

Predictive values of serum estradiol, calcium, and 25-hydroxyvitamin D levels for recurrence of benign paroxysmal positional vertigo in postmenopausal women

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ABSTRACT

Objectives: This study aims to explore the predictive values of serum estradiol, calcium and 25-hydroxyvitamin D [25(OH)D] levels for benign paroxysmal positional vertigo (BPPV) recurrence in postmenopausal women.

Patients and methods: A total of 156 postmenopausal women (mean age: 59.5±7.4 years; range, 46 to 75 years) diagnosed with primary BPPV between January 2015 and August 2018 were included. After follow-up for one year, they were divided into non-recurrence (n=126) and recurrence groups (n=30). Fifty healthy females (mean age: 60.3±7.4 years; range, 48 to 75 years) with natural menopause for over one year were enrolled as the control group. Serum estradiol, calcium and 25(OH)D levels were compared, and their correlations in the recurrence group were analyzed by Pearson method. The predictive values of these levels for recurrence were evaluated using the receiver operating characteristic curve. Predisposing factors were determined by univariate and multivariate logistic regression analyses.

Results: Serum estradiol, calcium, and 25(OH)D levels of the control group were significantly higher than the non-recurrence and recurrence groups (p<0.05). The levels of recurrence group exceeded those of non-recurrence group (p<0.05). In recurrence group, estradiol level was positively correlated with those of calcium and 25(OH)D (r=0.7501, 0.7871, p<0.001), and calcium level was positively correlated with that of 25(OH)D (r=0.7904, p<0.001). The three levels had diagnostic values for recurrence. The maximum Youden's index of their combination was 0.476, and the corresponding prognostic index was 13.04, suggesting a higher recurrence probability. Number of repositioning, Self-Rating Depression Scale score, levels of estradiol, calcium and 25(OH)D were predisposing factors for recurrence.

Conclusion: Serum estradiol, calcium, and 25(OH)D levels are significantly positively correlated in postmenopausal women with BPPV recurrence and their combination can be used to predict recurrence.

Keywords: 25-hydroxyvitamin D, benign paroxysmal positional vertigo, calcium, estradiol, postmenopause.

Benign paroxysmal positional vertigo (BPPV) is a transient vertigo induced by the movement of the head to a specific place, which is a self-limited peripheral vestibular disease accounting for 20 to 30% of all vertigo cases.^[1,2] Currently, it is well-accepted that BPPV is induced by the falling of otoliths from utricles to migrate into the semicircular canal and,

then, to be translocated under the influence of gravity, when the head position is altered, leading to an inappropriate endolymph flow and tumbling the crista ampullaris.^[3,4] As a result, the vestibular afferents of the affected semicircular canal are changed, triggering positional vertigo and nystagmus. Females are more vulnerable to BPPV than males, and the incidence rate

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of BPPV is rising constantly with aging. Particularly, postmenopausal women have high incidence and recurrence rates of BPPV.^[5]

Osteoporosis often occurs in postmenopausal women due to changes in their estrogen level. Otoliths form through the crystallization of calcium carbonate and, therefore, their synthesis and function are affected by calcium metabolic disorder.^[6] In the present study, we aimed to the predictive values of serum estradiol, calcium and 25-hydroxyvitamin D [25(OH)D] levels for BPPV recurrence in postmenopausal women and to identify related risk factors for the purpose of providing clinical evidence for the prevention of BPPV recurrence.

PATIENTS AND METHODS

This study was conducted at Huzhou Central Hospital, Affiliated Central Hospital of Huzhou University, Department of Operating Room between January 2015 and August 2018. A total of 156 postmenopausal women (mean age: 59.5±7.4 years; range, 46 to 75 years) diagnosed with primary BPPV in our hospital were selected as the study population. The diagnosis of BPPV was made according to the Practice Guidelines for the Diagnosis and Management of BPPV (2017).^[7] Inclusion criteria were as follows: (i) recurrent transient vertigo or dizziness (usually shorter than 1 min) seen after the head position is changed relative to the gravity direction; (ii) vertigo, as well as characteristic and positional nystagmus occur in positional test; (iii) having no other diseases, such as vestibular migraine, vestibular paroxysmia, central positional vertigo, Meniere's disease, vestibular neuritis, labyrinthitis, superior canal dehiscence syndrome, posterior-circulation ischemia, postural hypotension and

psychogenic vertigo. Besides, 50 healthy females (mean age: 60.3±7.4 years; range, 48 to 75 years) who underwent physical examination in our hospital in the same time period and had natural menopause for over than one year were enrolled as the control group. These females had a similar age distribution to that of the enrolled BPPV patients, suffered from no other types of vertigo or balance-related diseases within the past one year, and not receiving calcitonin, calcium tablets, or hormonal drugs. After follow-up every three months during one year, the postmenopausal women with primary BPPV were assigned into either the non-recurrence group (n=126) or the recurrence group (n=30). A written informed consent was obtained from each patient. The study protocol was approved by the Huzhou Central Hospital, Affiliated Central Hospital of Huzhou University Ethics Committee (date: January 21st, 2015; approval no. 20150604534126). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The Self-Rating Depression Scale (SDS) contains 20 items and its design is originally based on the diagnostic criteria for depression. The participants rated each item with regard to how they felt during the past several days using a four-point Likert scale. The raw sum score of the SDS ranges from 20 to 80; however, the results are usually presented as the SDS index obtained by expressing the raw score which is converted to a 100-point scale: ≤53 points, psychologically healthy and without depression; >53 points, depression. A higher score indicates a greater severity of depression.

Measurement of serum estradiol, calcium, and 25(OH)D levels

All participants were tested on the next day after the first diagnosis after an 8-h fasting period and a

TABLE 1
Serum estradiol, calcium, and 25(OH)D levels

Group	Estradiol (ng/L)	Calcium (mmol/L)	25(OH)D (ng/mL)
	Mean±SD	Mean±SD	Mean±SD
Control (n=50)	28.6±3.3	2.4±0.1	24.0±2.2
BPPV non-recurrence group (n=126)	16.7±1.4*	2.3±0.1*	19.3±2.3*
BPPV recurrence group (n=30)	14.3±1.5*#	2.1±0.1*#	16.7±2.1*#
<i>F</i>	29.281	10.287	24.316
<i>p</i>	<0.001	<0.001	<0.001

25(OH)D: 25-hydroxyvitamin D; SD: Standard deviation; BPPV: Benign paroxysmal positional vertigo; * Compared to control group, p<0.05; # Compared with BPPV non-recurrence group, p<0.05.

20 to 30-min rest in quiet conditions. The cubital venous blood was collected at 8:00 to 9:00 AM, placed in tubes without anticoagulants, left still and centrifuged at 3,000 rpm for 15 min. Afterwards, the supernatant was collected. The serum levels of estradiol and 25(OH)D were measured using the

chemiluminescent microparticle immunoassay analyzer (Beckman Coulter, USA), and that of calcium was detected with a semi-automatic analyzer. The endpoint of follow-up was one year; however, the follow-up was terminated at any time point, if a patient developed recurrence (e.g., after three months) and treatment was given immediately.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean \pm standard deviation, median (min-max) or number and frequency, where applicable. The independent t-test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was employed for multiple comparisons. The rank sum test was performed for comparisons of the groups. The correlations among serum estradiol, calcium, and 25(OH)D levels were analyzed using the Pearson method. The definitions of r value are given as follows: $r \geq 0.8$: high correlation; $0.5 \leq r < 0.8$: moderate correlation; $0.3 \leq r < 0.5$: low correlation; and $r < 0.3$: negligible correlation.^[8] The receiver operating characteristic (ROC) curve was plotted to evaluate the predictive values of these levels for BPPV recurrence in postmenopausal women. The predisposing factors for BPPV recurrence in postmenopausal women including

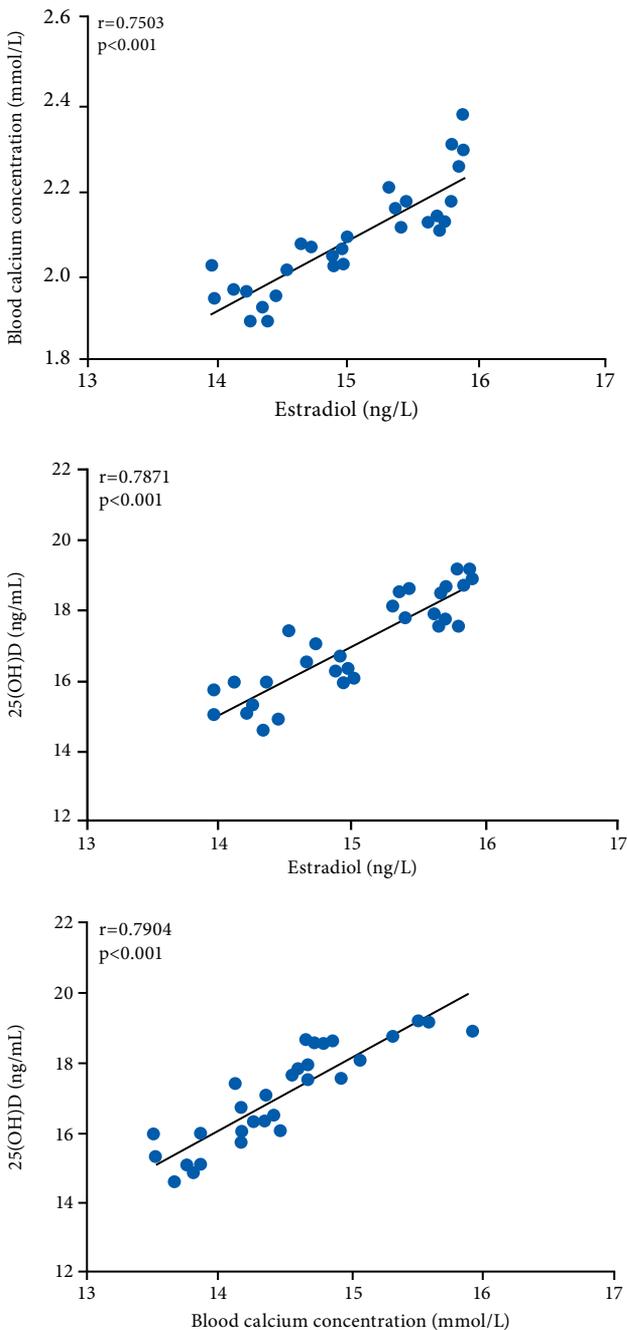


Figure 1. Correlation between serum estradiol, calcium and 25(OH)D levels in BPPV recurrence group.

25(OH)D: 25-hydroxyvitamin D; BPPV: Benign paroxysmal positional vertigo.

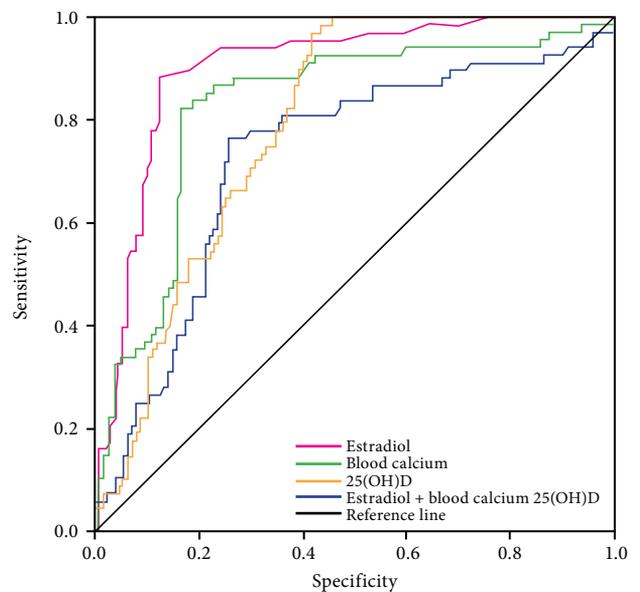


Figure 2. ROC curve for predictive values of serum estradiol, calcium and 25(OH)D levels for BPPV recurrence.

25(OH)D: 25-hydroxyvitamin D; ROC: Receiver operating characteristics; BPPV: Benign paroxysmal positional vertigo.

underlying diseases, injured side, affected semicircular canal, number of repositioning, SDS scores, duration of vertigo upon diagnosis, and serum estradiol, calcium, and 25(OH)D levels were analyzed in the univariate and multivariate logistic regression analyses. A *p* value of <0.05 was considered statistically significant.

RESULTS

In the non-recurrence group, there were 92 cases of posterior and 34 cases of horizontal semicircular canal BPPV with a mean age of 58.9±7.2 (range, 46 to 73) years. Among the recurrence group, 22 were diagnosed with posterior semicircular canal BPPV and eight with horizontal semicircular canal BPPV with a mean age of 60.2±7.3 (range, 47 to 75) years. The three groups had similar menopause duration, age distribution, and underlying diseases such as hypertension and diabetes mellitus (*p*>0.05).

The serum levels of estradiol, calcium, and 25(OH)D in the control group were significantly higher than those of BPPV non-recurrence group and recurrence group (*p*<0.05). The levels of the recurrence group were significantly higher than the non-recurrence group (*p*<0.05) (Table 1).

In the BPPV recurrence group, the serum estradiol level was positively correlated with those of calcium and 25(OH)D (*r*=0.7503, 0.7871, *p*<0.001), and the

serum calcium level was also positively correlated with that of 25(OH)D (*r*=0.7904, *p*<0.001) (Figure 1). Therefore, the patients with lower serum estradiol, calcium, and 25(OH)D levels were more prone to BPPV.

The ROC curve revealed that the three levels had diagnostic values for BPPV recurrence in postmenopausal women. The serum estradiol level was 13.83 mmol/L with the predictive sensitivity and specificity of 86.3% and 83.2%, respectively. The serum calcium level was 2.02 ng/L with the predictive sensitivity and specificity of 87.5% and 85.6%, respectively. The serum 25(OH)D level was 15.21 ng/mL with the predictive sensitivity and specificity of 87.5% and 71.4%, respectively. The Hosmer-Lemeshow test showed that the predicted probability was close to the true one (chi-square [χ^2]=0.348, *p*=0.555). The above three indices were included in logistic regression analysis to fit the predictive model of BPPV recurrence in postmenopausal women. The Prognostic index (PI) = 0.967X1 + 0.899X2 + 0.738X3, where X1, X2 and X3 were the levels of estradiol, calcium and 25(OH)D, respectively. A smaller PI indicated a higher risk of BPPV recurrence in postmenopausal women. The maximum Youden's index of their combination was 0.476, and the corresponding PI was 13.04. A PI of ≤13.04 suggested a higher probability of BPPV recurrence (Figure 2 and Table 2). Multivariate

TABLE 2
Predictive values of serum estradiol, calcium, and 25(OH)D levels for BPPV recurrence assessed by ROC curve

Index	AUC	95% CI	Predictive cutoff value	Sensitivity (%)	Specificity (%)
Calcium (mmol/L)	0.872	0.815~0.930	13.83	86.3	83.2
Estradiol (ng/L)	0.854	0.799~0.909	2.02	87.5	85.6
25(OH)D (ng/mL)	0.725	0.648~0.803	15.21	75.9	71.4
Estradiol + calcium + 25(OH)D	0.899	0.853~0.945	13.04	93.8	92.3

25(OH)D: 25-hydroxyvitamin D; BPPV: Benign paroxysmal positional vertigo; ROC: Receiver operating characteristics; AUC: Area under the curve; CI: Confidence interval.

TABLE 3
Multivariate regression analysis results for the effects of serum estradiol, calcium, and 25-(OH)D levels on BPPV recurrence

	β	SE	<i>p</i>	OR	95% CI
Estradiol	0.967	0.238	0.023	1.287	1.029-1.723
Calcium	0.899	0.323	0.011	1.827	1.098-3.241
25(OH)D	0.738	0.281	<0.001	2.376	1.325-2.984

25(OH)D: 25-hydroxyvitamin D; BPPV: Benign paroxysmal positional vertigo; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

TABLE 4
Univariate analysis of predisposing factors for BPPV recurrence

	BPPV non-recurrence group (n=126)				BPPV recurrence group (n=30)				χ^2/z	p
	n	%	Median	Min-Max	n	%	Median	Min-Max		
Underlying diseases									0.021*	0.885
Yes	48	38.10			11	36.67				
No	78	61.90			19	63.33				
Injured side									0.060*	0.806
Left	45	35.71			10	33.33				
Right	81	64.29			20	66.67				
Affected semicircular canal									0.001*	0.972
Horizontal semicircular canal	34	26.98			8	26.67				
Posterior semicircular canal	92	73.02			22	73.33				
Number of repositionings									26.877*	<0.001
Once	119	94.44			18	60.00				
Many	7	5.56			12	40.00				
SDS score (point)									12.264*	<0.001
Normal	110	87.30			7	23.33				
Depressed	16	12.70			23	76.67				
Duration of vertigo upon diagnosis (d)			3.4	3-7			9.1	7-14	2.214#	0.042
Latency period (s)			2	2.00-3.45			4	2.00-5.00	1.128#	0.312
Disease course (d)			24.5	17.0-29.0			25.0	17.5-29.5	1.453#	0.208

BPPV: Benign paroxysmal positional vertigo; SDS: Self-Rating Depression Scale; * χ^2 test results; # Rank-sum test results.

TABLE 5
Multivariate logistic analysis of predisposing factors for BPPV recurrence

Factor	β	SE	Wald	p	OR	95% CI
Number of repositionings	-2.478	0.589	5.107	0.003	2.356	1.769~2.841
SDS score (point)	-1.617	0.814	4.645	<0.01	5.480	2.043~6.125
Duration of vertigo upon diagnosis (d)	-0.524	0.532	7.728	0.402	1.207	0.612~2.536
Calcium (mmol/L)	-2.369	0.487	6.875	0.024	1.982	1.395~2.024
Estradiol (ng/L)	-1.793	0.753	10.083	0.026	4.964	3.578~6.723
25(OH)D (ng/mL)	-2.145	0.625	4.659	0.021	3.045	1.467~4.638

BPPV: Benign paroxysmal positional vertigo; SE: Standard error; OR: Odds ratio; CI: Confidence interval; SDS: Self-Rating Depression Scale; 25(OH)D: 25-hydroxyvitamin D.

regression analysis results for the effects of serum estradiol, calcium, and 25(OH)D levels on BPPV recurrence are listed in Table 3.

Univariate analysis showed that BPPV non-recurrence and recurrence groups had significantly different numbers of repositioning, SDS scores, and durations of vertigo upon diagnosis ($p < 0.05$) (Table 4). Multivariate logistic regression analysis indicated that the number of repositioning (odds ratio [OR]=2.356, 95% CI: 1.769~2.841), SDS score (OR=5.480, 95% CI: 2.043~6.125), estradiol level (OR=4.964, 95% CI: 3.578~6.723), calcium level (OR=1.982, 95% CI: 1.395~2.024), and 25(OH)D level

(OR=3.045, 95% CI: 1.467~4.638) were the predisposing factors for BPPV recurrence (Table 5).

DISCUSSION

The incidence rate of BPPV vary largely among different age groups.^[9] According to the etiology, BPPV is either primary or secondary. About 60 to 90% of the patients have unknown etiology upon diagnosis, as primary BPPV.^[10] The otolith is mainly composed of calcium-rich organic matter and carbonate crystals, which is a dynamic structure.^[11] Benign paroxysmal positional vertigo occurs, when otoliths have absorption

disorders or fall off to a certain extent. Vitamin D metabolism plays a critical role in the process of bone renewal, and serum 25(OH)D is the best index for the content and function of vitamin D in human body.^[12] Compared to the healthy controls, patients with BPPV have significantly lower serum 25(OH)D levels.^[13] Moreover, as a steroid hormone with biological activity, estrogen essentially participates in bone and calcium metabolism. In the case of estrogen deficiency, the dynamic balance of calcium ions outside bones is affected. In postmenopausal women, the estrogen secretion decreases significantly, leading to insufficient calcium secretion and, then, osteoporosis. Estrogen deficiency also affects the otolith stability and finally induces BPPV.^[14,15] Yang et al.^[16] found that estradiol deficiency was probably a risk factor for idiopathic BPPV in postmenopausal females. They also found in rats receiving bilateral ovariectomy that 17 β -estradiol replacement reversed the reduction in otoconin 90 level. In addition, Zhang et al.^[17] reported that the postmenopausal females with recurrent BPPV had low estrogen levels and bone mineral density. In this study, the serum levels of estradiol, calcium, and 25(OH)D in the control group were significantly higher than those of non-recurrence group and recurrence group. The levels of the recurrence group were significantly lower than those of the non-recurrence group. Furthermore, the Pearson analysis showed that the serum level of estradiol was significantly positively correlated with those of calcium and 25(OH)D in postmenopausal women with BPPV recurrence, and that there was also a significant positive correlation between serum calcium and 25(OH)D levels, possibly as the decrease of estrogen secretion after menopause further reduced calcium and 25(OH)D levels.

Benign paroxysmal positional vertigo recurrence refers to the occurrence of similar previous symptoms after successful repositioning.^[18] The probability of BPPV recurrence after follow-up for one year is 15 to 20% and, therefore, the researchers have endeavored to predict its recurrence.^[19] In this study, the plotted ROC curve exhibited that serum estradiol, calcium, and 25(OH)D levels had diagnostic values for BPPV recurrence in postmenopausal women. Additionally, the univariate and multivariate logistic regression analyses results showed that the number of repositioning, SDS score, together with serum levels of estradiol, calcium, and 25(OH)D were the predisposing factors for BPPV recurrence in postmenopausal women.

Although the psychological state of BPPV patients has been closely related to residual dizziness after repositioning, the relationship between recurrence and depression has rarely been studied.^[20] In this study, we found that the more depressed menopausal women were more prone to recurrence, which may be associated with incomplete central compensation or depression-induced changes in the intravascular environment.

Regardless, the sample size of this study is small. Further in-depth multicenter studies with larger sample sizes are ongoing in our group.

In conclusion, the serum estradiol, calcium, and 25(OH)D levels of postmenopausal women with recurrent BPPV are all positively correlated. The combination of the three indices can be used to diagnose the recurrence of BPPV, and postmenopausal women with BPPV should be restored as soon as possible. Appropriate psychological counseling may be also helpful.

Declaration of conflicting interests

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