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The Relationship Between Serum 25-hydroxyvitamin D and Calcium Levels and Idiopathic Benign Paroxysmal Positional Vertigo

Serum 25-hidroksivitamin D ve Kalsiyum Düzeyleri ile İdiyopatik Benign Paroksismal Pozisyonel Vertigo Arasındaki İlişki

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ABSTRACT

Aim: We aimed to compare 25-hydroxy vitamin D (25-OH vitamin D) and Ca2+ levels of patients admitted to our clinic with the complaint of dizziness and diagnosed with idiopathic benign paroxysmal positional vertigo (BPPV) with those of healthy control group without dizziness and investigate the role of Ca2+ and 25-OH vitamin D in the development of BPPV.

Material and methods: This study is a retrospective case-control study. The study sample consisted of 409 patients admitted to Alanya Training and Research Hospital Neurology outpatient clinic and diagnosed with idiopathic BPPV between 01.01.2018 and 01.08.2021, and of 338 control patients without any physician consultation due to vertigo, dizziness or imbalance in the last 1 year before admission to our clinic and whose serum vitamin D levels were measured, the Chi-square and T-test were utilized for statistical analysis.

Results: Mean blood 25-OH vitamin D levels were 15.74 ng/mL and 17.91 ng/mL in BPPV and control groups, respectively. Serum 25-OH vitamin D levels were significantly lower in BPPV group than control group (p=0.01, p<0.05). Mean serum Ca2+ levels did not exhibit any difference in BPPV and control groups.

Conclusion: Decreased serum levels of 25-OH vitamin D have been associated with the occurrence of BPPV independently of other key markers.

Key Words: Benign paroxysmal positional vertigo, 25-OH vitamin D, Ca2+

ÖZ

Amaç: Kliniğimize baş dönmesi şikâyeti ile başvurup idiopathic benign paroksismal pozisyonel vertigo (BPPV) tanısı alan hastalar ile baş dönmesi olmayan sağlıklı kontrol grubunun 25-hidroksi vitamin D (25-OH vitamin D) ve Ca2+ düzeylerinin karşılaştırılması Ca2+ ve 25-OH vitamin D'nin BPPV gelişimindeki rolünün araştırılmasıdır.

Gereç ve Yöntem: Çalışmamız geriye dönük vaka kontrol çalışması olup, 01.01.2018-01.08.2021 arası Alanya Egitim ve Araştırma Hastanesi Nöroloji polikliniğine başvuran İdiopatik BPPV tanısı alan 409 hasta ile kontrol grubu olarak kliniğimize başvuru öncesi son 1 yıl içerisinde vertigo, dizziness ya da dengesizlik nedeniyle hekim başvurusu olmayan serum D vitamini düzeyi ölçümü yapılmış 338 hasta seçilerek oluşturuldu. İstatiksel değerlendirmeler için ki-kare ve T testi testi kullanıldı.

Bulgular: Ortalama serum 25-OH vitamin D düzeyleri BPPV ve kontrol grubunda sırasıyla 15,74 ng/mL ve 17,91 ng/mL idi. Serum 25-OH vitamin D düzeyleri BPPV grubunda kontrol grubuna göre anlamlı derecede düşük bulundu (p=0,01, p<0,05). Ortalama serum Ca2+ düzeyleri BPPV ve kontrol grubunda anlamlı farklılık göstermedi.

Sonuç: Düşük 25-OH vitamin D serum seviyeleri BPPV gelişimi ile diğer anahtar belirteçlerden bağımsız olarak ilişkilidir.

Anahtar kelimeler: Benign paroksismal pozisyonel vertigo, 25-OH vitamin D, Ca2+

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INTRODUCTION

Vertigo is derived from the Latin verb “vertere” meaning to turn. Vertigo may occur both secondary to visual pathologies, proprioceptive system disorders, metabolic disturbances and cardiological abnormalities and to peripheral and central vestibular disorders, as well as side effects of drugs [1]. Among the peripheral vestibular disorder [2] Benign paroxysmal positional vertigo (BPPV) is a reported very common [2]. The prevalence of BPPV is reported to be around 2%, its annual prevalence 1.6%, and 1-year incidence 0.6% [3]. Schuknecht asserted that BPPV is mechanistically linked with attachment of basophilic staining deposits to the cupula within the posterior semicircular canal and called this pathological finding cupulolithiasis [4]. According to the widely accepted cupulolithiasis theory, vertigo and nystagmus occur when the rotation of the canal changes the direction of the cupula, associated with the adherence of the otoconia to the cupula rendering it sensitive to gravity. Furthermore, the canalolithiasis theory has been defined as the formation of stimulation in the hairy cells and the development of vertigo and nystagmus, as a result of stimulating the canal cupula by the endolymph, that they move along due to gravitational displacement of otoconia or canaliths separated from utricle macula into the semicircular canal [1,5,6]

Otoconia are calcite-based nanocomponents containing calcite crystals (>90%) and organic materials (<10%). The average size of otoconia is about 10 μm (within the range of 2 to 25 μm) [7,8]. Otoconia could be damaged by drugs. Also age-related decalcification and trauma, are commonly reported. Herein, an accelerated demineralization process associated with advancing age might lead to dissolution and disintegration of the otoconia, ultimately resulting in balance disorder [9].

Vitamin D, is a fat-soluble vitamin, produced in the skin related to UVB radiation exposure . Around 90-95% of the vitamin D present in the body is produced upon skin’s exposure to sunlight. Most of the circulating vitamin D is 25-OH vitamin D, of which half-life is 20 days. Therefore, 25-OH vitamin D is the first value to measure when determining vitamin D levels in the body. There is a significant balance between vitamin D and its metabolites and calcium and phosphorus in the body. Vitamin D helps regulate hormonally the serum calcium levels by acting on intestinal absorption of calcium taken up from outside, into the body [10].

Vitamin D plays maintains normal otolith function by stabilizing the calcium level in the vestibular endolymph, which ensures proper mineralization of the otoconia [11]. In this respect, many studies evaluated the role of vitamin D deficiency in BPPV development. Therefore, there are limited studies investigating the association between deficient vitamin D levels and vertigo, and their interrelationship has not been fully explored [12].

Here, we assessed blood 25-OH vitamin D and Ca2+ levels in patients with BPPV. In this respect, we investigated the relationship between the occurrence of BPPV and low 25-OH vitamin D and Ca2+ levels.

PATIENTS AND METHOD

In this retrospective case-control study the patients’ general characteristics were expressed as, mean, SD (standard deviation), percentage and frequency. Chi-square analysis was adopted for proportional variables to examine the general characteristics, disease states, Ca 2+ and Vit D OH groups of the patients. Probability values based on Fisher’s correction were given if the number of groups was insufficient. In addition, the independent-samples t-test and ANOVA test were performed to examine patient measurements according to groups. The study sample consisted of 409 patients admitted to Alanya Training and Research Hospital Neurology outpatient clinic and diagnosed with idiopathic BPPV between 01.01.2018 and 01.08.2021, and of 338 control patients without any physician consultation due to vertigo, dizziness or imbalance in the last 1 year before admission to our clinic, and whose serum vitamin D levels were measured. The BPPV diagnosis was based on observation of typical nystagmus during the characteristic tests (Dix-Hallpike, hyperextension tests and supine roll). Non- cooperation, presence of secondary factors for BPPV, and chronic disease conditions were defined as exclusion criteria. Patients who took vitamin and/or calcium supplements during the study and had systemic disease affecting vitamin

D levels were omitted from the study. Local ethics committee approval was obtained for this study (with the decision no: 14-04 of September 22, 2021) and accordance with the Declaration of Helsinki Ethical Principles.

Statistical analysis

The data was analyzed through the statistical program (SPSS, IBM Corp., Armonk, NY, USA) 18.0 package program for Windows. Intergroup comparisons were made through independent 2-sample T- test and chi-square test, p value < 0.05 was deemed statistical significance.

RESULTS

Age, calcium and vitamin D levels were evaluated in the control and vertigo groups. Of the patients, 35.6% were male, 64.4% were female, and 45.2% were in the control group and 54.8% in the vertigo group. Of the patients, 48.5% were aged 50 and under, 51.5% were aged 50 and over. Calcium values were below 8.5 ng/mL in 3.7% of the patients, 8.6-10 ng/mL in 84.7% and 10 ng/mL and over in 11.5%. 25-OH vitamin D values were below 20 ng/mL in 68,9% of the patients, 20-29 ng/mL in 20.2%, and 30 ng/mL and over in 10.8%. The calcium and 25-OH vitamin D levels (ng/mL) in the control and vertigo groups were different. The vertigo group had greater calcium levels compared to the control group (p = 0,03, p<0,05), but showed lower levels of 25-OH vitamin D (p = 0,01, p<0,05)(Table 1).

Table 1: Assessment of Age, Calcium and Vitamin D Levels by Groups

Measurement	Category	Group				p
		Control		Vertigo		
		n	%	n	%	
Age group	50 and below	207	61,2%	155	37,9%	0,01*
	50 and over	131	38,8%	254	62,1%	
Calcium levels (ng/mL)	below 8,5	18	5,3%	10	2,4%	0,02*
	8,6-10	309	91,4%	324	79,2%	
	over 10	11	3,3%	75	18,3%	
25-OH vit D levels (ng/mL)	below 20	205	60,7%	310	75,8%	0,02*
	20-29	101	29,9%	50	12,2%	
		32	9,5%	49	12,0%	

* Indicates a significance level of 0.05

There were differences in 25-OH vitamin D levels (ng/mL), but not calcium levels (ng/mL) (p = 0.83, p>0.05), according to age groups in the control group. Patients aged 50 and under had greater 25-OH vitamin D levels (ng/mL) than patients aged 50 and over, which explained the control group difference (p = 0.03, p<0.05). However, calcium levels (ng/mL), but not the levels of 25-OH vitamin D (ng/mL) (p = 0,06, p>0,05), changed among age groups in the vertigo group. This difference explains why patients under 50 showed greater 25-OH vitamin D levels (ng/mL) than those over 50 (p = 0.03, p<0.05)(Table 1).

The age range of the patients was different between the control and vertigo groups. Most patients in the vertigo group were over 50, and most of those in the control group were under 50 (p = 0,01, p < 0,05). The calcium levels (ng/mL) were different in the control and vertigo groups. Calcium levels in the vertigo group were largely 10 ng/mL and higher, whereas calcium levels in the control group varied from 8.6 to 10 ng/mL (p = 0.02, p<0.05). In terms of 25-OH vitamin D levels (ng/mL), we found no difference between the control and vertigo groups. The vertigo group's 25-OH vitamin D levels were predominantly below 20 ng/mL , while the control group's levels were between 20 and 29 ng/mL (p = 0.02, p<0.05) (Table2).

Table 2: Assessment of Age, Calcium and Vitamin D Levels in Groups by Gender

Measurement	Control		p	Vertigo		p
	Male	Female		Male	Female	
	X±s.s.	X±s.s.		X±s.s.	X±s.s.	
Age	43,07± 14,75	43,64± 13,78	0,23	56,96± 17,86	52,22± 17,05	0,09
Calcium levels (ng/mL)	9,36± 1,29	9,21± 0,54	0,04*	10,2± 7,03	9,54± 0,69	0,01*
25-OH vit D levels (ng/mL)	18,87± 7,94	17,45± 9,39	0,03*	16,91± 13,9	15,02± 12,73	0,02*

* Indicates a significance level of 0.05

Patient ages were no different in the control and vertigo groups according to gender (p>0.05). Gender differences in calcium and 25-OH vitamin D levels (ng/mL) were seen in the control group. The gender difference was attributable to the fact that male patients had greater calcium and 25-OH vitamin D levels (ng/mL) than female patients (p=0.04, p<0.05 for Ca2+; p=0,03, p<0,05 for 25-OH vitamin D). In the vertigo group, there were gender-specific variations in calcium and 25-OH vitamin D levels (ng/mL). Male patients had

greater calcium and 25-OH vitamin D levels (ng/mL) than female patients (p = 0,01, p<0,05 for Ca2+; p = 0,02, p<0,05 for 25-OH vitamin D), resulting in gender-specific differences (Table2).

D level measurements were found to be 17.91 ng/mL in the control group and 15.74 ng/mL in the vertigo group. The calcium level of the patients was found to be 9.26 ng/mL in the control group and 9.79 ng/mL in the vertigo group (Table 3).

Table 3: Assessment of Calcium and Vitamin D Levels in Groups by Age

Measurement			p			p
	50 and below	50 and over		50 and below	50 and over	
	X±s.s	X±s.s		X±s.s	X±s.s	
Calcium levels (ng/mL)	9,26± 1	9,26± 0,58	0,83	9,58± 0,9	9,92± 5,51	0,03*
25-OH vit D levels (ng/mL)	18,33± 9	17,26± 8,88	0,03*	15,99± 13,94	15,59± 12,77	0,06

* Indicates a significance level of 0.05

DISCUSSION

This study compared patients with idiopathic BPPV to those without vestibular complaints, regarding serum 25-OH vitamin D and calcium levels. When compared to control patients, serum 25-OH vitamin D levels were found to be decreased in BPPV patients, although total blood Ca2+ levels were not different. Furthermore, we found that lower blood 25-OH vitamin D levels may be an independent factor associated with BPPV development.

It has been considered that the presence of cupulolithiasis or canalithiasis lead to BPPV. Its exact etiology is uncertain, however calcium metabolism is important for the production and absorption of calcium carbonate-based otoconia, being a possible etiological factor for BPPV [4].

Vitamin D regulates the production of several Ca2+ binding proteins through specific vitamin D receptors (VDR) localized in the inner ear and epithelial cells. The epithelial Ca2+ channel system along with Na+/Ca2+ exchangers, and membrane-located Ca2+ pumps help balance the calcium levels through Ca2+ absorption from the endolymph [13]. A study of VDR-deficient mice showed that mice with mutant VDR have poor balance function, indicating that vitamin D deficiency may lead to vestibular dysfunction [14].

Vitamin D levels of BPPV patients were assessed only at the time of diagnosis in our study, but their post-treatment status was not examined. Further studies are required to obtain robust evidence as to whether vitamin supplementation may help cure BPPV patients, particularly those with vitamin D deficiency. Sheikhzadeh et al. showed that returning serum vitamin D levels to normal significantly reduced the recurrences of BPPV [15]. Buki et al. obtained similar results, showing that BPPV did not recur after supplementation with vitamin D was corrected the deficiency [16]. Gu et al. showed that treatment with 1α-hydroxy vitamin D3 could decrease the symptoms of BPPV, and that amin D3 levels and disease conditions such as osteopenia / osteoporosis are clinical indications of whether treatment regimen would be successful in preventing BPPV [17]. Talaat et al. revealed that vitamin D supplementation therapy improved the recurrence of BPPV [12].

Vivert et al. found that the rate of osteoporosis was higher in female patients with BPPV than the control group, and that impaired calcium metabolism was related to the BPPV development [18]. Another study reported that the recurrence of BPPV in female patients aged 50 years and over with osteoporosis was approximately 3.5-fold higher than same age group patients with normal bone mineral density. In their investigation on the link between osteoporosis and BPPV, Jeong et al. found that the T scores of both male and female patients with BPPV were lower than the control group, whereas the osteoporosis and osteopenia incidence in these patients was greater than the control group [11]. Buki et al. discovered that patients with BPPV had lower blood 25-OH vitamin D levels, and that vitamin D deficiency and osteoporosis were risk factors that could considerably affect BPPV recurrence in these patients [16]. These findings fit well with our findings, which showed that total Ca2+ levels and 25-OH vitamin D levels were decreased in female patients over 50 than in male patients (Table 2-3).

Results fromboth Rhim et al. and Güler et al.'s studies have reported that vitamin D insufficiency play an important role in BPPV development,

regardless of age, gender or type of BPPV [19]. However, Karataş et al. and Parham et al. suggested that BPPV and 25-OH vitamin D deficiency were not significantly associated and such a finding may be a mere coincidence [20,22]. In the present study, 25- OH vitamin D levels were decreased in 68.9% of all patients, with BPPV patients having significantly lower levels than the control group (Table 1). Furthermore, we found lower blood 25-OH vitamin D levels play a critical role in the development of BPPV, independently of age or gender.

Some studies have asserted that vitamin D deficiency causes aberrant otoconia production leading to otolith malfunction, and is linked to the development and recurrence of BPPV [3,8,9,12,21]. Other studies have reported, however, that low vitamin D levels are not linked to the development and/or recurrence of BPPV [20, 22]. Therefore the association of BPPV with vitamin D deficiency is still debated because of these discrepancies.

Limitations

Our study has some limitations since patients with idiopathic BPPV are only assessed at the diagnostic stage and it is unknown how much symptoms and attack frequency are relievedin BPPV patients, who have 25-OH vitamin D deficiency and receive replacement therapy.

CONCLUSION

Our findings suggest that 25-OH vitamin D deficiency is a potential causal factor in the development of BPPV, independent of age or gender. Further research could better delineate the strong link between BPPV and 25-OH vitamin D deficiency.

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