



# Audiovestibular findings in celiac patients

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## Abstract

**Aim:** Celiac is a small intestine disease that occurs in susceptible individuals with a cellular and humoral immunological response that develops against gluten, a cereal protein. There are few studies evaluating the audiovestibular system in celiac patients. This study aims to evaluate audiovestibular findings in celiac patients.

**Materials and Methods:** 40 patients with celiac disease and 40 healthy volunteers were enrolled in this study. Each subject underwent a neurotologic examination including pure tone audiometry (PTA), transient evoked otoacoustic emission (TEOAE) with 1000 Hz, 1500 Hz, 2000 Hz, 3000 Hz and 4000 Hz, videonystagmography (VNG), and binaural bithermal caloric test. It was evaluated whether the test results indicated significant differences between the celiac patient and control group.

**Results:** Sensorineural hearing loss was detected in the right and left ear of the 7 patients. In the pure tone audiometry (PTA) test, there was no statistically significant difference between celiac patients and controls in both air conducted and bone conducted hearing thresholds ( $p=0.389$  for the right ear,  $p=0.083$  for the left ear). Speech reception thresholds of celiac patients were significantly higher than the controls ( $p=0.000$  for right ear,  $p=0.001$  for the left ear) While OAE response was obtained in the right ear of 24 patients and in the left ear of 23 patients; OAE response was obtained in the entire control groups. In the OAE test, in response to 2000 Hz stimuli, there was no significant difference in the right ear responses, although there was a lower signal-to-noise ratio in patients compared to the control group. At all other frequencies, a statistically significant lower signal-to-noise ratio was found in the patient group. Statistically significant pathological differences were found in spontaneous nystagmus, gaze, saccade, smooth pursuit, optokinetic nystagmus and caloric tests in celiac patients compared to the control group ( $p < 0.05$ ).

**Conclusion:** Pure tone audiometry, otoacoustic emission, oculomotor and caloric tests findings indicated that auditory system, peripheral and central vestibular system may be affected in individuals with celiac disease.



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## Introduction

Celiac diseases (CD) is an autoimmune disease and gluten intolerance which occurs when genetically prone individuals ingest food containing gluten [1-2]. It is known that many systems are affected by celiac disease. However, very few studies evaluate the hearing function and/or vestibular system in celiac disease. Therefore, the current study aims to evaluate whether celiac disease impacts the auditory system, peripheral and central vestibular system.

## Materials and Methods

The study subjects comprised 40 patients with celiac disease, aged between 12 and 65 years (16 male, 24 female;

mean age of 35), and age and sex-matched 40 healthy volunteers. The sample size decided with power analysis. The average age of diagnosis of celiac patients was 31.05 years. The control group consists of healthy participants without complaints of vertigo. It has been questioned whether patients have complaints of vertigo, and 18 patients had complaints of vertigo. It has been questioned whether patients adhere to the celiac diet. Twenty-nine patients adhered to the celiac diet, while others did not. Exclusion criteria were anatomical problems associated with the outer ear and middle ear, the history of chronic otitis media, and an acoustic tumor.

Each subject underwent neurotologic examination. Pure tone audiometry (PTA) and speech audiometry tests were performed with Interacoustics Clinical Audiometer AC40. 125, 250, 500, 1000, 2000, 4000, 6000 and 8000 Hz air conduction hearing thresholds were obtained with THD-

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39 earphone with MX41/AR ear cushion. 250, 500, 1000, 2000 and 4000 Hz bone conduction hearing threshold were obtained with a radio ear B-71 vibrator. Arithmetic mean of 500, 1000 and 2000 Hz air conduction thresholds and 500, 1000, and 2000 Hz bone conduction thresholds were evaluated. In the speech audiometry test, monosyllabic and multisyllabic word list developed at Marmara University Audiology Unit was used.

Transient Evoked Otoacoustic Emission (TEOAE) test with 1000, 1500, 2000, 3000 and 4000 Hz performed with Otodynamics' OAE ILO V6. When signal-to-noise ratio is six or more, the OAE response was accepted in that frequency. When responses of three out of five frequencies (3/5) were accepted, then the OAE response was positive in that ear. It was evaluated separately for each ear. Right and left ear of 1000 Hz, 1500 Hz, 2000 Hz, 3000 Hz and 4000 Hz signal-to-noise ratio values were compared between patients and controls.

Videonystagmography (VNG) and binaural bithermal caloric test were done with micromedical by Interacoustics visual eyes. VNG test battery comprised of gaze test, spontaneous nystagmus evaluation, saccade test, smooth pursuit test, optokinetic test and caloric test. Subjects were informed not to use a sedative or other drug (except heart, blood pressure or diabetes medications) and to take alcohol before the test day.

VNG tests were performed in a dimly lit environment. The light bar was 1 meter away from the subject and adjusted to the eye level of the subject in a sitting position. The goggles with fire-wire see-through lenses were fitted to the subjects. Horizontal and vertical calibrations were performed.

Gaze horizontal and gaze vertical tests were performed, and the subjects were asked to look at the light on the light bar. At certain angles, when the eye is unable to fixate, or nystagmus was observed, gaze test was considered pathological.

In the spontaneous nystagmus evaluation, goggles were covered, and eye movements with and without fixation were recorded.

In the saccade test, subjects were instructed to catch the lights that are lit randomly on the light bar. The patient is asked to follow the visual stimulus given in the most accurate way possible. The LED on the light bar is adjusted to light at the right and at the left (horizontal saccade) or up and down (vertical saccade) at an angle of 15-20° with respect to the center of the light bar at 2-3 second intervals. Responses to 30 randomized stimuli in the light bar were recorded and analyzed. The latency, velocity and accuracy of saccadic movement were assessed. Saccade latency of more than 200 ms is considered pathological.

The smooth pursuit test recorded the subject's eyes while tracking the light moving in sinusoidal trajectory. The target accelerates at 0.1 Hz, 0.2 Hz, and 0.4 Hz. Smooth pursuit gain was calculated as the ratio of eye velocity to target velocity. When the gain was lower than 0.8, smooth pursuit test was accepted pathological.

Optokinetic nystagmus was evaluated with rapidly rightward and leftward flowing stimuli on the light bar. The LED moves first from right to left then from left to right at

velocity of 30-60 degrees/sec for 1 minute. Gain and phase were evaluated. Gain was the ratio of velocity of eyes to the velocity of target. When the gain was lower than 0.5, the optokinetic nystagmus test was accepted pathological. It was evaluated whether there was asymmetry between the test results on both sides.

The subjects underwent air-stimulated binaural bithermal caloric test with the order of left cold, right cold, left warm and right warm. During the test, the subject's head was brought to 30 degree flexion. Physiological nystagmus caused by cold and warm stimulation was evaluated with the Jongkee's formula.

The study was carried out by Turgut Ozal University, Faculty of Medicine Clinical Research Ethics Committee (Approval No. 99950669/332, dated October 17, 2014). Both verbal and written informed consent was obtained from all participants.

### Statistical analysis

Data were analyzed with Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) version 22 software. In order to test whether there was a difference between the control and patient groups in terms of categorical variables, the Pearson chi square test was used in cases where parametric test assumptions were provided, and Fisher's exact test was used in cases where parametric test assumptions were not provided. The t-test was used to evaluate whether there was a difference between the control and patient groups in terms of continuous variables.

## Results

Sensorineural hearing loss was detected in the right and left ear of the 7 celiac patients. According to Clark [3], the degrees of hearing loss of the participants are given in Table 1. In the pure tone audiometry (PTA) test, there was no statistically significant difference between celiac patients and healthy participants in hearing thresholds ( $p=0.389$  for the right ear,  $p=0.083$  for the left ear). The mean of speech reception threshold was 12.10 dB ( $\pm 16.05$ )

**Table 1.** Degrees of sensorineural hearing loss of all participants.

		Patients	Controls
Right Ear	Normal Hearing	33	38
	Slight HL	3	1
	Mild HL	1	1
	Moderate HL	1	-
	Moderately severe HL	-	-
	Severe HL	2	-
	Profound HL	-	-
Left Ear	Normal Hearing	30	38
	Slight HL	4	1
	Mild HL	-	1
	Moderate HL	3	-
	Moderately severe HL	-	-
	Severe HL	2	-
Profound HL	1	-	

**Table 2.** The otoacoustic emission signal-to-noise ratio values at different frequencies.

		Patients	Controls	p value
Right Ear	1000 Hz	5.03 ( $\pm$ 5.72)	10.25 ( $\pm$ 5.92)	0.000
	1500 Hz	9.27 ( $\pm$ 8.08)	14.75 ( $\pm$ 3.95)	0.000
	2000 Hz	8.42 ( $\pm$ 7.51)	10.30 ( $\pm$ 3.32)	0.152
	3000 Hz	8.19 ( $\pm$ 6.45)	11.10 ( $\pm$ 1.93)	0.008
	4000 Hz	6.04 ( $\pm$ 4.78)	8.20 ( $\pm$ 3.74)	0.027
Left Ear	1000 Hz	6.33 ( $\pm$ 7.75)	10.08 ( $\pm$ 7.55)	0.032
	1500 Hz	7.68 ( $\pm$ 7.18)	11.80 ( $\pm$ 5.85)	0.006
	2000 Hz	9.46 ( $\pm$ 7.14)	15.36 ( $\pm$ 3.43)	0.000
	3000 Hz	7.50 ( $\pm$ 6.66)	15.73 ( $\pm$ 4.40)	0.000
	4000 Hz	6.10 ( $\pm$ 6.01)	14.85 ( $\pm$ 2.50)	0.000

in the right ear of patients, 14.15 dB ( $\pm$  21.53) in the left ear of patients; 1.25 dB ( $\pm$  2.19) in the right ear of controls, and 2.50 dB ( $\pm$  2.53) in the left ear of controls. Speech reception thresholds of celiac patients were significantly higher than the controls ( $p=0.000$  for the right ear,  $p=0.001$  for the left ear).

While OAE response was obtained in the right ear of 24 patients and in the left ear of 23 patients; OAE response was obtained in the entire control group. In the OAE test, in response to 2000 Hz stimuli, there was no significant difference in the right ear responses, although there was a lower signal-to-noise ratio in patients compared to the control group. In the OAE test with 2000 Hz, there was statistically significant lower signal-to-noise ratio was found in the left ear of patients. In the OAE tests with 1000 Hz, 1500 Hz, 3000 Hz and 4000 Hz, statistically significant lower signal noise ratio were found in the patients compared to the controls in both right and left ears (Table 2). Pathological gaze horizontal findings were found in 5 patients and pathological gaze vertical findings were found in 8 patients. All gaze test findings were normal in the control group. In the gaze horizontal and gaze vertical tests, there was a statistically significant difference between celiac patients and controls ( $p=0.027$  for gaze horizontal and  $p=0.003$  for gaze vertical). Spontaneous nystagmus was observed in 9 patients.

Spontaneous nystagmus was not observed in the healthy participants. A statistically significant difference was found between celiac patients and healthy individuals in the spontaneous nystagmus test ( $p=0.001$ ). Spontaneous nystagmus was observed in 4 of the 29 patients who adhered to the celiac diet and in 5 of the 11 patients who did not. There was a statistically significant difference in observing spontaneous nystagmus between patients who adhered to celiac diet and those who did not ( $p=0.047$ ).

Pathological saccade test findings were observed in 6 patients. All saccade test findings were normal in the healthy participants. Statistically, a significant difference was found between celiac patients and healthy individuals in saccade test findings ( $p=0.001$ ).

Pathological smooth pursuit test results were observed in 16 patients. All smooth pursuit test findings were normal in the control group. A statistically significant difference

was found between celiac patients and healthy participants in smooth pursuit test ( $p=0.000$ ).

Asymmetric optokinetic test findings were found in 20 patients. All optokinetic test findings were symmetrical in the controls. There was a statistically significant difference between patients and controls in optokinetic test findings ( $p=0.000$ ).

In the caloric test, the average of reduced vestibular response (RVR) percentage was 8.15 % ( $\pm$  3.31) in controls, 19.82% ( $\pm$  14.33) in the patients. Statistically significant difference was found between celiac patients and healthy individuals in RVR percentage ( $p=0.000$ ). It is considered pathological when the percentage of air caloric RVR is above 20%. Caloric RVR was pathological in 19 patients. All caloric RVR were normal in the control group. There was statistically significant difference between patients and controls in pathological RVR ( $p=0.000$ ).

## Discussion

Celiac is a small intestine disease that occurs in susceptible individuals with a cellular and humoral immunological response that develops against gluten, a cereal protein. Celiac disease is considered a multisystem disease since many systems can be affected [4]. Neurological symptoms are observed in 6-10% of celiac patients. The most commonly observed neurological symptoms are ataxia, epilepsy, anxiety, peripheral neuropathy, encephalitis and migraine [5]. Demonstration of lymphocyte infiltration in the central nervous system and peripheral nerves, the appearance of inflammatory cells in the cerebrospinal fluid, the detection of autoantibodies in the circulation, and response to immunomodulatory therapy with a gluten-free diet support the relationship of neurological symptoms with autoimmunity [6,7].

The pathogenesis of inner ear disorders associated with autoimmunity is not completely known. However, different mechanisms, such as immune complex accumulation, humoral antibody production, vasculitis and autoreactive T cells, are responsible [8]. The development of sensorineural hearing loss in celiac patients associated with mineral and vitamin absorption disorders (vitamin B12, folate, vitamin D, E, and pyridoxine for bipter), cerebral vasculitis, the presence of antineuronal antibodies, lymphocyte filtration in the labyrinth, accumulated immune complexes are causing tissue damage, and immunopathological events causing an immune response in the inner ear [9].

There is limited number of studies evaluating auditory system in celiac patients. However, previous studies were conducted in the pediatric group. In literature, a higher prevalence of sensorineural hearing loss was observed in pediatric celiac patients [10]. In the current study, sensorineural hearing loss was detected in seven of fourthy adult celiac patients. There was no significant difference in hearing thresholds between adult celiac patients and controls. However, OAE findings indicated that auditory system is affected in celiac patients.

In the literature, the study in which the vestibular system was examined in adult celiac patients was not found. In the study conducted in the pediatric group, celiac patients were evaluated with electronystagmography [11]. Abnor-

mal gaze, eye-tracking and optokinetic nystagmus test responses were observed. In the present study, peripheral and central vestibular systems were analyzed with bin-aural bithermal caloric test and oculomotor tests. Statistically significant pathological differences were found in spontaneous nystagmus, oculomotor tests and caloric tests in celiac patients compared to the control group.

Gaze, saccade and smooth pursuit findings may be pathological in the use of drugs affecting the central nervous system, brainstem and cerebellar pathologies, diseases involving the basal ganglia, insomnia, and tiredness. Asymmetrical optokinetic nystagmus findings may be observed in occipitoparietal lesions. Pathological RVR is observed in lesions of peripheral vestibular structures, vestibular nerve and the region of entry of the eighth nerve into the brainstem. Oculomotor and caloric test findings of the current study indicated that peripheral and central vestibular system is affected in the celiac patients.

Additionally, statistically higher numbers of spontaneous nystagmus were observed in celiac patients who did not adhere to the celiac diet, indicating the effect of diet on the vestibular system in celiac disease.

The limitation of the current study was that it is not evaluated whether the findings correlated with clinical symptoms. In further studies, larger number of celiac patients should be evaluated with VNG and VHIT tests.

## Conclusion

Sensorineural hearing loss was detected in the right and left ear of the 7 out of 40 celiac patients. Abnormal gaze, saccade, and optokinetic test findings indicated that central vestibular system may be affected in celiac patients. Caloric test findings showed that the peripheral vestibular system can be affected in the celiac patients. In con-

clusion, pure tone audiometry, otoacoustic emission, oculomotor and caloric tests findings indicated that auditory system, peripheral and central vestibular system may be affected in individuals with celiac disease.

## Ethics approval

The study was carried out by Turgut Ozal University Faculty of Medicine Clinical Research Ethics Committee (Approval No. 99950669/332, dated October 17, 2014).

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