Otology & Neurotology
37:1388–1392 © 2016, Otology & Neurotology, Inc.

Calcium Homeostasis During Attack and Remission in Patients With Idiopathic Benign Paroxysmal Positional Vertigo

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Objective: To evaluate changes in calcium metabolism in patients with idiopathic benign paroxysmal positional vertigo (BPPV) on initial presentation and at the follow-up visit.
Subjects and Methods: The study comprised a total of 31 patients aged greater than 18 years who presented at the otorhinolaryngology outpatient clinic of our hospital, newly diagnosed as idiopathic BPPV based on the history compatible with BPPV and positive provocative maneuver (either Dix-Hallpike or Roll test). The first blood sample was obtained on the day of initial presentation when the patient was found to have active unilateral BPPV. After 6 months, a blood sample was again drawn in accordance with the procedure. Blood samples were analyzed for data on 25-hydroxyvitamin D (25(OH)-D), total calcium, parathormone and ionized calcium on initial presentation, and at the follow-up visit.
Results: The patients comprised 20 (64.5%) women and 11 (35.5%) men with a mean age of 49.78 years (range, 23–75 years). During an attack a higher prevalence of decreased serum Vitamin D is less than 20 ng/ml, was determined (93.5% versus 38.7%). There were statistical differences between the Vitamin D values, parathormone, and corrected by pH ionized calcium in both periods ($p < 0.05$).
Conclusion: A statistically significant association was determined between Vitamin D and calcium metabolism in patients with idiopathic BPPV. It can be considered that Vitamin D deficiency and decreased ionized Ca level may be a risk for BPPV, not only in patients with osteoporosis but also in all patients. Very low levels of 25(OH)-D seem to be associated with recurrence of BPPV. The recurrences might possibly be prevented with supplementary Vitamin D especially in those with recurrent idiopathic BPPV but further studies would be necessary to determine this. **Key Words:** Attack—BPPV—Calcium—Homeostasis—PTH—Remission—Vitamin D.

Otol Neurotol **37:**1388–1392, 2016.

Head trauma, advanced age, various disorders affecting the inner ear such as vestibular neurinitis and Meniere's disease, and women sex are known predisposing factors of benign paroxysmal positional vertigo (BPPV) but the triggers of otoconial degeneration and detachment of calcium (Ca) crystals from the otoconial beds are not known (1).

Ca metabolism plays a primary role in the synthesis/absorption of otoconia made of Ca carbonate, and may therefore be an etiological factor in the onset of BPPV (2–4). Although several studies have implied that abnormal Ca metabolism may underlie BPPV (5–7) and a number of studies have investigated the association between BPPV and osteoporosis, few studies have corroborated these findings by examining serum markers of bone turnover (8). In the current study, since corrected by pH ionized calcium (pHiCa), parathormone (PTH), and 25-hydroxyvitamin D (25(OH)-D) provided more information regarding disturbed Ca homeostasis, it was aimed to evaluate changes in Ca metabolism in patients with idiopathic BPPV on initial presentation and at the follow-up visit.

SUBJECTS AND METHODS

A total of 37 patients older than 18 years who presented at or were referred to the otorhinolaryngology outpatient clinic of our hospital, newly diagnosed as idiopathic BPPV based on the on the history compatible with BPPV and positive provocative maneuver (either Dix-Hallpike [DH] or Roll test). The patients were treated with the canalith-repositioning maneuver (modified Epley's method or Lempert). The number of recurrences, the number of treatment maneuvers, and demographic data were recorded. At the follow-up examinations, patients determined with positive DH maneuver were evaluated as recurrence, and those with negative DH maneuver as non-recurrence. Patients were called for follow-up twice for evaluation in respect of recurrence after therapeutic maneuver. Patients

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The authors disclose no conflicts of interest.
DOI: 10.1097/MAO.0000000000001167

showing recurrence were called for regular treatment until the DH test was determined negative. In addition, the patients were interviewed by telephone every month by the second author to confirm the absence of recurrence of BPPV. They were instructed to return to the clinic immediately if they suspected BPPV recurrence. The patients were followed up for at least 6 months.

The first blood sample was obtained on the day of initial presentation when the patient was found to have active unilateral BPPV. Blood samples were drawn from the antecubital vein by careful vein puncture in a 21 G sterile syringe without stasis at 08.00 to 11.00 AM after a fasting period of 12 h and then centrifuged at $4000 \times g$ for 5 min to separate plasma for 25(OH)-D. If the diagnosis of BPPV was not made in the morning, patients were requested to attend on the following morning. After 6 months from the initial blood sample, each patient was invited to a follow-up examination. Of the total 37, 31 responded and presented for the check-up at which the Dix-Hallpike test was repeated, so the six patients who did not attend follow-up were excluded from the study. From patients with a negative Dix-Hallpike test, a blood sample was again drawn in accordance with the procedure. All the blood samples were rapidly frozen in vials after centrifugation and stored at $-80\,^{\circ}C$ until analysis. Ionized calcium (iCa) and pH levels were measured with an electrolyte analyzer (Cornley AFT500AU). As iCa values were affected by pH, the calculation was made as corrected by pH iCa. Albumin and total Ca levels were also measured as evaluation was made of all calcium related parameters including albumin total Ca and iCa. Thus total evaluation was ensured for Ca levels (ionized and bound to albumin) and excluded possible interferences because of albumin levels. All blood samples were analyzed for data on PTH, albumin, total Ca, and iCa on the initial and follow-up visits. Laboratory testing was performed in the biochemistry laboratory of Mustafa Kemal University, Turkey.

In this study, patients were excluded with diseases that affect Vitamin D and Ca homeostasis, and those who had received Vitamin D and Ca therapy or osteoporosis treatment. The following exclusion criteria were also applied to patients: inability to provide consent (e.g., presence of mental retardation or dementia), focal findings on routine cranial nerve examination, history of other vestibular disorders (e.g, labyrinthitis, Meniere's disease, Paget's disease, otosclerosis, vestibular neuritis, vestibular schwannoma, Cogan's syndrome), history of balance disorders of other etiology (e.g., peripheral neuropathy, vertebrobasilar insufficiency, hypotension, arrhythmia, Arnold Chiari malformation), history of ear surgery, history of previous BPPV attack, history of head trauma, presence of otitis media, multivitamin use, inability to undergo positional testing (i.e., Dix-Hallpike maneuver)-because of neck musculoskeletal disorder, and inability to lie supine. From the details obtained on first presentation, patients who had experienced an attack similar to a BPPV attack were considered to possibly have recurrent BPPV and were excluded from the study. Approval for the study was granted by the Clinical Research Ethics Board of Mustafa Kemal University Hospital.

Statistical Analysis

Statistical analysis of the results was performed using SPSS for Windows 22.0(Chicago, IL). Values were expressed as mean ± standard deviation (SD). Comparisons of data during at the initial and follow-up visit were made using the Paired Samples test or Wilcoxon test. A value of $p < 0.05$ was determined as statistically significant.

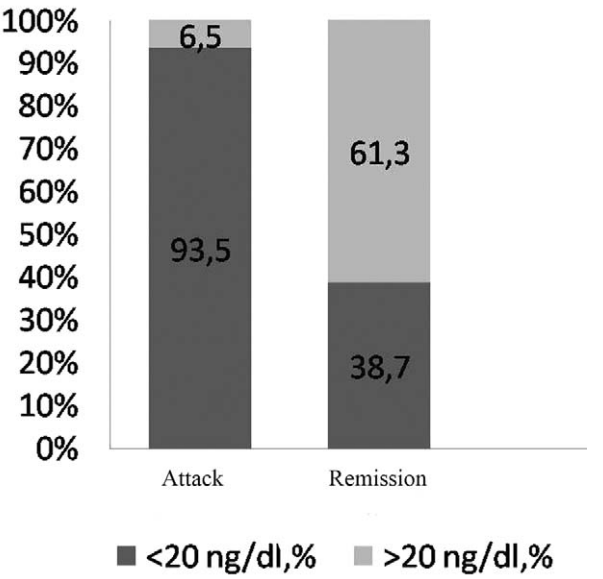

FIG. 1. Graphic showing 25(OH)-D (≥20/<20 ng/ml) levels on initial presentation and at the follow-up visit.

RESULTS

The mean age of the patients was 49.78 years (range, 23–75 years). Of the 31 study patients, 20 (64.5%) were women and 11 (35.5%) were men. There was a statistical difference between the groups in gender distribution ($p = 0.01$). The duration of BPPV symptoms until the clinical evaluation and enrollment in the present study varied from 1 to 12 days (median = 4.0). Most (90%) of the patients were evaluated within 5 days from the onset of symptoms. BPPV most commonly involved the posterior canal (n = 29; 93.6%), followed by the horizontal canal (n = 2; 6.4%). Canalolithiasis was observed to be clinically responsible for the etiology in the vast majority of patients. Recurrent attacks of BPPV were reported in five patients with very low levels of Vitamin D in early periods (within 3 months).

The mean Vitamin D values at the initial and follow-up visits were 9.73 ± 8.77 ng/ml, 19.08 ± 5.92 ng/ml, respectively. Serum 25(OH)-D levels is less than 20 ng/ml were considered as deficiency and levels less than 10 ng/ml were considered as severe deficiency (9). A higher prevalence of decreased serum 25(OH)-D is less than 20 ng/ml was seen on initial presentation (93.5% versus 38.7%, $p < 0.001$, Fig. 1). The mean PTH values at the initial and follow-up visits were 43.84 ± 18.48 pg/ml, 25.08 ± 11.58 pg/ml, respectively (normal range, 12.0–65.0 pg/ml). On initial presentation, six patients were determined with increased serum PTH value (>65 pg/ml). At the follow-up visit, increased PTH value was not determined in any patient. The mean pHiCa values at the initial and follow-up visits were 0.87 ± 0.22 mg/dl, and 1.03 ± 0.56 mg/dl, respectively. There were statistical differences between the 25(OH)-D values, PTH, and pHiCa in both periods ($p < 0.05$). No statistically significant differences were

TABLE 1. *Patient characteristics, the values of biochemical parameters on initial presentation and at the follow-up visit and also 25(OH)-D classification of both periods*

Characteristics	Period (n = 31) (mean ± SD)		
	Attack	Remission	*p*
Age, y	49.78 ± 11.80	49.78 ± 11.80	–
Sex	11M/20F	11M/20F	<0.05
25(OH)D, ng/ml	9.73 ± 8.77	19.08 ± 5.92	<0.001
PTH, pg/ml	43.84 ± 18.48	25.08 ± 11.58	<0.001
PhiCa, mg/dl	0.87 ± 0.22	1.03 ± 0.56	0.001
Total Ca, mg/dl	9.65 ± 0.32	9.54 ± 0.46	NS
Albumin, g/dl	4.43 ± 0.19	4.41 ± 0.30	NS

Ca indicates calcium; F, female; M, male; NS, non significant; pHiCa, corrected by pH ionized calcium; PTH, parathormone; y, years.

determined between the two periods in respect of albumin and total Ca levels ($p > 0.05$). The laboratory findings of the patients are shown in Table 1.

DISCUSSION

The results of the study showed decreased 25(OH)-D levels and pHiCa levels and elevated PTH levels on initial presentation of idiopathic BPPV in both men and women compared with the values at the follow-up visit.

The otoconia, like bone are composed of Ca carbonate (Ca phosphate in bone) as calcite crystals and an organic core consisting predominantly of glycoproteins (10,11). Ca and carbonate ions are the fundamental requirements for producing vertebrate otoconia. In addition, Ca is required to mineralize otoconia and to maintain any turnover in the otolith because the otoconia are in a dynamic state (12,13). Sanyelbhaa and Sanyelbhaa (14) suggested that Vitamin D deficiency results in production of abnormal otoconia, which results in otolith dysfunction. Jeong et al. (15) reported that a normal serum level of Vitamin D is essential for the development of normal otoconia through keeping the Ca concentration in the vestibular endolymph at a normal critical level, as either low or high Ca would result in abnormal otoconia. This critical balance is achieved by the epithelial Ca channel transport system expressed in the inner ear, which is regulated by Vitamin D receptor (VDR).

Vitamin D plays a part in the homeostasis of Ca and phosphorus. The VDR is present in the cells throughout the body, and is involved in cell proliferation and differentiation as well as immunomodulation (16). A recent experimental study demonstrated that all components of epithelial Ca channel transport system are expressed as transcripts in the semicircular canal duct and cochlea. Even though lesser than the bone, the otolith of utriculi is also generated by dynamic Ca^{2+} uptake, and this process is related to Ca^{2+} binding proteins that are up-regulated by Vitamin D (12,17,18). Mice without vestibular D receptor have been determined to show vestibular dysfunction (19).

A recent clinical study showed an apparent correlation between BPPV and osteopenia or osteoporosis and it was hypothesized that mechanisms of increased resorption and decreased fixation of Ca might also be implicated in the onset of repeated dislocation of otoconia. It has been assumed that Vitamin D deficiency contributes to the generation of BPPV via deranged Ca metabolism in the vestibular organs (20). Another clinical study reported that postmenopausal women with BPPV have a high prevalence of osteopenia/osteoporosis, and postmenopausal women with osteopenia/osteoporosis have a higher than expected prevalence of BPPV. A previous study has reported that levels of biochemical markers of bone turnover correlate with the presence of BPPV but not Ca or VitD (8). Buki et al. (21) reported that the mechanism of the beneficial effect of Vitamin D may involve improvement of pathological biomineralization of otoconia similar to that of bone and teeth and in that study, low levels of serum 25(OH)-D were measured in four cases with chronically recurrent severe BPPV episodes. Talaat et al. (22) showed that 25(OH)-D was significantly lower in recurrent BPPV compared with a non-recurrent subgroup of BPPV. In the current study, recurrence in the early period (0–90 days) was detected in five cases with low levels of serum 25(OH)-D. This may suggest that 25(OH)-D and calcium contribute to the stability of the hair cells of the support tissues. Their absence can lead to disease and in cases of severe deficiency may lead to recurrence of the disease. Decreased fixation of Ca may generate failures in the remodeling of the internal structure of the otoconia themselves, as well as in their attachment on the otoconial membrane, although a decreased concentration of free Ca in the endolymph might induce reduction in its capacity to dissolve the dislodged otoconia, in addition to affecting electromechanical transduction of the sensory epithelium (23,24).

Although several studies showed that abnormal Ca metabolism might underlie BPPV (5–7), there is no study showing that PTH is extremely vulnerable to abnormal Ca metabolism. In the current study, elevated PTH levels, vitamin D deficiency and decreased pHiCa levels were detected on initial presentation compared with those at the follow-up visit in patients with idiopathic BPPV. This is consistent with a recent report that 25(OH)-D was significantly and inversely correlated with markers of

bone formation and resorption and that Vitamin D supplementation may prevent BPPV recurrences (21,25). A recent study has also indicated an association between reduced bone mineral density and development/recurrence of BPPV and that low levels of 25(OH)-D were related to the development of BPPV while very low levels were associated with recurrence of BPPV (26). We have posited that Vitamin D prophylaxis may prevent recurrent attacks of idiopathic BPPV, especially in those with recurrent idiopathic BPPV. Further studies are needed to demonstrate this clinical significance.

In the current study, 25(OH)-D and pHiCa were also found to be decreased in men. This finding suggests that not only hormonal changes such as estrogen, but also other factors related to Ca homeostasis such as 25(OH)-D and PTH may cause BPPV. In elderly patients, the linking filaments of the otoconia may be weakened or broken.

While the rate of 25(OH)D is less than 20 ng/ml and 25(OH)D $\geq$20 ng/ml patients was 93.5% (2 of 29) on initial presentation, it was determined as 38.7% (19 of 12) at the follow-up visit. As the blood samples were obtained from patients at the end of the study, at the time of the attack and 6 months later during follow up and were all assayed at the same time, vitamin supplements were not given after the attack, and during the follow-up period the patients were questioned whether or not they were taking medications including vitamins. There was no information of Vitamin D levels in this region during the study as there was no control group. However, the geographic area where the study patients lived is in the southern most region of Turkey, which is a sunny region for the vast majority of the year. When all the laboratory results were examined of the blood samples obtained on first presentation and during follow-up, the patients with very low levels of Vitamin D were determined to be the patients with recurrence within the first 3 months and whore quired a greater number of treatment maneuvers. When the results were known of the blood samples obtained at the first visit and at the 6-month follow-up visit, which were analyzed at the same time, it was determined that the Vitamin D levels of most of the patients were low at the time of the attack and increased in the follow-up period. Vitamin supplements were not given after the attack.

In 78% of the patients, the attacks occurred during the winter months. However, the geographic area where the study patients lived is in the southern most region of Turkey, which is a sunny region for the vast majority of the year. We think that the BPPV attacks showed a seasonal increase, especially in the winter. As there was no control group, it is not possible to provide more information regarding this. Vitamin D levels are known to show a difference according to nutritional habits and seasons. In literature, a level of Vitamin D less than 20 ng/dl is accepted as deficiency (9). Therefore, although it is thought that Vitamin D deficiency could play a role in the pathogenesis of BPPV, it could also be a trigger factor.

The spontaneous increases in Vitamin D can be related to seasonality of the Vitamin D level and/or nutrition. Whitman and Baloh assessed the number of BPPV visits seen at a hospital in Boston in March, April, and May and compared this with the number of visits during the remaining months of the year to explore the possibility of BPPV seasonality. They concluded that the incidence of BPPV in Boston may be higher during the period between March and May, compared with other months (27). We think that BPPV and changes in Vitamin D levels are seen in parallel with seasonal predisposition. In patients with Vitamin D deficiency and calcium homeostasis problems, this condition of the forming of abnormal otoconia may prepare the ground for disease. We suggest that BPPV may be a sequela of low Vitamin D and disturbed calcium homeostasis.

In conclusion, there seems to be a correlation between BPPV and low levels of 25(OH)-D and pHiCa. It should be considered that Vitamin D deficiency and decreased iCa level may be a risk for BPPV not only in patients with osteoporosis but also in all patients. Elevated PTH levels can show the attack period of the BPPV. Very low levels of 25(OH)-D seem to be associated with recurrence of BPPV. The recurrences might possibly be prevented with supplementary Vitamin D especially in those with recurrent idiopathic BPPV but further studies would be necessary to determine this. Although it is thought that Vitamin D deficiency could play a role in the pathogenesis of BPPV, it could also be a trigger factor.

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