

Serum Vitamin D and Recurrent Benign Paroxysmal Positional Vertigo

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Objectives: The objective of the present study was to examine the effects of serum 25-hydroxyvitamin D concentrations on patients diagnosed with benign paroxysmal positional vertigo (BPPV) on BPPV recurrence.

Study Design: Case series.

Methods: A retrospective review of 232 patients diagnosed with BPPV visiting the clinic between June 2014 and June 2015 was performed. All patients underwent a complete otolaryngological, audiologic, and neurologic evaluation. The appropriate particle-repositioning maneuver was performed depending on the type of BPPV. The patients were divided into the recurrence group and the nonrecurrence group. Age, gender, follow-up period, type of BPPV, and vitamin D concentrations in the two groups were compared and analyzed through binary logistic regression analyses.

Results: The average follow-up period after treatment was 10.2 months. Forty-one (17.7%) of 232 patients suffered a recurrence during the follow-up period. The mean vitamin D concentration of 191 patients who did not suffer any recurrence was 16.63 ng/mL, whereas that of 41 patients who suffered a recurrence was 13.64 ng/mL. This difference in vitamin D concentrations was statistically significant ($P < 0.019$). The patients' age, gender, follow-up period, and type of BPPV had no statistically significant impact.

Conclusion: Vitamin D is assumed to affect BPPV as a recurrence factor independent of age, gender, follow-up period, and type of BPPV.

Key Words: Vitamin D, benign paroxysmal positional vertigo, recurrence, logistic regression.

Level of Evidence: 4.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a disease known to cause clinical symptoms when body positions change due to otoconia that has become dislodged from the macula of the utricle or the saccule and has entered the semicircular canal or attached to the cupula. Otoconia consist of the crystals of its main components, calcium carbonate and glycoproteins, and are connected to hair cells with protein fibers. The crystals of otoconia are formed by the active calcium metabolic process of the vestibular organ.¹

The calcium channel proteins that are associated with vitamin D in the epithelium are known to be involved in the calcium metabolism of the vestibular organ, and the interactions between calcium-related diseases and BPPV have been studied. There are study results indicating that bone mineral density,

osteoporosis, and osteopenia are associated with BPPV.²⁻⁴ Recently, along with study results indicating that the vitamin D levels of BPPV patient groups are lower compared to controls, there were case studies indicating that the vitamin D deficiency of patients who chronically suffer recurrences of BPPV was quite severe.⁵⁻⁷

Although BPPV has been named a benign disease, a number of BPPV patients suffer recurrences, and BPPV patients show 1-year recurrence rates of approximately 20% and 5-year recurrence rates of approximately 50%.⁸ In particular, some patients experience severe difficulties in their daily lives due to frequent recurrences of BPPV.

Vitamin D is mostly synthesized in the skin and is changed into 25-hydroxyvitamin D (25-OH vitamin D) in the liver and into 1,25-dihydroxyvitamin D [1,25 (OH)₂ vitamin D] in the kidney to act on various parts of the human body. Among metabolites, 25-OH vitamin D has the highest serum concentration, and the concentration level is a good indicator of the vitamin D held in vivo. The present study was intended to examine the effects of serum 25-OH vitamin D concentrations on patients diagnosed with BPPV on BPPV recurrence.

MATERIALS AND METHODS

At the Yonseimiraе Otorhinolaryngology Clinic (Paju, Republic of Korea), 232 consecutive patients (169 women and 63 men) with a diagnosis of idiopathic BPPV were recruited between June 2014 and June 2015, after excluding eight patients with a history of previous BPPV, three patients with a

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history of head trauma during the preceding month, and seven patients who declined the study. Thirty-six patients treated with vitamin D were also excluded. Two hundred and thirty-two patients were retrospectively followed up until October 2015. Patient information was obtained from patient records, and direct patient telephone calls were made to ensure accuracy of the recurrence data.

All patients were subjected to otologic tests with videonystagmography and video Frenzel glasses when they first visited the hospital, and all patients were diagnosed and treated by one doctor. Dix-Hallpike, supine roll, and cephalic hyperextension tests were conducted to identify the locations of lesions, and the patients were treated using the modified Epley maneuver for posterior semicircular canalolith, the Barbecue rotation maneuver for horizontal semicircular canalolith, the Appiani maneuver and the Gufoni maneuver for horizontal semicircular cupulolith, and the Yacovino maneuver for superior semicircular canalolith. As treatment, otoconia replacement was conducted one to two times per day, and the patients were instructed to visit the hospital at intervals of 2 to 3 days. The disappearance of symptoms and of nystagmus identified in otological tests were regarded as the criteria for complete cures.

As a criterion for recurrence, the occurrence of vertigo 1 month or more after a complete recovery, which led to the identification of nystagmus with video Frenzel glasses and consequently to the diagnosis of BPPV, was regarded as a recurrence. All 232 patients had blood tests done upon first presentation, regardless of recurrence. As a serum test, the 25-OH vitamin D concentration was measured using Chemiluminescence Immunoassay (CIA) (Centaur, Siemens Healthineers, Erlangen, Germany).

The patients were divided into a recurrence group and a nonrecurrence group by defining only those patients who had a relapse and visited the hospital during the follow-up period. The patients' age, gender, follow-up period, type of BPPV, and vitamin D concentrations were examined. In addition, age, gender, follow-up period, type of BPPV, and vitamin D concentrations of the recurrence group and the nonrecurrence group were compared and analyzed through binary logistic regression analyses. Statistical analyses were conducted using PASW version 19 (SPSS Inc., Chicago, IL). Results with the *P* value below 0.05 were regarded as statistically significant.

RESULTS

The mean age of the 232 subjects of the present study was 50.35 years (13–88 years). Of the patients, 63 were males (17–81 years, mean age 50.13 ± 17.16) and 169 were females (13–88 years, mean age 50.43 ± 16.31); the number of females was 2.68 times larger than the number of males. The average follow-up period after treatment was 10.2 months (4–16 months, mean period 10.2 ± 3.64).

The mean vitamin D concentration of the 232 patients was 16.10 ng/mL (4–52, 16.10 ± 7.40 ng/mL), that of males was 16.43 ± 6.22 ng/mL, and that of females was 15.97 ± 7.80 ng/mL. Of the 232 patients, 41 (17.7%) suffered a recurrence during the follow-up period. Of the 41 patients, 10 were males and 31 were females. The mean vitamin D concentration of 191 patients who did not suffer any recurrence was 16.63 ng/mL (4–52, 16.63 ± 7.40 ng/mL), whereas that of the 41 patients who suffered a recurrence was 13.64 ng/mL (5–33, 13.64 ± 6.97 ng/mL). BPPV most commonly involved the lateral canal (n = 159, 68%), followed by the posterior canal (n = 39, 17%) and the anterior canal

TABLE I.
Clinical Characteristics of No Recurrence Group and Recurrence Group in Benign Paroxysmal Positional Vertigo.

Variable	No Recurrence (n = 191)	Recurrence (n = 41)
Age, mean ± SD (years)	50.77 ± 17.00	48.37 ± 13.93
Gender		
Male	53	10
Female	138	31
Follow-up period, mean ± SD (months)	10.14 ± 3.7	10.24 ± 3.31
25-hydroxyvitamin D (ng/mL)	16.63 ± 7.4	13.64 ± 6.97
Type		
Posterior canal	32	7
Lateral canal	133	26
Anterior canal	4	2
Multiple canal*	22	6

*Multiple canal involved or both ears involved.
SD = standard deviation.

(n = 6, 3%). In 25 patients (11%), both posterior and horizontal canals were affected. In three patients (1%), both ears were affected (Table I). Binary logistic regression analyses were conducted to verify the factors that affect recurrence had included all the variables set forth in Table I. There was no significant difference in age, gender, follow-up periods, or type of BPPV between the two groups. The vitamin D concentration of the recurrence group was significantly lower than that of the nonrecurrence group (*P* < 0019); therefore, vitamin D concentrations were identified as a factor that affects recurrence of BPPV (Table II).

DISCUSSION

During the formation and maintenance processes of otoconia, calcium flows from the epithelial cells of the utricle and saccule into cells through Ca²⁺-selective

TABLE II.
Variables on Benign Paroxysmal Positional Vertigo Using Binary Logistic Regression Analysis.

Variable	B	SE	Sig.	Exp(B)
Age	-.006	.011	.580	.994
Gender	-.125	.413	.762	.882
Follow-up period	.024	.049	.624	1.025
25-hydroxyvitamin D	-.068	.029	.019	.882
Type				
Posterior canal			.624	
Lateral canal	-.409	.641	.523	.664
Anterior canal	-.422	.523	.420	.656
Multiple canal*	.593	1.011	.557	1.810

*Multiple canal involved or both ears involved.
B = unstandardized coefficient; SE = standard error, Exp (B) = exponential function (B).

transient receptor potential vanilloid (TRPV)5, TRPV6 channels involved in active calcium movements. Thereafter, the Ca^{2+} ions are combined with both calcium buffer proteins (calbindin-D9K, calbindin-D28K), which are intracellular-binding proteins discharged from hair cells through sodium-calcium exchangers (NCX), and plasma membrane Ca^{2+} -ATPases, which are Ca^{2+} exit pathways existing in cytosolic membranes. In addition, along with the HCO_3^- discharged through carbonic anhydrase, locally high concentrations of Ca^{2+} and HCO_3^- are formed in the endolymph to constitute CaCO_3 vitreous bodies (crystallite). The CaCO_3 vitreous bodies are induced to form otoconia through the actions of NADPH oxidases (Nox3) and otopetrin-1 (Otop1), which are membrane-bound enzymes. The vitreous bodies formed are combined with otolithic proteins, such as Oc90, Otolin-1, keratan sulfate proteoglycan (KSPG), and Sc1, so that otoconia can grow. Matured otoconia are attached to the otolithic membranes through anchoring. In this case, glycoproteins, such as otogelin, otogelin-like, α -tectorin, β -tectorin, otoancorin, and KSPG(s), become involved in the formation of otolithic membranes.^{1,9,10}

In some animal experiments, researchers reported that 1,25-(OH)₂ vitamin D₃ increased the expression of TRPV5, calbindin-D9K, and calbindin-D28K by the semicircular canal duct (SCCD), and increased the expression of PMCA3 and NCX2 by the cochlear lateral wall (LW), while reducing the expression of PMCA4 by the SCCD and the expression of PMCA3 by the LW.^{10,11}

Given study results indicating that the density of otoconia of mice with osteoporosis and the size of otoconia of the same mice increased abnormally over the processes of generation, maintenance, and extinction of otoconia; those indicating that the expression of TRPV5, TRPV6 proteins decreased in the inner ear of aged mice; and those indicating that otoconia excessively deposited with Sparc-like 1 proteins were made in genetically manipulated Oc90 protein-deficient mice, diverse elements are factors assumed to be involved in the generation, maintenance, and degeneration of otoconia.¹²⁻¹⁴

In a study conducted by Vivert et al.,² 332 female BPPV patients were compared with the control group, and the authors reported that the ratio of osteoporosis was higher among BPPV patients and assumed that calcium metabolism disorders were associated with the occurrence of BPPV. The authors presented two mechanisms of the relationships between BPPV and osteopenia or osteoporosis. First, the decrease of estrogen in reducing the natural regulators of bone mass might disturb the internal structure of the otoconia and/or their interconnection and attachment to the gelatinous matrix. Second, an increase of calcium resorption might generate increased concentration of free calcium in the endolymph and reduce its capacity to dissolve the dislodged otoconia.

In a study related to osteoporosis that was conducted with postmenopausal women aged 50 years or more, Yamanaka et al.³ reported in BPPV patients with osteoporosis a recurrence incidence of 56.3%, which was significantly higher than that observed in patients with normal bone mineral density (BMD) (16.1%).

Furthermore, the frequency of BPPV recurrence increased as BMD decreased.

As a study of osteoporosis and BPPV that included both males and females, Jeong et al.⁴ compared 209 BPPV patients (males 67, females 142) with the control group. Both the male and female patients showed lowest T scores lower than the control group and showed higher ratios of osteopenia and osteoporosis than the normal control group. Female patients showed wider ranges of bone regions with different bone density values from normal persons and male patients also showed lower bone mineral density in some bone regions compared to the normal control group.

According to a study conducted by Jeong et al.,⁵ when 100 BPPV patients were compared with a control group of 192 persons, 25-OH vitamin D concentrations were different. The values were 14.4 ± 8.4 ng/mL among the BPPV patients and 19.0 ± 6.8 ng/mL in the control group, and vitamin D insufficiency (10–20 ng/mL), vitamin D deficiency (< 10 ng/mL), and osteoporosis were observed as factors that significantly affected the occurrence of BPPV.

Buki et al.⁷ compared 14 patients who had no relapse of BPPV with four patients who had a relapse of BPPV. They reported a serum vitamin D concentration of 14 ng/mL in patients who had a relapse of BPPV, which was lower than the serum vitamin D concentration of 27 ng/mL in patients who had no relapse of BPPV. When vitamin D-supplementing therapy was implemented with the patients for 8 months, there was no additional recurrence of BPPV.

As a study result similar to that of the present one, Talaat et al.⁶ defined as recurrence patients those patients diagnosed with BPPV in the follow-up period and those who had been definitely diagnosed 1 year before the present diagnosis. Both the BPPV recurrence group and nonrecurrence group showed statistically significant differences in T scores of bone mineral density and vitamin D concentrations compared to the control group. When the recurrence group and the nonrecurrence group were compared with each other, although a difference in vitamin D was shown (16.04 ng/mL vs. 11.93 ng/mL), no difference was shown in T scores. In the study, bone mineral density showed inverse correlations with age but no correlation with vitamin D. In addition, according to a study by Talaat et al., the effect of vitamin D treatment of severe vitamin D deficiency has an impact on the recurrence rate of BPPV.¹⁵ Specifically, Talaat et al. reported an improved recurrence rate of BPPV among the patients with low serum vitamin D level during the treatment with oral vitamin D supplements.

The study conducted by Jeong et al.⁵ had a limitation in identifying clear recurrences because recurrences were defined by asking the patients whether they had similar symptoms in the past. The study conducted by Talaat et al.⁶ had a definition of recurrences that was slightly different from that in the present study because patients who contracted BPPV 1 year before the follow-up were included in the study. The present study defined only those patients who suffered

a recurrence during the follow-up period as recurrence patients and might have underestimated recurrence rates due to those patients who did not visit the hospital when they suffered a recurrence. However, given that existing studies have reported 1-year recurrence rates as 15% to 20%, previous studies conducted in this hospital⁸ showed a 1-year recurrence rate of 18.6%, which was not much different from that shown by other studies. In addition, the mean follow-up period of the present study was 10 months; the recurrence rate of 17.7% can be regarded as indicating that most recurrence patients visited this hospital again.

The mean vitamin D serum concentrations may differ by the country-of-study institutions.⁵⁻⁷ Therefore, direct comparison of values in study results requires quite some attention.

In a previous study regarding Koreans' vitamin D concentrations,¹⁶ the mean serum concentration was identified as 19.1 ± 6.8 ng/mL, and 47% of males and 64.5% of females were observed as having insufficient vitamin D concentrations not exceeding 20 ng/mL. In the present study, 69.8% of males and 73.9% of females showed 20 ng/mL or lower vitamin D concentrations, indicating higher ratios of deficiency groups when compared indirectly.

CONCLUSION

Given the results of the present study, serum vitamin D concentrations are assumed to affect BPPV as a factor for recurrences independent of age, gender, follow-up period, and type of BPPV.

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