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Reduction of recurrence rate of benign paroxysmal positional vertigo by treatment of severe vitamin D deficiency

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ABSTRACT

Objective: Several studies correlated between vitamin D deficiency and the development, and the recurrence of benign positional paroxysmal vertigo (BPPV), but none of them proved that treatment of vitamin D deficiency would reduce the recurrence rate of BPPV. This study aims to detect the effect of treatment of severe vitamin D deficiency on the recurrence rate of BPPV.

Methods: The inclusion criteria of the study group were: (1) Unilateral, idiopathic, posterior canal BPPV with no history suggestive of secondary BPPV and (2) 25-hydroxyvitamin D3 level $\leq$10 ng/ml. All subjects enrolled in the current study underwent detailed clinical history, audiovestibular evaluation consisting of pure-tone audiometry, Immittancemetry, Videonystugmography, serum 25-hydroxyvitamin D3 assessment, and Dual-energy X-ray absorptiometry (DXA). Vitamin D therapy was prescribed for the study group. Serum 25-hydroxyvitamin D3 level was evaluated twice, on recruitment into the study group and 3 months after commencing vitamin D therapy. According to the results of the second evaluation of serum 25-hydroxyvitamin D3, the study group was subdivided into two subgroups: Subgroup (I): including 28 subjects who disclosed elevation of serum 25-hydroxyvitamin D3 level; improvement $\geq$10 ng/ml. Subgroup (II): including 65 patients who disclosed elevation of serum 25-hydroxyvitamin D3 levels $<$10 ng/ml. The study group was followed up for 18 months in order to observe the recurrence of BPPV.

Results: The differences between both study subgroups (I) & (II) regarding age, sex distribution, and bone mineral density were insignificant. The number of subjects who had recurrence of BPPV in subgroup (I) was 4 (14%) versus 28 subjects (43%) in subgroup (II). The mean values for recurrent attacks/subject in subgroups (I) & (II) were 0.18, and 0.66 attack/subject respectively; these differences between both subgroups were of high statistical significance ($p < 0.01$). The Odds Ratio for development of recurrence of BPPV in subjects with severe vitamin D deficiency was 4.54 (95% CI: 1.41–14.58, $p < 0.01$). The relapse attacks of BPPV affected both ears irrespective of the ear showing the original BPPV attack.

Conclusion: The present study indicates that improvement of serum 25-hydroxyvitamin D3 levels is associated with substantial decrease in recurrence of BPPV.

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1. Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo; it is believed to be an otoconia-related balance disorder. It is caused by dislocation of degenerated otoconia into the semicircular canals rendering the canals sensitive to gravity. BPPV has a lifetime prevalence of 2.4% [1]. BPPV may be found in isolation, idiopathic BPPV, in approximately 80% of all cases. BPPV may be secondary to head trauma, vestibular neuritis,

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Meniere's disease, migraines, otologic surgery, and prolonged bed rest [1]. Canalith repositioning maneuvers (CRM) provide a convenient and rapid method for treatment of BPPV. CRM would resolve the positional nystagmus in 80–100% of cases through moving the canalith from the affected semicircular canal to the vestibule where they are absorbed [2]. Although CRM is very effective, BPPV often recurs. In one study, within 2 years of follow-up, 44% of patients treated successfully with the CRM redevelop BPPV [3]. Furthermore, recurrence was higher in secondary BPPV, especially BPPV secondary to head injury [4], but it was not related to the age or sex of the patient [5].

Vitamin D plays an important role in maintaining normal otolith function through keeping the vestibular endolymph calcium at a critical level that allows mineralization of the otoconia properly [6]. Several studies correlated between vitamin D deficiency and the development, and the recurrence of BPPV [6,7]. Severe vitamin D deficiency is considered whenever serum 25-hydroxyvitamin D3 levels $\leq$10 ng/ml [8], and such low levels of 25-hydroxyvitamin D3 were significantly associated with recurrence of BPPV [7]. In the present study, we aimed to detect the effect of treatment of severe vitamin D deficiency on the recurrence rate of BPPV.

2. Materials and methods

2.1. Subjects

This study was conducted in a tertiary referral center, Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia between February 2013 and April 2015. The study group included 93 subjects (42 males, 51 females; age range 28–70 years (50.4 $\pm$ 10.8)). They were recruited from the outpatient clinic. Informed consent was obtained from all subjects participating in the study, and the study was approved by the Ethics Committee at Dr Soliman Fakeeh Hospital.

2.2. Methods

Five hundred and sixty-two subjects with BPPV were examined in order to select the study group of the present study. *The inclusion criteria of the study group were*: (1) Unilateral, idiopathic, posterior canal BPPV with no history suggestive of secondary BPPV, e.g. head trauma, Meniere's disease, labyrinthitis, Migraine; (2) 25-hydroxyvitamin D3 level $\leq$10 ng/ml; *The exclusion criterion from the study group was*: Loss of contact during the study period with the participant, with subsequent inability to determine if BPPV recurrence developed or not.

All subjects enrolled in the current study underwent the following: (i) detailed clinical history, audiovestibular evaluation consisting of pure-tone audiometry, Immittancemetry, Videonystugmography; (ii) Initial therapeutic session for curing BPPV; (iii) serum 25-hydroxyvitamin D3 assessment, followed by prescription of vitamin D therapy; (iv) dual-energy X-ray absorptiometry (DXA).

The first therapeutic session, 25-hydroxyvitamin D3 assessment and DXA all were done within 3 days. 25-Hydroxyvitamin D3 was re-evaluated 3 months after commencing vitamin D therapy. According to the results of this re-evaluation, the study group was divided into two subgroups: *Subgroup (I):* including 28 subjects who disclosed elevation of serum 25-hydroxyvitamin D3 level, with improvement $\geq$10 ng/ml. *Subgroup (II):* including 65 patients who disclosed elevation of serum 25-hydroxyvitamin D3 levels $<$10 ng/ml. An important point should be overstressed regarding this subdivision; the investigators of this study had no role in assigning subjects into *Subgroups (I) or (II)* and they were merely observers. The medical treatment for vitamin D deficiency was prescribed for the entire study group. Those who complied to the prescribed treatment had their serum 25-hydroxyvitamin D3 level improved, and were included in *Subgroup (I).* On the other hand, those who did not follow the therapeutic regimen, for their own reasons (e.g. lack of motivation or awareness, intolerance to side effects of the therapy like gastritis), did not show improvement on follow-up and were included in *Subgroup (II)*. So it was the subjects' own compliance to medical treatment that assigned the study group into either subgroups, not the investigators.

The subjects of the study group were followed up for 18 months; they 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.

2.2.1. Diagnosis and treatment of posterior canal BPPV

The diagnosis was based on presence of recurrent, brief, vertigo which was related to the head movement and head position, together with positive Dix-Hallpike (DH) test. The DH test was considered positive when fatigable, geotropic torsional nystagmus (i.e., the upper poles of the eyes beating to the lowermost ear) with an up-beating component was recorded when the patient lied flat in the supine position with his affected ear downwards, and the nystugmus reversed when the patient resumed the sitting position [9]. The treatment of BPPV was based on multiple Epley's maneuver, three or four maneuvers, in the first therapeutic session. The patients were instructed to do Brandt-Daroff redistribution exercises at home for 1 week, and then a re-evaluation session was held to determine if the BPPV was cured completely; BPPV recovery was considered whenever the vertigo disappears and DH test is negative. Epley maneuver and Brandt-Daroff redistribution exercises are described in detail in many references elsewhere [10–12].

2.2.2. Vitamin D assessment & therapy

25-Hydroxyvitamin D3 was assessed using fasting, early morning, venous blood samples. Those with levels $\leq$10 ng/ml were recommended to get vitamin D therapy; loading dose for 1 month, 50,000 IU oral vitamin D3, three times/week. This is followed by maintenance dose, 50,000 IU oral vitamin D3, once every 2 weeks [8]. Calcium supplementation therapy, Calcium citrate 600 mg tablets twice daily, was provided as well. 25-Hydroxyvitamin D3 was re-assessed after 3 months of starting vitamin D therapy to evaluate the outcome of the therapy.

2.2.3. Dual-energy X-ray absorptiometry (DXA) assessment

Bone mineral density (BMD) of the study group was assessed using DXA. BMD was measured at lumbar spine (L1–L4) and proximal femur. The lowest *T*-score for each subject was used for the subsequent analysis. Normal *T*-score should be ≥ -1 SD. *T*-scores less than -2.5 SD is considered osteoporosis [13].

2.2.4. Statistical analysis

For statistical analysis, the parametric, quantitative data were compared using Student's *t*-test. One sample *t*-test and two samples *t*-test between percents were used to compare the different percentages in the study. Fisher's exact test was used to compare the distribution of qualitative data. Odds Ratio was used to test the correlation between development of recurrent attacks of BPPV and severe vitamin D deficiency. A "p" value of $\leq$0.05 indicated statistical significance. The computer program used was SPSS, release 18.0.

3. Results

3.1. Demographics and clinical features of the study group

One hundred subjects were initially included in the present study. Seven of them were excluded as we lost contact with them

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Table 1
Demographic, BMD and vitamin D levels of both study subgroups.

	Subgroup (I) ($n=28$)	Subgroup (II) ($n=65$)
Age (years)	50.8 ± 12.8	50.5 ± 11.4
Males (%)	13 (46%)	29 (45%)
T-score (mean ± SD)	−1.17 ± 1.2	−1.35 ± 1.3
25-Hydroxyitamin D level		
Before treatment	6.7 ± 2	6.8 ± 2.1
After treatment	28.3 ± 5	8.7 ± 3.5

Non-significant differences ($p > 0.05$) were detected between subgroups I, II regarding the Age, sex distribution, T-score, and vitamin D level (before treatment). Significant differences were detected between both subgroups regarding vitamin D level after treatment ($p < 0.0001$). Vitamin D levels after treatment were significantly higher than before treatment in both subgroups ($p < 0.0001$).

after short follow-up period. Table 1 shows that both study subgroups had the same age, gender distribution, and BMD, as indicated by the *T*-score. Failure of subjects in subgroup (II) to show improvement in their vitamin D level was attributed to non-compliance to the recommended vitamin D therapy regimen. They either stopped the vitamin therapy after short period or did not start it at all.

3.2. Description of the BPPV

Most of the patients (86 subjects; 92%) were examined within 1 week of development of the symptoms of BPPV, and the rest of the study group (seven subjects, 8%) reported insidious vestibular complaints of ill-defined period. Seventy-six subjects (82%) were cured after one therapeutic session with multiple repetitions of Epley's maneuver in the session, and then doing Brandt-Daroff redistribution exercises at home for 1 week. Seventeen subjects (18%) needed another session of multiple Epley's maneuver and another week of home-based Brandt-Daroff redistribution exercises. Table 2 shows that the recurrence of BPPV in subgroup (I) was lower than subgroup (II). Subgroup (I) had fewer subjects with recurrence (4 versus 28 subjects), less attacks of recurrence (5 versus 43 attacks), and less attack/subject ratio (0.18 versus 0.66 attacks/subject). The Odds Ratio (OR) for development of recurrence of BPPV in subjects with severe vitamin D deficiency = 4.54 (95% CI: 1.41–14.58, $p < 0.01$).

BPPV relapses in subgroup (I) were as follows: three relapses affecting the ipsilateral posterior canal and two affecting the contralateral posterior canal. Fig. 1 shows the distribution of affected semicircular canals in the study group during the relapse of BPPV. The affected canals laterality in the figure was reported in relation to the ear affected in the original BPPV episode. Thirty-three percent of the BPPV relapses affected the same posterior canal which was affected in the initial attack. The affected canals were posterior canals (71%), and horizontal canals (30%); all of them were canalithiasis. One sample *t*-test between percents

Table 2
Number of subjects with BPPV recurrence.

	Subgroup (I) ($n=28$)	Subgroup (II) ($n=65$)
Number of subjects with recurrence		
Single recurrence	3 (11%)	16 (25%)
Two recurrences	1(4%)	9 (14%)
Three recurrences	0	3 (5%)
Total	4 (14%)	28 (43%)
Total number of recurrence attacks	5	43
Attacks/subject ratio	0.28	0.66

Significant differences were detected between both subgroups regarding the total number of subjects with recurrence of BPPV ($p < 0.001$), total number of recurrence attacks ($p < 0.001$), and attacks/subject ratio ($p < 0.01$).

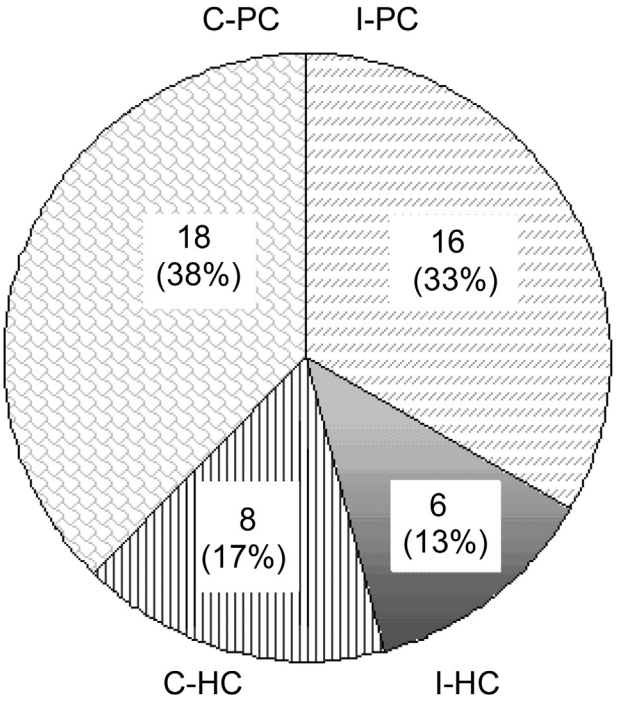

Fig. 1. Number of semicircular canals affected during the BPPV recurrent attacks in the study. I-PC: ipsilateral posterior canal; I-HC: ipsilateral horizontal canal; C-PC: contralateral posterior canal; C-HC: contralateral horizontal canal. Total number of recurrence attacks = 48. Ipsilateral and contralateral sides are considered in respect to the laterality of effected ear in the original episode of BPPV group.

disclosed this difference to be significant ($p < 0.01$). None of the reported relapses affected more than one canal. Ipsilateral ears were affected in 46%, and contralateral ears were affected in 55% of recurrences, and this difference was found to be insignificant ($p > 0.05$).

The earliest relapse of BPPV occurred 7 weeks after recovery of the initial BPPV attack. The last relapse was after 16 months; Fig. 2 discloses the incidence of relapses over time after recovery of the initial BPPV attack.

4. Discussion

Otoconia are made of ordered deposition of inorganic calcium carbonate crystallites onto a framework of organic matrix of glycoproteins, mainly otoconin 90. Several studies suggested the importance of vitamin D for development and maintenance of normal otoconia and subsequently normal otolith function [14–16]. Normal serum level of vitamin D is essential for

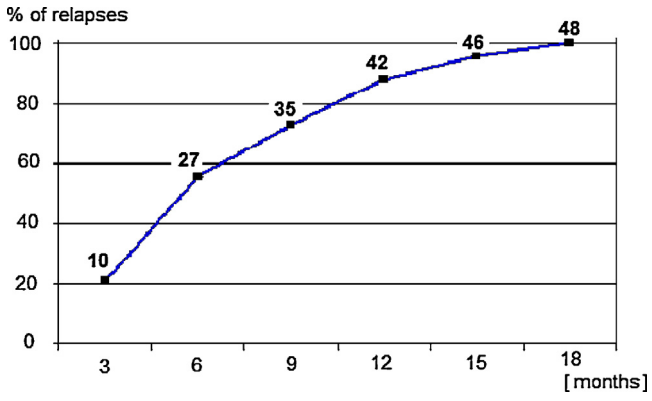

Fig. 2. The cumulative incidence of BPPV relapses in the study.

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development of normal otoconia through keeping the calcium concentration in the vestibular endolymph at a normal critical level, as either low or high calcium would result in abnormal otoconia. This critical balance is achieved by the epithelial calcium channel transport system expressed in the inner ear, which is regulated by Vitamin D receptor [6]. Several studies correlated between vitamin D deficiency and development and recurrence of BPPV [6,7,14]. Sanyelbhaa et al. [15] reported abnormal ocular and cervical vestibular evoked myogenic potentials (VEMP) in subjects with vitamin D deficiency. They suggested that vitamin D deficiency results in production of abnormal otoconia, which results in otolith dysfunction.

The present study is a prospective study that follows up subjects with both BPPV and severe vitamin D deficiency to study the effect of treatment of severe vitamin D deficiency on the recurrence of BPPV. Selection of the study group was restricted to those with unilateral, idiopathic, posterior canal BPPV as the recurrence rate is higher in multi-canal BPPV, anterior canal BPPV [17], and BPPV secondary to endolymphatic hydrops [18], head trauma [4]. According to the study group level of serum 25-hydroxyvitamin D3 after 3 months of prescribing vitamin D therapy, the study group was subdivided into subgroups (I) & (II). We confirmed that both subgroups have the same age, sex distribution, and bone mineral density (BMD) to exclude any confounding factor.

Eighteen-month follow-up period was adopted in the present study, and this was based on the previous findings reporting that 50% of BPPV recurrences occur within 6 months of the initial repositioning maneuver, and nearly all of the recurrences recur within 18 months of the initial repositioning maneuver [17]. The recurrence rate in subgroup (I) and subgroup (II) was 14% and 43% ($p < 0.01$). Previous studies reported the rate of BPPV recurrence within the first 2 years to be 10.9% [19], up to 44% [3]. Five years of follow-up raised the recurrence up to 50% [20]. The recurrence rate reported in the present study still falls within this range. The relapses in the present study did not show predilection to the originally affected ear (Fig. 1). The prevalence of horizontal canals BPPV (HC-BPPV) during the relapses was 30%, which was higher than previously reported in the literature among BPPV. Soto-Varela et al. [21] reported the prevalence of HC-BPPV to be 6.4% in a series of 614 patients with BPPV. Cakir et al. [22] reported HC-BPPV prevalence to be 13.6% in a series of 169 patients. Statistical analysis using two-sample *t*-test for percentages revealed the differences between the present study and the above mentioned two studies to be highly significant ($p < 0.01$). The equal affection of both ears, and the high prevalence of HC-BPPV disclosed in the present study may indicate that vitamin D deficiency causes lesions in the maculae of both ears.

5. Conclusions

The present study indicated that improvement of serum 25-hydroxyvitamin D3 levels is associated with substantial decrease in recurrence of BPPV.

Conflict of interest

None.

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