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Serum vitamin D levels and peak cough flow in patients with subacute ischemic stroke

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Abstract

Aspiration pneumonia is a major, potentially fatal complication after ischemic stroke. Decreased coughing function is a significant risk factor for aspiration in ischemic stroke survivors. Peak cough flow (PCF) is a useful tool for assessing cough function. Vitamin D deficiency is frequent after ischemic stroke and is linked to a variety of muscle functions and physical activities. There has been no investigation of the correlation between vitamin D levels and PCF in ischemic stroke survivors. This study aimed to examine the relationship between serum vitamin D levels and PCF in patients with ischemic stroke. Patients with ischemic stroke who underwent PCF evaluation and serum vitamin D level measurements within 1 month of onset were retrospectively recruited. The association between PCF parameters and serum vitamin D levels was also analyzed. In total, 142 patients with ischemic stroke were included. PCF parameters and serum vitamin D levels were found to be significantly correlated. Moreover, serum vitamin D levels were shown to be a significant predictor of PCF parameters. Serum vitamin D levels were related to PCF parameters in patients with ischemic stroke. In addition, serum vitamin D level may serve as a predictor of coughing function in patients with ischemic stroke.

Abbreviations: FEV-1 = forced expiratory volume in 1 second, MBI = modified Barthel index, MMSE = Mini-Mental State Examination, PCF = peak cough flow, PEF = peak expiratory flow, VDR = vitamin D receptor.

Keywords: ischemic stroke, peak cough flow (PCF), peak expiratory flow, vitamin D

1. Introduction

Aspiration pneumonia is a major complication which can lead to death after ischemic stroke.[1,2] The prevalence of pneumonia among ischemic stroke survivors is reported to be approximately 11 to 31%.[3–5] To decrease respiratory mortality in patients with ischemic stroke, it is crucial to understand the physiology of coughing dysfunction following stroke. Aspiration risk may be increased in many individuals with respiratory complications due to reduced cough reflex, poor clearance of secretions, and swallowing abnormalities.[6] Peak cough flow (PCF) is a measure used to objectively evaluate cough function.[7] A low PCF has been reported as one of the predictors of an increased risk of aspiration pneumonia.[8] Reflex cough is caused by afferent activation and is controlled by the brainstem[6]; this serves to protect the airway from aspiration.[6] Voluntary cough is achieved by respiratory muscles including the diaphragm, and is controlled by the cerebral cortex.[6] It is known that patients with ischemic stroke have poor PCF due to diminished cortical respiratory movement and weakened respiratory muscles.[6] Previous studies have shown that although the center for controlling cough is in the brain stem, diaphragmatic movement is facilitated by cortical-respiratory projections across the cortex, which are involved in the supra-medullary regulation of coughing.[9] Further studies have reported that cough is induced through electrical stimulation in the cortex, such as the supplementary motor areas and suprasylvian gyrus.[10] Therefore, depending on the brain lesion, the effect on cough function may be different.

In patients with ischemic stroke, the prevalence of vitamin D insufficiency was greater than in general medical patients,[11,12] reported to reach approximately 70%.[13] Ischemic stroke and vitamin D insufficiency are both associated with a high inflammatory burden and characterized by elevated inflammatory markers.[14,15] Decreased vitamin D levels may also be a hallmark of inflammatory conditions.[16,17] Therefore, evaluation of vitamin D levels in patients with ischemic stroke is warranted. Vitamin D is known as a micronutrient that affects calcium and bone metabolism. However, recent studies have shown that it has diverse physiological functions, with particular effects on the immune system and muscular function. Furthermore, vitamin D levels have been related to the presence of the vitamin D receptor (VDR) in the tissues.[18] Decreased serum vitamin D concentrations are known to be linked to decreased muscle strength and endurance.[19–22] Vitamin D affects calmodulin and insulin-like growth factor binding proteins involved in the synthesis of muscle cytoskeletal proteins,[23,24] and further affects the metabolism of phospholipids involved in muscle contraction, promoting muscle proliferation and differentiation.[25,26] Vitamin D also impacts

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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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muscle development and cell proliferation via stimulation of the mitogen-activated protein kinase signaling pathway.[27,28] Vitamin D deficiency has previously been linked with muscular atrophy and fat infiltration, which leads to prolonged muscle relaxation time and muscle fatigue and reduced maximal muscle contractility.[29] The respiratory muscles, like other musculoskeletal muscles, are susceptible to muscle dysfunction due to vitamin D deficiency. In addition, vitamin D has been linked to cough function and pulmonary function in several studies.[30–32]

As yet, there has been no study investigating the correlation between vitamin D levels and PCF in patients with ischemic stroke. This study therefore aimed to examine the relationship between serum vitamin D concentration and PCF in patients with ischemic stroke.

2. Methods

2.1. Subjects

A retrospective study was performed on patients with ischemic stroke admitted to Kyung Hee University Hospital in Gangdong from January 2019 to October 2022. Patients who underwent blood tests to measure serum vitamin D concentration and PCF tests to evaluate cough function within 1 month of onset were enrolled. To ensure the selection of patients with sufficient cognitive function to perform the PCF test, patients with a Mini-Mental State Examination (MMSE) score of ≥20 were selected. Patients with a history of stroke, traumatic brain injury, or brain tumor were excluded to rule out brain lesions that may influence the test findings. Neurological conditions that could affect PCF, such as motor neuron disease, spinal cord injury, pulmonary diseases such as restrictive lung disease and chronic obstructive pulmonary disease, cardiac disease such as heart failure, and coronary artery disease, were excluded. Patients with a history of urolithiasis, fractures, dysphagia, and medical conditions affecting nutrient absorption, such as celiac disease, Crohn disease, liver disease, chronic kidney disease, hyperparathyroidism, and history of steroid therapy, which may be secondary causes, were also excluded.

Despite the fact that vitamin D levels are a continuous variable, the groups were separated into a normal and vitamin D deficiency group for comparison to determine whether there was a difference in PCF between groups. Vitamin D deficiency has previously been indicated at serum concentrations of <20 ng/mL of 25-hydroxyvitamin D.[33] In the analysis to confirm the association, since the effect on cough function may be different depending on the brain lesion, the analysis was performed by dividing the non-brain stem lesion and the brain stem lesion. The study was performed according to a protocol authorized by the Institutional Review Board of Kyung Hee University Hospital in Gangdong, Korea (IRB approval number: 2022-11-036).

2.2. Serum vitamin D level

Serum 25-hydroxyvitamin D levels were measured using the Architect 25-OH D vitamin kit (Abbott Diagnostics, Lake Forest, IL), within 1 month of ischemic stroke onset.

2.3. PCF

The PCF test was performed by a rehabilitation specialist and physical therapist using a peak flow meter (Philips Respironics Inc., Murrysville, PA). The patient was instructed to inhale deeply and cough as forcefully as possible while sitting upright. The PCF test was performed 3 times, and the highest peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV-1) values were chosen for the study.

2.4. Statistical analysis

Variables were examined statistically using SPSS version 20.0 for Windows (IBM Corp., Armonk, NY). Levene test was used to examine the homogeneity of the variance. The Kolmogorov–Smirnov test was used to assess the distributional normality of continuous variables, including age, body mass index, MMSE, modified Barthel index (MBI), serum vitamin D level, PEF, and FEV-1. In the comparison between groups, continuous variables were analyzed using the independent *t* test, while categorical variables including gender, smoking, regular alcohol use, brain lesion location, and comorbidities were analyzed using the chi-square test. The relationship between serum vitamin D levels and PCF parameters was analyzed using the Pearson correlation analysis. Multiple linear regression analysis was performed with stepwise adjustment for sociodemographic variables, lifestyle factors, comorbidities, MBI, MMSE, and the effect of serum vitamin D level on PCF parameters. In all statistical tests, a P value <.05 was deemed statistically significant.

3. Results

3.1. Baseline characteristics

A total of 142 patients with a mean age of 62.65 ± 14.28 years comprising 67 males and 75 females were recruited. The mean MMSE was 20.78 ± 1.81, the MBI was 38.65 ± 17.37, and the serum vitamin D level was 21.49 ± 8.26 ng/mL. In terms of PCF parameters, the mean PEF was 375.51 ± 145.76 L/min, and the mean FEV-1 was 1.95 ± 0.84 L. Baseline characteristics, lifestyle factors, brain lesions, and comorbidities are shown in Table 1.

3.2. Comparison of PCF between vitamin D deficiency and normal groups

Sociodemographic and lifestyle factors, brain lesions, comorbidities, MMSE, MBI, PEF, and FEV-1 between the vitamin D deficiency group and the normal group are shown in Table 2.

Table 1

Demographic characteristics of the study participants.

Characteristic	Value
Sociodemographic characteristics	
Age (yr)	62.65 ± 14.28
Male	67 (47.20)
Female	75 (52.80)
Lifestyle characteristics	
BMI (kg/m^2)	23.38 ± 3.04
Smoking	28 (19.70)
Regular alcohol use	60 (42.30)
Brain lesion location	
Brain stem	53 (37.30)
Non-brain stem	89 (62.70)
Comorbidities	
Hypertension	88 (62.00)
Arrhythmia	50 (35.20)
Diabetes mellitus	85 (59.9)
Dyslipidemia	124 (87.30)
MMSE	20.78 ± 1.81
MBI	38.65 ± 17.37
Serum vitamin D level (ng/mL)	21.49 ± 8.26
PEF (L/min)	375.51 ± 145.76
FEV-1 (L)	1.95 ± 0.84

Values are presented as mean ± standard deviation or number (%).

BMI = body mass index, FEV-1 = forced expiratory volume in 1 second, MBI = modified Barthel index, MMSE = Mini-Mental State Examination, PEF = peak expiratory flow.

Using the Kolmogorov–Smirnov test, all continuous variables were normally distributed. There were no statistically significant differences between the groups in terms of sociodemographic factors, lifestyle factors, or brain lesions. Regarding comorbid diseases, 71 (68.90%) and 29 (28.20%) patients in the vitamin D deficiency group had a history of hypertension and arrhythmia, respectively, and 17 (43.60%) and 21 (53.80%) patients in the normal group, had a history of arrhythmias, which showed a statistically significant difference. The PEF and FEV-1 were 352.62 ± 132.40 L/min and 1.91 ± 0.84 L in the vitamin D deficiency group, respectively, which were significantly lower than 435.95 ± 163.13 L/min and 2.25 ± 0.78 L in the normal group, respectively.

3.3. Association between serum vitamin D level and PCF

The results of the correlation analyses between PEF, FEV-1, and serum vitamin D levels are shown in Table 3. Using the Kolmogorov–Smirnov test, all continuous variables were normally distributed. In the correlation analysis of all patients, we observed a statistically significant correlation between serum vitamin D levels and PEF (R = 0.198, P = .018) and FEV-1 (R = 0.234, P = .005). In the brainstem lesion group, there was a statistically significant correlation between serum vitamin D levels and PEF (R = 0.076, P = .048) and FEV-1 (R = 0.290, P = .035). In the non-brainstem lesion group, there was a statistically significant correlation between serum vitamin D levels and PEF (R = 0.245, P = .021, FEV-1 (R = 0.319, P = .002).

Table 4 presents the results of multiple regression analysis. This analysis revealed that the serum vitamin D level (standardized β = 0.335, B = 6.006, P < .001) was a significant predictor of PEF (adjusted R^2 = 0.106) in all patients, and was also a significant predictor (standardized β = 0.370, B = 0.039, P < .001) of FEV-1 (adjusted R^2 = 0.131). Serum vitamin D level (standardized β = 0.362, B = 5.868, P = .002) was a significant predictor of PEF (adjusted R^2 = 0.119) in the brainstem lesion group. The serum vitamin D level (standardized β = 0.417, B = 0.038, P < .001) was a significant predictor of FEV-1 (adjusted R^2 = 0.162). Serum vitamin D level (standardized β = 0.300, B = 6.618, P = .012) was a significant predictor of PEF (adjusted R^2 = 0.077) in the non-brainstem lesion group. The serum vitamin D level (standardized β = 0.340, B = 0.047, P = .004) was a significant predictor of FEV-1 (adjusted R^2 = 0.102).

4. Discussion

To the best of our knowledge, this is the first study to analyze the relationship between serum vitamin D levels and PCF parameters in patients with subacute ischemic stroke. Our investigation showed that PEF and FEV-1 levels were significantly lower in subacute ischemic stroke patients with vitamin D deficiency. Serum vitamin D levels, PEF, and FEV-1 were all significantly correlated in both the brain stem lesion and non-brain stem lesion groups. These results suggest that serum vitamin D level may be a significant predictor of cough function in patients with subacute ischemic stroke.

Several studies have investigated how vitamin D affects cough function; however, the underlying mechanism is not fully understood. Nevertheless, it is well known that vitamin D has a significant impact on the musculoskeletal function associated with

Table 2

Comparison of peak cough flow between vitamin D deficiency and normal groups.

	Vitamin D deficiency group (n = 103)	Normal group (n = 39)	*P* value
Sociodemographic characteristics			
Age (yr)	62.36 ± 14.43	63.41 ± 14.05	.700
Male	49 (47.60)	18 (46.20)	.880
Female	54 (52.40)	21 (53.80)	
Life style characteristics			
BMI (kg/m^2)	23.27 ± 3.07	23.66 ± 2.97	
Smoking	11 (10.70)	6 (15.40)	.441
Regular alcohol use	40 (38.80)	20 (51.30)	.180
Brain lesion location			
Brain stem	36 (35.00)	17 (43.60)	.342
Non-brain stem	67 (65.00)	22 (56.40)	
Comorbidities			
Hypertension	71 (68.90)	17 (43.60)	.005*
Arrhythmia	29 (28.20)	21 (53.80)	.004*
Diabetes mellitus	65 (63.10)	20 (51.30)	.199
Dyslipidemia	88 (85.40)	36 (92.30)	.272
MMSE	20.73 ± 1.81	20.89 ± 1.84	.642
MBI	38.07 ± 18.24	40.17 ± 14.94	.522
PEF (L/min)	352.62 ± 132.40	435.95 ± 163.13	.002*
FEV-1 (L)	1.91 ± 0.84	2.25 ± 0.78	.028*

Values are presented as mean ± standard deviation or number (%).

BMI = body mass index, FEV-1 = forced expiratory volume in 1 second, MBI = modified Barthel index, MMSE = Mini-Mental State Examination, PEF = peak expiratory flow.

* P < .05.

** P < .001.

Table 3

Correlation between serum vitamin D level and peak cough flow.

	PEF	FEV-1
Total	R = 0.198 P = .018*	R = 0.234 P = .005*
Brain stem lesion	R = 0.076 P = .048*	R = 0.290 P = .035*
Non-brain stem lesion	R = 0.245 P = .021*	R = 0.319 P = .002*

FEV-1 = forced expiratory volume in 1 second, PEF = peak expiratory flow.

* P < .05.

Table 4

Multiple linear regression of serum vitamin D level as a predictor of peak cough flow.

	Dependent variable	Independent variable	Standardized β	B	95% CI	*P* value	VIF	Adjusted R^2
Total	PEF	Constant		259.813				0.106
		Serum vitamin D level	0.335	6.006	(3.183, 8.829)	<.001**	1.000	
	FEV-1	Constant		1.231				0.131
		Serum vitamin D level	0.370	0.039	(0.023, 0.056)	<.001**	1.000	
Brain stem lesion	PEF	Constant		266.462				0.119
		Serum vitamin D level	0.362	5.868	(2.267, 9.470)	.002*	1.000	
	FEV-1	Constant		1.315				0.162
		Serum vitamin D level	0.417	0.038	(0.018, 0.058)	<.001**	1.000	
Non-brain stem lesion	PEF	Constant		241.532				0.077
		Serum vitamin D level	0.300	6.618	(1.527, 11.709)	.012*	1.000	
	FEV-1	Constant		0.995				0.102
		Serum vitamin D level	0.340	0.047	(0.016, 0.078)	.004*	1.000	

Variables were based on their order of listing in the multiple regression analysis.

CI = confidence interval, FEV-1 = forced expiratory volume in 1 second, PEF = peak expiratory flow, VIF = variance inflation factor.

* $P < .05$,

** $P < .001$.

physical performance.[34] Additionally, it is connected with muscular strength, fatigability, and endurance.[19] Calcitriol stimulates the nuclear VDR, which, through a transcription factor, begins the genomic route and promotes the synthesis of muscular cytoskeletal protein, comparable to growth factor-binding proteins and calmodulin that are essential for muscular function.[34] It is believed that the activation of VDR affects phospholipid metabolism, a crucial component in muscle contraction.[29] In addition, in vitro studies have shown that vitamin D regulates the function of immune cells.[35] There is also evidence to suggest that vitamin D deficiency may impair lung host defense, leading to the development of aberrant flora that induces inflammation.[35] High concentrations of vitamin D-binding protein are correlated with low concentrations of free vitamin D metabolites, which may promote macrophage activation and decrease FEV-1.[36] In addition, VDR mutant mice exhibited an increase in inflammatory cell infiltration, phosphorylation of nuclear factors, proinflammatory mediators, and pulmonary matrix metalloproteinases,[37] which was related to pulmonary function decrease and emphysema.[37] These findings suggest that the loss of the VDR may result in the initiations of emphysema at an earlier age, presumably owing to inflammation, immunological dysregulation, and lung damage.[37]

Several muscles are also involved in coughing. Ischemic stroke survivors are known to have compromised corticodiaphragmatic circuits, which may result in aberrant diaphragmatic movement.[38] Due to the disruption of the medullary and cortical regions involved in cough formation, both reflexive and voluntary cough may be altered by ischemic stroke.[39,40] These 2 forms of cough have comparable characteristics, including a 3-phase inspiration pattern followed by evacuation by respiratory muscles.[41] The temporal region and supramarginal gyrus comprise sensorimotor areas and are known to be related to poor motor activation in cough.[42] Reflex cough and voluntary cough have similarities in terms of muscle activation, suggesting a possible role for the supramarginal gyrus and temporal regions in the motor component of cough, as well as a potentially important role in protection against aspiration.[42]

A decreased coughing function is a significant risk factor for aspiration in patients with ischemic stroke. Therefore, proper evaluation and management of coughing function are important to maintain a good prognosis in ischemic stroke survivors and to maximize the outcome of rehabilitation treatment. According to the results of this study, serum vitamin D levels are a significant predictor of cough function. Therefore, measuring vitamin D concentration in patients with ischemic stroke may be helpful in predicting coughing function. Accurately predicting the coughing function of patients with ischemic stroke may help predict the risk of fatal aspiration pneumonia and lower mortality. It may also provide objective evidence for the usefulness of measuring serum vitamin D levels in patients with ischemic stroke.

The limitations of this study are its retrospective cross-sectional design, and the small number of participants. Second, only PEF and FEV-1, which can be measured using a peak flow meter, were performed to evaluate cough function. Therefore, a large-scale prospective longitudinal study that includes other indicators to evaluate coughing function is needed in the future.

In conclusion, serum vitamin D levels are associated with PCF parameters in patients with ischemic stroke. In addition, serum vitamin D level may serve as a predictor of coughing function in patients with ischemic stroke.

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