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ORIGINAL ARTICLE

Early vestibulospinal reflex changes in type 2 diabetes mellitus in relation to peripheral neuropathy

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ABSTRACT

BACKGROUND: Diabetes mellitus (DM) and its complications are rapidly becoming the world's most significant cause of morbidity and mortality. Most of patients with DM complain of imbalance and/or dizziness. The aim of this study was to assess the cervical vestibular evoked myogenic potential (cVEMP) in diabetic patients as an indicator of the integrity of the vestibulo-spinal reflex (VSR) that plays a pivotal role in balance.

METHODS: Forty adult patients (mean age=49.12±9.03 years) with a confirmed diagnosis of type II DM underwent cVEMP. Results were compared with those of 40 age and gender matched control subjects selected randomly. Patients and controls were not known to have neither peripheral nor central vestibular disorders. The grade of peripheral neuropathy, level of HbA1c and duration of DM were compared with cVEMP results.

RESULTS: Patients had higher cVEMP threshold with longer P13 and N23 wave latencies than controls. Neuropathic patients, those with poorer glycemic control and those with disease duration >5 years had significant higher cVEMP threshold and prolonged wave latencies in both ears than other patients. Severity of neuropathy had the strongest correlation with cVEMP results followed by level of HbA1c and finally the disease duration.

CONCLUSIONS: Diabetic patients have altered VSR in the form of delayed waves and elevated threshold of cVEMP response which is correlated with neuropathic changes found in these patients. DM affects both labrynthine and retro-labrynthine parts of the VSR pathway. Also, diabetic patients have a subclinical vestibular deficit that may appear with progression of diabetic complications.

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KEY WORDS: Diabetes mellitus - Diabetic neuropathies - Vestibular evoked myogenic potentials.

Diabetes mellitus (DM) is a disease of abnormal carbohydrate metabolism that is characterized by hyperglycemia. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin.[1] There are two broad categories of diabetes, type 1 and type 2 diabetes mellitus. Type 1 diabetes represents about 4% to 5% of the cases and is characterized by autoimmune destruction of the beta pancreatic cells. Type 2 diabetes accounts for about 90% to 95% of the cases, and the pathogenesis includes insulin resistance and a relative lack of insulin production.[2]

Diabetes mellitus symptoms include frequent urination (including nocturia), excessive thirst, extreme hunger, increased fatigue, irritability, unusual weight loss, and blurred vision.[3] Diabetes Mellitus and its complications are rapidly becoming the world's most significant cause of morbidity and mortality.[4] Acute metabolic complications associated with mortality include diabetic ketoacidosis, hypoglycemia. Chronic microvascular complica-

tions include retinopathy, nephropathy and neuropathy. The major macrovascular complications include accelerated cardiovascular disease resulting in myocardial infarction and cerebrovascular disease manifesting as strokes.[5]

Although diabetic sensory neuropathy and retinopathy are well-researched topics, relatively few studies have focused on the effects of DM on the vestibular system. Some studies have reported evidence of vestibular dysfunction,[6-8] while others found no significant abnormalities.[9, 10]

Our aim was to assess the cervical vestibular evoked myogenic potential (cVEMP) in diabetic patients as an indicator of the integrity of the vestibulo-spinal reflex (VSR) that plays a pivotal role in balance function.

Materials and methods

The study was designed as an observational case control study. It was approved by the Otolaryngology Research Ethical Committee (ORL-REC) in Faculty of Medicine, Cairo University and an informed consent was signed by all subjects who participated in the study.

Subjects

Eighty subjects were included in the study, 40 patients as a study group and 40 subjects as a control group. Patients included in the study were adults, with an age less than 60 years old, diagnosed previously as type 2 diabetes mellitus (T2DM) of variable durations, without any other medical disorder and with absence of a considerable complaint of dizziness. They were selected from the diabetes mellitus Outpatient Clinic in Kasr Al-Ainy Hospital, Cairo University during their regular follow-up visits.

Exclusion criteria of patients in the study group included patients with chronic medical disorders other than DM (*e.g.* hypertension, neurological disease, vascular insufficiency, etc.), patients with otologic disease, complaint of hearing impairment, history of major head trauma, any history of vestibular dysfunction before the onset of diabetes and musculoskeletal disorders that contribute to postural instability. Patients who showed known vestibular disorder during testing (*e.g.* BPPV, unilateral vestibular hypofunction, etc.) were also excluded.

Subjects in the control group were adults not known to be diabetics. They were selected randomly to match the age range and gender distribution in the study group. The same above exclusion criteria were applied on the control group.

Methods

All subjects included in the study were submitted to the following assessment protocol: detailed history taking of vertigo, diabetes mellitus and general diseases. Otolaryngology examination. Neurological examination of cranial nerves, sensory system, motor system, deep reflexes and coordination. Administration of Michigan Neuropathy Screening Instrument (MNSI) for detection of peripheral neuropathy grade (score >2.5 was considered positive).[11] Laboratory tests including: Fasting plasma glucose (FBG), Two hours postprandial blood glucose (2HPP) and Glycated hemoglobin (HbA1c). HbA1c more than 7% indicates poor glycemic control.[12]

Cervical vestibular evoked myogenic potential (cVEMP) was done for all participants via Bio-logic Navigator® Pro AEP system using 500 Hz rarefaction polarity tone burst stimulus with 2 ms rise/fall time and zero ms plateau (2-0-2). The stimulus was delivered monaurally via air conduction route at 100 dBHL with 5 dB steps till the threshold. The stimulus rate was 5.1Hz with 53.3 ms analysis time. A band pass filter (10-1500 Hz) was used. A total of 128 sweeps were averaged. The measurement was repeated twice to check wave reproducibility. P13 and N23 waves latencies for both ears stimulation were measured. The electrode montage was: non-inverting (+ve) on the upper third of the sternoclenomastoid muscle, inverting (-ve) on the sternoclavicular junction and common (ground) on the forehead. During recording the patient was asked to sit upright on a chair and turns his head to the contralateral side of stimulation with pushing his chin against his fist. Figure 1 shows an example of a cVEMP response obtained from a patient included in this study.

Statistical analysis

Data were statistically described in terms of range, mean±standard deviation (±SD), frequencies and percent-

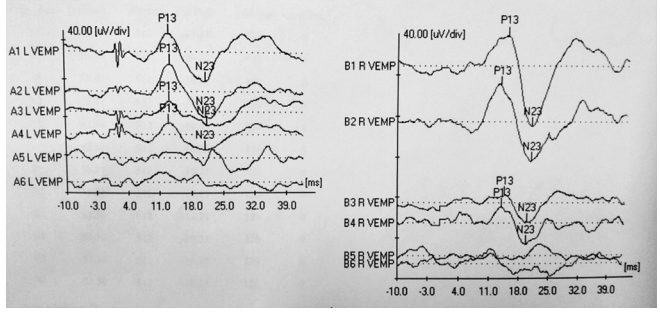

Figure 1.—cVEMP response of both ears recorded from a patient in the study.

ages when appropriate. Comparison of numerical variables between the study groups was done using Independent Student *t*-test for independent samples when comparing 2 groups. For comparing categorical data, χ^2 test was performed. Correlation between continuous variables was done using Pearson correlation coefficient. The P values less than 0.05 was considered statistically significant. R value for correlation was considered weak when R<0.5, moderate when R from 0.5 to 0.7 and strong when R>0.7. All statistical calculations were done using IBM personal computer program SPSS (Statistical Package for the Social Science) version 21. Linear regression analysis (Enter method) was used as the method for performing multivariate analysis for assessment of different predictors, each wave latency and threshold value was used separately as dependent variable and others as independent variables.

Results in some statistical analysis processes were divided into 2 subgroups according to MNSI Score "as an indicator of neuropathy grade" into neuropathic group (24 patients with score >2.5) and non-neuropathic (16 patients with score ≤2.5), according to HbA1c level "as an indicator of glycemic control" into poor control group (27 patients with HbA1c >7 mg/dL) and good control group (13 patients with HbA1c ≤7 mg/dL) and finally according to diabetes mellitus duration into group A (24 patients with a duration >5 years) and group B (16 patients with a duration ≤5 years).

Results

There were no significant differences between the study group and the control group regarding age and gender distribution (Table I). Twenty four patients (60%) out of 40 in the study group had peripheral neuropathy (MNSI Score >2.5), while no subject in the control group had peripheral neuropathy (MNSI Score ≤2.5). The score among patients ranged from 1 to 5.5 with a mean =3.27±1.28, while in the control group the range was 0 to 2.5 with a mean =0.94±0.74 (Figure 2).

Thirty five patients in the study group (87.5%) had cVEMP as a response to right ear stimulation and 32 (80%) had cVEMP as a response to left ear stimulation.

TABLE I.—*Comparison between the study group and the control group regarding age and gender distribution.*

		Study group N.=40	Control group N.=40	P value
Mean of age in years (±SD)		49.12 (±9.03)	45.62 (±11.6)	0.13*
Gender distribution (%)	Male	10 (25%)	14 (35%)	0.33**
	Female	30 (75%)	26 (65%)	

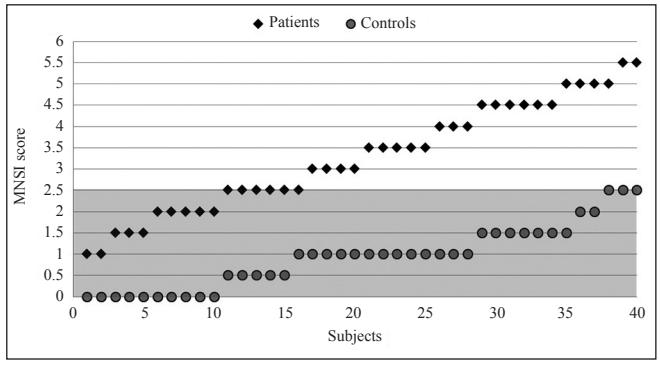

Figure 2.—MNSI Score of patients and controls.

In the control group 39 (97.5%) had cVEMP as a response to right ear stimulation and 37 (92.5%) had cVEMP as a response to left ear stimulation. There were no significant differences between the 2 groups regarding presence of cVEMP as a response to either right or left ear stimulation (P=0.09 and 0.1 for right and left sides respectively). Patients in the study group had significantly higher mean values of threshold and waves latencies (*i.e.* delayed P13 and N23 waves) than the study group as a response to both right and left ear stimulation (Table II).

When comparing neuropathic patients with non-neuropathic patients, out of the 24 neuropathic patients 19 (79%) had cVEMP as a response to right ear stimulation and 17 (71%) had cVEMP as a response to left ear stimulation. All the non-neuropathic patients had cVEMP as a response to right ear stimulation, while 15 (93.75%) out of 16 had cVEMP as a response to left ear stimulation. There were no significant differences between the 2 groups regarding presence of cVEMP as a response to either right or left ear stimulation (P=0.051 and 0.076 for right and left sides respectively). Patients in the neuropathic group had significantly higher man values of threshold and waves

TABLE II.—*Comparison between the study group and the control group regarding threshold and waves latencies of cVEMP in both ears.*

cVEMP	Study group Mean (±SD)	Control group Mean (±SD)	P value
Right ear			
Threshold (dBHL)	93 (±5.45)	86.54 (±4)	<0.001
P 13 latency (ms)	16.43 (±1.57)	13.21 (±0.77)	<0.001
N 23 latency (ms)	24.26 (±1.80)	22.9 (±1.06)	0.002
Left ear			
Threshold (dBHL)	92.65 (±5.07)	86.62 (±3.34)	<0.001
P 13 latency (ms)	15.95 (±1.74)	13.48 (±0.5)	<0.001
N 23 latency (ms)	23.93 (±1.65)	22.97 (±0.99)	0.006

The study group had 35 responses in from Rt ear and 32 from Lt ear. The control group had 39 responses from Rt ear and 37 from left ear.

TABLE III.—*Comparison between the neuropathic group and the non-neuropathic group.*

cVEMP	Neuropathic group Mean (±SD)	Non-neuropathic group Mean (±SD)	P value
Right ear			
Threshold (dBHL)	96.31 (±4.66)	89.06 (±3.27)	<0.001
P 13 latency (ms)	17.49 (±0.92)	15.17 (±1.22)	<0.001
N 23 latency (ms)	25.32 (±1.05)	23 (±1.69)	<0.001
Left ear			
Threshold (dBHL)	96.17 (±3.32)	88.66 (±3.51)	<0.001
P 13 latency (ms)	17.04 (±0.99)	14.71 (±1.59)	<0.001
N 23 latency (ms)	25 (±1.12)	22.71 (±1.27)	<0.001

The neuropathic group had 19 responses from Rt ear and 17 from Lt ear. The non-neuropathic group had 16 responses from Rt ear and 15 from left ear.

TABLE V.—*Comparison between group "A" and group "B" regarding threshold and waves latencies of cVEMP in both ears.*

cVEMP	Group A (>5 years) Mean (±SD)	Group B (<5 years) Mean (±SD)	P value
Right ear			
Threshold (dBHL)	96 (±4.47)	89 (±3.87)	<0.001
P 13 latency (ms)	17.3 (±1.01)	15.26 (±1.43)	<0.001
N 23 latency (ms)	24.92 (±1.58)	23.38 (±1.72)	0.01
Left ear			
Threshold (dBHL)	95.88 (±3.17)	89 (±4.3)	<0.001
P 13 latency (ms)	16.87 (±1.15)	14.91 (±1.74)	0.001
N 23 latency (ms)	24.78 (±1.37)	22.96 (±1.41)	0.001

The "A" group had 20 responses from Rt ear and 17 from Lt ear. The "B" group had 15 responses from Rt and Lt ears.

latencies (*i.e.* delayed P13 and N23 waves) than the non-neuropathic group as a response to both right and left ear stimulation (Table III).

When comparing patients with poor glycemic control against patients with good glycemic control, out of the 27 poor control patients 22 (81%) had cVEMP as a response to right ear stimulation and 20 (74%) had cVEMP as a response to left ear stimulation. All patients in the good control group had cVEMP as a response to right ear stimulation, while 12 (92.3%) out of 13 had cVEMP as a response to left ear stimulation. There were no significant differences between the 2 groups regarding presence of cVEMP as a response to either right or left ear stimulation (P=0.097 and 0.117 for right and left sides respectively). Patients in the poor control group had significantly higher mean values of threshold and waves latencies (*i.e.* delayed P13 and N23 waves) than the good control group as a response to both right and left ear stimulation (Table IV).

When comparing results of patients having DM duration >5 years "group A" with results of patients with DM duration <5 years "group B", out of the 24 patients in group "A" 20 (83.3%) had cVEMP as a response to right ear stimulation and 17 (70.8%) had cVEMP as a response to left ear stimulation. In group "B" 15 patients (93.75%) had cVEMP as a response to right and left ear stimulation separately. There were no significant differences between the two groups regarding presence of cVEMP as a response to either right or left ear stimulation (P=0.329 and 0.076 for right and left sides respectively). Patients in group "A" had significantly higher mean values of threshold and waves latencies (*i.e.* delayed P13 and N23 waves) than that of group "B" as a response to both right and left ear stimulation (Table V).

TABLE IV.—*Comparison between the poor control group and the good control group threshold and wave latencies of cVEMP in both ears.*

cVEMP	Poor control group Mean (±SD)	Good control group Mean (±SD)	P value
Right ear			
Threshold (dBHL)	95 (±5.11)	89.61 (±4.31)	0.003
P 13 latency (ms)	17.34 (±1)	14.41 (±1.5)	<0.001
N 23 latency (ms)	24.87 (±1.31)	23.22 (±2.07)	0.019
Left ear			
Threshold (dBHL)	94.75 (±4.43)	89.16 (±4.17)	0.001
P 13 latency (ms)	16.87 (±1.13)	14.71 (±1.59)	<0.001
N 23 latency (ms)	24.52 (±1.41)	22.94 (±1.59)	0.007

The poor control group had 22 responses from Rt ear and 20 from Lt ear. The good control group had 13 responses from Rt ear and 12 from left ear.

All cVEMP parameters increased with increased DM duration, level of HbA1c and MNSI Score (*i.e.* +ve correlation). The threshold of both ears had moderate correlation with DM duration and level of HbA1c with a strong correlation with MNSI Score. Wave P13 latency of the right ear had a moderate correlation with DM duration and a strong correlation with both level of HbA1c and MNSI Score, but stronger with the later. Wave N23 latency of the right ear had a weak correlation with DM duration and a moderate correlation with both level of HbA1c and MNSI Score, but more with the later. In the left ear, wave P13 latency had a weak correlation with DM duration, a moderate correlation with the level of HbA1c and a strong correlation with MNSI Score. Wave N23 latency had a weak correlation with DM duration and a moderate correlation with both level of HbA1c and MNSI Score, but more with the later (Table VI).

Multivariate analysis for assessment of different predictors was done to detect which one of the 3 correlated factors has more effect on the cVEMP parameters. It showed that MNSI Score was a significant predictor of wave P13 latency in both ears in addition to the cVEMP threshold of the right ear (Table VII).

TABLE VI.—*Correlation between cVEMP results and DM duration, level of HbA1c and MNSI Score.*

cVEMP		DM duration	Level of HbA1c	MNSI Score
Right ear				
Threshold	R	0.588	0.668	0.817
	P value	0.000	0.000	0.000
P13 latency	R	0.557	0.805	0.841
	P value	0.001	0.000	0.000
N23 latency	R	0.466	0.637	0.653
	P value	0.005	0.000	0.000
Left ear				
Threshold	R	0.689	0.563	0.728
	P value	0.000	0.001	0.000
P13 latency	R	0.464	0.677	0.760
	P value	0.008	0.000	0.000
N23 latency	R	0.499	0.560	0.689
	P value	0.004	0.001	0.000

TABLE VII.—*Linear regression analysis of different predictors affecting cVEMP results.*

cVEMP		DM duration	Level of HbA1c	MNSI Score
Right ear				
Threshold	Constant		82.641	
	Coefficient	0.047	-0.177	3.675
	P value	0.789	0.808	0.005
P13 latency	Constant		11.558	
	Coefficient	0.034	0.546	0.38
	P value	0.438	0.088	0.048
N23 latency	Constant		19.505	
	Coefficient	0.09	-0.053	0.89
	P value	0.314	0.783	0.071
Left ear				
Threshold	Constant		83.388	
	Coefficient	0.364	0.209	1.644
	P value	0.055	0.785	0.209
P13 latency	Constant		12.363	
	Coefficient	-0.033	0.071	1.07
	P value	0.607	0.789	0.023
N23 latency	Constant		21.366	
	Coefficient	0.008	-0.044	0.93
	P value	0.905	0.876	0.061

Discussion

Although the study showed a higher percentage of absent cVEMP responses in both ears than control group, the difference did not reach a significant value. Ward et al found 32% of tested ears in T2DM patients have absent cVEMP in comparison to 12% in controls.[6] Also Konukseven *et al.* found 12% of T2DM ears not showing cVEMP response in comparison to zero% in controls.[13] On the other hand Kamali *et al.*, who investigated T1DM, and Bektas *et al.*, who investigated T2DM, had cVEMP response from all diabetic patients included in their studies.[14, 15]

Patients had significant higher threshold and delayed cVEMP waves in both ears than that of controls. To our Knowledge, no one studied the threshold of cVEMP in diabetics up till now. Delayed waves were found by Konukseven *et al.* who investigated T2DM and Kamali *et al.* who investigated T1DM.[13, 14] On the other hand, Neither Ward *et al.* nor Bektas *et al.* reported any delay in wave latencies in T2DM patients who had preserved cVEMP in their studies.[15, 16]

In our results, patients with peripheral neuropathy, patients with poorer glycemic control and patients with disease duration >5 years had significant higher cVEMP threshold and prolonged waves latencies in both ears than other patients in the study group. In sake of detecting which factor is related more to cVEMP changes the correlation of these 3 factors with cVEMP results was studied. The MNSI Score (grade of neuropathy) had the strongest correlation with cVEMP results followed by level of HbA1c (glycemic control) and finally the disease duration came. Kamali *et al.* found that cVEMP waves are delayed in neuropathic T1DM patients more than non-neuropathics.[14] Konukseven *et al.* found a significant positive correlation between P13 latency and HbA1c in T2DM patients. Unexpectedly, they found that cVEMP latencies decrease with increased DM duration (*i.e.* inversely correlated). They did not study the correlation with peripheral neuropathy as they investigated only non-neuropathic diabetic patients.[13] Bektas *et al.* worked on T2DM patients and found no significant difference in wave latencies between neuropathic, non-neuropathic and normals.[15] Although Ward *et al.* found more absent cVEMP in T2DM patients with less response amplitude, they reported no association of HbA1c, duration of DM and MNSI Score with cVEMP results.[6]

In sack of detecting which factor is directly affecting the cVEMP results, a multivariate analysis was done. The MNSI Score was found to be directly affecting latency of wave P13 in both ears in addition to cVEMP threshold in right ear. In spite of absence of significant effect of MNSI Score on N23 latency, it tends to cause a prolongation of N23 latency of both ears as we noticed that P values are low and near to the significant value (0.061 and 0.071 to right and left ears respectively) in comparison to P values of DM duration and level of HbA1c.

In addition to vestibular impairment, hearing affection in diabetic patients was reported by many researchers. Özel *et al.* reported that DM patients have significant higher PTA threshold at all frequencies than normals.[17] Kla-

genberg *et al.* found that 10% of patients with DM have moderate SNHL.[7] High frequencies SNHL was found in 20% of patients with DM in a study done by Al-Rahman *et al.*[16]

Many authors have tried to identify the underlying cause of audio-vestibular affection in diabetic patients. In conclusion, the predominant mechanisms are microangiopathy of the inner ear, neuropathy of the 8th nerve, outer hair cell dysfunction and disruption of endolymphatic potential.[16]

Changes in ultrastructure of inner ear capillaries in a rat model of DM, including thickened basement membrane, was reported by Wang *et al.*[18] Tomisawa found atrophy and thickening changes of stria vascularis in DM patients in comparison to non-diabetics.[19] In studies based on autopsy results of diabetic patients with neuropathy, Schwann and perineural cells and endoneural vascular elements were found to be affected by neuropathy.[20] This is supported by histopathologic studies that showed changes in myelin sheaths of the nerves in animals with experimental DM,[17] and eighth nerve demyelination in DM patients.[21]

In DM there is decreased lipid synthesis and increased lipid breakdown, which lead to elevated blood lipid levels and contribute to arthrosclerosis. With constricted or blocked supplying vessels, nerves and receptor cells become malnourished and their cellular membrane demonstrate dysplasia or necrosis. In addition, lipid metabolism disorders have been found to lead to deposit of fatty droplets in hair cells and are thought to be a direct cause of audio-vestibular alternation in DM.[22]

The labyrinthine structures have a very intense metabolic activity and therefore a constant expenditure is necessary to keep proper concentrations of sodium and potassium in the endolymph. Glucose is fundamental for ATP production within the cells and energy supply for the sodium and potassium pump to work properly. As such, the metabolic alterations which involve the glucose metabolism can impair energy supply, altering the concentration of ions in the endolymph and perilymph, causing a change in the labyrinthine electric potentials.[23]

In VEMPs, the stimulus is thought to be primarily transduced via type I vestibular hair cells which are known to have greater sensitivity to ototoxic medications, oxygen deprivation and metabolic disturbances.[24] Histopathologic studies of rats with induced diabetes identified atrophy restricted to type I vestibular hair cells in those rats with the longest duration of diabetes.[25]

Prolonged response latencies in nerve conduction studies are considered diagnostic in case of peripheral neuropathy among diabetic patients.[26] In this study, the worsening of peripheral neuropathy significantly causes delay in wave N13 meaning it affects the conduction along the nerve. This delay may be indicative of a neuropathy similar to the neurovascular damage seen with peripheral neuropathy in diabetics.

Latencies of VEMP waves are more reliable indicator than the amplitude in brainstem lesions.[27] Besides, damage only to the vestibular nerve may be insufficient for VEMP latency prolongation. Therefore, prolonged latencies of the VEMP suggest lesions in the retrolabyrinthine pathway, especially in the vestibulospinal tract.[27, 28] In addition, musculoskeletal degeneration may affect test results because DM causes altered glucose metabolism in peripheral tissues, such as muscle and adipose tissue.[29] Our consistent results in both ears are accepted in DM being a systemic disease and could be of value for early detection of neuropathy. This wave delay should be compared with age specific normative data as it is bilateral and could be missed in case of inter aural comparisons only.

In the present study, the neuropathy grade was more correlated to alternation in cVEMP results than glycemic control and disease duration. American Diabetes Association reported that neuropathy can develop despite strict regulations and normoglycemia and other mechanisms may play a role in its pathogenesis.[30] In addition, Patients had delayed P13 and N23 waves similar to findings were reported by 2 studies who worked on T1DM[14] and T2DM.[13] So, it seems that both types alter the cVEMP.

In spite of altered vestibuo-spinal reflex found in this study, patients did not have a major complaint of dizziness. Rigon *et al.* reported that vestibular involvement might occur despite the absence of vestibular symptoms in diabetic patients.[31] Konukseven *et al.* determined that dizziness symptoms were absent in 70% of diabetic patients.[13] This situation could be explained by two factors: the first is absence of asymmetry in the system as the metabolic disorders are expected to affect it equally; the second is the gradual onset of vestibular insult that promote vestibular compensation process. The vestibular system has a high plasticity that may change the clinical manifestations of vestibular abnormalities.

Conclusions

From our findings, we can conclude that diabetic patients have altered VSR in the form of delayed waves and elevated threshold of cVEMP response which is correlated with neuropathic changes found in these patients. Diabetes mel-

litus affects both labyrinthine and retro-labyrinthine parts of the VSR pathway. Also, diabetic patients have a subclinical vestibular deficit that may appear with progression of diabetic complications. However, the study of cVEMP in diabetic patients is still limited to few researches, with different patients' selection criteria and different parameters analysis. So, comparison is difficult and a large scale study of that test in diabetics is important.

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