Original Article

Benign paroxysmal positional vertigo and serum transthyretin in Chinese older adults

Zexing Cheng MS, Ming Wang MS, Juebo Yu MD

Department of Otolaryngology, Affiliated Hospital of Yangzhou University, Yangzhou university, Yangzhou, China

Background and Objectives: Poor nutritional status is associated with benign paroxysmal positional vertigo (BPPV). Transthyretin (TTR) is a more sensitive marker than is albumin for nutritional status assessment. This study was conducted to confirm an association between serum transthyretin levels and BPPV. **Methods and Study Design:** In total, 320 patients with BPPV and 320 age- and gender-matched controls were recruited between July 1, 2018, and July 1, 2020. All patients underwent audiovestibular tests, including the Dix–Hallpike test for the posterior semicircular canal and the supine roll test for the horizontal semicircular canal. Furthermore, serum transthyretin levels and other biochemical indicators were tested. Risk factors, including a history of heart and cerebral vascular diseases, were examined, and compared between groups. Hematolgical and biochemical tests were performed and subjected to between-group analysis. Multiple logistic regression models were employed to evaluate the TTR–BPPV. Interaction and stratified analyses were conducted. **Results:** Patients with BPPV had significantly lower TTR levels than controls (213±49.3 vs 284±56.4 $p<0.001$). Alcohol consumption and anemia played an interactive role in the association between BPPV and low TTR levels. After adjustments for triglycerides, BMI, uric acid, HbA1C, 25-OH vitamin D_3, alcohol consumption, and anemia, the multiple logistic regression revealed that participants with low TTR levels had a significantly increased risk of BPPV (OR: 5.5; 95% CI, 2.55–11.9; $p<0.001$). **Conclusions:** Chinese older adults with low serum transthyretin levels have an increased risk of BPPV.

Key Words: nutrition, benign paroxysmal positional vertigo, transthyretin, older adults, vertigo

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) presents as an intermittent vertigo attack over a brief period and torsional or horizontal nystagmus triggered by provocative head movement. A common peripheral vestibular condition, BPPV is usually diagnosed in otorhinolaryngology clinics. BPPV severely affects the quality of life of older adults and is closely related to falls, depression, and impairments in the ability to perform activities of daily living.[1] With a lifetime prevalence of 2.4%,[2] BPPV accounts for approximately 20%–30% of vestibular vertigo cases,[3,4] and the age of onset ranges from 11–84 years. The risk of BPPV development increases with aging. Its annual incidence among people aged 18–39 years is 0.7%. Among people aged >60 years, its annual incidence increases to 3.4%.[1,2]

Each year, approximately 5.6 million patients in the United States present with dizziness as a primary concern, and 17%–42% of patients with vertigo receive a BPPV diagnosis.[5] Fortunately, BPPV is easily treated, with repositioning manoeuvres being the most effective approach. The 2-year recurrence rate is 10%–43%. The 5-year recurrence rate can reach 50%.[1,2]

The pathogenesis of BPPV is unclear, but a general belief is that the otolith detaches from the otolith bed, entering the semicircular canal and stimulating the vestibular hair cells on the ampullary crest during head movement, resulting in a vertigo attack. Although the etiology of BPPV has yet to be elucidated, this condition is clinically divided into primary and secondary BPPV according to whether the etiology is known or unknown. The specific etiology of BPPV includes head trauma, sudden deafness, Meniere's disease, vestibular neuritis, otitis media, and vestibular migraine, and the related risk factors include hypertension, diabetes, cervical spondylosis, and coronary heart disease. Age is one of the major risk factors for BPPV; aging may be accompanied by the functional degradation of the semicircular canals, formation of ear stones, reduction of the elliptical capsule, displacement of the otolith, and balloon spots in type I and type II hair cells. However, the etiology remains unknown in 50%–70% of BPPV cases; this is called idiopathic or primary BPPV.

In recent years, various studies have found that osteoporosis incidence and vitamin D deficiency rates in patients with BPPV are considerably higher than those in

Corresponding Author: Dr Juebo Yu, Department of Otolaryngology, Affiliated Hospital of Yangzhou University, Yangzhou university, Yangzhou, China.
Tel: +021 0514-82981199
Email: yujuebo2004@163.com
Manuscript received 27 November 2021. Initial review completed 08 January 2021. Revision accepted 16 May 2021.
doi: 10.6133/apjcn.202109_30(3).0005

the general population. Antiosteoporosis treatment or vitamin D deficiency correction has been found to reduce the recurrence rate of BPPV, suggesting that calcium metabolism disorder may be an underlying mechanism of BPPV.[6-8] Nutritional risk, BMI reduction, male sex, and older age are factors influencing osteoporosis.[9,10]

Malnutrition may be a cause of BPPV. Serum album and transthyretin (TTR; also known as prealbumin) are the nutritional biomarkers of principal relevance.[11,12] TTR is mainly synthesized by hepatocytes and is less likely to be the product of a hepatic disease, unlike other serum proteins.[11,12] Serum TTR is the earliest laboratory indicator used to evaluate nutritional status. Moreover, TTR is considered the earliest laboratory indicator of nutrition and is preferred over albumin as a biomarker of malnutrition.[11] To the best of our knowledge, no study has investigated the association between serum TTR levels and BPPV. In examining BPPV risk, most studies have considered vitamin D or uric acid (UA) rather than TTR.[13,14] However, the reliability of self-reported dietary data in nutritional research is questionable,[15] and serum TTR is only widely accepted in reflecting recent nutritional intake.

This study investigated whether the levels of TTR in Chinese older adults with BPPV differed from those of older adults in the general population and whether low TTR was an independent risk factor for BPPV in Chinese older adults. The findings serve as a reference for clinical practice and the prevention of BPPV in older adults.

METHODS

Ethical approval statement

This study was part of a retrospective analysis of BPPV efficacy, the protocol of which was approved by the Local Ethics Committee of the Affiliated Hospital of Yangzhou University, China. The participants underwent only routinely performed tests. Written informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Participants

This study was conducted using the geriatric BPPV database of our hospital. In total, 568 older adults with BPPV aged >60 years were recruited by the Department of Otorhinolaryngology between July 2018 and August 2020. All patients had received an otolaryngological consultation within 1 week of the acute onset of vertigo, undergone complete positional manoeuvres (including the Dix–Hallpike test for posterior semicircular canals and the supine head-turning test for horizontal semicircular canals), and received a diagnosis of BPPV. All the patients revisited the hospital for a postural test 1 week after their initial reduction. Overall, 23 of the participants could not complete the procedures due to disability, and 87 refused to participate. Thus, 458 participants were included in the analyses.

Diagnostic criteria

Patients who met the 2017 American Academy of Otolaryngology—Head and Neck Surgery Foundation diagnostic criteria of BPPV were considered.[16] These criteria are (1) a history of temporary vertigo when the head moves to a specific position and (2) characteristic nystagmus induced by the Dix–Hallpike test or the roll test, with a short incubation period (<30 s) and the onset of fatigue.

Inclusion criteria

Patients who met the following inclusion criteria were eligible for participation: (1) Adequately understood the purpose of the study, agreed to participate, and signed the informed consent form and (2) had a diagnosis of BPPV.

Exclusion criteria

Patients were excluded in the case of any of the following: (1) Presence of conditions affecting nutritional status, including Cushing syndrome, renal failure, chronic liver disease, nephrotic syndrome rheumatoid arthritis, acute inflammatory diseases, hypothyroidism, hyperthyroidism, autoimmune disease, and malignant tumours; (2) medical treatment that could significantly affect nutritional status, including past or present oral hormone therapy, antiosteoporosis drug therapy, and other factors affecting prealbumin levels. (3) inability to reduce treatment, refusal to reduce treatment, or ineffective treatment reduction; (4) Secondary BPPV—specifically, a history of migraine, Meniere's disease, vestibular neuronitis, labyrinthitis, head trauma, inner ear surgery, or related conditions; (5) pregnancy or unavailable laboratory data. The final sample comprised 320 older adults with BPPV (Figure 1).

Control groups

The control group comprised individuals without BPPV who underwent physical examination in the outpatient department of Yangzhou University Hospital from July 2018 to August 2020. The exclusion criteria were the same as those applied to the experimental group. In total, 320 participants (153 men and 167 women) with an average age of 68.8±6.26 years were enrolled.

Risk factor selection

Based on the literature, a standardized questionnaire was administered to assess potential risk factors for BPPV, including serum vitamin D concentrations; history of chronic disease, hypertension, or smoking and drinking; high BMI; and vascular risk factors (mainly hypertension, glycosuria, hyperlipidaemia, and coronary heart disease).

Biochemical measurements

On the morning of the second day after admission, blood was drawn from the participants on an empty stomach and sent to the Laboratory of Yangzhou University Affiliated Hospital for determining serum levels of TTR, 25-OH vitamin D_3 ($25(OH)D_3$), homocysteine (Hcy), LDL cholesterol, serum blood glucose, HDL cholesterol, total cholesterol, triglycerides (TGs), glycosylated Hb (HbA1c), Hb, creatinine, alanine aminotransferase, aspartate aminotransferase, albumin, and UA. Low serum TTR levels were defined as <170 mg/L.[17]

Statistical analysis

Analyses were conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

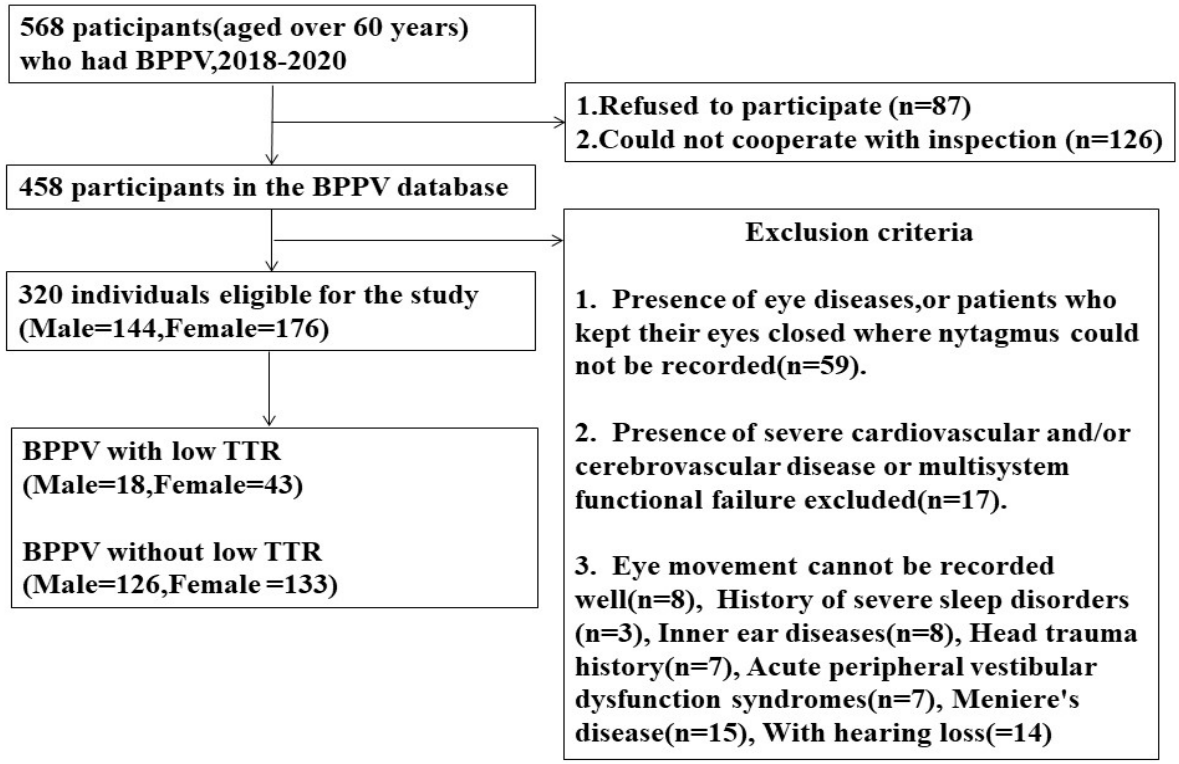

Figure 1. Flow diagram of the participant selection criteria. BPPV: benign paroxysmal positional vertigo; TTR: transthyretin.

The measurement data of normal distribution were expressed as the mean ± standard deviation, and the mean comparisons involved either an independent samples t test or a Mann–Whitney U test. Categorical variables are expressed as frequencies and percentages, and a chi-square test was performed. Correlations among TTR and age, sex, HbA1c, UA, Hcy, BMI, and 25(OH)D_3 were assessed using Pearson correlation analysis. Interaction and stratified analyses were performed based on age (<70 or ≥70 years), alcohol consumption (nondrinkers and drinkers), smoking habits (never-smokers and smokers), and history of risk factors for BPPV. Multivariate logistic regression models were employed to identify the association between TTR levels and BPPV. The regression modeling results are presented as odds ratios (ORs) and 95% Confidence intervals (CIs). Both nonadjusted and multivariate adjusted models, comprising variables of age, sex, HbA1c, BMI, 25(OH)D_3, and low TTR, were applied. All tests were two sided, and a p value of <0.05 was considered statistically significant.

RESULTS

The characteristics of the participants are presented in Table 1. The BPPV group consisted of 320 participants (144 men and 176 women) with a mean age of 68.2±6.02 years. The control group contained 320 participants (153 men and 167 women) with a mean age of 68.9±6.26 years. No significant between-group difference in either age or sex was observed (p>0.05). Furthermore, no significant difference was observed in vascular risk factors (e.g., a history of hypertension, diabetes, coronary heart disease, hyperlipidaemia, and smoking or drinking; p>0.05). However, the proportion of patients with osteoporosis significantly differed between the BPPV and control groups.

As shown in Table 2, no significant differences were noted in age, systolic blood pressure, diastolic blood pressure, blood lipid levels, albumin, Hb, or urea nitrogen between groups (p>0.05). However, differences in UA, HbA1c, TGs, BMI, and 25(OH)D_3 were significant. Specifically, their levels group were significantly lower in the BPPV group than in the control group (p<0.05). Furthermore, TTR levels in patients with BPPV were significantly lower than that in the controls (213±49.3 vs 284 4±56.4, respectively). The proportion of patients with low serum TTR levels was significantly higher in the BPPV group than in the control group (19.1% vs 8.13%, respectively).

Stratified analyses of associations between BPPV and low PA are presented in Table 3. The interaction analysis revealed that alcohol consumption and anemia played an interactive role in the association between BPPV and low PA. The OR between BPPV and low PA was higher in those who consumed alcohol (OR=5.51; 95% CI, 2.46–12.4; p<0.001) than in those who did not (OR=1.51; 95% CI, 0.82 –2.93; p=0.0173). In addition, considerably higher ORs between BPPV and low PA were detected in patients with anemia (OR=21.3; 95% CI, 2.68 –170

; p<0.001) compared with in patients without anemia (OR=2.05; 95% CI, 1.20–3.44; p=0.006). The interactions are presented in Figure 2.

Table 4 presents the results of the multivariate logistic regression analysis between BPPV and potential association factors. A multivariate logistic regression model indicated that TTR and the risk factors are associated with BPPV. UA, HbA1c, TGs, BMI, 25(OH)D_3, anemia (present or absent), alcohol consumption (present or absent),

Table 1. Demographic characteristics of the participants

Variable	BPPV groups (n=320)	Control groups (n=320)	t or chi-statistic	*p* value
Age (years)†	68.2±6.02	68.9±6.26	-0.93	0.352
Gender‡				
Male (n, %)	144 (45)	153 (47.8)	0.50	0.476
Female (n, %)	176 (55)	167 (52.2)		
Alcohol consumption (n, %)	171 (53.4)	165 (51.6)	0.23	0.635
Smoking habits (n, %)	135 (42.2)	128 (40.0)	0.78	0.377
SBP (mmHg)†	111±18.3	108±16.7	1.04	0.308
DBP (mmHg)†	75.3±12.5	74.9±11.3	0.71	0.745
Type 2 diabetes (n, %) ‡	84 (26.3)	72 (22.5)	1.12	0.269
Hypertension (n, %) ‡	85 (26.7)	90 (28.1)	0.20	0.567
Osteoporosis (n, %) ‡	68 (21.3)	50 (15.6)	5.36	0.021
Anemia (n, %) ‡	46 (14.4)	41 (12.8)	0.33	0.564
Dyslipidaemia (n, %) ‡	93 (29.1)	81 (25.3)	1.14	0.286

BPPV: benign paroxysmal positional vertigo; SBP: systolic blood pressure; DBP: diastolic blood pressure.
†Independent t-test.
‡Chi test.

Table 2. Biochemical markers of the participants

Variable	BPPV groups (n=320)	Control groups (n=320)	t or chi-statistic	*p* value
HbA1c (%) †	5.56±1.25	5.15±0.88	4.7	<0.001
SBG (mmol/L) †	4.97±0.67	4.94±0.74	0.59	0.555
ALT (g/L) †	12.7±5.68	12.1±5.58	0.87	0.383
AST (g/L) †	13.0±6.26	12.5±4.82	1.01	0.311
Albumin (g/L) †	42.3±5.37	41.9±4.56	1.57	0.137
Transthyretin (mg/L) †	213±49.2	284±56.4	-14. 2	<0.001
Low TTR (n, %) ‡	61 (19.1)	26 (8.13)	16.3	<0.001
Hemoglobin (g/l) †	133±16.1	133±18.1	0.05	0.962
25(OH)D_3 (mmol/L) †	23.2±4.09	25.8±3.43	-8.68	<0.001
Hcy (μm/L) †	7.09±2.38	7.34±1.88	-1.34	0.179
UA (mmol/L) †	312±48. 5	306±24.2	2.23	0.26
BMI (kg/m^2) †	23.47±1.03	25.12±1.22	-21.9	<0.001
CA (mmol/L) †	72.7±15.0	73.1±13.6	0.27	0.785
CHO (mmol/L) †	4.51±1.08	4.66±0.88	-1.66	0.097
TG (mmol/L) †	2.39±1.32	2.20±1.11	2.01	0.045
LDL-C (mmol/L) †	2.61±0.88	2.68±0.84	-1.09	0.276
HDL-C (mmol/L) †	1.08±0.32	1.13±0.37	-0.86	0.066

SBG: serum blood glucose; 25(OH)D_3: 25-OH vitamin D_3; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HbA1c: hemoglobin A1c; UA: uric acid; CA: creatinine; Hcy: homocysteine; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; TGs: triglycerides; BPPV: benign paroxysmal positional vertigo; TTR: transthyretin.
Data are presented as means ± standard deviations or as frequencies (percentages).
Low transthyretin levels were defined as a transthyretin concentration of <170 mg/L.
†Independent t-test.
‡Chi test.

and low TTR levels (present or absent) were included in the multivariate logistic regression model. Low TTR levels were significantly associated with an increased risk of BPPV (OR: 5.50, 95% CI, 2.55–11.9). HbA1c, TGs, BMI, 25(OH)D_3, and anemia were risk factors for BPPV. UA and alcohol consumption were not independent risk factors for BPPV.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the potential association between BPPV and serum TTR levels. In this case–control study, low TTR levels were identified as a significant and independent risk factor of BPPV in Chinese older adults. Patients with low levels of TTR had a 2.7-fold greater risk of BPPV. Moreover, alcohol consumption and anemia significantly influenced this correlation, suggesting that these low TTR levels, alcohol consumption, and anemia may exert interactive effects on BPPV development. The association remained significantly independent of the following confounders: HbA1c, TGs, BMI, UA, and 25(OH)D_3.

The prevalence of malnutrition among hospitalized patients in recent decades is 50%.[18] Mounting evidence suggests that malnutrition weakens the immune system, raises infection rates, and reduces sensitivity to drugs in older patients. For people with malnutrition, the mortality rate is high, hospitalization is long, and hospitalization costs are high. However, the relationship between malnutrition and BPPV has received little scholarly attention. Serum TTR, as a serological indicator of nutrition, has a short half-life and can sensitively reflect changes in nutritional status. To the best of our knowledge, few studies

Table 3. Association between low TTR and BPPV according to baseline characteristics

Subgroup	BPPV groups (n=320)		Control groups (n=320)		OR, 95%CI	*p* value	*p* value for interaction
	TTR <170 mg/L	TTR ≥170 mg/L	TTR <170 mg/L	TTR≥170 mg/L			
Age							0.426
<70years	33	164	15	178	2.34 (1.25, 4.56)	0.007	
≥70years	28	95	11	116	3.12 (1.47, 6.57)	0.002	
Gender							0.053
Female	43	133	13	141	1.45 (0.68, 3.12)	0.335	
Male	18	126	13	153	3.92 (2.03, 7.60)	<0.001	
Alcohol consumption							0.015
No	30	134	18	131	1.55 (0.82, 2.30)	0.173	
Yes	31	125	8	163	5.51 (2.46, 12.36)	<0.001	
Smoking habits							0.075
No	21	113	14	177	4.22 (2.10, 8.47)	<0.001	
Yes	40	146	12	117	1.66 (0.84, 3.31)	0.144	
Dyslipidaemia							0.376
No	45	182	22	215	2.44 (1.41, 4.22)	0.001	
Yes	17	76	4	79	4.31 (1.39, 13.34)	0.007	
Anemia							0.032
No	51	237	18	261	2.05 (1.20, 3.44)	0.006	
Yes	10	22	8	33	21.3 (2.68, 170)	<0.001	
Osteoporosis							0.220
No	31	221	19	251	2.03 (1.12, 3.67)	0.017	
Yes	29	39	7	43	4.04 (1.58, 10.3)	0.002	
Type 2 diabetes							0.463
No	46	190	18	230	2.49 (1.44, 4.28)	0.001	
Yes	15	69	8	64	4.00 (1.27, 12.6)	0.012	
Hypertension							0.215
No	42	183	15	215	1.62 (0.63, 4.18)	0.316	
Yes	19	76	11	79	0.85 (0.64, 1.23)	0.392	

TTR: transthyretin; BPPV: benign paroxysmal positional vertigo; OR: Odds ratio; CI: Confidence interval; Low transthyretin levels were defined as a transthyretin concentration of <170 mg/L.

Table 4. Multivariable logistic regression models of risk factors for BPPV

	Model 1†			Model 2‡			Model 3§		
	Unadjusted OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value
Low TTR	2.72	1.67-4.43	<0.001	5.26	2.44-11.3	<0.001	5.50	2.55-11.9	<0.001
HbA1c	/	/	/	1.58	1.25-1.99	<0.001	1.62	1.27-2.05	<0.001
25(OH)D_3				0.89	0.84-0.95	<0.001	0.88	0.83-0.94	<0.001
BMI	/	/	/	0.13	0.09-0.19	<0.001	0.13	0.07-0.18	<0.001
TG	/	/	/	1.30	1.09-1.55	<0.001	1.32	1.10-1.58	0.003
Uric acid	/			1.00	0.99-1.01	0.781	1.00	0.99-1.00	0.351
Anemia	/	/	/	/	/	/	3.16	1.33-7.50	0.009
Alcohol consumption	/	/	/	/	/	/	0.66	0.41-1.07	0.092

BPPV: benign paroxysmal positional vertigo; TTR: transthyretin; HbA1c: hemoglobin A1c; TGs: triglycerides. Low transthyretin levels were defined as a transthyretin concentration of <170 mg/L.
†Model 1: Unadjusted. ‡Model 2: Adjusted for HbA1c, 25(OH)D_3, BMI, TGs, and uric acid.
§Model 3: Adjusted for Model 2 + anemia and alcohol consumption

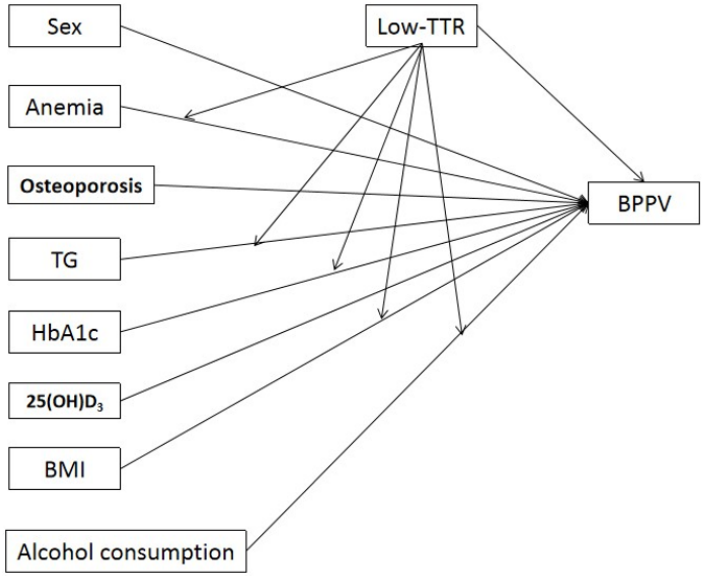

Figure 2. Conceptual diagram presenting the effect of TTR on BPPV pathogenesis, along with their interactions. TTR: transthyretin; 25(OH)D_3: 25-OH vitamin D3; HbA1c: hemoglobin A1c; TGs: triglycerides; BPPV: benign paroxysmal positional vertigo.

have demonstrated a relationship between nutritional status and BPPV. One study suggested that poor dietary habits and inadequate nutritional intake are associated with BPPV.[19] However, the researchers did not analyze the correlation between nutritional indicators and BPPV. Several studies have reported that osteoporosis is a risk factor for BPPV, probably because abnormal calcium metabolism may underlie BPPV.[20,21] Furthermore, a large population-based study including 6,649 patients with osteoporosis and 26,596 matched controls observed that BPPV risk in patients with osteoporosis was 1.82 times higher than that in controls. However, a recent study found that reduced levels of serum prealbumin is related to osteoporosis in older adults with type 2 diabetes mellitus.[22] The literature suggests that malnutrition risk can lead to osteoporosis and that osteoporosis can induce BPPV. In addition, low prealbumin levels are associated with osteoporosis. Therefore, we postulated that low TTR levels and BPPV are associated. The present study confirmed that older adults with low TTR levels, especially those with osteoporosis, are more susceptible to BPPV. Specifically, the stratification analysis revealed a fourfold increased risk of BPPV in these patients. However, an interaction analysis of the osteoporosis subgroup indicated that osteoporosis was not a risk factor for BPPV. The relatively small sample size, as well as population bias, may limit the accuracy of these results. Large-scale studies on the relationship between TTR and BPPV and osteoporosis are required to determine the reliability of these results.

Several studies have found an association between high serum UA levels and BPPV.[23,24] However, high serum UA levels are complexly correlated with BPPV occurrence. Studies conducted in China have reported that a high serum UA concentration is a risk factor for BPPV, and one study conducted in Turkey presented similar findings.[25,26,27] Similar to the present study, several investigations have observed a negative association between high UA levels and peripheral vertigo in older adults with BPPV.[27] Several studies have suggested that hypertension, diabetes, hyperlipidemia, and a smoking habit are risk factors for BPPV.[28,29,30] Herein, TGs, BMI, and anemia were determined to be risk factors for BPPV, whereas hypertension, diabetes, hyperlipidaemia, and osteoporosis were not. As mentioned, we performed this study to confirm the correlation between low PA and BPPV. We conducted subgroup analyses after adjusting for confounders, and patients with low TTR were found to have an increased incidence of BPPV regardless of whether they had systemic diseases (e.g., diabetes, hyperlipidaemia, or osteoporosis). Moreover, a subgroup analysis revealed that individuals with low TTR levels who also had anemia or consumed alcohol had significantly higher BPPV risks than did individuals with normal TTR levels. However, the interaction analyses indicated that age, sex, smoking habits, diabetes, hyperlipidemia, osteoporosis, and hypertension did not influence the association between BPPV and low TTR, whereas alcohol consumption and anemia played an interactive role in this association. Notably, the participants who had both anemia and hypoprealbuminemia were significantly more likely—specifically, 10- times more likely—to develop BPPV. The participants without these risk factors were also significantly more likely to develop BPPV, but only 2.05 times more likely. These results suggest that normal clinical parameters may prevent BPPV. Therefore, we should devote special attention to the clinical care of older adults with anemia. Considering that the limited sample size of this study may affect the reliability of the results, we will conduct a multicenter prospective study to further observe the relationship between anemia and BPPV.

No consensus has been reached on the etiology or pathogenesis of BPPV. Fragmented otoconial particles that enter the semicircular canal and either lie loose or adhere to the ampulla, thus stimulating the ampulla, may result in vertigo and nystagmus symptoms.[31] Yamauchi et al reported that vitamin D affected calcium ion concentrations in the endolytic lymph through the regulation of the calcium channel–related activity in the inner ear.[32] Furthermore, other studies have revealed that mice with vitamin D receptor gene knockout exhibit impaired balance function, as indicated by head deflection and body roll.[33] These findings suggest that vitamin D deficiency leads to otolith dysfunction and contributes crucially to BPPV development. Consistent with the literature, we observed significant differences in vitamin D levels between the BPPV and control groups. However, vitamin D levels are also affected by latitude, age, sex, season, hormone levels, nutritional status, lifestyle habits, and associated diseases.[34] Studies have not considered all these factors, resulting in inconsistent conclusions. Therefore, a multicenter and multiethnic study with a large sample size is warranted to explore the correlation between BPPV and vitamin D levels.

Mean serum TTR levels were lower in the BPPV group than in the control group. In addition, the proportion of individuals with low TTR levels was significantly lower in the BPPV group than in the control group. A multivariate regression analysis model demonstrated that BPPV risk was 5.5 times greater in those with low TTR levels (OR=5.50; 95% CI, 2.55–11.9). Our findings suggest that low levels of serum TTR are associated with a high risk of BPPV. This has great clinical significance given the rapidly aging Chinese population. Falls have been reported to be the main cause of death and disability in people aged >65 years, whereas vertigo is the main risk factor for falls in older adults.[35,36] The comprehensive clinical evaluation of serum TTR in high-risk populations may facilitate the early detection of BPPV and the prevention of falls or disability caused by sudden vertigo episodes. Early BPPV detection and BPPV therapy initiation with corresponding management, including vitamin D supplements, lifestyle changes, and dietary habit adjustments, might prevent falls and improve quality of life in older adults. However, our conclusions should be interpreted with caution considering the risk of publication bias and the following limitations. First, because of the case–control design, we could determine whether the association between reduced TTR levels and BPPV is causal. Randomized controlled trials, which are more reliable than case–control studies, must be conducted to confirm the association between BPPV and TTR. Second, our study provides an overview of evidence suggesting that reduced serum TTR levels are associated with and may be

an independent risk factor for BPPV. Furthermore, we examined older adults. Future studies could confirm our results by using a sample of individuals over a broader age range drawn from a more diverse population. Finally, the nutritional habits of the participants and their use of drugs affecting calcium metabolism and TTR/albumin levels were not considered.

Conclusion

Our findings suggest that low serum TTR levels in Chinese older adults are associated with an increased risk of BPPV, particularly if anemia is present or alcohol consumption is habitual. Further longitudinal studies and large-scale prospective studies are warranted to explore the precise risk factors for BPPV and to determine whether serum TTR levels and BPPV are causally related.

ACKNOWLEDGEMENTS

We thank the physicians and participants for their involvement in this study.

AUTHOR DISCLOSURES

The authors declared no potential conflicts of interest with respect to the research, authorship, or publication of this article. This work was not supported by funding.

REFERENCES

1. Kim JS, Zee DS. Clinical practice. Benign paroxysmal positional vertigo. N Engl J Med. 2014;370:1138-47. doi: 10.1056/NEJMcp1309481.
2. von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, Neuhauser H. Epidemiology of benign paroxysmal positional vertigo: a population based study. J Neurol Neurosurg Psychiatry. 2007;78:710-5. doi: 10.1136/jnnp.2006.100420.
3. Bhattacharyya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T. Clinical practice guideline: benign paroxysmal positional vertigo (update). Otolaryngol-Head Neck Surg. 2017;156(Suppl 3):S1-S47. doi: 10.1177/0194599816689667.
4. Halmagyi GM, Thurtell MJ, Curthoys IS. Vertigo: clinical syndromes. In: Gleeson M, ed. Scott-Brown's Otorhinolaryngology, head and neck surgery, 7th ed. Great Britain, England: Edward Arnold Ltd; 2008. pp. 3760-3.
5. Hanley K, O'Dowd T, Considine N. A systematic review of vertigo in primary care. Br J Gen Pract. 2001;51:666-71.
6. Jeong SH, Kim JS, Shin JW, Kim S, Lee H, Lee AY et al. Decreased serum vitamin D in idiopathic benign paroxysmal positional vertigo. J Neurol. 2013;260:832-8. doi: 10.1007/s00415-012-6712-2.
7. Mikulec AA, Kowalczyk KA, Pfitzinger ME, Harris DA, Jackson LE. Negative association between treated osteoporosis and benign paroxysmal positional vertigo in women. J Laryngol Otol. 2010;124:374-6. doi: 10.1017/S002221510999209X.
8. Talaat HS, Kabel AM, Khaliel LH, Abuhadied G, El-Naga HA, Talaa AS. Reduction of recurrence rate of benign paroxysmal positional vertigo by treatment of severe vitamin D deficiency. Auris Nasus Larynx. 2016;43:237-41. doi: 10.1016/j.anl.2015.08.009.
9. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev. 2000;21:115-37. doi: 10.1210/edrv.21.2.0395.
10. Li Y, Hui M, Chang X, Wang YP, Zhang BZ, Yu JC. BMI reduction and vitamin D insufficiency mediated osteoporosis and fragility fractures in patients at nutritional risk: a cross-sectional study. Eur J Clin Nutr. 2018;72:455-9. doi: 10.1038/s41430-017-0067-9.
11. Ingenbleek Y, Van Den Schrieck HG, De Nayer P, De Visscher M. Albumin, transferrin and the thyroxine-binding prealbumin/retinol-binding protein (TBPA-RBP) complex in assessment of malnutrition. Clin Chem Acta. 1975;63:61-7. doi: 10.1016/0009-8981(75)90379-4.
12. Jeong JU, Lee HK, Kim YJ, Kim JS, Kang SS, Kim SB. Nutritional markers, not markers of bone turnover related predictors of bone mineral density in chronic peritoneal dialysis patients. Clin Nephrol. 2010;74:336-42. doi: 10.5414/cnp74336.
13. Sheikhzadeh M, Lotf Y, Mousavi A, Heidari B, Monadi M, Bakhshi E. Influence of supplemental vitamin D on intensity of benign paroxysmal positional vertigo: a longitudinal clinical study. Caspian J Intern Med. 2016;7:93-8.
14. Dong L, Wang Z, Zhang W, Bao L, Cui GY, Ye XC. The correlation between serum uric acid level and benign paroxysmal position vertigo. Chin J Pract Nervous Dis. 2017;20:21-3. doi: 10.3969/j.issn.1673-5110.2017.21.005.
15. Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML et al. Addressing current criticism regarding the value of self-report dietary data. J Nutr. 2015;145:2639e45. doi: 10.3945/jn.115.219634.
16. Bhattacharyya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T et al. Clinical practice guideline: benign paroxysmal positional vertigo (update). Otolaryngol Head Neck Surg. 2017;156(3 suppl):S1-S47. doi: 10.1177/0194599816689667.
17. Zhang SQ, Peng B, Stary CM, Jian ZH, Xiong XX, Chen QX. Serum prealbumin as an effective prognostic indicator for determining clinical status and prognosis in patients with hemorrhagic stroke. Neural Regen Res. 2017;12:1097-102. doi: 10.4103/1673-5374.211188.
18. Coats KG, Morgan SL, Bartolucci AA, Weinsier RL. Hospital-associated malnutrintion: a reevaluation 12 years later. J Am Diet Assoc. 1993;93:27-33. doi: 10.1016/0002-8223(93)92126-i.
19. Schultz AR, Neves-Souza RD, de Souza Pinho Costa V, Meneses-Barriviera CL, Franco PPR, de Moraes Marchiori LL. Is there a possible association between dietary habits and benign paroxysmal positional vertigo in the elderly? The importance of diet and counseling. Int Arch Otorhinolaryngol. 2015;19:293-7. doi: 10.1055/s-0035-1551551.
20. Chan K-C, Tsai Y-T, Yang Y-H, Chen P-C, Chang P-H. Osteoporosis is associated with increased risk for benign paroxysmal positional vertigo: a nationwide population-based study. Arch Steoporos. 2017;12:106. doi: 10.1007/s11657-017-0403-7.
21. Kim SY, Han SH, Pank MH. Clinical features of recurrence and osteoporotic changes in benign paroxysmal positional vertigo. Auris Nasus Larynx. 2017;44:156-61. doi: 10.1016/j.anl.2016.06.006.
22. Xiu S, Chetri JK, Sun L, Mu Z, Wang L. Association of serum prealbumin with risk of osteoporosis in older adults with type 2 diabetes mellitus: a cross-sectional study. Ther Adv Chronic Dis. 2019;10:2040622319857361. doi: 10.1177/2040622319857361.
23. Xia F, Wang N, Wang Y, Liang L, Liu M, Li J, Liu H, Fu X. The relationship between benign paroxysmal positional Vertigo and cerebrovascular disease in the elderly. Chin J Geriatr. 2017; 36:1087-91. doi: 10.3760/cma.j.issn.0254-9026.2017.10.008.
24. Xu M, Chen W, Liu L, Wang F, Ling Y, Huang Z. Study on the correlation between uric acid level and benign

paroxysmal positional vertigo. J Xiangnan Univ. 2015;17: 11-3. doi: 10.16500/j.cnki.1673-498x.2015.03.004.
25. Yang X, Yang B, Wu M, Wang F, Huang X, Li K, Mao Z, Xu Z, Ren H. Association between serum uric acid levels and benign paroxysmal positional vertigo: A systematic review and meta-analysis of observational studies. Front Neurol. 2019;15;10:91. doi: 10.3389/fneur.2019.00091.
26. Lin YT, Lin HW, Huang YC, Ho WT, Li YC, Chen TJ. Association between gout and vertigo in a Taiwanese population. J Clin Neurosci. 2013;20:857-61. doi: 10.1016/j.jocn.2012.05.036.
27. Celikbilek A, Gencer ZK, Saydam L, Tanik N, Ozkiris M. Serum uric acid levels correlate with benign paroxysmal positional vertigo. Eur J Neurol. 2014;21:79-85. doi: 10.1111/ene.12248.
28. D'Silva LJ, Staecker H, Lin J, Lin J, Sykes KJ, Phadnis MA et al. Retrospective data suggests that the higher prevalence of benign paroxysmal positional vertigo in individuals with type 2 diabetes is mediated by hypertension. J Vestib Res. 2016;25:233-9. doi: 10.3233/VES-150563.
29. Cohen HS, Kimball KT, Stewart MG. Benign paroxysmal positional vertigo and comorbid conditions. ORL J Otorhinolaryngol Relat Spec. 2004;66:11-5. doi: 10.1159/000077227.
30. Sunami K, Tochino R, Tokuhara Y, Yamamoto H, Tomita S, Koshimo N, Yamane H. Effects of cigarettes and alcohol consumption in benign paroxysmal positioning vertigo. Acta Otolaryngol. 2006;126:834-8. doi: 10.1080/00016480500527474.
31. Bhattacharyya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T et al. Clinical Practice Guideline: Benign Paroxysmal Positional Vertigo (Update) Executive Summary. Otolaryngol Head Neck Surg. 2017;156:403-16. doi: 10.1177/0194599816689660.
32. Yamauchi D, Nakaya K, Raveendran NN, Harbidge DG, Singh R, Wangemann P, Marcus DC. Expression of epithelial calcium transport system in rat cochlea and vestibular labyrinth. BMC Physiol. 2010;10:1. doi: 10.1186/1472-6793-10-1.
33. Minasyan A, Keisala T, Zou J, Zhang Y, Toppila E, Syvälä H, Lou YR, Kalueff AV, Pyykkö I, Tuohimaa P. Vestibular dysfunction in vitamin D receptor mutant mice. J Steroid Biochem Mol Biol. 2009;114:161-6. doi: 10.1016/j.jsbmb.2009.01.020.
34. Karataş A, Yüceant GA, Yüce T, Hacı C, Cebi IT, Salviz M. Association of benign paroxysmal positional vertigo with osteoporosis and vitamin d deficiency: a case controlled study. J Int Adv Otol. 2017;13:259-65. doi: 10.5152/iao.2016.2640.
35. Kannus P. Fall-induced injuries and deaths among older adults. JAMA. 1999;281:1895-9. doi: 10.1001/jama.281.20.1895.
36. Mueller M, Strobl R, Jahn K, Linkohr B, Peters A, Grill E. Burden of disability attributable to vertigo and dizziness in the aged: results from the KORA-Age study. Eur J Public Health. 2014;24:802-7. doi: 10.1093/eurpub/ckt171.