-(OH) Vitamin D was 3 weeks. Given that blood was collected within 48 hours after hospitalization, it can be expected that it preceded ischemic stroke, not due to hormone synthesis or a decrease in the existing vitamin D after ischemic stroke.[6]

Turetsky et al[14] reported that in a study comparing the relationship between serum vitamin D levels and lesion size, NIHSS

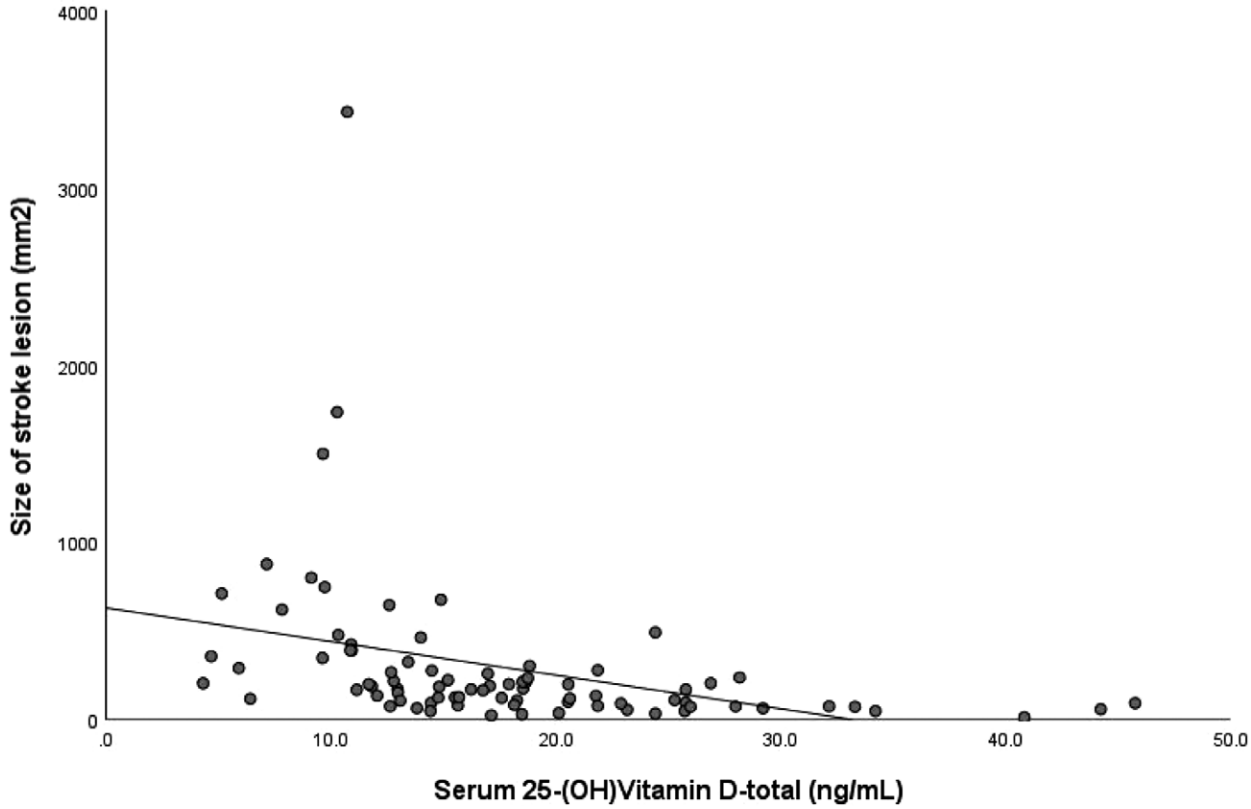

Figure 1. The association between the serum 25-(OH) Vitamin D and size of stroke lesion (mm^2) in all the patients. R^2 was −0.602.

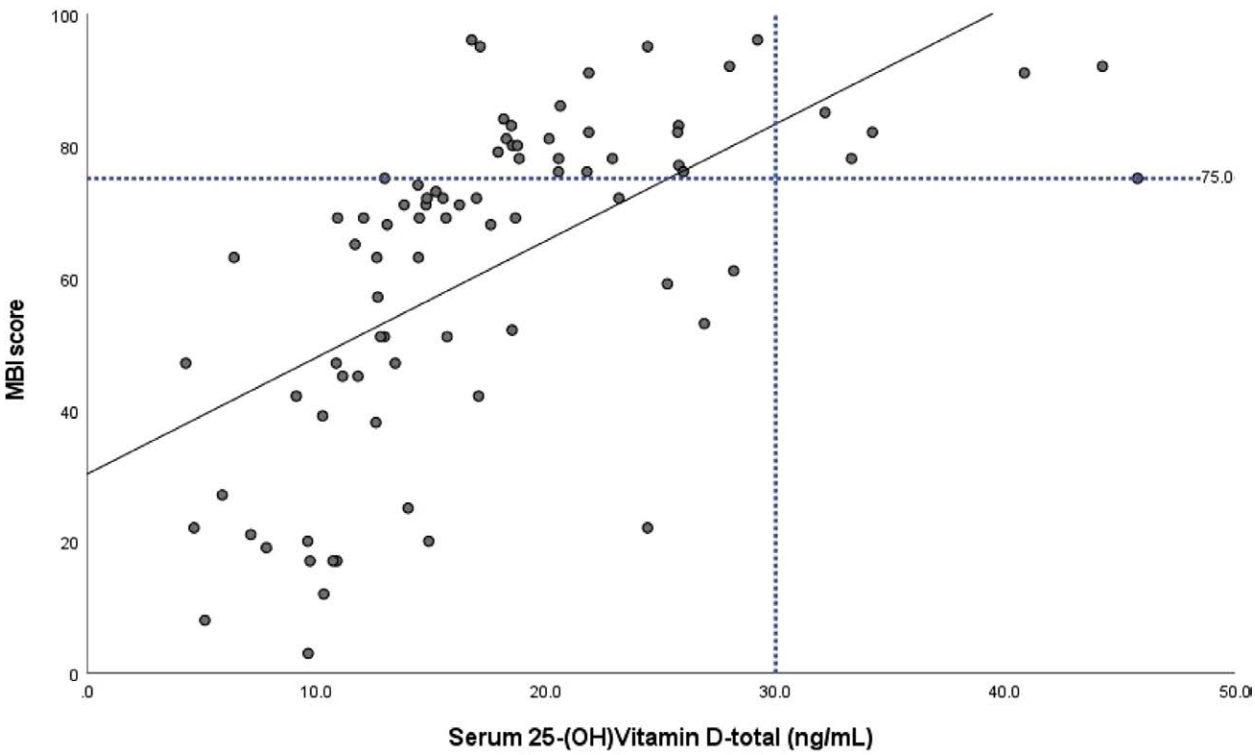

Figure 2. The association between the serum 25-(OH) Vitamin D and MBI in all the patients. R^2 was 0.372. In all the patients with serum vitamin D level of 30 ng/mL or higher (vertical dotted line), the MBI score was 75 or higher (horizontal dotted line), which was classified as mild or minimal dependence. MBI = modified Barthel index.

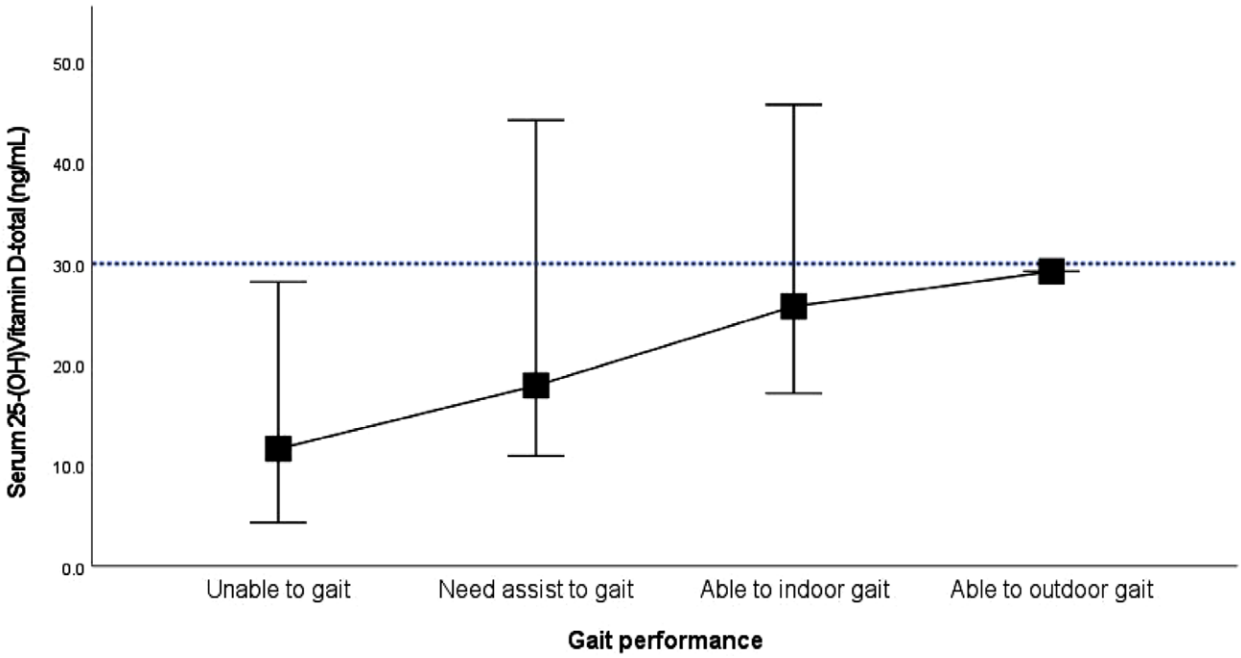

Figure 3. The association between the serum 25-(OH) vitamin D level and gait performance in all the patients. In all the patients with serum vitamin D levels of 30 ng/mL or higher (horizontal dotted line), gait was possible with or without assistance.

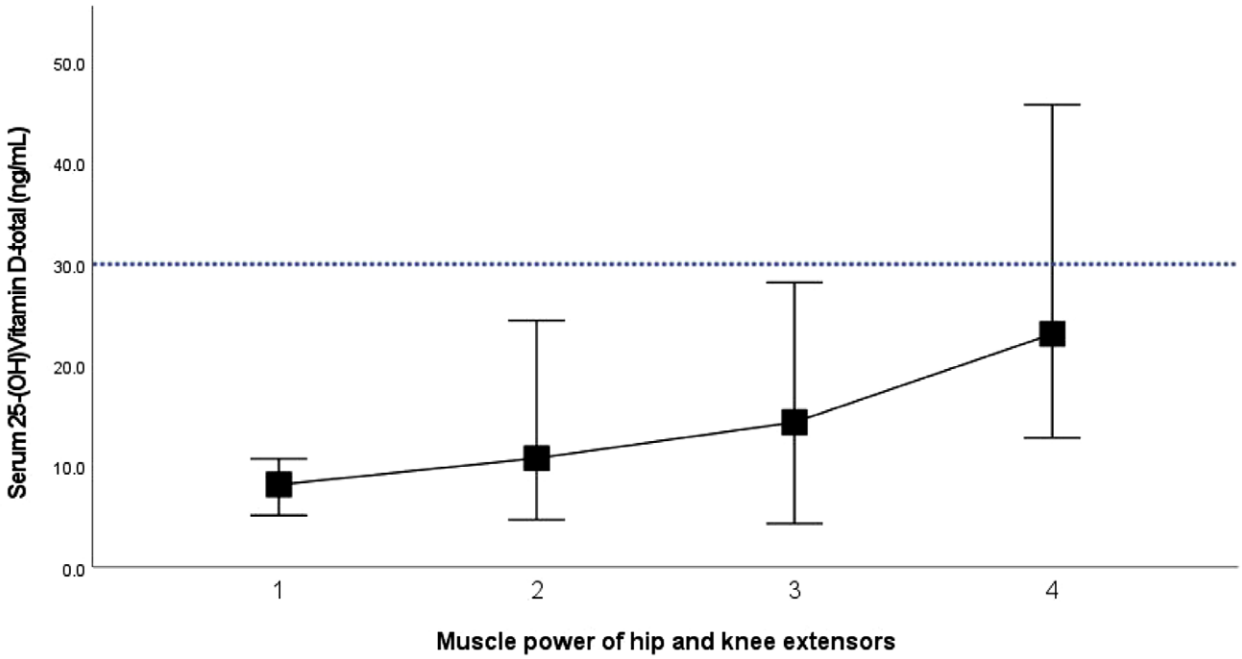

Figure 4. Association between the serum 25-(OH) Vitamin D and the muscle power of hip and knee extensors on hemiplegic side in all the patients. In all patients with serum vitamin D levels of 30 ng/mL or higher (horizontal dotted line), the muscle power of hip and knee extensors was grade 4.

score at hospitalization in ischemic stroke patients, the lower the serum vitamin D level, the larger the size of the ischemic stroke lesion, and the higher the NIHSS score. In our study, when ischemic stroke occurred, the serum vitamin D levels and the size of the ischemic stroke lesion showed a negative correlation with the correlation coefficient of –0.620 ($P < .005$). When ischemic stroke occurred, there was a positive correlation with a correlation coefficient of 0.742 ($P < .005$) with the MBI score, a positive correlation with a correlation coefficient of 0.718 with the gait performance ($P < .005$), and a positive correlation with a correlation coefficient of 0.735 with the hip muscle power and knee extensors on the hemiplegic side ($P < .005$). The results of this study are similar to Turetsky et al's[14] study comparing serum vitamin D levels and ischemic stroke lesion sizes; The higher the blood vitamin D levels, the smaller the ischemic stroke lesion size, and the better the preservation of functional abilities, including gait.

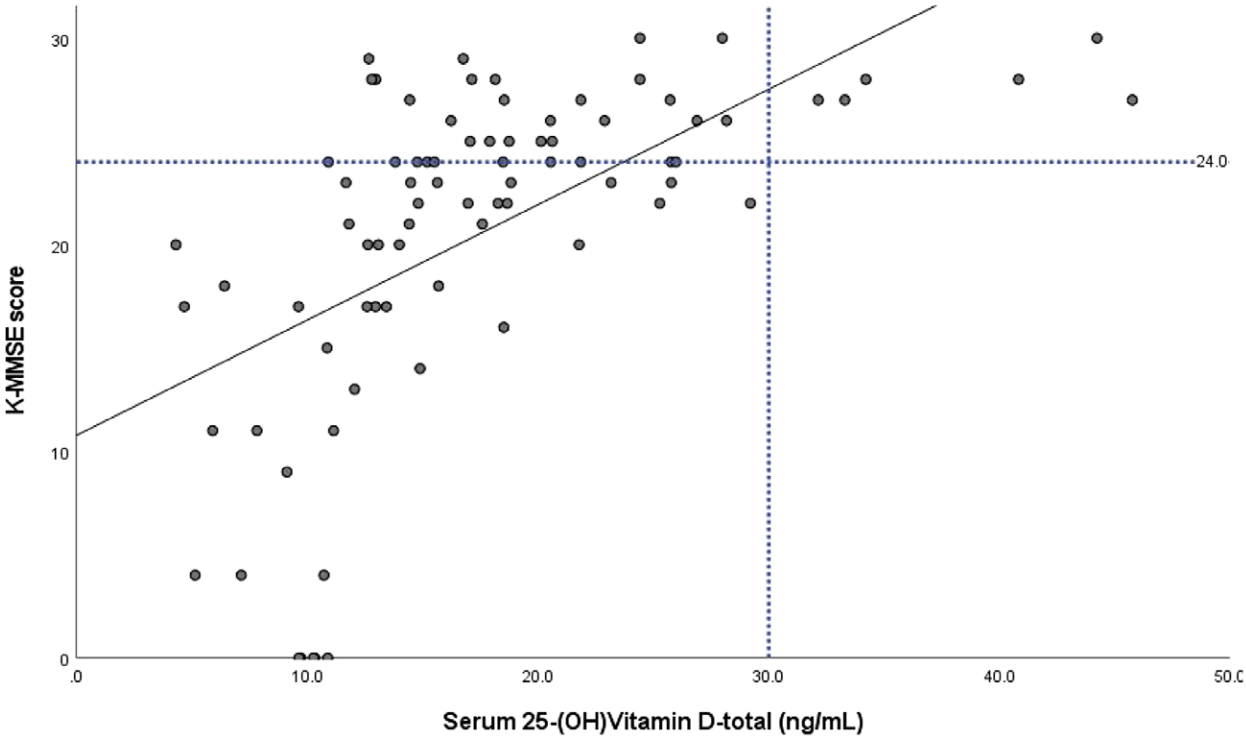

Figure 5. The association between the serum 25-(OH) Vitamin D and cognitive function in all patients. R^2 was 0.352. In all patients with serum vitamin D levels of 30 ng/mL or higher (vertical dotted line), the K-MMSE score was ≥ 24 (horizontal dotted line), which is diagnostic score for mild cognitive impairment. K-MMSE = Korean mini mental screening examination.

Kim et al[26] reported that in a study of the relationship between serum vitamin D levels and poststroke depression in 126 stroke patients, there was no significant correlation between the serum vitamin D levels and MBI score. These findings are contrary to those of the present study where we demonstrated a significant positive correlation between the two. Kim et al[26] did not measure the serum vitamin D levels and MBI score at the time of stroke and performed the above 2 tests without specifying the period from the onset of the disease to the test period. This difference is thought to have occurred because the serum vitamin D levels and the MBI score were evaluated within one week after the onset of the ischemic stroke.

Park et al[27] reported that in a study of 818 ischemic stroke patients with high vitamin D levels showed particularly good functional recovery results when assessed by mRS, whereas low vitamin D levels resulted in poor functional recovery results. These findings suggest that vitamin D levels are one of the predictors of ischemic stroke prognosis in patients. In addition, Markišić et al[28] studied the association of serum vitamin D levels and functional recovery results in patients with first-ever ischemic stroke using NIHSS at the time of hospitalization, 3 months, and 6 months after hospitalization. There was no clear association between vitamin D and functional recovery results after 3 and 6 months of the onset of the disease.[28] However, they reported that there was a positive correlation between serum vitamin D levels and the NIHSS results at the time of hospitalization, the lower the blood vitamin D levels, the worse prognosis for ischemic stroke patients. This indicates that serum vitamin D levels can help predict the severity of the disease when ischemic stroke occurs.

Sato et al[29] did a case-control study of 96 elderly poststroke hemiplegic female patients with 25-(OH) Vitamin D deficiency (<10 ng/mL). They were divided into 2 groups; 48 experimental groups as patients were given 1000 international unit of ergocalciferol daily and control group and followed for 2 years. In 48 patients taking 1000 international unit ergocalciferol, an increase in the number and size of type 2 muscle fibers, and an improvement in muscle strength were observed. In addition, the fall was reduced by 84%.[29] These findings suggest that maintaining adequate serum vitamin D levels may help restore functional abilities in elderly stroke patients.

Yalbuzdag et al[13] reported a negative correlation between the serum 25(OH)D levels and cognitive function in a retrospective study including 120 stroke patients who participated in a neurological rehabilitation program. In another prospective study including 354 patients with ischemic stroke, Chen et al[30] reported a negative correlation between the serum vitamin D levels and cognitive function. This is consistent with the results of this study where the serum vitamin D levels and the MMSE score had a positive correlation of 0.692 ($P < .005$). In addition, Ozdemir et al[31] studied the association between cognitive function evaluated through MMSE and functional ambulation evaluated through functional independence measure (FIM) and Adapted Patient Evaluation Conference System in 54 stroke patients diagnosed with stroke. They reported that the better the score of the MMSE, the greater the improvement of the patient's FIM score and functional ambulation at discharge.[31] This suggests that the degree of cognitive impairment in the event of a stroke may affect the degree of the patient's functional recovery and may be an important prognostic factor.

In this study, we observed a negative correlation between the serum vitamin D levels and lesion size of Korean ischemic stroke patients aged 65 to 85 and a positive correlation with the functional ability, gait performance, the muscle power of hip and knee extensors on the hemiplegic side and cognitive function. The gait performance and the muscle power of hip and knee extensors on the hemiplegic side had a stronger correlation with the serum vitamin D levels in men and cognitive function in women. Considering that previous studies had shown that the size of ischemic stroke lesions is correlated with the neurological and functional recovery results,[32] indicating that the serum vitamin D levels influenced the size of the lesion, and as a result, it influenced the degree of impairment of motor function and cognitive function. And we think that the reason why there were

no significant differences when divided by season and sex is that outdoor activities decrease with age.

Currently, the precise mechanism through which serum vitamin D levels influence the size, functional impairment, and cognitive impairment of stroke lesions is not known. However, in this study, there was a significant difference between the vitamin D deficiency patient group and the normal patient group divided based on the serum vitamin D level of 20 ng/mL. Considering the positive correlation between the serum vitamin D levels and functional ability, gait performance, and the muscle power of hip and knee extensors on the hemiplegic side, we suggest that in elderly Koreans aged 65 to 85 years with a high incidence of ischemic stroke, prevention of vitamin D deficiency can reduce the size of ischemic stroke when it occurred and further reduces the degree of functional and cognitive impairment. In addition, in this study, when the serum vitamin D levels were ≥ 30 ng/mL, MBI score, gait performance, the muscle power of hip and knee extensors on the hemiplegic side, and MMSE score were especially good (Figs. 2, 3, 4, 5). Accordingly, we strongly recommend that Koreans aged 65 to 85 years should maintain their serum vitamin D level above 30 ng/mL as this may help preserve the patient's functional and cognitive function in the event of a stroke.

The limitation of this study is a small sample size which was not sufficient because patients with underlying diseases were excluded and after the ischemic stroke, follow-up on vitamin D levels was not performed. To clearly elucidate the relationship between the serum vitamin D levels and ischemic stroke severity, continuous follow-up studies including an evaluation of long-term prognosis of chronic state patients with ischemic stroke are required.

5. Conclusion

In this study, we found that the lower the serum vitamin D levels in ischemic stroke Korean patients aged 65 to 85, the larger the lesion size at the time of the disease, and the worse functional impairment including gait and cognitive impairment. Therefore, considering the increase in the incidence of ischemic stroke due to old age among the Koreans aged 65 to 85 years without underlying disease, we strongly recommended that the serum vitamin D level should be maintained at > 30 ng/mL. Based on the previous studies and the present study findings, this will help preserve the motor and cognitive functions and the size of the lesion.

Author contributions

Conceptualization: Jun Young Park, Ju Hyeon Kim, Jae Hyun Lee, Young Joo Sim, Ho Joong Jeong, Ghi Chan Kim.
Data curation: Jun Young Park, Ju Hyeon Kim, Ghi Chan Kim.
Formal analysis: Jun Young Park.
Investigation: Ghi Chan Kim.
Methodology: Ghi Chan Kim.
Project administration: Ghi Chan Kim.
Software: Ghi Chan Kim.
Supervision: Jae Hyun Lee, Young Joo Sim, Ho Joong Jeong.
Validation: Ghi Chan Kim.
Writing – original draft: Jun Young Park, Jae Hyun Lee.
Writing – review & editing: Jun Young Park, Young Joo Sim, Ho Joong Jeong, Ghi Chan Kim.

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