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Benign Paroxysmal Positional Vertigo from the Perspective of Vitamin D

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Abstract

Vitamin D (VIT D) is involved in maintaining Ca^{2+} homeostasis in the endolymph playing a primary role in synthesis of otoconia made up of calcium carbonate. VIT D deficiency which has been associated with Benign Paroxysmal Positional Vertigo (BPPV), results in an abnormal morphological structure of otoconia and subsequent otolith dysfunction. Although the association between VIT D deficiency and recurrence of BPPV was indefinite, many studies indicated that VIT D supplementation was beneficial for BPPV.

Keywords: Vitamin D; Otoconia; Drugs; Vertigo

Introduction

Benign Paroxysmal Positional Vertigo (BPPV) is the most common disease in vestibular disorders, characterized by sudden, repeated and rotational vertigo attacks when the head moves in a specific direction. BPPV has been reported to account for 8% of patients with moderate or severe dizziness/vertigo. The one-year prevalence of BPPV was seven times higher in patients aged ≥ 60 years than the 18-39 years age group, with a cumulative incidence up to 10% at the age of 80 [1]. Recurrent episodes and residual dizziness even after successful treatment using Canalith Repositioning Maneuvers (CRM) affect a significant percentage of BPPV patients. The one-year recurrence rate has been reported to be 22.79% and 28.89% in young and older patients, while the incidence rate of residual dizziness was 61% [2]. Acute rotational vertigo and residual dizziness increase imbalance and the risk of falls. Studies have shown that the most severe complication in BPPV was fall-related fracture and injuries, leading to high morbidity and mortality rates in older patients [2]. In terms of pathogenesis, dislodged otoconia from maculae utriculi float in the semicircular canals, which may generate abnormal luminal endolymph to flow and result in vertigo. Unfortunately, the pathogenesis of otoconia detachment remains uncertain. An increasing body of evidence suggests that Vitamin D (VIT D) is involved in the formation of otoconia, and VIT D deficiency would be a risk factor for BPPV. Much controversy surrounds the role of VIT D in BPPV. A prospective observational study in Egypt demonstrated that VIT D deficiency was related to BPPV development [3]. However, the significant relationship between occurrence and VIT D deficiency for BPPV was not certified in another study [4]. The present review discusses the relationship between VIT D and BPPV in terms of mechanism, occurrence, recurrence, and prevention aspects.

Vitamin D and Otoconia

The mechanism of vitamin D

The Human otoconia include the organic core and inorganic outside shell, consisting of about 10% glycoproteins and 90% carbonate. The carbonate component is extremely sensitive to chemical influences such as changes in pH, ion concentrations and complexation reactions and produces a chemical reaction that leads to irreversible morphological alterations *in vitro*, similar to conditions in BPPV. Accordingly, maintaining endolymph homeostasis is important to keep the otoconia structure intact and stable [5]. A Ca^{2+} absorption system has been discovered in the vestibular tissues, including calcium channels and calcium buffer proteins predominantly regulated by $1,25\text{-}(OH)_2D$ through activating the VIT D receptor. Interestingly, $1,25\text{-}(OH)_2D$ can up-regulate gene expression of the absorption system to sustain the low endolymph levels of Ca^{2+} and preserve normal otoconia function [6].

The influence of vitamin D deficiency

VIT D could play an important role in the pathogenesis of BPPV by influencing the calcium homeostasis in the vestibular organ through the absorption system. Buki, et al. investigated the relationship between VIT D deficiency and BPPV and found degenerative features of otoconia such as fissure, fusion, and smaller particles were presented in VIT D receptor null mice which was similar with the condition of VIT D deficiency [7]. Another study found that the serum VIT D levels and otoconia-associated protein expression in BPPV patients were lower than healthy controls. Moreover, otoconia-associated protein expression levels were significantly lower in VIT D receptor knockout mice than in controls. In the VIT D receptor knockout mice injected with VIT D or saline, no statistically significant difference in protein expression levels was found between the two treatment groups; these results indicated that the VIT D receptor might be underexpressed in BPPV patients [8].

Furthermore, globular substances, precursors of mature otoconia, were found to be present under otoconial membrane in mice, pig ,chick embryo etc., by many investigators. In the study ,the mice were in a state of VIT D deficiency by eliminating detectable ultraviolet radiation for five weeks, Globular substances of larger diameter and higher density were found in the VIT D-deficiency group compared to the VIT D-sufficient group. The rough and grainy surface of these globular substances became increasingly smoother, along with VIT D deficiency [9].

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The Relationship between Vitamin D Deficiency and Bppv

BPPV occurrence

VIT D deficiency can change the structure of the otoconia, which are made of calcium carbonate. Such structural changes may induce otoconia to easily detach from the otolith organ, leading to BPPV attacks. A prospective study in Egypt suggested that low VIT D levels were related to BPPV development; the mean VIT D level in the BPPV group (16.04 ng/ml) was significantly lower than the healthy control (19.53 ng/ml) [3]. Another prospective study demonstrated a significantly lower VIT D level in BPPV patients, including those who experienced their first episodes and recurrent vertigo patients. This observation suggested that VIT D deficiency might be a risk factor for BPPV [10]. In a Korean study where postmenopausal BPPV female patients were classified into three groups (normal, osteopenia and osteoporosis) according to the Bone Mineral Density (BMD), multiple logistic regression analyses showed that VIT D deficiency was positively related to osteoporosis in BPPV. VIT D deficiency and osteoporosis were found to be risk factors for BPPV [11]. In a retrospective study that included 380 BPPV patients and 3125 control subjects, divided into age-and gender-based subgroups, differences in the serum VIT D existed among different age groups and genders. Lower VIT D level was a risk factor in both male and female patients aged less than 40 and females aged 40-69 and 60-69 years. Interestingly, a recent study reported that the mean age years of male BPPV subjects and healthy controls were 62.1 ± 10.6 and 59.4 ± 13.2, with no statistically significant difference in age between the two groups. The mean VIT D level was 20.99 ± 6.76 ng/ml and 23.17 ± 6.49 ng/ml in the BPPV patients and controls, and 25(OH)D was identified as a risk factor of BPPV in males [12].

Otolin-1 is an inner ear protein exclusively expressed in otoconia and cells of the vestibule and cochlea. Interestingly, a prospective study found high otolin-1 levels in BPPV patients, suggesting that it may be a potential serum marker for BPPV patients. However, no statistical significance in low VIT D levels was found between BPPV patients and controls [4]. Two limitations of that study included the small sample size and the high percentage of post-traumatic BPPV patients (13%).

BPPV recurrence

In the previously mentioned Egyptian prospective study, the BPPV patients were divided into a non-recurrent and recurrent group according to BPPV recurrence at one-year follow-up. VIT D levels in the non-recurrent group (16.04 ng/ml) were significantly higher than in the recurrent group (11.93 ng/ml) (P=0.046), which suggested that recurrent attacks of BPPV were associated with lower VIT D levels [3]. Similarly, in another prospective cohort study, a statistically significantly greater proportion of VIT D deficiency (serum 25(OH)D ≤ 20 ng/ml) patients was found in the recurrent BPPV group, compared to the non-recurrent BPPV group (68% *vs* 37%), with significantly higher mean VIT D levels in the latter group (19.53 ± 15.33 *vs* 25.85 ± 14.10 ng/ml) [13]. Wang et al. reported lower serum 25-(OH)VIT D levels in middle-aged and elderly women with recurrent BPPV (17.15 ± 2.028 ng/ml) compared to an age-matched healthy control group (23.84 ± 3.125 ng/ml) [14]. During the comparison between non-postmenopausal and postmenopausal women within the recurrent BPPV group, decreased serum VIT D levels (16.231 ± 2.102 ng/ml) were found in women over 50, especially postmenopausal ones. In a study by Gu Il Rhim, during a 2-year follow-up period, BPPV recurrence rates were significantly different at different VIT D levels, while two cut-off points for 25-(OH) VIT D were 10 ng/ml and 15 ng/ml. Setting the cut-off point was 15 ng/ml, greater and less than 15 ng/ml the recurrence rates respectively were 60% and 40%, the recurrence was increasing with the declining of serum VIT D level, it indicated that the low serum VIT D levels significantly affected the recurrence of BPPV [15].

On the contrary, no significant difference in 25-(OH) VIT D level was found in patients first diagnosed with BPPV (21.0 ± 5.9 ng/ml) and recurrent BPPV patients (21.9 ± 4.9 ng/ml) in a prospective study [10]. A meta-analysis that assessed the risk factors for BPPV recurrence concluded that VIT D did not contribute to BPPV recurrence [16].

The Effects of Vitamin D Supplementation

Given that VIT D deficiency has been associated with the occurrence and recurrence of BPPV, the use of VIT D supplementation to treat VIT D deficiency in BPPV patients is still a matter of debate. Gu, et al. conducted a double-blind, randomized controlled trial where 100 BPPV patients were randomly and equally divided into treatment and control groups [17]. Treatment with Canalith Repositioning Maneuver (CRM) was given to both groups and 1α-Hydroxyvitamin D3 to the treatment group for two weeks. After using the logistic regression analysis, the level of 25-(OH) D3 and Bone Mineral Density in patients were the clinical reminders of whether the supplement therapy for BPPV was effective (P<0.05). In the treatment group, the level of serum 25-(OH) D3 and BMD were significantly improved after 1α-Hydroxyvitamin D3 treatment (P<0.05). Moreover, BPPV-related symptoms were also relieved. In a recent study where BPPV patients were randomly divided into the VIT D supplementation (n=20) and control groups (n=20), the level of 25-(OH) D3 was significantly increased from 12.4 ± 2 ng/ml to 26.3 ± 4.1 ng/ml after six months in the VIT D supplementation group. The recurrence respectively were 0.2 ± 0.4 and 1.5 ± 0.7 in the VIT D supplementation group and control group, the difference was highly significant (P=0.000). Apparently, the recurrence was obviously lower in the supplementation group during the six months follow up [18]. Our previous meta-analysis study showed that supplementation of VIT D could significantly reduce recurrence in BPPV patients with VIT D deficiency, suggesting VIT D supplementation was beneficial for BPPV patients [19]. Among the seven studies included in our meta-analysis, only one concluded that the VIT D supplements did not significantly reduce BPPV recurrence. The remaining six studies concluded that VIT D could be a prophylactic medication to decrease the risk of BPPV recurrence, although the heterogeneity among the included studies was significant due to differences in study design, therapeutic medications used and inconsistent BPPV subtypes.

VIT D deficiency can lead to adverse effects on bone metabolism, including fractures and bone loss. Severe VIT D deficiency (serum 25(OH)D<12 ng/ml) has been documented to increase the risk of mortality, infections, cancers and should be avoided as far as possible. The high safety and inexpensive costs associated with VIT D make it an attractive option, as VIT D supplementation may be used as adjuvant therapy for many diseases [20].

Conclusion

BPPV is a disease with high prevalence and recurrence in dizziness/vertigo disorders can seriously affect the quality of life and work performance, even resulting in severe complications, especially in the elderly. VIT D predominantly up-regulates protein expression of the Ca^{2+} absorption system in the vestibular system and maintains the low endolymph Ca^{2+} for otoconia synthesis. VIT D deficiency can result in the abnormal morphological structure of otoconia. Such structural changes may induce otoconia to easily detach from the otolith organ, leading

to BPPV attacks. Most clinical trials found that VIT D deficiency was a risk factor for BPPV occurrence. Although the association between VIT D deficiency and recurrence for BPPV was indefinite, many studies indicated that VIT D supplements were beneficial to BPPV patients with VIT D deficiency. VIT D supplementation not only reduced BPPV recurrence but also helped prevent injury caused by VIT D deficiency to other body organs. Accordingly, we recommend quantifying serum VIT D levels in BPPV patients and dietary or drug supplementation for hypovitaminosis D. Although most trials supported the VIT D supplementation, high-quality clinical trials were sparse. Currently, there is no consensus on VIT D supplementation for VIT D deficiency.

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Conflict of Interest

The authors declare no conflicts of interest.

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