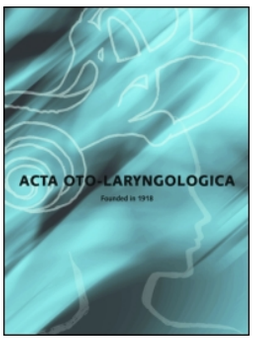

Acta Oto-Laryngologica

ISSN: 0001-6489 (Print) 1651-2251 (Online) Journal homepage: http://www.tandfonline.com/loi/ioto20

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To cite this article: Weiwei Han, Zhenyi Fan, Min Zhou, Xu Guo, Wang Yan, Xiaoxiong Lu, Li Li, Chengyao Gu, Caijing Chen & Yunqin Wu (2017): Low 25-hydroxyvitamin D levels in postmenopausal female patients with benign paroxysmal positional vertigo, Acta Oto-Laryngologica, DOI: 10.1080/00016489.2017.1416168

To link to this article: https://doi.org/10.1080/00016489.2017.1416168

Published online: 22 Dec 2017.

ACTA OTO-LARYNGOLOGICA, 2017
https://doi.org/10.1080/00016489.2017.1416168

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RESEARCH ARTICLE

Low 25-hydroxyvitamin D levels in postmenopausal female patients with benign paroxysmal positional vertigo

Weiwei Han[a,b], Zhenyi Fan[a], Min Zhou[a], Xu Guo[b], Wang Yan[a], Xiaoxiong Lu[a], Li Li[a], Chengyao Gu[a], Caijing Chen[a] and Yunqin Wu[a]

[a]Department of Neurology, Ningbo No.2 Hospital, Ningbo, Zhejiang, PR China; [b]Department of Rehabilitation, Ningbo No.2 Hospital, Ningbo, Zhejiang, PR China

ABSTRACT

Objective: Several studies have reported the association of benign paroxysmal positional vertigo (BPPV) with vitamin D deficiency. This study aimed to evaluate serum 25-hydroxy vitamin D (25 (OH) D) levels in native Chinese postmenopausal women with de novo idiopathic BPPV and to investigate the possible relationship between the occurrence of BPPV and low 25 (OH) D levels.

Methods: This retrospective study comprised of 85 postmenopausal women with de novo idiopathic BPPV and 80 age-matched healthy controls. All subjects had bone mineral density (BMD) and serum 25 (OH) D levels measurements recorded, and the results were compared.

Results: The prevalence of reduced BMD (T score <-1.0) was significantly higher in female patients with BPPV than in healthy controls (71.8% vs. 51.2%, $p = .004$). The mean serum 25 (OH) D levels were also significantly lower in female patients with BPPV than in healthy controls (19.1 ± 5.2 vs. 22.5 ± 5.8, $p < .001$). The regression analyses demonstrated that vitamin D deficiency was associated with BPPV with an odds ratio of 2.1 (95% confidence interval = 1.1–3.1, $p = .031$).

Conclusion: Our study suggests that low 25 (OH) D may be a risk factor for BPPV in postmenopausal women.

ARTICLE HISTORY
Received 14 October 2017
Revised 18 November 2017
Accepted 27 November 2017

KEYWORDS
Occurrence; osteopenia; osteoporosis; 25-hydroxy vitamin D; benign paroxysmal positional vertigo

Introduction

Benign paroxysmal positional vertigo (BPPV) is one of the most common forms of vertigo. Although the mechanism of otoconial degeneration and detachment from otoconial beds remains unknown, the widely accepted opinion is that BPPV is caused by dislodged otoconia floating into one of the semicircular canals, thereby making them sensitive to gravity [1]. BPPV can develop in the setting of head trauma, vestibular neuritis, migraines, Meniere's disease, or ear surgery, but for 50 to 70% of BPPV cases, the aetiology is still unknown and is referred to as idiopathic. BPPV can occur at any age, but the incidence increases with age. The 1-year prevalence of individuals with BPPV ranges from 0.5% in 18- to 39-year-olds to 3.4% in individuals above 60 years old [1,2]. Idiopathic BPPV is predominant in females above 50 years old, consistent with the menopausal age range of women. Decreased female hormones after menopause may be involved in the aetiology of BPPV [3].

Several studies have demonstrated that diabetes, hypertension, hyperlipidemia, stroke, autoimmune thyroiditis, osteoporosis and vitamin D deficiency may be associated with BPPV occurrence [4–6]. Among these, the relationship between BPPV and both osteoporosis and vitamin D deficiency have attracted much interest, indicating that abnormal calcium metabolism may be a pathogenic process of BPPV. Most studies have suggested that a low vitamin D level was involved in the occurrence and/or recurrence of BPPV [6–8]. Additionally, studies have also demonstrated a positive effect in treating osteoporosis or vitamin D deficiency among BPPV patients [7,9–11]. Nevertheless, a few recent studies reported that a low vitamin D level was not associated with BPPV occurrence and/or recurrence [12–15]. These discrepancies among the results of the association between BPPV and vitamin D deficiency may be caused by different clinical settings. In addition, serum 25-hydroxy vitamin D (25(OH) D) levels are affected by various factors, such as age, sex, seasonal factors, hormonal factors, nutrition and lifestyle habits, and pre-existing metabolic disorders [16]. Not all of the studies take these factors into account, so the results of the relationship between BPPV and vitamin D deficiency may be controversial.

Until now, there have been no reports on serum 25 (OH) D levels in BPPV patients from China. In this study, we assessed serum 25 (OH) D levels in native Chinese postmenopausal women with de novo idiopathic BPPV and analysed whether low vitamin D levels were associated with BPPV occurrence.

Materials and methods

Participant selection

This study retrospectively enrolled postmenopausal women who were diagnosed with de novo idiopathic BPPV at the

CONTACT Yunqin Wu wu_yunqin@126.com Department of Neurology, Ningbo No. 2 Hospital, Ningbo, Zhejiang 315010, PR China

Department of Neurology, Ningbo No. 2 Hospital, between January 2016 and August 2017. BPPV diagnosis was based on a characteristic history and observation of typical nystagmus during the Dix-Hallpike manoeuvre, supine roll, and cephalic hyperextension tests. The detailed methods of diagnosis have been described in several studies [1]. The BPPV group inclusion criteria were: (1) postmenopausal women with idiopathic BPPV; (2) agreeing to participate in the study; (3) bone mineral density (BMD) and 25 (OH) D levels measured after diagnosis of BPPV. The healthy control group was recruited from the health check-up centre of our hospital with a mean daily patient number of 4500 based on the following criteria: (1) agreeing to participate in the study, (2) without a history of vertigo or imbalance, (3) availability of integral data, including age, height, weight, ongoing health problems, medication history and physical activity habits, and (4) living in Ningbo city. The criteria for exclusion were non-cooperation, a history of similar symptoms or confirmed BPPV diagnosis previously, having secondary factors for BPPV, such as a history of head trauma, vestibular neuritis, Meniere's disease, migraines, ear surgery or sudden hearing loss, having a hip or lumbar spine fracture, long-term steroid therapy, vitamin D supplementation or osteoporosis treatment and systemic diseases influencing BMD or vitamin D levels.

This study was approved by the Ethics Committee of Ningbo No. 2 Hospital, Zhejiang, China. Informed consent was obtained from all subjects.

Bone mineral densitometry

Dual-energy X-ray absorptiometry (GE Lunar Prodigy Scanner, GE Lunar Corporation, WI, USA) was used to measure the BMD. The BMD measurement value was based on the lowest T score of either the lumbar spine (L1–L4) or proximal femur. The T score was expressed as standard deviations (SD) compared to the mean BMD of a young normal female from manufacturer provided references. The patients with T score higher than −1.0 SD were considered to have normal BMD, those with a T score from −1.0 to −2.5 SD were considered to have osteopenia and those with a T score lower than −2.5 SD were considered to have osteoporosis.

Measurement of serum 25-hydroxyvitamin D

Fasting early morning venous blood was collected from all subjects. Serum 25(OH) D was measured using the API3200 liquid chromatography-mass spectrometer/mass spectrometer system (Applied Biosystems, Foster City, CA). The 25 (OH) D level was classified as normal (≥30 ng/ml), insufficient (≥20 to <30 ng/ml), and deficient (<20 ng/ml).

Statistical analysis

The data were analysed using SPSS 22.0 (SPSS Inc., Chicago, IL). Values were expressed as the mean ± SD and then analysed using the unpaired *t*-test to determine differences between the groups. To compare the frequency of reduced BMD between the groups, a Chi-square test was used. The differences were considered significant when $p < .05$.

Results

Demographic characteristics

Eighty-five postmenopausal women with a new diagnosis of idiopathic BPPV were enrolled after excluding 13 patients who refused measurements of BMD or serum 25 (OH) D, 11 who declined to participate in the study, and 10 suspected of and/or diagnosed with BPPV relapse. Six patients who took hormone therapy and five patients who took medications for osteoporosis or vitamin D deficiency were also excluded.

Overall, 165 subjects participated in this study. The mean age of the 85 BPPV patients was 63.5 ± 9.72 years (range, 44–88 years), and the mean age of the 80 healthy controls was 63.9 ± 9.87 years (range, 43–92 years). There were no significant differences in age distribution, body mass index, or comorbidities between the groups ($p > .05$) (Table 1). In addition, the subjects selected as BPPV patients and healthy controls were evaluated over a similar in time frame.

Bone mineral densitometry

Osteopenia was observed in 35.3% of BPPV patients (30/85), osteoporosis was observed in 36.5% (31/85) and normal was observed in 28.2% (24/85; Table 1). The frequency of osteopenia was 37.5% (30/80), osteoporosis was 13.7% (11/80) and normal was 48.8% (39/80) in healthy controls (Table 1). The prevalence of reduced BMD (T score < −1.0) was significantly higher in patients with de novo BPPV than in healthy controls (71.8% vs. 51.2%, $p = .004$; Table 1).

Serum 25-hydroxyvitamin D level

The mean serum 25 (OH) D levels were significantly lower in patients with de novo BPPV than in healthy controls (19.1 ± 5.2 vs. 22.5 ± 5.8, $p < .001$; Table 1). The prevalence of vitamin D deficiency was also significantly higher in

Table 1. Clinical characteristics of BPPV patients and healthy controls.

Characteristic	BPPV (85)	Control (80)	*p* value
Age, mean ± SD (years)	63.5 ± 9.72	63.9 ± 9.87	.796
BMI (kg/m^2)	23.8 ± 3.02	23.6 ± 3.29	.766
Diabetes mellitus (%)	13 (15.3)	13 (16.2)	.866
Hypertension (%)	34 (40.0)	36 (45.0)	.516
25-hydroxyvitamin D (ng/ml)	19.1 ± 5.2	22.5 ± 5.8	<.001
25-hydroxyvitamin D			
Normal (%)	3 (3.5)	9 (11.3)	
Insufficiency (%)	34 (40.0)	43 (53.8)	
Deficiency (%)	48 (56.5)	28 (35.0)	.006
Bone mineral density			.004
Normal (%)	24 (28.2)	39 (48.8)	
Osteopenia (%)	30 (35.3)	30 (37.5)	
Osteoporosis (%)	31 (36.5)	11 (13.7)	

BPPV: benign paroxysmal positional vertigo; BMI: body mass index is the weight in kgs divided by the square of the height in metres; SD: standard deviation.

p values were calculated using independent *t*-test or Chi-square test. The differences were considered significant if *p* values < .05.

Table 2. Logistic regression analysis of the association between BPPV and variables.

	Odds ratio	*p* value	95%CI
25-hydroxyvitamin D Deficiency	2.1	.031	1.1–3.9
Bone mineral densitometry			
Osteopenia	3.9	.002	1.6–9.5
Osteoporosis	2.6	.033	1.1–6.1

patients with BPPV than in healthy controls (56.5% vs. 35.0%, $p = .006$; Table 1).

Multiple logistic regression analysis

Multiple logistic regression analysis was used to assess the relationship between BPPV and related variables including age, BMI, diabetes, hypertension, osteopenia, osteoporosis and vitamin D deficiency. The regression analyses demonstrated that osteopenia, osteoporosis and vitamin D deficiency were risk factors for BPPV (Table 2).

Discussion

Otoconia consists of calcium carbonate and a number of proteins, of which otoconin-90 and otolin-1 are the most important. Calcium and carbonate ions are essential for the formation of the otoconia [7]. Calcium ion should be increased locally to initiate and maintain the mineralization of the protein matrix of the otoconia. It is important to maintain low calcium ion levels to prohibit the unnecessary mineralization of the rest of the labyrinth. Vitamin D plays an important role in keeping calcium ion at a normal level, as either low or high levels may result in abnormal otoconia. In animal experiments, 1,25-(OH)2 vitamin D3 increased the expression of transient receptor potential vanilloid 5 and calcium buffer proteins (calbindin-D9K and calbindin-D28K) in the semicircular canal duct, and increased the expression of plasma membrane-type Ca^{2+}-ATPase 3 and sodium-calcium exchangers 2 in the cochlear lateral wall [6,7,9]. Vitamin D receptor deficient ($VDR^{-/-}$) mice showed balance dysfunction [17]. Subjects with vitamin D deficiency have abnormal ocular and cervical vestibular evoked myogenic potentials, indicating that vitamin D deficiency results in otolith dysfunction [18].

Accumulating studies imply that disturbance of calcium metabolism may underlie the pathogenesis of BPPV. Osteopenia and osteoporosis are more prevalent in middle-aged and elderly subjects, particularly in postmenopausal women, which is consistent with the incidence peak of BPPV. In 2003, Vibert et al. first observed that osteoporosis and osteopenia are more prevalent in older female BPPV patients than in healthy controls. Since then, several studies have found that the prevalence of reduced BMD is significantly higher in both men and women with BPPV than in controls and BPPV patients with reduced BMD have a higher recurrence rate than those without reduced BMD [4,5]. We also found a higher prevalence of reduced BMD (71.8%) in postmenopausal women with BPPV. In 2007, Vibert et al. [19] found a reduced density and increased volume of otoconia in osteoporotic rats compared to the control group. In addition, otoconin-90 expression levels were decreased in an osteoporotic rat model compared to those in rats with normal BMD, and oestrogen replacement therapy could reverse these changes. The oestradiol level in postmenopausal female BPPV patients was significantly lower than in healthy controls [3].

Numerous studies have investigated the role of vitamin D in the pathogenesis of BPPV. Some studies have reported that low vitamin D level is associated with occurrences and recurrences of BPPV. Vitamin D levels during BPPV episodes were significantly lower than those during BPPV remission [20]. Furthermore, normalization of serum vitamin D level in BPPV patients can reduce the recurrence and intensity of BPPV [7,9,10]. Additionally, a retrospective study from the USA confirmed that treatment of osteoporosis in 260 women with calcitriol, bisphosphonates, or vitamins D3 had a protective effect against BPPV [11].

Nevertheless, there are some controversies regarding the relationship between vitamin D and the occurrence or recurrence of BPPV. According to studies conducted by Jeong et al. [6], decreased vitamin D only showed a significant relationship with BPPV occurrence, but the vitamin D level did not differ between the de novo and recurrent groups. Büki et al. [7] compared vitamin D levels in BPPV patients who had no relapse of BPPV with patients who had a relapse BPPV. They reported that serum vitamin D levels in BPPV patients were similar to the general population but that the levels in the recurrent BPPV patients were significantly lower than those in de novo BPPV patients. Similarly, a study conducted in Paju found that vitamin D levels in recurrent BPPV patients were significantly lower than in de novo BPPV patients [8]. In contrast, a study conducted in Croatia reported no significant differences in the vitamin D level in BPPV patients with and without recurrences [15]. Unlike the general tendency, another study could not establish any link between the onset of BPPV and vitamin D and serum calcium ion [12]. Similar to this study, Karataş et al. [13] found that the prevalence of osteoporosis and vitamin D deficiency was high in both BPPV patients and the general population. They suggested that osteoporosis and vitamin D deficiency were not risk factors for BPPV. Similarly, Çıkrıkçı et al. [14] did not find that vitamin D deficiency was associated with BPPV incidence or recurrence.

These paradoxical research conclusions may be caused by the different clinical settings, such as the definition of BPPV recurrence, follow-up time, and age and sex distribution. In addition, vitamin D levels can also be influenced by season, skin colour, living style, supplement use, geographical conditions, nutritional status and methodologies to measure. To exclude confounding factors, we only selected postmenopausal women with de novo idiopathic BPPV. To minimize the effect of the weather, we recruited healthy controls living in the same local community from the health check-up centre of our hospital in the corresponding month. Moreover, we compared the possible influencing factors such as age, BMI, and comorbidities between the two groups. These features make our study more reliable.

Previous studies have shown that vitamin D deficiency is a common health issue in the southeastern coastal areas of China. The prevalence of vitamin D deficiency in women from Shanghai and Hangzhou was 46.0% and 72.4%,

respectively [16]. In our study, the prevalence of vitamin D deficiency in healthy controls was 35.0%, which indicates that hypovitaminosis D is still prevalent. The prevalence of vitamin D deficiency in BPPV patients was 56.5%, which was significantly higher than in healthy controls. Ningbo, a city in Zhejiang, is located in temperate zones (28°51'–30°33') where people have sufficient ultraviolet B radiation for their body to synthesize vitamin D. Additionally, Ningbo is a coastal city with abundant fish resources where the population consumes fish and fish oil, resulting in higher vitamin D levels than in Shanghai and Hangzhou. Similarly, a study was conducted by Talaat et al. [5] reported that vitamin D deficiency to be endemic in Egypt. The study found that reduced BMD and low vitamin D levels were associated with both development and recurrence of BPPV.

To our knowledge, this is the first study to investigate whether serum vitamin D level and BMD are altered in postmenopausal women with idiopathic de novo BPPV patients from China. We found that reduced serum vitamin D and BMD were associated with occurrence of BPPV in postmenopausal women. However, there are some limitations in our study. First, this is a single centre, retrospective study, lacking an appropriate control group and epidemiological data of vitamin D in Ningbo. Further studies should investigate vitamin D status in Ningbo. Second, this study only recruited postmenopausal women with de novo idiopathic BPPV. We will evaluate the relationship of BMD and vitamin D in younger women and men with idiopathic BPPV in a future study. Finally, we did not perform follow-ups to determine the vitamin D levels at different stages of disease. Some BPPV patients with osteoporosis or vitamin D deficiency have received drug treatments. Because the follow-up time is short, the therapeutic effect could not be determined. Thus, we cannot confirm a causal relationship between them. Further studies are needed to explore the causality and the underlying mechanism.

Conclusion

In summary, we found a lower level of 25(OH) D in postmenopausal women with de novo idiopathic BPPV than in healthy controls. Low 25 (OH) D may be a risk factor for BPPV occurrence in postmenopausal women. Future studies are needed to explore the role of 25 (OH) D in the pathogenesis of BPPV.

Acknowledgements

The authors thank the participants of the study.

Disclosure statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Funding

This study was supported by the Zhejiang Province Regional Center for Neurology, 2015, and the Huamei Foundation of Ningbo No. 2 Hospital under Grant No. 2017HMKY18.

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