ORIGINAL ARTICLE

The Association Between Idiopathic Benign Paroxysmal Positional Vertigo and Calcium Metabolism

Joon-Seok Ko, Seong-Ki Ahn, Sea-Yuong Jeon, Dong Gu Hur, Ho-Yeop Kim, Jong Ryeal Hahm, Soo Kyung Kim

Department of Otolaryngology (JSK, SKA, SYJ, DGH, HYK)
Institute of Health Sciences, (SKA)
Department of Internal Medicine, School of Medicine, Gyeongsang National University, Jinju, South Korea (JRH, SKK)

Objective: The aim of this study was to demonstrate an association between the pathophysiology of idiopathic benign paroxysmal positional vertigo (BPPV) and calcium metabolism by urinary deoxypyridinoline (D-Pyr) a known bone resorption factor.

Materials and Methods: During the period March 2011 to April 2012, twenty-three women aged less than 65 years with a diagnosis of idiopathic BPPV underwent bone mineral density (BMD) of the lumbar spine and urinary D-Pyr analysis. The same tests were performed in a sex and age-matched control group.

Results: The incidence of osteopenia or osteoporosis in this study were significantly higher in idiopathic BPPV group than in the BMD control group ($p = 0.038$). Furthermore, 11 of the 23 patients in the idiopathic BPPV group and 10 of 44 in the D-Pyr control group had significantly elevated urinary D-Pyr levels ($p = 0.044$).

Conclusion: The present study shows an association between idiopathic BPPV and a change in calcium metabolism. The authors believe that this disturbance in calcium metabolism, in terms of increased bone resorption, could induce changes in otolithic organs.

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Introduction

The term benign paroxysmal positional vertigo (BPPV) was coined by Dix and Hallpike in 1952.[1] BPPV is one of the most common vestibular disorders, and various etiologies. However, although 50 to 70% of cases occur in isolation (termed idiopathic or primary BPPV), BPPV can also develop after head trauma, viral neurolabyrinthitis, Ménière's disease, migraine, ear or dental surgery, or prolonged bed rest, which are representative examples of secondary BPPV.[2] In particular, idiopathic BPPV is encountered more often in women, with a female-to-male ratio of 2~3:1, and has a peak age onset in the sixth decade of life.[3]

The high prevalence of BPPV in middle-aged women suggests that hormonal factors play a role in its pathogenesis.[4] In recent studies, the prevalence rates of osteopenia and osteoporosis were found to be higher in patients with idiopathic BPPV than in a normal control group.[4,5]

The diagnosis of osteoporosis depends on measures of bone mineral density (BMD) at various sites, but usually the distal radius, lumbar spine, and hip. However, as BMD changes are small and the average postmenopausal bone loss over 1 year in only about 2%, slower rates of losses may be undetected.[6] Therefore, recently much interest has been focused on various biochemical markers of bone

Corresponding address:
Seong-Ki Ahn
Department of Otolaryngology, School of Medicine, Gyeongsang National University,
Jinju, 660-702, Republic of Korea
Tel: +82-55-750-8176
Fax: +82-55-759-0613
e-mail: skahn@gnu.ac.kr

turnover that represent the products of bone formation and resorption released into the circulation (Table 1). These biochemical markers of bone metabolism can provide better real-time assessments of bone resorption, formation, and turnover.[7] Urinary deoxypyridinoline (D-Pyr) is a representative bone resorption marker, and its level in urine as determined by high-performance liquid chromatography (HPLC) is widely regarded as the best method available for assessing bone resorption.[8] However, no attempt has been made to compare bone resorption markers in an idiopathic BPPV group and a control group. Therefore, the aim of this study was to investigate whether an association exists between the pathophysiology of idiopathic BPPV and calcium metabolism, as determined by urinary D-Pyr, or BMD, as determined by dual energy X-ray absorptiometry (DXA).

Table 1. Representative biochemical markers for bone turnover.

Bone Formation Markers	
Serum	Bone-specific alkaline phosphatase
	Osteocalcin
	Carboxyterminal propeptide of type I collagen
	Aminoterminal propeptide of type I collagen
Bone Resorption Markers	
Serum	Cross-linked C-telopeptide of type I collagen
	Tartrate-resistant acid phosphatase
	N-telopeptide of collagen cross-links
	C-telopeptide of collagen cross-links
Urine	Hydroxyproline
	Pyridinolines
	Deoxypyridinolines
	N-telopeptide of collagen cross-links
	C-telopeptide of collagen cross-links

Materials and methods

This prospective study was carried out on 23 women aged less than 65 years with a diagnosis of idiopathic BPPV made at the Department of Otolaryngology, Gyeongsang National University Hospital between March 2011 and April 2012. The institutional review board of our hospital approved the study protocol and written informed consent was obtained all study subjects. BPPV was diagnosed based on a history of recurrent positional vertigo and the results of the Dix-Hallpike[1-3, 9] for BPPV of the posterior semicircular canal (PSC-BPPV) and based on the results supine head-turning[10-13] for BPPV of the horizontal semicircular canal (HSC-BPPV). The exclusion criteria applied for idiopathic BPPV were as follows: (1) a history of head trauma, (2) vestibular neuritis or labyrinthitis, (3) Ménière's disease, (4) otitis media, (5) a history of ear or dental surgery, (6) current or a history of osteopenia/osteoporosis, and (7) a history other metabolic related disorders. The Dix-Hallpike test for PSC-BPPV was considered positive if nystagmus was recorded with appropriate positioning, latency, duration, and fatigability, and if it reversed when the patient resumed a sitting position. With the affected ear down, geotropic torsional nystagmus (i.e., the upper poles of the eyes beating to the lowermost ear) occurs with an up-beating component for PSC. Patients with HSC-BPPV were classified as canalolithiasis type (horizontal geotropic nystagmus) or cupulolithiasis (horizontal apogeotropic nystagmus) type according to the direction of nystagmus.[13-15]

In addition, BMD was measured using a Lunar Prodigy DXA (GE Medical Systems, Madison, WI) in the lumbar spine. Results are presented as T-scores, which were calculated using by dividing differences between measured BMDs and the mean BMD of healthy young adults matched for sex and ethnic group by the SD of the same healthy young adult population. BMD were considered normal when the T-score was within -1.0 SD of the normative value, and osteopenia and osteoporosis were diagnosed when lumbar spine BMDs were between -1.0 and -2.5 SD or < -2.5 SD of normative values. According to the World Health Organization criteria, individuals with a T-score of -1.0 SD are twice as likely to experience a fracture as individuals with a T-score of zero.[16]

Using age-matched groups, we compared the T-scores of the 23 patients with those of 44 healthy women without a history of dizziness who visited our hospital for a physical check-up.

An immunoassay for urinary D-Pyr (Metra Biosystems Mountain View, CA) was used to determine amounts of bone resorption. The normal range of values for urinary D-pyr is 2.5~6.5 nM/mM creatinine. We also compared the urinary D-Pyr values of patients in 44 healthy women without a history of dizziness who visited our hospital for a physical check-up.

All data were collected prospectively. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, USA). Pearson's $\chi 2$ test and Fisher's exact test were used to compare BMD and urinary D-Pyr in the above-mentioned groups. Statistical significance was accepted for p values < 0.05.

Results

Clinical characteristics

Twenty-three patients who fulfilled the selection criteria were analyzed. Ages ranged from 20 to 64 years (mean age 48.0 years ± 11.3 years). The characteristics of the 23 patients are summarized in Table 2. Twelve patients had PSC-BPPV and 11 had HSC-BPPV. All patients with PSC-BPPV had the canalolithiasis type. Six of the 11 patients with HSC-BPPV had the canalolithiasis type, and 5 had the cupulolithiasis type. The values of BMD in idiopathic BPPV ranged from -3.7 to 1.0, and urinary D-Pyr levels ranged from 2.78 to 13.33 nM/mM creatinine.

Bone mineral density by dual energy X-ray absorptiometry

Osteopenia (-2.5 < T-score < -1.0) and osteoporosis (T score ≤ -2.5) were found in 30% of the idiopathic BPPV group. Osteopenia and osteoporosis proportions were significantly higher in the idiopathic BPPV group than in the BMD control group (Fig. 1).

Urinary deoxypyridinoline

The proportion with an elevated urinary D-Pyr value (normal; 2.5~6.5 nM/mM creatinine) in the idiopathic BPPV group was significantly higher than in the D-Pyr control group ($p < 0.05$) (Fig. 2).

Table 2. Clinical features of patients with idiopathic benign paroxysmal positional vertigo.

No	Age	Side/Type	T-score	Urinary D-Pyr
1	30	Rt. PSCC canalolithiasis	0.6	7.89
2	34	Rt. PSCC canalolithiasis	-0.8	5.83
3	46	Rt. HSCC canalolithiasis	0.7	3.68
4	52	Rt. PSCC canalolithiasis	-0.7	4.12
5	63	Rt. HSCC canalolithiasis	-2.5	5.37
6	62	Lt. PSCC canalolithiasis	-3.3	8.53
7	41	Lt. HSCC cupulolithiasis	-1.3	5.09
8	61	Lt. PSCC canalolithiasis	-1.5	14.94
9	35	Rt. PSCC canalolithiasis	-0.6	7.01
10	38	Rt. PSCC canalolithiasis	1.0	3.49
11	52	Rt. HSCC cupulolithiasis	-1.7	6.68
12	64	Rt. HSCC cupulolithiasis	-3.7	13.33
13	62	Lt. PSCC canalolithiasis	-1.7	6.58
14	47	Rt. PSCC canalolithiasis	0.9	7.11
15	50	Rt. HSCC cupulolithiasis	0.9	4.57
16	48	Rt. PSCC canalolithiasis	1.0	6.53
17	54	Lt. HSCC canalolithiasis	0.3	2.78
18	42	Lt. HSCC cupulolithiasis	-0.9	5.87
19	42	Rt. PSCC canalolithiasis	0.2	4.77
20	62	Lt. HSCC canalolithiasis	0.2	5.15
21	52	Lt. HSCC canalolithiasis	-0.8	8.54
22	20	Lt. HSCC canalolithiasis	0.0	6.57
23	48	Rt. PSCC canalolithiasis	-0.7	5.56

No: number, PSCC: posterior semicircular canal, HSCC: horizontal semicircular canal, T-score: T-score of bone mineral density by dual energy X-ray absorptiometry, D-Pyr: deoxypyridinoline

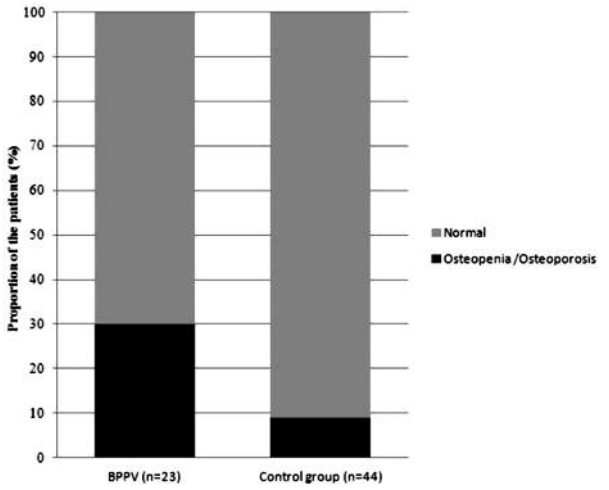

Figure 1. Result of bone mineral density. Proportions of patients with osteopenia and osteoporosis were higher in idiopathic BPPV group (30%) than in the BMD control group (9%) (p = 0.038). BPPV: benign paroxysmal positional vertigo, BMD: bone mineral density

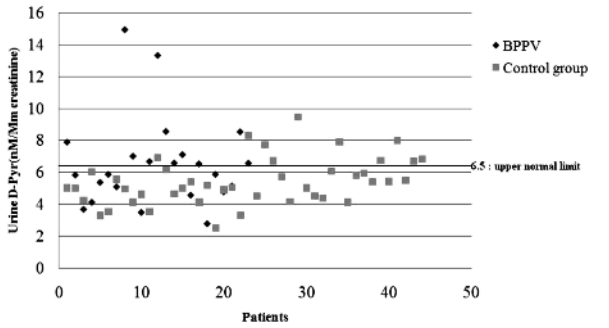

Figure 2. Result of urine deoxypyridinoline. Eleven of the 23 (48%) idiopathic BPPV patients and 10 of the 44 (22%) in the D-pyr control group had an elevated urinary D-Pyr level (p = 0.044). Idiopathic BPPV patients are shown using filled rhombus and D-pyr control group using filled rectangular. D-Pyr: deoxypyridinoline, BPPV: benign paroxysmal positional vertigo

Discussion

We report for the first time an association between the pathophysiology of idiopathic BPPV and calcium metabolism as determined urinary D-Pyr level. Dizziness represents a serious public health problem worldwide and has substantial societal costs. In particular, BPPV, which is one of the most common peripheral vestibular disorders, occurs when otoconia become dislodged and move into the semicircular canals.[10,11]

Otoconia are composed of calcite crystals with an organic core consisting predominantly of glycoproteins.[17] Otoconia are dynamic in nature, and take up 45Ca at a rate comparable to that of bone. It has been proposed that a reduction in bone formation may be the main reason for the lower calcium content of otoconia, and thus, similarities between bone and otoconia formation may help answer questions raised about bone minearalization.[18] In particular, three possible mechanisms could explain the correlation between BPPV and osteopenia or osteoporosis. First, reductions in estrogen, the natural generator of bone mass, may disturb the internal structure of otoconia and/or their interconnection and attachment to the gelatinous matrix.[5] Second, increased calcium resorption may increase the concentration of free calcium in endolymph and reduce its capacity to dissolve dislodged otoconia.[5] Third, the capacity ability to dissolve otoconia is inversely dependent on the free calcium concentration in endolymph.[19] In this animal study, otoconia were completely dissolved by normal endolymph with a calcium concentration of 20 μM, but not when the calcium concentration was increased to 500μM.

Furthermore, the etiology of BPPV remains to be elucidated in many cases. In previous clinical studies, the prevalences of osteopenia and osteoporosis were found to be higher in patients with idiopathic BPPV than in healthy controls.[4,5] Vibert et al. confirmed that ultrastructural modifications of otoconia occur, in terms of changes in aspect, size, and density, in ovariectomized osteopenic/osteoporotic female adult rats.[20] These results were interpreted to occur as a consequence of a disturbed calcium metabolism in the utricle induced by osteopenia or osteoporosis. Furthermore, it has been hypothesized that the pathogenetic mechanism of BPPV could involve a disturbance in calcium homeostasis associated with a systemic disorder, such as, osteoporosis or another skeletal disease. Since, BPPV is frequently due to a menopause-related hormonal deficiency, a preponderance of otoconial degeneration would be expected in menopausal women.[5,21] In the present study, as has been reported previously, the proportion patients with osteopenia or osteoporosis diagnosed with BMD was significantly higher in the idiopathic BPPV group than in the BMD control group.[4,5]

Biochemical bone markers can be valuable tools for the management of metabolic bone diseases. Their most

recognized application in clinical practice is for monitoring the treatment for osteoporosis as an adjunct to BMD measurement. Other diagnostic tests can also be used as predictive markers for bone loss and the risk of bone fracture. [22] Biochemical markers available for the assessment of bone formation and bone loss (resorption) are summarized in Table 1.

Of these biochemical markers, D-Pyr, which is mainly present in bone and dentine, is considered a specific biomarker of bone resorption, and to be useful for predicting fracture risk associated with osteoporosis or bone cancer and for growth assessments in children with growth hormone deficiency.[23] D-Pyr measured in urine is likely to be derived from bone because of the mass and high turnover of bone.[24] Thus, urinary D-Pry provide a straightforward, cheap, non-invasive means for detecting bone resorption,[23] which is why we chose to used it in the present study. We found that the proportion of patients increased urinary D-Pyr values in the patients group was significantly higher than in the D-Pyr control group, which suggests that idiopathic BPPV and bone metabolism are closely related, irrespective of menopausal status.

Conclusion

The present study shows an association between idiopathic BPPV and a change in calcium metabolism. It is suggested that disturbances of calcium metabolism, as manifested by increased bone resorption, induce changes in otolithic organs. Further studies will be conducted to clarify the pathophysiology of idiopathic BPPV from the perspective of calcium metabolism.

Conflict of interest: The authors declare that they have no vested interest that could be construed to have inappropriately influenced this study.

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