Research Article

Blood Serum Levels of Magnesium in Patients with Benign Paroxysmal Positional Vertigo

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Highlights

- Elevated serum Mg levels is seen in the BPPV patients than in the control group
- Subjects with low Ca/Mg ratio have more BPPV than subjects with medium ratio

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ABSTRACT

Background and Aim: Magnesium is essential for the morphogenesis of otoconia. The imbalance in the chemical composition of otoconia can make people susceptible to Benign Paroxysmal Positional Vertigo (BPPV). The primary outcome was to compare serum magnesium levels in BPPV patients with controls. The Ca/Mg ratios in participants are also recorded and analyzed in the present study.

Methods: In this case-control study, we measured the serum Mg, Ca, and vitamin D in BPPV patients and age-, sex-matched subjects without BPPV. The results were adjusted for Ca, vitamin D, hypertension, and body mass index.

Results: A total of 123 BPPV patients participated in this study. The mean Mg value was higher in patients than controls (2.01 vs. 1.95 mg/dL, p=0.030). Condition logistic regression analyses showed a higher rate of BPPV among subjects with low Ca/Mg ratio (quartile 1), relative to subjects with medium ratio (quartiles 2 and 3) (adjusted OR: 3.92, p=0.003).

Conclusion: The present study demonstrated an imbalance of Ca and Mg in the BPPV patients as significantly higher Mg levels and lower serum Ca/Mg ratio. Although it appears decreased Ca/Mg ratio to be a risk factor for BPPV, this result should be confirmed in confirmatory studies.

Keywords: Magnesium; calcium; benign paroxysmal positional vertigo; otolithic membrane; matched-pair analysis

Introduction

Benign Paroxysmal Positional Vertigo (BPPV) is a prevalent peripheral vestibular end-organ disease, characterized by a sudden and transient feeling of spinning along with nystagmus. Symptoms occur due to changes in head position in relation to gravity and can vary in intensity, ranging from mild dizziness to severe episodes that may result in nausea or vomiting, significantly affecting daily activities. In general, idiopathic BPPV tends to affect older individuals and females more frequently, with women being affected 2–3 times more often than men and typically occurring in their sixth decade of life [1-3]. Studies suggest that certain factors, including being female, having hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, and a vitamin D deficiency, can elevate the likelihood of BPPV recurring [4, 5].

BPPV has the ability to impact any of the three semicircular canals, but the most common type is BPPV in the Posterior Semicircular Canal (PSCC). The primary symptom of PSCC BPPV is recurring vertigo, which is always triggered by specific changes in head position relative to gravity and lasts for less than a minute. This vertigo tends to improve or disappear after repeated head positioning. Positioning nystagmus following the Dix–Hallpike test is characterized by geotropic and torsional movement, short latency and limited duration, and it diminishes with repeated testing and reverses when sitting up. The Particle Repositioning Maneuver (PRM), such as the Epley maneuver, is a safe and effective treatment for this disease [6, 7].

The underlying mechanism of this condition is widely accepted to be the detachment of otoliths from the macula utriculi and their displacement into the semicircular canals. The otolith debris that becomes detached can either attach to the cupula, leading to cupulolithiasis, or float freely in the semicircular canals, resulting in canalolithiasis. BPPV is a mechanical issue of the inner ear that occurs due to abnormal stimulation of a semicircular canal.

It is believed that most cases of BPPV are caused by otoconia detaching from the otolithic membrane and moving to the lowest point of the inner ear, typically the posterior canal [3].

The chemical composition of otoconia is important for understanding of pathological effects. Earlier research has indicated that human otoconia consist of calcium, which is in line with the existence of the stable trigonal polymorph of calcium carbonate. Mammalian species have been found to contain small quantities of other elements, including magnesium (Mg), sodium, potassium, phosphorus, sulfur, and chloride [8]. The explanation for the existence of these non-calcium elements is still unknown. Magnesium is essential for the development of otoconia, which is achieved by incorporating it into an artificial system and creating a nanocomposite (artificial otoconia) in a laboratory setting. Incorporating magnesium during the growth of artificial otoconia results in the inclusion of magnesium and subsequent changes in shape, which moves towards a closer resemblance to human otoconia. This suggests that comparable processes of magnesium incorporation occur in human otoconia, which explains the presence of magnesium content found in them [8]. The primary aim of the present study was to compare the level of magnesium in BPPV patients and healthy controls. The secondary aim was to compare Ca/Mg ratios between the two groups.

Methods

In this case-control study, BPPV patients were included in the case group from March 2020 to September 2021. Inclusion criteria included BPPV patients within 3 days of the onset of symptoms, not taking anti-vertigo drugs, and age≥18 years old. The diagnosis of BPPV was established based on patient history and characteristic nystagmus during Dix-Hallpike and head-roll tests. Subjects were excluded if they had Suspicious of other causes of vertigo such as trauma or involvement of the central neurological system; any evidence of spine and neck vertebral problems; malnutrition; use of hypo– or hypermagnesemia–inducing drugs (within at least 2 weeks ago), chronic renal failure. One hundred twenty-three consecutive BPPV patients were included in this study. Control subjects were selected from healthy volunteers who had no complaints of vertigo or chronic illness and matched on sex and age (±2 years) during the same time period. We evaluated the controls to determine whether they met the same inclusion and exclusion criteria described above. We evaluated the major comorbidities in the two groups

such as hypertension, dyslipidemia, diabetes, thyroid disease, musculoskeletal disease, etc. Blood samples were collected from both BPPV patients and the control group. The Xylidyl Blue method using commercial kits from Pars Azmoon, Tehran, Iran was used to measure serum Mg concentration (mg/dL). Total serum calcium levels were quantified based on a colorimetric method using Arsenazo III reagent (Darman Faraz Kave, Iran). Ionized serum calcium was determined by using a plasma mass spectrometer. The concentration of 25-hydroxyvitamin D in serum was determined through High-Pressure Liquid Chromatography (HPLC). In our analyses, serum vitamin D and Ca levels were considered as continuous variables. In our study, we utilized the following cut-off points for serum Mg levels: symptomatic hypomagnesemia (<1.22 mg/dL), asymptomatic hypomagnesemia (1.22–1.82 mg/dL), chronic latent magnesium deficit (CLMD; 1.82–2.07 mg/dL), interval for health (2.07–2.32 mg/dL), asymptomatic hypermagnesemia (2.32–4.86 mg/dL), and symptomatic hypermagnesemia (>4.86 mg/dL) [9]. Also, serum Ca/Mg ratios were calculated and categorized into quartiles. We combined the second and third quartiles into a single reference group, resulting in a low (quartile 1), moderate (quartiles 2 and 3), and high (quartile 4).

Statistical analysis

We provided means and Standard Deviations (SD) for quantitative variables, and absolute frequencies and percentages for categorical variables. Paired t-tests were used to analyze continuous variables. Non-normally distributed continuous data were log-transformed prior to analysis. Effect sizes were calculated using Hedges's g. According to Cohen, effect sizes of 0.80, 0.50, and 0.20 represent large, medium, and small effect sizes, respectively [10]. The chi-square test was used to analyze categorical variables. Crude Odds Ratios (ORs) and 95% Confidence Interval (95% CI) were calculated to assess the association between Mg levels and the presence of BPPV. Conditional logistic regression was used to account for the matching factors. The logistic regression was adjusted in 3 steps. In the first model, ORs were adjusted for the total Ca level. In the second model, ORs were adjusted for the potential confounding variables (total Ca level and vitamin D). As patients with BPPV had significantly higher Body Mass Index (BMI) and more hypertension compared to controls, in the third model, ORs were adjusted for potential cofounders, having hypertension, and BMI. Secondary analyses were exploratory without formal sample size estimation. All statistical analyses were performed using the stata 14.0 statistical program (StataCorp LP, College Station, TX, USA). Statistical tests were two-sided. P values of 0.05 or less were considered statistically significant.

Sample size

The sample size for the study was estimated using G*power version 3.1.9.2 with a confidence level of 95% and power of 80%. According to the study of Kaya et al. [3], mean Mg concentration in the case and control groups was 1.89 (0.23) mg/dL and 1.80 (0.27) mg/dL, respectively. The sample size was determined to be 123 patients in each group.

Results

In total, 123 BPPV patients were included in the study. Table 1 shows demographic characteristics of participants in the two groups. Out of the total

Table 1. Demographic characteristics of patients with benign paroxysmal positional vertigo and controls

	BPPV patients (n=123)	Controls (n=123)	p*
Age [mean(SD)]	46.9(13.5)	46.8(13.6)	0.179
Female [n(%)]	83(67.5)	83(67.5)	1.000
Other chronic disease [n(%)]			
Diabetes mellitus	4(3.3)	2(1.6)	0.423
Hypertension	19(15.4)	7(5.7)	0.013
Other disease	4(3.3)	0(0.0)	1.000
BMI [n(%)]	28.1(3.7)	24.9(3.5)	<0.001

BPPV; benign paroxysmal positional vertigo, BMI; body mass index
* According to matched design of the study, continuous and categorical variables were analyzed between the two groups by paired t test and conditional logistic regression.

participants, 83 (67.5%) were females and 40 (32.5%) were males. In the patient group, the mean age was 46.9 (13.5) years. In the control group, the mean age was 46.8 (13.6) years. The mean BMI value was 28.1 kg/m^2 (3.7) in the patient group and 24.9 kg/m^2 (3.5) in the control group. The analysis showed a significant difference in BMI value between the two groups (paired t-test, p<0.001). Comorbidities in the cases and controls were found in 27 and 9 subjects, respectively. In 11 out of 123 BPPV patients (8.9%), bilateral involvement of posterior SCCs was observed. Duration of vertigo and residual dizziness were 3.0 (2.1) days and 9.1 (7.9) days, respectively. Table 2 describes the characteristics of BPPV in the case group.

Distribution of vitamin D in the two groups was skewed. Therefore, we used the logarithmic transformation of vitamin D for further analysis. Although the median vitamin D value in the patient group was higher than in the control group (28.0 ng/mL versus 25.0 ng/mL, respectively), this difference was not statistically significant (paired t-test, p=0.170). Other measured biochemical parameters are shown in Table 3.

Moreover, the mean Mg value was higher in the BPPV group compared to the control group (2.01 (0.22) mg/dL

Table 2. Characteristics of patients with benign paroxysmal positional vertigo

	Frequency (%)
Side of involvement [n(%)]	
Right	75(61.0)
Left	37(30.1)
Bilateral	11(8.9)
Past history of BPPV [n(%)]	35(28.5)
Frequency of Epley maneuver	
1–2 times	105(85.4)
≥3 times	18(14.6)
Time to improvement	
<24 hours	105(85.4)
≥24 hours	18(14.6)
Duration of residual dizziness	
≤3 days	33(26.8)
4–7 days	37(30.1)
≥8 days	53(43.1)

BPPV; benign paroxysmal positional vertigo

Table 3. Mean and standard deviation of biochemical parameters in the patients with benign paroxysmal positional vertigo and healthy controls

	BPPV patients	Healthy controls	p*
Total Ca, mg/dL	9.39(0.03)	9.37(0.04)	0.697
Ionized Ca, mg/dL	1.25(0.01)	1.25(0.01)	0.294
Log vitamin D**	3.21(0.05)	3.12(0.05)	0.170
Mg, mg/dL	2.01(0.22)	1.95(0.23)	0.029
Ca/Mg ratio	4.71(0.52)	4.88(0.06)	0.040

BPPV; benign paroxysmal positional vertigo
* Paired t test, ** The back transformed of mean vitamin D in the case and control groups are 22.69 and 24.91 ng/mL, respectively.

Table 4. Conditional logistic regression analysis for odds of benign paroxysmal positional vertigo according to Mg and Ca/ Mg ratio categories

	Crude OR (95% CI)	Model 1	Model 2	Model 3
Mg level				
Hypomagnesemia	0.63 (0.31, 1.27)	0.63 (0.31, 1.28)	0.53 (0.25, 1.12)	0.33 (0.13, 0.87)
CLMD	0.61 (0.33, 1.13)	0.60 (0.33, 1.12)	0.58 (0.31, 1.10)	0.50 (0.23, 1.09)
Normal	Ref	Ref	Ref	Ref
Hypermagnesemia	1.37 (0.44, 4.31)	1.36 (0.43, 4.30)	1.47 (0.46, 4.79)	2.02 (0.48, 8.60)
Ca/Mg ratio				
Low	**1.98 (1.01, 3.86)**	**2.02 (1.02, 3.97)**	**2.44 (1.19, 4.99)**	**3.92 (1.58, 9.71)**
Medium	Ref	Ref	Ref	Ref
High	1.06 (0.55, 2.06)	1.03 (0.53, 2.02)	0.93 (0.47, 1.85)	0.74 (0.29, 1.86)

OR; odds ratio, CI; confidence interval, CLMD; chronic latent magnesium deficit
Model 1: adjusted for total Ca level, Model 2: adjusted for total Ca level, and vitamin D, Model 3: adjusted for total Ca level, vitamin D, hypertension, and body mass index. Significant associations are in bold.

versus 1.95 (0.23) mg/dL, respectively). The difference in Mg levels between the two groups was statistically significant (paired t-test, p=0.030). The effect size for Mg levels was small (0.20, 95% CI: 0.02 to 0.38).

In the case and control groups, low Mg levels (hypomagnesemia or CLMD) were found in 76 (61.8%) and 90 (73.2%) subjects, respectively. Condition logistic regression analyses showed that there was little evidence of an association between different Mg levels and odds of BPPV (Table 4). However, we observed a higher rate of BPPV among subjects with low Ca/Mg ratio (quartile 1), relative to subjects with medium ratio (quartiles 2 and 3), in both unadjusted and adjusted analyses (adjusted OR: 3.92, 95% CI: 1.58 to 9.71, p=0.003).

Discussion

To the best of our knowledge, this is the first study in which matched control-case methodology was used to assess the potential correlation between BPPV and serum Mg levels. The mean age of participants in our study was 46.8 years, and the majority of patients were women (67.5%). These finding align with previous literature [3]. Furthermore, our study found no significant differences in total Ca, ionized Ca and vitamin D levels between the two groups. Although some studies have reported a deficiency in vitamin D among BPPV patients, a recent review study showed a non-significant relationship between the occurrence of BPPV and low vitamin D levels (standardized mean difference –2.20, p=0.33) [11]. However, low vitamin D levels were significantly evident among patients with recurrent episodes of BPPV [5, 12].

Compared to the control group, we observed higher levels of serum Mg in the BPPV patients. However, the effect size was small and the clinical significance of the average difference of 0.06 mg/dL is unknown. Over 90% of otoconial structure is composed of calcite (crystalized calcium carbonate) [13, 14]. Normal otoconial function relies on appropriate levels of calcium and carbonate in the endolymph, which are regulated by a calcium channel transport system expressed in the inner ear [15]. Walther et al. [8] conducted a study on the ultrastructural dysmorphology of human otoconia and found Mg and Ca have an impact on the size and shape of otoconia. Vibert et al. [16] also observed that rats with induced osteoporosis showed a less dense and low calcium in otoconia, which could potentially play a role in the development of BPPV.

In addition to aforementioned studies, researchers have been studying the relationship between BPPV and calcium metabolism. Talaat et al. [17] found that low bone mineral density and vitamin D deficiency may be relate to BPPV. Similarly, Kaya et al [3] discovered that BPPV patients had slightly higher levels of Mg compared to the control group, although this difference was not statistically significant. In addition to the small sample

size, this study had several methodological problems, such as the use of a t-test for a group-matching design and the presentation of only crude analyses. It seems that redistribution of Mg is primary factor contributing to the variation of Mg concentration in the two groups. The higher level of serum Mg may correspond to a decrease of Mg in the inner ear, similar to what is observed in cases of hyperparathyroidism, where there is an increase in serum Ca but a decrease in bone mineral density [18]. In order to support and confirm this hypothesis, further research involving animal studies and assessment of ionized Mg levels is necessary.

Interestingly, we discovered that there is a noticeable discrepancy in the levels of Ca and Mg in the blood of BPPV patients, with elevated levels of serum Mg and a low Ca/Mg ratio. The odds of BPPV were approximately four times higher in individuals with a low Ca/Mg ratio compared to those with a medium ratio (control group). This association was statistically significant (p=0.003) and indicated that a low Ca/Mg ratio could potentially be a risk factor of BPPV. It is worth noting that these two electrolytes have an opposite effect on each other and serum Ca/Mg ratios may provide a more accurate representation of homeostasis compared to serum Mg levels [19].

Methodological considerations/limitations

There are several limitations to the present study that should be noted. Firstly, the present study design is case-control, which means that it is impossible to establish causal relationships between variables. Secondly, while efforts were made to control for potential confounders such as sex, age, and BMI, there may still be residual confounding factors such as hormonal status that were not accounted for. However, even after adjusting for BMI, subjects with a low Ca/Mg ratio still showed a significantly higher likelihood of having BPPV compared to those with a moderate ratio (quartiles 2 and 3). Thirdly, we did not measure free Mg levels, which are considered the physiologically active form of Mg in the body. This is a limitation because total Mg measurement in serum may not accurately reflect intracellular concentrations or the available unbound fraction. It is worth mentioning that the measurement of free Mg is not commonly conducted in research studies, possibly due to varying levels of selectivity for Mg compared to other cations, the absence of standardized diagnostic reference intervals, and limited availability of specialized techniques for measuring free Mg [20]. Fourthly, our study only identified affected PSCC in our patients and did not find any other affected canals. This may limit the generalizability of our results. Fifthly, the diabetes mellitus status of participants was unknown, which is relevant because insulin administration can cause to intracellular shift of Mg and lead to low serum Mg levels in patients with type 2 diabetes mellitus [21].

Finally, blood samples for biochemical analysis were only obtained once at the onset of BPPV. Therefore, we could not assess the relationship between serum Ca/Mg ratio and clinical improvement over time. The aforementioned limitations may affect the reliability of the conclusion.

Conclusion

Magnesium is an important element in the size and shape of otoconia of the inner ear, so it is important to evaluate this ion in Benign Paroxysmal Positional Vertigo (BPPV) patients. The present study showed that Mg levels were higher in the BPPV patients than the controls, which could disturb the architecture of otoconial complexes in the inner ear. However, the results were not confirmed in the logistic regression analysis. Therefore, clinical importance of the Mg level needs to be confirmed in more studies with large sample size. Interestingly, a significant low Ca/Mg ratio was observed in BPPV patients compared to subjects with medium ratio. This result should be confirmed in confirmatory studies.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Guilan University of Medical Sciences (approval code: IR.GUMS.RES.1399.333) and all patients participated in the study were informed of the study procedure and signed written consent forms.

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Authors' contributions

MA: Study design and supervision, drafting the manuscript; MMJ: Study design and supervision, statistical analysis, interpretation of the results and critical revision of the manuscript; NS: Acquisition of data, and drafting the manuscript.

Conflict of interest

No potential conflict of interest was reported by the author(s).

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