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Original Research

Investigating the Role of Oxidative Stress in Benign Paroxysmal Positional Vertigo with Spot Urine

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Abstract

Objectives: The objectives of this study were to evaluate the role of oxidative stress in benign paroxysmal positional vertigo (BPPV) by measuring urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), 8-hydroxy-guanosine (8-OHG), and 8-hydroxy-guanine levels.

Methods: Thirty-one adult female patients diagnosed with BPPV were included in this study. Patients with central pathologies and other peripheral causes of vertigo were excluded from the study. The patients were evaluated for oxidative stress during and after the BPPV attack with blood samples and spot urine tests. Depression, anxiety, and stress scale (DASS) questionnaire was used to evaluate emotional stress. A control group consisting of 30 age-matched healthy women was formed.

Results: Urinary oxidative stress values during the attack were significantly higher than the post-treatment group and the healthy control group ($p<0.05$). There was no significant difference between the urinary oxidative stress values of the BPPV group after treatment and the healthy control group ($p>0.05$). DASS scores were significantly higher during the attack and after the treatment compared to the healthy control group ($p<0.05$).

Conclusion: The increase in spot urinary 8-OHdG, 8-OHG, and 8-hydroxy-guanine levels can be used as a biomarker for oxidative stress in patients with BPPV. Furthermore, emotional stress can also trigger BPPV attacks by increasing oxidative stress.

Keywords: DNA damage, guanosine, oxidative stress, positional vertigo

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Benign paroxysmal positional vertigo (BPPV) is defined as brief attacks of rotatory nystagmus and vertigo provoked by changes in head posture. It is the most common peripheral vestibular disorder (50%) and women are affected 2–3 times more frequently than man. The etiology of BPPV is otoconial debris floats within the semicircular canal (canalolithiasis) or settles in the cupula (cupulolithiasis).[1] Posterior canalolithiasis is the most common subtype (70–90%) and the Dix-Hallpike (DHP) test is used for the diagnosis. The horizontal canal is the second most frequently affected canal after the posterior canal (5–30%). In the DHP maneuver, torsional nystagmus lasting shorter than 45 s with latency and fatigability was considered BPPV. In the treatment, repositioning maneuvers are performed and this maneuver is called the Epley maneuver for the posterior canal.[2]

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Reactive oxygen species (ROS), which damage proteins, lipids, and nucleic acids when in excessive concentration, is defined as oxidative stress. Oxidized DNA products are excreted in the urine and the most stable marker showing DNA damage in spot urine is 8-hydroxy-2'-deoxyguanosine (8-OHdG).[3] Chromatographic methods and immunohistochemical techniques can be used for urine 8-OHdG measurement. Although the chromatographic method is the gold standard, enzyme-linked immunosorbent assay (ELISA) is a less costly and rapid technique. Similarly, the urine 8-hydroxy-guanosine (8-OHG) level is used as a marker of RNA damage.[4]

Recently, the role of oxidative stress in the etiology of BPPV has been tried to be revealed by the levels of many enzymes and proteins in the serum. The objective of the current study was to evaluate the potential role of oxidative stress in acute BPPV attacks with spot urine.

Methods

Ethical Approval

The study was approved by the Instructional Review Board (decision no: 2799/date: April 02, 2021). All procedures were performed in accordance with the ethical standards set by the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patients and Study Design

Patients who applied to our outpatient clinic with acute vertigo attack between November 2021 and July 2022 and were diagnosed with BPPV were included in the study. After detailed otolaryngologic and neurologic examinations, the following groups of patients were excluded from the study: (a) central vertigo or other peripheral causes of vertigo, (b) patients with signs of chronic otitis media such as tympanic membrane perforations or retraction pockets, (c) having systemic or inflammatory diseases such as hypertension, diabetes, and hypothyroidism, (d) male patients, to avoid gender-related variables in spot urinary analysis, and (e) patients who need medical treatment and whose complaints do not regress with maneuvers in the acute period.

After the patients were treated with repositioning maneuvers, they were evaluated with blood tests, depression-anxiety-stress scale (DASS) questionnaire and spot urine samples. All patients with BPPV were called for control after 2 days, and repositioning maneuvers were repeated if necessary. Blood test, spot urine test, and DASS questionnaire were repeated 3 weeks after the acute attack. As the control group, 30 healthy young women without hearing loss, systemic disease, inflammatory disease, and any cochleovestibular disorders were formed. All groups were compared in terms of blood samples, spot urine oxidative stress parameters, and DASS questionnaires.

Vestibular Evaluation

All patients underwent a complete neuro-otologic examination. After otomicroscopic evaluation for chronic middle ear disease, third window diseases, such as perilymph fistula, were excluded with fistula test. Central pathologies were tried to be revealed by evaluating nystagmus and neurologic examination. Balance and gait were assessed using Romberg's sign and the Unterberger test. Dysmetria and dysdiadochokinesia tests were used to evaluate cerebellar dysfunction.

After exclusion of chronic middle ear diseases and central pathologies, for the diagnosis of BPPV, diagnostic maneuvers were performed on the patients with videonystagmography. Torsional nystagmus lasting <45 s with latency and fatigue in the DHP and supine roll tests were accepted as BPPV. The DHP test was positive in 27 of the 31 patients included in the study, and the supine roll test was positive in four of them. Epley maneuver for posterior canalolithiasis and Gufoni repositioning maneuver for lateral semicircular canal BPPV were performed in the treatment. All patients with BPPV were called for control after 2 days, and repositioning maneuvers were repeated if necessary. At the first admission during the attack and on the 21st day after the repositioning maneuvers, blood and urine samples were taken from the patients and DASS questionnaires were filled.

DASS-42

We used the DASS-42 item validated by Hekimoglu et al.[5] The DASS-42 consists of 3 subscales and 14 questions each evaluating depression, anxiety, and stress separately. Patients are asked to evaluate their emotional state in the last week and to rate the questions between 0 (not applied) and 3 (mostly). Points are calculated individually and on a total of 42 questions.

Laboratory Procedures

Peripheral venous blood and spot urine samples were obtained at the first admission during the attack, on the 21st day after repositioning maneuvers, and after routine examinations of healthy controls. To obtain serum samples, blood samples were centrifuged at 1500 × g for 15 min and both blood and spot urine samples were stored frozen at −80°C until biochemical analysis.

Serum glucose, creatinine, uric acid, albumin, total cholesterol, HDL, triglyceride, CRP, fibrinogen, sedimentation, urine uric acid, urine Na, and urine protein values were measured in all groups.

Urine 8-OHG, 8-OHdG, and 8-hydroxy-guanine levels were measured using the DNA/RNA Oxidative Damage (High Sensitivity) ELISA Kit. (Item No: 589320, Cayman Chemical, MI, USA) A single measure of oxidative stress was calculated, including all three biomarker levels.

Statistical Analysis

The IBM SPSS 28.0 package program (SPSS Inc.; Chicago, IL,USA) was used. Mean, standard deviation, and median values were used in the descriptive statistics of the data. Independent sample t-test and Mann–Whitney U-test were used in the analysis of quantitative independent data, and paired sample t-test and Wilcoxon test were used in the analysis of dependent quantitative data. Statistical significance was granted at P level < 0.05.

Results

The mean age was 35.5±4.6 years in the BPPV group, and 34.0±3.0 years in the healthy control group. The mean age of the groups did not differ significantly (p>0.05). Urinary oxidative stress values during the attack were significantly higher than the post-treatment group and the healthy control group (p<0.05). After the treatment, urine oxidative stress value did not differ significantly between the BPPV group and the healthy control group (p>0.05). Urine oxidative stress value was significantly decreased after treatment in the BPPV group (p<0.05, Table 1).

Similarly, serum total cholesterol, triglyceride, C-reactive protein (CRP), sedimentation, and urine protein values were significantly higher (p<0.05) compared to the healthy control group during the attack. After treatment, serum

Table 1. Parameters with significant difference between BPPV and control group

	BPPV Group (n=31)		Control Group (n=30)		p
	Mean±SD	Median	Mean±SD	Median	
Urine 8-OHdG + 8-OHG + 8-hydroxy-guanine (ng/mL)					
^{0}At admission	640.3±142.9	597.7	261.4±93.4	247.8	0.000^{m}
^{1}After treatment	313.6±150.3	319.3	261.4±93.4	247.8	0.330^{m}
P$^{0-1}$	0.000^{w}				
Total cholesterol (mg/dL)					
^{0}At admission	195.1±11.9	197.4	182.7±16.3	185.5	0.001^{t}
^{1}After treatment	184.6±13.5	182.3	182.7±16.3	185.5	0.710^{t}
P$^{0-1}$	0.003^{E}				
Triglyceride (mg/dL)					
^{0}At admission	125.9±20.7	120.8	113.3±13.3	115.7	0.019^{t}
^{1}After treatment	116.9±10.3	115.6	113.3±13.3	115.7	0.283^{t}
P$^{0-1}$	0.021^{E}				
HDL (mg/dL)					
^{0}At admission	55.4±12.0	53.9	66.5±10.3	65.4	0.002^{m}
^{1}After treatment	67.6±10.1	66.8	66.5±10.3	65.4	0.671^{m}
P$^{0-1}$	0.000^{w}				
CRP (mg/L)					
^{0}At admission	3.6±1.7	3.8	2.6±1.3	2.7	0.040^{t}
^{1}After treatment	2.5±1.3	2.2	2.6±1.3	2.7	0.623^{t}
P$^{0-1}$	0.006^{E}				
Sedimentation (mm/hr)					
^{0}At admission	19.6±7.3	19.0	10.1±5.4	10.5	0.000^{t}
^{1}After treatment	10.8±4.8	12.0	10.1±5.4	10.5	0.628^{t}
P$^{0-1}$	0.000^{E}				
Urine protein (mg/dL)					
^{0}At admission	73.2±27.3	73.0	47.4±19.9	48.0	0.001^{t}
^{1}After treatment	41.7±17.1	39.0	47.4±19.9	48.0	0.283^{t}
P$^{0-1}$	0.000^{E}				

^{t}t-test/^{m} Mann-whitney u test/^{E}Paired sample t-test/^{w}Wilcoxon test; BPPV: Benign paroxysmal positional vertigo; HDL: High-density lipoprotein; CRP: C-reactive protein; SD: Standard deviation.

total cholesterol, triglyceride, CRP, sedimentation, and urine protein values did not differ significantly between the BPPV group and the healthy control group (p>0.05). In the BPPV group, serum total cholesterol, triglyceride, CRP, sedimentation, and urine protein values were significantly decreased after treatment (p<0.05, Fig. 1).

High-density lipoprotein (HDL) cholesterol value during the attack was significantly (p<0.05) lower than in the healthy control group, and after the treatment, HDL value did not differ significantly between the BPPV group and the healthy control group (p>0.05, Table 1).

Serum glucose, creatinine, uric acid, albumin, fibrinogen, urine sodium, and urine uric acid values did not differ significantly between BPPV and the healthy control group (p>0.05). In the BPPV group, creatinine, uric acid, albumin, and urine sodium values did not change significantly after treatment (p>0.05, Table 2).

DASS scores during and after the BPPV attack were significantly (p<0.05) higher than the healthy control group. In the BPPV group, DASS scores decreased significantly after the treatment (p<0.05, Table 3).

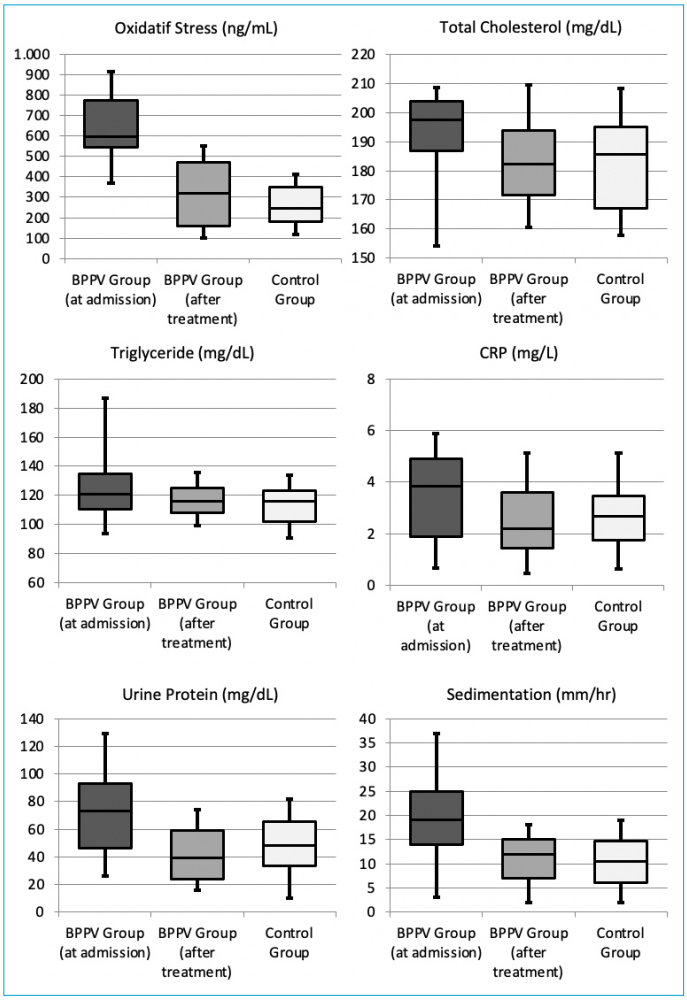

Figure 1. Significantly higher parameters during BPPV attack compared to the control group.

Discussion

Vertigo is defined as a false sense of spinning or the illusion of movement. Causes of vertigo are broad and include central and peripheral etiologies. Peripheral vertigo is more common and occurs in vestibulocochlear nerve or inner ear pathologies. Conversely, central vertigo is less common and typically occurs in pathologies of the brain parenchyma or vestibular nucleus. Differential diagnosis can be made with a detailed anamnesis and a complete neuro-otological examination, but in some cases, computed tomography and magnetic resonance imaging of the brain may be required.[6]

BPPV is the most common peripheral vestibular disorder (50%), and women are affected 2–3 times more frequently.[1] Many recent studies have revealed the role of oxidative stress in the occurrence of BPPV.[7-11] In these studies, the relationship between oxidative stress and BPPV was evaluated by measuring serum levels of superoxide dismutase, disulfide/total thiol, inflammatory mediators, prolidase, malondialdehyde, and catalase. In this study, we also demonstrated the role of oxidative stress in the development of BPPV with oxidative stress marker levels in spot urine.

There is a complex relationship between BPPV and oxidative stress. The balance of calcium and carbonate levels in the endolymph is important for normal otoconial function.[12] Increased secretion of calcium-rich material from the otoconia into the endolymph or otoconia containing less calcium is explained as the main cause of BPPV symptoms. Vibert et al.[13] showed that otoconia ultrastructure with less calcium can cause the development of BPPV in ovariectomized osteoporotic rats. Oxidative stress has been blamed for the close relationship between BPPV and calcium metabolism. ROS such as hydroxyl radicals, superoxide anions, and hydrogen peroxide increase the migration of calcium from the endoplasmic reticulum into the cell, causing rupture of the mitochondrial outer membrane and apoptosis.[14] Consequently, oxidative stress is thought to affect BPPV through calcium metabolism.

Consistent with our findings, Ozbay et al.[7] reported that malondialdehyde, the end product of lipid peroxidation induced by free radicals, and serum values of prolidase enzyme, which plays a role in collagen catabolism, are associated with increased oxidative stress, which causes peripheral vertigo. Şahin et al.[8] found significantly higher disulfide/native thiol and disulfide/total thiol ratios in pa-

Table 2. Parameters with no significant difference between BPPV and control group

	BPPV Group (n=31)		Control Group (n=30)		p
	Mean±SD	Median	Mean±SD	Median	
Glucose (mg/dL)					
[0]At admission	92.9±9.0	91.0	90.8±9.1	91.5	0.427[t]
[1]After treatment	86.2±7.7	86.0	90.8±9.1	91.5	0.059[t]
P[0-1]	0.008[E]				
Creatinine (mg/dL)					
[0]At admission	0.76±0.10	0.74	0.71±0.07	0.72	0.115[t]
[1]After treatment	0.72±0.07	0.71	0.71±0.07	0.72	0.648[t]
P[0-1]	0.108[w]				
Uric acid (mg/dL)					
[0]At admission	4.6±1.2	4.7	4.8±0.8	4.8	0.564[t]
[1]After treatment	4.7±0.9	4.6	4.8±0.8	4.8	0.597[t]
P[0-1]	0.852[E]				
Albumin (g/dL)					
[0]At admission	45.6±2.0	45.7	44.9±1.6	45.1	0.003[t]
[1]After treatment	44.9±1.6	44.7	44.9±1.6	45.1	0.662[t]
P[0-1]	0.139[E]				
Fibrinogen (mg/dL)					
[0]At admission	420.5±67.1	438.0	400.9±56.4	410.5	0.174[m]
[1]After treatment	387.3±48.8	384.0	400.9±56.4	410.5	0.354[m]
P[0-1]	0.025[w]				
Urine Sodium (mEq/L)					
[0]At admission	95.0±42.1	85.0	81.9±13.3	82.0	0.185[t]
[1]After treatment	87.4±13.3	88.0	81.9±13.3	82.0	0.158[t]
P[0-1]	0.335[E]				
Urine Uric Acid (mg/dL)					
[0]At admission	57.9±33.0	63.0	44.0±20.7	37.2	0.099[t]
[1]After treatment	42.0±23.8	35.4	44.0±20.7	37.2	0.753[t]
P[0-1]	0.026[E]				

[t]t-test/[m]Mann-whitney u test/[E]Paired sample t-test/[w]Wilcoxon test; BPPV: Benign paroxysmal positional vertigo; SD: Standard deviation.

Table 3. Comparison of DASS scores between BPPV and control group

	BPPV group (n=31)		Control group (n=30)		p
	Mean±SD	Median	Mean±SD	Median	
Depression					
[0]At admission	15.4±10.0	16.0	6.1±2.4	6.5	0.000[m]
[1]After treatment	11.8±7.0	10.0	6.1±2.4	6.5	0.001[m]
P[0-1]	0.013[w]				
Anxiety					
[0]At admission	15.8±8.9	15.0	3.4±1.8	4.0	0.000[m]
[1]After treatment	10.9±7.1	9.0	3.4±1.8	4.0	0.000[m]
P[0-1]	0.001[w]				
Stress					
[0]At admission	19.9±9.3	18.0	7.0±3.8	6.0	0.000[m]
[1]After treatment	13.7±7.3	11.0	7.0±3.8	6.0	0.000[m]
P[0-1]	0.001[w]				

[m]Mann-whitney u test/[w]Wilcoxon test, BPPV: Benign paroxysmal positional vertigo, SD: Standard deviation.

tients with BPPV, and these findings are consistent with the increase in oxidative stress in patients with BPPV. Güçlütürk et al.[9] studied the oxidative stress markers and the inflammatory mediators (IL-1β and IL-6) that may play roles in the pathogenesis of BPPV and reported results similar to ours. In addition to the increase in ROS, the decrease in antioxidant proteins has also been associated with BPPV in the literature. In a study by Li et al.[10], decreased serum levels of antioxidant proteins, such as superoxide dismutase, were associated with an increased risk of BPPV. Apart from these studies, this is the first study to investigate spot urinary oxidative stress markers in BPPV.

There are many studies showing that the oxidative DNA damage indicated by 8-OHdG is associated with mental illnesses such as schizophrenia and bipolar disorder, cardiovascular pathologies, and cancer.[15-17] The oxidized products of DNA strand damage are excreted in the urine, and 8-OHdG has been shown to be the most stable marker showing DNA damage in spot urine.[3] Similarly, the urine 8-OHG level is used as a marker of RNA damage.

Chromatographic methods and immunohistochemical techniques can be used for urinary 8-OHdG and 8-OHG measurement. Although the chromatographic method is the gold standard, ELISA is a less costly and rapid technique. In the same review study, it was shown that urinary 8-OHdG concentrations were higher in smokers but not related to gender and body mass index.[4] We also used the ELISA method in our study. To prevent urinary 8-OHdG and 8-OHG concentrations from being affected by variable factors, we included young female patients with no known disease in both BPPV and control groups. The smoking status of our groups was similar. Different studies have shown an association between creatinine excretion and 8-OHdG. It was deemed necessary to be evaluated together for healthy adults.[18,19] In our study, all patients were evaluated with normal creatinine values.

In the literature, it is stated that antioxidants decrease significantly in plasma, especially in major depression, and this situation increases oxidative stress and causes degenerative diseases. Maes et al.[20] revealed in their review studies that antioxidants decrease, oxidative damage increases, and some antioxidants have antidepressive effects in major depression. Consistent with these findings, we found high DASS scores in BPPV patients with increased oxidative stress in our study.

The limitation of our study is the inclusion of a limited number of patient populations. Further studies with larger case numbers are needed.

Conclusion

To the best of our knowledge, this is the first study to evaluate the role of oxidative stress in BPPV by spot urine samples. The increase in spot urinary 8-OHdG, 8-OHG, and 8-hydroxy-guanine levels can be used as a biomarker for oxidative stress in patients with BPPV, and being a non-invasive method is advantageous in some patients. Furthermore, emotional stress can also trigger BPPV attacks by increasing oxidative stress.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul Training and Research Hospital. (No: 2799/02.04.2021).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – O.O., H.A. ,O.Y.; Design – O.O., H.R., H.F.A.; Supervision – H.A., O.Y.; Materials – O.O., H.R., H.F.A.; Data collection – O.O., H.R., H.F.A.; Analysis – O.O., H.A., O.Y.; Literature search – O.O., H.A., H.R., H.F.A., O.Y.; Writing – O.O., H.R., H.F.A.; Critical review – O.O., H.A., O.Y.

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