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OTOLOGY

Low bone mineral density and vitamin D deficiency in patients with benign positional paroxysmal vertigo

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Abstract Several studies indicated the association between benign paroxysmal positional vertigo (BPPV) with osteoporosis and vitamin D deficiency implying that abnormal calcium metabolism may underlie BPPV. The aim of the present study is to confirm the correlation between BPPV and both decrease in bone mineral density (BMD) and vitamin D deficiency. The study group included 80 patients with idiopathic BPPV (52 females, 28 males), with age range 31–71 years (47.6 ± 9.1). The patients were divided into two groups; recurrent BPPV group including 36 subjects and non-recurrent group including 44 subjects. The control group included 100 healthy volunteers with age and gender distribution similar to the study group. All the subjects in the study were examined using Dual-energy X-ray absorptiometry to assess BMD, and serum 25-hydroxyvitamin D for vitamin D assessment. The accepted normal levels were T-score > −1, and 25-hydroxyvitamin D > 30 ng/ml. Twenty-six (26 %) subjects showed abnormal T-score in the control group; 26 (59 %) in the non-recurrent BPPV and 22 (61 %) in the recurrent BPPV group. Chi square test showed significant difference between the control group and both BPPV groups. The control group had significantly higher 25-hydroxyvitamin D levels than the BPPV subgroups ($p < 0.05$). Moreover, the 25-hydroxyvitamin D was significantly lower in the recurrent BPPV than it was in the non-recurrent subgroup ($p < 0.05$). The results of the current study associate between reduced BMD and development/recurrence of BPPV. Moreover, low levels of vitamin D were related to development of BPPV while very low levels were associated with recurrence of BPPV. The co-occurrence of two morbidities is not by itself supportive of a relationship, but the cumulating studies correlating between BPPV and both vitamin D deficiency and low BMD indicate the investigation and treatment of those disorders in cases with recurrent BPPV.

Keywords Otoconia · Osteopenia · Osteoporosis · Recurrence of BPPV · Vitamin D · Bone marrow density

Introduction and rationale

Otoconia are composites of protein and calcium carbonate located in the saccule and utricle of the inner ear. They are the only mammalian hard tissue mineralized by calcium carbonate, whereas the other two systems, bone and teeth, consist of calcium phosphate. Otoconia are subject to damage by drugs, inflammation, trauma, and most importantly age induced decalcification. Progressive demineralization with advancing age leads to degradation and fragmentation of otoconia, resulting in balance disorder [1]. Benign positional paroxysmal vertigo (BPPV) represents one of the most common peripheral vestibular diseases. BPPV occurs as a result of the otoconia detaching from the otolithic membranes and collecting in one or more of the

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semicircular canals [2]. Several studies correlate idiopathic BPPV with general disorders such as diabetes [3], chronic thyroiditis [4], hypertension, hyperlipidemia, stroke [5], osteoporosis/osteopenia [2], and vitamin D deficiency [6]. Among these, the associations with osteoporosis and vitamin D deficiency imply that abnormal calcium metabolism may underlie BPPV. The aim of the present study is to confirm the correlation between decrease in bone mineral density (BMD), vitamin D deficiency and BPPV.

Materials and method

The current study is a prospective cohort study at two tertiary medical centers.

Subjects

This study was conducted between August 2011 and December 2013 in Hadiclinic and Aladan hospitals, Kuwait. The study group included 80 patients with idiopathic BPPV (52 females, 28 males), with age range 31–71 years (47.6 ± 9.1). Patients with history of head trauma or other vestibular disorder, e.g. vestibular neuritis, were excluded. The patients were divided into two groups according to the recurrence of BPPV. Recurrence was defined as BPPV that occurred after 1-month or more of a successful reposition maneuver, or patients with confirmed attack(s) of BPPV that was successfully treated during the preceding year as indicated by the medical records. The recurrent group included 36 patients in whom initial BPPV was diagnosed during the study period with recurrence in the follow-up period or had confirmed attack(s) in the previous year. The non-recurrent group included 44 patients with BPPV who had no recurrence for a minimum of 1-year follow-up. The control group included 100 healthy volunteers with age and gender distribution similar to the study group. They had no neurotologic symptoms and no history of any dizziness or imbalance. None of the subjects in the present study received Calcium or vitamin D therapy for 1-year before the study. Informed consent was obtained from all subjects, and the study was approved by the Ethical Committee at Hadiclinic and Aladan Hospitals.

Methods

Clinical diagnosis of BPPV

The diagnosis was based on history of recurrent, brief positional vertigo, and the results of the Dix-Hallpike test (DH) or supine roll test. The eye movements were observed using videonystagmography. Either of DH or supine roll test was considered positive if nystagmus was observed with appropriate positioning, latency, duration, and fatigue. With the affected ear down, geotropic torsional nystagmus (i.e. the upper poles of the eyes beating to the lowermost ear) with an up-beating component should occur in posterior canal BPPV. While in horizontal canal BPPV, there would be geotropic or ageotropic pure horizontal nystagmus. The details of diagnosis of BPPV are discussed in Balatsouras et al. [7].

Data collection

Dual-energy X-ray absorptiometry (DXA) was used to assess BMD of both the study and control groups. DXA radiation exposure is about one-tenth that of a standard chest x-ray. A "T-score", derived from the DXA measurement, expresses an individual's BMD (in standard deviations) compared to the mean BMD of a "young normal" adult population of the same sex. The T-score was classified as normal (more than −1 SD), osteopenia (−1 to −2.5 SD), or osteoporosis (< − 2.5 SD) [8]. BMD was measured at lumbar spine (L1–L4) and proximal femur. The lowest T-score for each subject was used for the subsequent analysis.

Fasting early morning venous blood was collected from patients and controls to measure serum 25-hydroxyvitamin D and free ionized calcium (iCa). The serum level of 25-hydroxyvitamin D was measured using a electrochemiluminescence (EMC, Roche®- COBAS e411). The 25-hydroxyvitamin D level was classified as normal (≥30 ng/ml), insufficient (>20 to <30 ng/ml), or deficient (≤20 ng/ml) [9]. The iCa was assessed using whole blood heparinized sample. iCa level range between 1.1 and 1.4 mM/L was considered normal [10].

DXA, iCa and 25-hydroxyvitamin D were assessed within 48 h of the clinical diagnosis of BPPV.

Results

Demographics and clinical features

Overall, 180 subjects participated in this study. The age and gender distribution of the control and study subgroups is shown in Table 1. The differences in the age and gender distribution between the control, non-recurrent and recurrent study subgroups were statistically insignificant. The Body Mass Index (BMI) was nearly equal in the control and study groups (32.6 ± 5.9 versus 32.2 ± 5.2, $p = 0.895$).

The duration of BPPV symptoms until the clinical evaluation and enrollment in the present study varied from 1 to 9 days (median = 2.0). Most (90 %) of the patients were evaluated within 4 days from the onset of the symptom. All the BPPV cases were unilateral and affecting single

Table 1 Age and gender distribution in the control and study subgroups

	No	Age (year)		Gender	
		Mean ± SD	Range	Female	Male
Control	100	44.4 ± 11.2	27–72	67 (67 %)	33 (33 %)
Non-recurrent BPPV	44	47 ± 8.9	31–71	25 (61 %)	19 (39 %)
Recurrent BPPV	36	48.3 ± 9.4	33–71	27 (69 %)	9 (31 %)

Non significant differences, $p > 0.05$, were detected between the study subgroups as regards: age (using one way ANOVA), and gender distribution (using *Chi square* test)

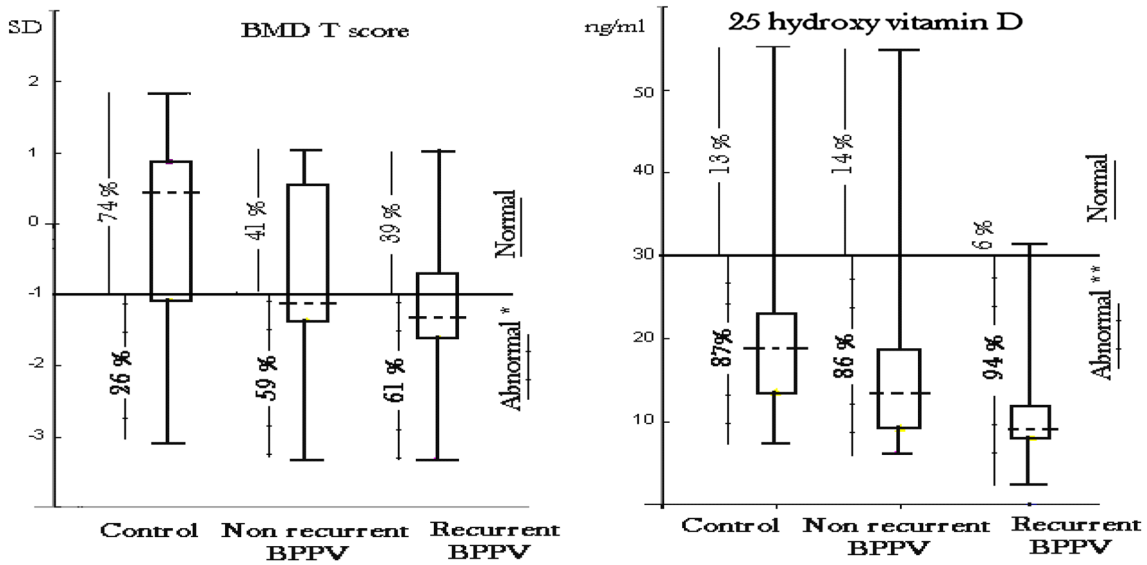

Fig. 1 Plot box of the different study subgroups for the 25-hydroxyvitamin D and T-score. Abnormal*: osteoporosis/osteopenia; Abnormal**: vitamin D deficiency/insufficiency. The percentage beside each box represents the percent of observations in each subgroup above and below the normal cut off values; −1 for the T-score and 30 ng/ml for 25-hydroxyvitamin D. Chi square test revealed significant statistical differences ($p < 0.05$) between the controls and both the recurrent and non-recurrent BPPV groups regarding the normal versus abnormal distribution of T-score only

semicircular canal; most commonly involved the posterior canal ($n = 71$, 88.8 %), which was followed by the horizontal canal ($n = 9$, 11.2 %),

BMD, free ionized calcium and 25-hydroxyvitamin D level

- All the subjects participating in the present study had normal free ionized calcium. The mean and SD of free ionized calcium levels in the control (68 subjects), non-recurrent, and recurrent BPPV groups were 1.25 ± 0.07, 1.25 ± 0.07, and 1.24 ± 0.06, respectively. One-way ANOVA test detected non-significant differences between the groups ($p > 0.05$).
- Figure 1 shows the box plot of the T-score of BMD and 25-hydroxyvitamin D level in the different study subgroups. The figure also discloses the percent of observations above and below the normal cut off values. The numbers of subjects showing abnormal T-score were 26 (26 %) in the control group, 26 (59 %) in the non-recurrent BPPV and 22 (61 %) in the recurrent BPPV group. Chi square test showed this difference between the control and study subgroups to be significant ($p < 0.001$). All the study subgroups had high prevalence of vitamin D insufficiency/deficiency.
- Quantitative results of T-score of BMD and serum 25-hydroxyvitamin D level are shown in Table 2. The control group had significantly higher T-score and 25-hydroxyvitamin D ($p < 0.05$). Moreover, the 25-hydroxyvitamin D was significantly lower in the recurrent BPPV compared to the non-recurrent subgroup ($p < 0.05$).
- Significant negative correlation was detected between the age and T-score of BMD in both the control ($r = -0.4973$) and the study group ($r = -0.45$). No correlation was detected between the T-score and 25-hydroxyvitamin D level in either the control and study subgroups.

Table 2 Mean and SD of "T-score" of the MBD and 25-hydroxyvitamin D level in the control and study subgroups

	T-score		25-hydroxyvitamin D	
	Mean	SD	Mean	SD
Control	0.06	1.16	19.53	8.45
Non-recurrent BPPV	−0.84	1.19	16.04	10.26
Recurrent BPPV	−0.97	1.24	11.93	7.57

One way ANOVA test revealed significant differences between the different groups ($p < 0.05$) regarding both T-score and vitamin D level. Student *t* test (Post-Hoc test) revealed significant statistical differences ($p < 0.05$) between the controls and both the recurrent and non-recurrent BPPV groups regarding the BMD T-score, and the 25-hydroxyvitamin D level. Significant statistical differences between the recurrent and non-recurrent BPPV groups was only disclosed regarding the 25-hydroxyvitamin D level ($p = 0.046$)

Discussion

Otoconia are made from inorganic calcium carbonate calcite deposited onto an organic matrix. The organic core is composed of a matrix protein of 90 kDa, otoconin 90, as 90 % of its content and other minor proteins [11]. This organic matrix protein is directly in contact with the endolymph through pore-like openings located on the crystalline surface. These openings play an important role in the homeostatic control of the chemical environment moving out of and into the core of otoconia [12]. Ca^{2+} and carbonate (CO^{3-}) levels in the vestibular endolymph should be kept at critical level to confirm normal otoconial function; it should be locally increased to initiate [13], and probably maintain [1], mineralization of the protein matrix of the otoconia. On the contrary, it is also important to maintain low Ca^{2+} level to prohibit unnecessary mineralization of the rest of the labyrinth [13]. This critical balance is achieved by the epithelial Ca^{2+} channel transport system expressed in the inner ear. This system includes the apical entry channels (TRPV5 and TRPV6), the cytosolic Ca^{2+} buffering proteins (calbindin-D9 K and calbindin-D28 K), and the basolateral Ca^{2+} extruding transporters (sodium–calcium exchangers and plasma membrane calcium ATPases). Vitamin D through vitamin D receptors in the inner ear upregulates the epithelial Ca^{2+} channel transport system [13]. However, the exact mechanism of upregulation of calcium flux induced by 1,25-dihydroxy vitamin D3 in primary culture of semicircular canal duct (SCCD) cells is not fully understood [14]. Yamauchi et al. confirmed the upregulation of TRPV5 at the transcript level [13, 14]. Immunoblot data did not show a significant difference in TRPV5 expression between control and 1,25-dihydroxy vitamin D3 treated SCCD cells [14]. This result was not consistent with the functional data from the same preparation that showed an upregulation by 1,25-dihydroxy vitamin D3 of radio-labeled calcium fluxes in primary cultures of SCCD [15].

Such discrepancy could be accounted for by an upregulation by 1,25-dihydroxy vitamin D3 of another controlling part of the transport system [14].

Vibert et al. reported ultrastructural modifications of the otoconia in terms of changes in their aspect, size and density in ovariectomized osteopenic/osteoporotic female adult rats; the otoconia were increased in size and decreased in their density as compared to a control group of rats. These changes were interpreted as the consequence, in the utricle, of the disturbance of the calcium metabolism induced by osteoporosis/osteopenia. They speculated that BPPV may be induced by such disturbance by different mechanisms; on one hand, the decreased fixation of calcium may generate failures in the remodeling of the internal structure of the otoconia themselves, as well as in their attachment on the otoconial membrane; on the other hand, an increased concentration of free calcium in the endolymph might induce reduction in its capacity to dissolve the dislodged otoconia, in addition to affecting electromechanical transduction of the sensory epithelium [1, 14].

Middle East receives abundant sunlight all year round. However, contemporary studies reported vitamin D deficiency to be endemic in the Middle East. It impacts all age groups and both genders. These findings are attributed mainly to inadequate exposure to sunlight, either because of the dressing style or avoidance of extremely hot sun [15]. Since vitamin D takes part in the regulation of calcium and phosphorus found in the body and plays an important role in maintaining proper bone structure, Vitamin D insufficiency, serum 25-hydroxyvitamin D < 30 ng/ml, is a risk factor of osteoporosis [16]. Recently several investigators reported that low vitamin D levels were found associated with recurrence of BPPV and the recurrence was relieved with vitamin D supplementation [6, 17]. Several studies reported Low BMD to be higher in both women and men with BPPV than in controls; patients with osteoporosis/osteopenia have increased recurrence rate of BPPV and require increased number of canalith repositioning maneuvers [18–21].

The results of the current study associate between reduced BMD and development/recurrence of BPPV. Moreover, low levels of vitamin D were related to development of BPPV while very low levels were associated with recurrence of BPPV.

The co-occurrence of two morbidities is not by itself supportive of a relationship. But the cumulating studies correlating between BPPV and both vitamin D deficiency and low BMD indicates the investigation and treatment of those disorders in cases with recurrent BPPV.

Conflict of interest The authors declare that they have no conflict of interest.

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