Original Research

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
1–7

DOI: 10.1177/0194599814527574
http://otojournal.org
SAGE

Effects of Type 2 Diabetes on Otoacoustic Emissions and the Medial Olivocochlear Reflex

Erdem Eren, MD[1], Ece Harman, MD[2], Seçil Arslanoğlu, MD[1], and Kazım Önal, MD[1]

No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. To demonstrate if cochleopathy in patients with type 2 diabetes with normal audiometric hearing threshold can be detected with otoacoustic emissions or medial olivocochlear (MOC) reflex measurements.

Study Design. Cross-sectional study.

Setting. Tertiary university teaching hospital.

Methods. The study involved 40 type 2 diabetic patients and 24 healthy volunteers. All participants who showed normal otoscopic findings, hearing thresholds, and acoustic admittance were included. Cochlear activity of participants was evaluated by means of distortion product otoacoustic emissions (DPOAEs) and transient otoacoustic emissions (TOAEs). The MOC reflex was evoked with contralateral acoustic stimulation and recorded with DPOAEs and TOAEs.

Result. A comparison of DPOAE and TOAE levels with a *t* test between patient and control groups revealed no significant difference ($P > .05$). A comparison of the MOC reflex response between the 2 groups also revealed no statistically significant difference ($P > .05$).

Conclusion. Although decreased OAE amplitude levels were found in diabetic patients, there was no statistically significant difference in OAEs and MOC reflex. Additional studies are needed to evaluate the role of OAEs and MOC reflex in normal-hearing patients with diabetes.

Keywords

Diabetes, otoacuostic emissions, medial olivocochlear, hearing

Received September 23, 2013; revised February 10, 2014; accepted February 20, 2014.

Type 2 diabetes mellitus is a major health problem affecting up to 7% of the adult population worldwide and associated with microvascular and neuropathic complications. Sclerosis of the internal auditory artery, thickened capillaries of the stria vascularis, atrophy of the spiral ganglion, and demyelination of the eighth cranial nerve have been demonstrated among autopsied patients with diabetes.[1,2] A temporal bone study Kariya et al[3] showed that compared with age-matched controls, the cochlear vessel wall is significantly thicker in both type 1 and type 2 diabetic patients. In the same study, the authors also demonstrated that patients managed with insulin therapy displayed a thicker vessel wall than patients receiving oral antidiabetic agents.[3] A similar study conducted by Fukushima et al[4] demonstrated greater atrophy of stria vascularis, greater loss of cochlear outer cells, thicker basilar membrane, and more stria vascularis vessel walls in the group of patients with diabetes compared with that of controls. They found no significant difference in the number of spiral ganglion cells or inner hair cells between groups.

Although diabetes-associated hearing loss has been described in the literature,[5,6] some studies do not report such an association.[7,8] In a cross-sectional analysis conducted on 5140 adults, Bainbridge et al[9] reported that the frequency of low-/mid-frequency hearing impairment of mild or greater severity assessed in the worse ear was 21.3% among 399 adults with diabetes and 9.4% among 4741 adults without diabetes. For high-frequency hearing impairment of mild or greater severity assessed in the worse ear, the incidence was 54.1% among those with diabetes and 32.0% among those without. In light of recent published articles, there is growing evidence that diabetic patients are prone to hearing loss, but characterization of that loss is uncertain.[10]

Otoacoustic emissions (OAEs) comprise a noninvasive method of evaluating cochlear reserve. OAEs are used for detection of ototoxicity,[11] hearing screening, and intactness of the entire ascending and descending auditory pathway.[12] The medial olivocochlear (MOC) efferent system that

[1]İzmir Katip Çelebi University Atatürk Research and Education Hospital, Otolaryngology Head and Neck Surgery Clinic, Konak/İzmir, Turkey
[2]İzmir Katip Çelebi University Atatürk Research and Education Hospital, Endocrinology Clinic, Konak/İzmir, Turkey

Corresponding Author:
Erdem Eren, Piri Reis Mh İnönü Cd No 252/17 Konak/İzmir 35280, Turkey.
Email: erd2eren@yahoo.com

innervates outer hair cells is subject to an increasing number of clinical research studies by means of OAEs. MOC activity reduces basilar membrane responses to sound by reducing the gain of cochlear amplification.[13] It has been speculated that MOC efferents help to reduce acoustic trauma and aid in speech comprehension in noise.[14] The MOC reflex compromise has been proposed as an early warning for an impending complications of diabetes.[15,16]

Literature on the effect of diabetes mellitus on OAEs of normal-hearing patients is confusing. In a study conducted with patients with type 2 diabetes, a statistically significant decrease was found at 4 kHz in distortion product otoacoustic emission (DPOAE) in diabetic patients compared with controls.[17] On the contrary, Sasso et al[18] demonstrated no difference in evoked OAE amplitudes between diabetic and nondiabetic patients in an acute hyperglycemic state. In a study investigating the effect of hyperglycemia on stimulus frequency (SF) OAEs, the authors found that mean SFOAE levels were elevated following glucose consumption.[19]

A few studies have investigated the auditory function of middle-aged diabetic patients with normal hearing by means of OAE and evaluated the MOC reflex in these patients. Our aim is to demonstrate whether cochleopathy in type 2 diabetic patients with a normal audiometric hearing threshold can be detected with OAEs or MOC reflex measurements.

Materials and Methods

This prospective study involved patients with type 2 diabetes mellitus who were referred from the endocrinology department and healthy volunteers. The mean age of the diabetes group was 47.6 ± 9.8 years, and that of the control group was 47 ± 9.4 years. There were 14 men (35%) and 26 women (65%) in the patient group (40 subjects) and 8 men (33.3%) and 16 women (66.7%) in the control group (24 subjects).

The study was performed in accordance with Helsinki Committee requirements and was approved by the Ethics Committee of İzmir Katip Çelebi University. Written informed consent was obtained from all participants before the study.

All diabetes patients met each of the criteria of the American Diabetes Association (ADA).[20] According to the ADA, 1 of the following should be present: fasting plasma glucose ≥126 mg/dL, hemoglobin A1C (HbA1C) level ≥6.5%, 2-hour plasma glucose ≥200 mg/dL during an OGTT, patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or a random plasma glucose ≥200 mg/dL.

The health of the control group was determined on the basis of medical history, physical otolaryngologic examination, blood chemistry, and audiologic evaluations. Patients who had previously undergone otologic surgery; who had chronic otorrhea, chronic tinnitus, otitis media/externa, or congenital ear deformity; or who were smokers were excluded.

All participants who showed normal otoscopic findings, hearing thresholds, and acoustic admittance were included. Correlation analysis was based on plasma glucose levels that were analyzed before the audiologic evaluation. The audiometric evaluation was performed within 1 month after HbA1C levels were measured. Normal-hearing thresholds were defined as being <20 dB HL (no air-bone gap) at 500, 1000, 2000, 4000, 5000, 6000, 7000, and 8000 kHz (Interacoustics AC40 Audio Electronics Inc, Austin, TX). DPOAE measurements at the frequencies used in the main experiments—0.5, 1, 2, 2.5, 3,4, 5, 6, 7, and 8 kHz—and transient otoacoustic emission (TOAE) measurements at the frequencies used in the main experiments—1, 2, 3, and 4 kHz—were recorded using a Vivosonic integrity K500 (Vivosonic Inc, Ontario, Canada) measurement system. DPOAEs were recorded with stimulus levels of L1 = 65 and L2 = 55 dB SPL and f2/f1 = 1.22. Emissions were considered to be normal when signal-to-noise ratio levels exceeded 3 dB (considered valid and presented in **Tables 1** and **2**).

To investigate the effects of contralateral acoustic stimulation (CAS) on MOC reflex contralateral, a continuous, broadband white noise (bandwidth, 50-8000 kHz) was presented at 60-dB SPL, corresponding to 30-dB HL, to minimize interaural transmission and activation of the stapedial reflex. Reduction/suppression may be defined numerically as the amplitude difference of the OAE response without and with CAS; the value of this difference shows that CAS-induced DPOAE/TOAE enhancement is present. Reduction is present when the difference is positive with a decrease in the response amplitude of TOAE/DPOAE with CAS; suppression is present when the TOAE/DPOAE responses are extinguished. TOAE reduction/suppression is absent when the difference is zero or negative. When the difference is zero or negative, DPOAE/TOAE enhancement is present.

Tympanometric measurements were recorded using an Interacoustics AZ26 (Audio Electronics Inc) middle ear analyzer with a 226-kHz probe tone. Values within the range of 0.30 to 1.50 mm H_2O were considered to be normal. Acoustic reflex thresholds, using steady-state broadband noise, were also recorded with the Interacoustics AZ26 (Audio Electronics Inc). All participants with an acoustic reflex threshold lower than 80 dB HL were excluded in an effort to exclude middle ear muscle activity as a potential cause of OAE level changes and MOC reflex suppression.

A Shapiro-Wilk test was used to assess the normal distribution of the data. If data were normally distributed, a t test was used; otherwise, the Mann-Whitney U test and Wilcoxon signed-rank test were used. For categorical data, χ^2 test was used. A Spearman test was used for correlation analysis. Statistical analyses were conducted using the SPSS software (version 16 for Windows). The statistical significance level was established at $P < .05$, and confidence intervals were 95%. Power analysis were conducted with G*Power 3.1.7.[21]

Results

The mean hearing levels of diabetes patients and control groups are presented in **Table 1**. The number of valid

Table 1. Mean (SD) Hearing Levels (dB) of Diabetic and Control Groups.

Side	Group	0.5 kHz	1 kHz	2 kHz	2.5 kHz	3 kHz	4 kHz	5 kHz	6 kHz	7 kHz	8 kHz
Left	DM	7.6 (1.6)	10.7 (4.1)	12.1 (1.8)	13.2 (2.3)	13.5 (3)	12.8 (3.2)	14.1 (2.3)	13.9 (1.9)	14.5 (2.3)	15.6 (2.7)
	Control	7.3 (2)	10.9 (3)	12.5 (1.1)	14.3 (2.4)	12.8 (2.9)	13.2 (2.5)	12.2 (2.2)	13.9 (1.6)	14.2 (2.1)	15.5 (1.7)
Right	DM	7.5 (2.4)	15.8 (1.9)	15.1 (3.2)	14.1 (2.3)	15.5 (2.4)	15.6 (1.9)	14.7 (1.6)	14.7 (1.9)	15.3 (1.5)	15.8 (1.9)
	Control	7.9 (2.3)	14.4 (3)	16.1 (1.9)	15.5 (2.9)	15.4 (2.6)	15.1 (2.2)	15.2 (2.1)	15.4 (1.6)	14.7 (2.2)	14.7 (1.7)

Table 2. Number of Valid and Nonvalid Otoacoustic Emissions Based on Frequency.[a]

	Patient				Control					
	Left		Right		Left		Right		Power[b]	
DPOAE (Frequency)	N1	N2	N1	N2	N1	N2	N1	N2	Left	Right
0.5	19	21	26	14	11	12	15	8	0.53	0.67
1	36	4	33	7	22	1	21	2	0.82	0.80
2	36	4	36	4	23	0	21	2	0.83	0.81
2.5	34	6	35	5	21	2	22	1	0.80	0.82
3	36	4	31	9	22	1	20	3	0.82	0.78
4	33	7	35	5	20	3	18	5	0.79	0.77
5	30	10	31	9	18	5	21	1	0.74	0.79
6	33	7	30	10	22	1	20	3	0.81	0.77
7	34	6	32	8	18	5	20	3	0.76	0.78
8	34	6	34	6	20	3	20	3	0.79	0.79

[a]N1, number of valid otoacoustic emissions; N2, number of nonvalid otoacoustic emissions.
[b]Effect size (d) = 0.8.

Table 3. Number of Valid Otoacoustic Emissions Based on Frequency.[a]

	Patient				Control					
	Left		Right		Left		Right		Power[b]	
TOAE (Frequency)	N1	N2	N1	N2	N1	N2	N1	N2	Left	Right
1	30	10	35	5	21	2	19	4	0.78	0.78
2	27	13	31	9	20	3	20	3	0.75	0.78
3	24	16	23	17	12	11	14	9	0.59	0.63
4	12	28	16	24	7	16	12	11	0.35	0.52

[a]N1, number of valid otoacoustic emissions; N2, number of nonvalid otoacoustic emissions.
[b]Effect size (d) = 0.8.

OAEs and achieved power of t-test analysis for each frequency (effect size d = 0.8) in the patient and control groups are presented in **Tables 2** and **3**. Comparison of valid/invalid OAEs (DPOAE/TOAE) revealed no statistically significant difference between groups ($P > .05$).

Ophthalmologic evaluation showed diabetic retinopathy in 7 patients (17.5%). Peripheral neuropathy was identified in 10 patients (25%). Microalbuminuria was identified in 4 (10%) patients. Thirteen patients had at least 1 complication.

No statistically significant difference was found between the 2 genders. Although gender differences in OAE measurements were present,[22] only on the left side at 3 kHz was a statistically significant difference found (P = .001, DPOAE).

All groups are compared according to left and right sides. A comparison of DPOAE levels with paired t test at all 10 frequencies between patient and control groups revealed no significant difference ($P > .05$). We found no significant side difference in emission levels ($P > .05$). The amplitude values of the DPOAEs are presented in **Figures 1** and **2** (left ear of both groups, right ear of both groups, respectively).

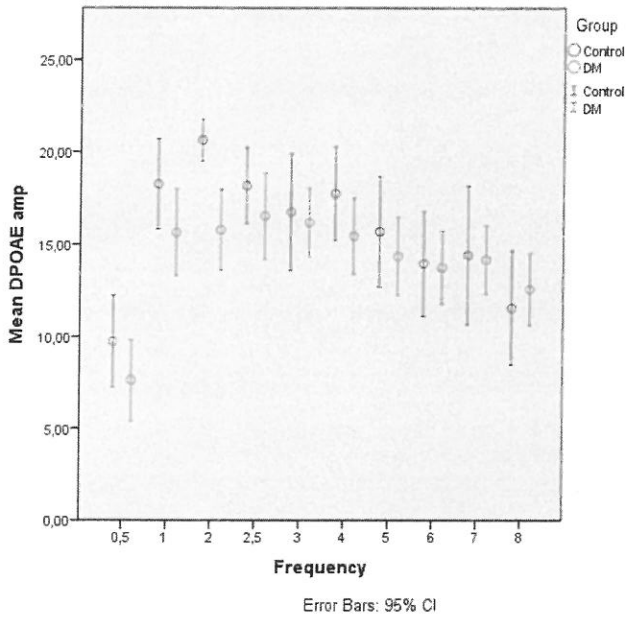

Figure 1. Distortion product otoacoustic emissions levels of the left ears of the patient and control group. The first bar of each frequency represents the control group.

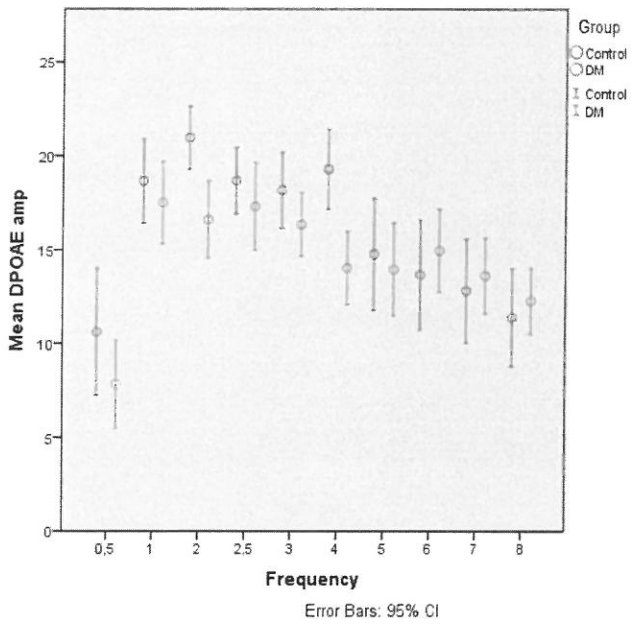

Figure 2. Distortion product otoacoustic emission levels of the right ears of the patient and control group. The first bar of each frequency represents the control group.

In both groups, suppression or enhancement of emission levels was observed as a result of CAS (the MOC reflex). Intergroup comparison of the MOC reflex revealed no statistically significant difference (**Table 4**).

All groups are compared according to left and right sides. A comparison of TOAE levels with paired t test at all 4 frequencies between patient and control groups revealed no significant difference ($P > .05$). We found no significant side difference in emission levels ($P > .05$). The amplitude values of the TOAEs are presented in **Figures 3** and **4** (left ear of both groups, right ear of both groups, respectively).

In both groups, suppression or enhancement of emission levels was observed as a result of CAS (the MOC reflex). Intergroup comparisons of MOC reflex differences showed no statistically significant result (**Table 5**).

A correlation analysis demonstrated no statistically significant relation between blood glucose levels and OAE amplitude levels in DPOAE except 0.5 kHz of both ears (left P = .016, right P = .002, Spearman's ρ =–0.429, –0.429, respectively), 2 kHz of the left ear (P = .002, ρ = –.392), and 4 kHz of the right ear (P = .008, ρ = –0.362). Except for 8 kHz in both ears and 6 and 7 kHz in the right ear, a negative correlation coefficient was found. A correlation analysis demonstrated no statistically significant relation between blood glucose levels and OAE amplitude levels in TOAE. Except for 4 kHz in both ears, a negative correlation coefficient was found (statistically insignificant).

A correlation analysis demonstrated a negative correlation between HbA1C levels and OAE amplitude at 1, 2.5, and 7 kHz (only at 2 kHz was a statistically significant correlation found, P = .02, ρ = –0.3) of the left ear and at 0.5, 1, 2.5, 3, 5, 6, and 8 kHz of the right ear. Correlations of HbA1C levels and DPOAE at 2 kHz are presented in Supplemental Figures S1 and S2 (available at otojournal.org; left ear and right ear, respectively).

In TOAE, a negative correlation was found at 1, 2, and 4 KHz of the left ear and at 1, 2, and 3 kHz of the right ear (no statistically significant correlation was found). Correlation of HbA1C levels and TOAE at 2 kHz are presented in Supplemental Figures S3 and S4 (left ear and right ear, respectively).

Discussion

Metabolic functioning is disturbed in diabetes. Mitochondrial dysfunction, oxidative stress, and the deposition of glycated products in body tissues lead to disturbed energy metabolism. Microangiopathy, advanced glycation end products, and reactive oxygen species are underlying mechanisms that lead to complications.

A study on type 1 diabetic children with normal hearing demonstrated no difference in TOAE amplitude levels but limited suppression of TOAE (involvement of MOC bundle) in diabetic adolescents. The authors of that study also found that abnormalities of cochlear integrity was evident in patients with retinopathy but not related to neuropathy or nephropathy.[15] In a similar study conducted in normal-hearing children with type 1 diabetes, the authors found no statistically significant difference in TOAE or DPOAE amplitude levels. A defective suppression of TOAE was found at 2 and 4 kHz in the diabetic group.[16] Both studies indicate that dysfunction in the MOC system can be regarded as an early central manifestation of diabetic neuropathy.

Table 4. Mean (SD) Medial Olivocochlear Reflex Values (Distortion Product Otoacoustic Emissions).

Side	Group	0.5 kHz	1 kHz	2 kHz	2.5 kHz	3 kHz	4 kHz	5 kHz	6 kHz	7 kHz	8 kHz
Left	Diabetes mellitus	−0.3 (5.9)	1.4 (6.5)	0.2 (6.2)	−1.8 (5.7)	1.9 (7.2)	0.9 (5.4)	−0.7 (4.9)	0.09 (4.6)	−0.03 (5.8)	−0.2 (3)
	Control	0.05 (5.1)	0.7 (4.9)	0.4 (5.4)	−0.9 (4.7)	−0.2 (5.8)	0.5 (5.3)	−0.8 (7.3)	1 (4)	0.5 (5.1)	−0.1 (4.4)
Right	Diabetes mellitus	0.9 (8.4)	0.5 (6.2)	0.4 (6.9)	1.1 (6.3)	−0.02 (4.2)	0.8 (4.9)	−0.7 (5.6)	0.3 (5.5)	−1.4 (4.6)	−0.9 (4.2)
	Control	0.7 (5.5)	0.8 (5.6)	0.2 (4.6)	−1 (4.1)	0.1 (5.5)	−0.1 (4.8)	−0.8 (4.3)	−0.4 (3.9)	0.9 (5.1)	−1.3 (4.7)

[a]There was no statistically significant differences between groups.

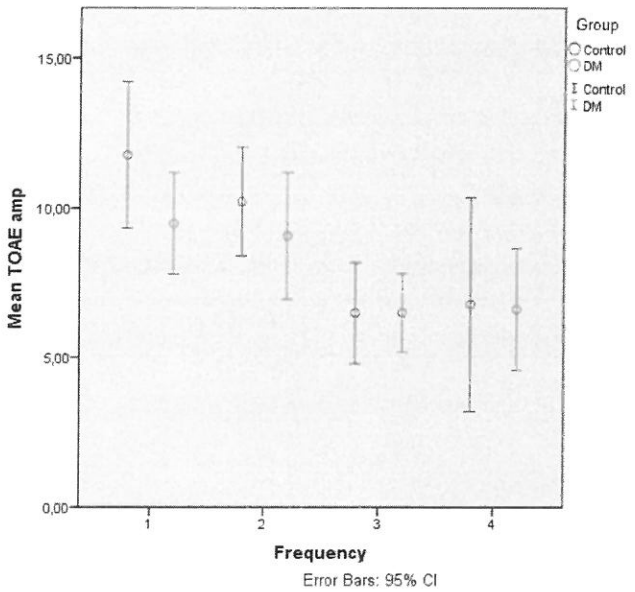

Figure 3. Transient otoacoustic emission levels of the left ears of the patient and control group. The first bar of each frequency represents the control group.

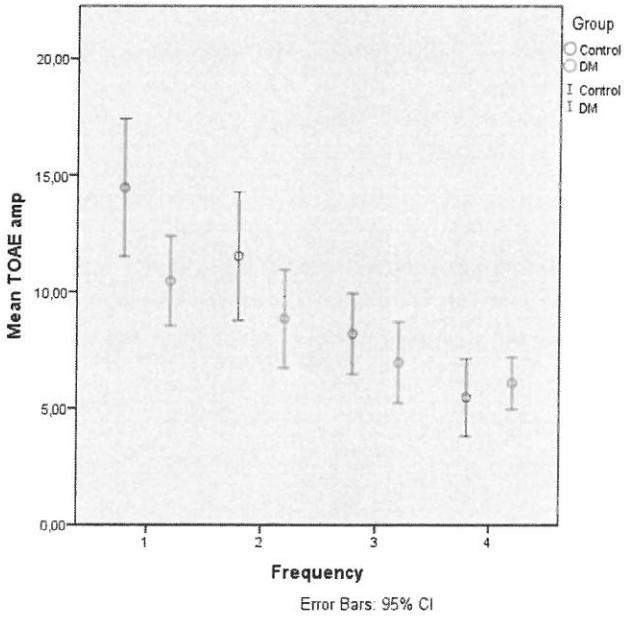

Figure 4. Transient otoacoustic emissions levels of the right ears of the patient and control group. The first bar of each frequency represents the control group.

Ottoviani et al[23] demonstrated a reduction in DPOAEs and TOAE amplitude levels in adults with type 1 diabetes. Their study group consisted of normal-hearing subjects, and they found no relationship between reduction in OAE amplitudes and complications. The major drawback of the study is that the authors did not set up a criterion for valid OAE amplitude levels, which decreases the reliability of the results.

A higher prevalence of evoked OAE compromise has been demonstrated in patients with type 2 diabetes.[18] No association has been found between OAE compromise and diabetic complications. In addition, in this study, the authors demonstrate no significant change in OAE intensities in the acute hyperglycemic state either in the diabetic or control group. An increase in mean SFOAE amplitude levels was observed during hyperglycemia in a study conducted by Jacobs et al.[19] A statistically significant increase in MOC inhibition amplitude was also observed during the hyperglycemic state. A negative correlation between blood glucose levels and both DPOAE and TOAE amplitude levels was found in our study.

In our study, we did not demonstrate a statistically significant decrease in DPAOE or TOAE amplitude levels between diabetic patients and controls. Our results are contrary to those of other studies that report such a decrease in OAE amplitude in diabetic patients.[24,25] Although the current opinion in the literature suggests that the amplitudes of diabetic patients' OAEs levels are significantly lower compared with healthy controls, our results demonstrate that there is no clinical significance between these groups. But our results might have suffered from a type 2 error, and that is the main limitation of our study. In a bigger study group, there might be pronounced difference.

We use a contralateral noise to elicit MOC reflex. The main effect of MOC efferents is to inhibit cochlear responses by decreasing the gain of the cochlear amplifier. The MOC reflex is expected to be suppressive when SOAEs are used. Guinan[14] commented that the most important difficulty with using DPOAEs is that the effect can be in either direction and could change greatly with small changes in stimulus parameters, thereby making a single measurement difficult to interpret. As stated, activation of the MOC system can result in either enhancement of OAEs or suppression of OAEs.[26] In our study group, activation of the

Table 5. Mean (SD) Medial Olivocochlear Reflex Values (Transient Otoacoustic Emissions).[a]

Side	Group	1 kHz	2 kHz	3 kHz	4 kHz
Left	Diabetes mellitus	1.5 (4.3)	−0.6 (4.6)	0.5 (4.4)	−0.5 (3.5)
	Control	3.1 (4.8)	1.8 (3.9)	−0.05 (4.2)	−0.9 (5.2)
Right	Diabetes mellitus	2.2 (5.1)	0.7 (3.6)	−0.2 (5)	−0.2 (3.5)
	Control	0.9 (5.6)	0.3 (5)	0.7 (4.6)	0.3 (2.8)

[a]There was no statistically significant difference between groups.

MOC reflex with DPOAEs revealed suppression and enhancement. We did not detect any compromise in MOC activity (in DPOAEs). In an animal model of diabetes, MOC reflex (in DPOAEs) compromise was demonstrated after the 25th week in rats without any evidence of hearing loss, but DPOAE amplitudes did not change.[27] Contrary to previous studies, we did not demonstrate any statistically significant difference in MOC reflex activity (in TOAEs) between diabetic patients and controls.[15,16]

MOC reflex compromise has been proposed as an early warning for an impending complication of diabetes. In our study, MOC reflex compromise was not detected. We have found no clinically significant difference between diabetic patients and the control group. Studies investigating this relationship have reported confusing results. In an animal study of diabetes, the authors reported a protective role of insulin against MOC reflex compromise,[27] but clinical studies on insulin-dependent diabetic patients did not reveal such protection. The use of the MOC reflex to assess the status of a disease is a difficulty faced by such studies.[27] To permit clinical use of CAS as a test of the human MOC efferent system, further data must be collected to determine the range of normal and expected results for different disorders.

Conclusions

We evaluate the effect of type 2 diabetes on cochlear function in patients without hearing loss. Although we found decreased OAE amplitude levels in diabetic patients, there was no statistically significant difference in OAEs or MOC reflex. Additional studies are needed to evaluate the role of OAEs and MOC reflex in diabetic patients.

Author Contributions

Erdem Eren, substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be published; **Ece Harman**, substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be published; **Seçil Arslanoğlu**, substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be published; **Kazım Önal**, substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be published.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

Supplemental Material

Additional supporting information may be found at http://otojournal.org/supplemental.

References

1. Makishima K, Tanaka K. Pathological changes of the inner ear and central auditory pathway in diabetics. *Ann Otol Rhinol Laryngol*. 1971;80:218-228.
2. Jorgensen MB. The inner ear in diabetes mellitus: histological studies. *Arch Otolaryngol*. 1961;74:373-381.
3. Kariya S, Cureoglu S, Fukushima H, et al. Comparing the cochlear spiral modiolar artery in type-1 and type-2 diabetes mellitus: a human temporal bone study. *Acta Med Okayama*. 2010;64:375-383.
4. Fukushima H, Cureoglu S, Schachern PA, Paparella MM, Harada T, Oktay MF. Effects of type 2 diabetes mellitus on cochlear structure in humans. *Arch Otolaryngol Head Neck Surg*. 2006;132:934-938.
5. Axelsson A, Sigroth K, Vertes D. Hearing in diabetics. *Acta Otolaryngol Suppl*. 1978;356:1-23.
6. Kurien M, Thomas K, Bhanu TS. Hearing threshold in patients with diabetes mellitus. *J Laryngol Otol*. 1989;103:164-168.
7. Colletti V, Fiorino FG, Sittoni V, Bonanni GAuditory evaluation in diabetes mellitus. *Adv Audiol*. 1985;3:121-132.
8. Gibbin KP, Davis CG. A hearing survey in diabetes mellitus. *Clin Otolaryngol*. 1981;6:345-350.
9. Bainbridge KE, Hoffman HJ, Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. *Ann Intern Med*. 2008;149:1-10.
10. Hong O, Buss J, Thomas E. Type 2 diabetes and hearing loss. *Dis Mon*. 2013;59:139-146.
11. Başoğlu MS, Eren E, Aslan H, Bingölballı AG, Oztürkcan S, Katılmış H. Prevention of cisplatin ototoxicity: efficacy of micronized flavonoid fraction in a guinea pig model. *Int J Pediatr Otorhinolaryngol*. 2012;76:1343-1346.
12. Lonsbury-Martin BL, Martin GK. Otoacoustic emissions. *Curr Opin Otolaryngol Head Neck Surg*. 2003;11:361-366.

13. Guinan JJ Jr.Cochlear efferent innervation and function. *Curr Opin Otolaryngol Head Neck Surg*. 2010;18:447-453.
14. Guinan JJ Jr.Olivocochlear efferents: anatomy, physiology, function, and the measurement of efferent effects in humans. *Ear Hear*. 2006;27:589-607.
15. Elbarbary N, El-Kabarity RH, El-desouky ED. Cochleapathy in Egyptian adolescents with type 1 diabetes mellitus. *Int J Pediatr Otorhinolaryngol*. 2012;76:1558-1564.
16. Ugur AK, Kemaloglu YK, Ugur MB, et al. Otoacoustic emissions and effects of contralateral white noise stimulation on transient evoked otoacoustic emissions in diabetic children. *Int J Pediatr Otorhinolaryngol*. 2009;73:555-559.
17. Aladağ I, Kurt S, Eyibilen A, Güven M, Erkorkmaz U. Early evaluation of auditory dysfunction in patients with type 2 diabetes mellitus. *Kulak Burun Bogaz Ihtis Derg*. 2008;18:203-210.
18. Sasso FC, Salvatore T, Tranchino G, et al. Cochlear dysfunction in type 2 diabetes: a complication independent of neuropathy and acute hyperglycemia. *Metabolism*. 1999;48:1346-1350.
19. Jacobs PG, Konrad-Martin D, McMillan GP, et al. Influence of acute hyperglycemia on otoacoustic emissions and the medial olivocochlear reflex. *J Acoust Soc Am*. 2012;131:1296-1306.
20. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36(suppl 1):S67-S74.
21. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39:175-191.
22. McFadden D, Martin GK, Stagner BB, Maloney MM. Sex differences in distortion-product and transient-evoked otoacoustic emissions compared. *J Acoust Soc Am*. 2009;125:239-246.
23. Ottaviani F, Dozio N, Neglia CB, Riccio S, Scavini M. Absence of otoacoustic emissions in insulin-dependent diabetic patients: is there evidence for diabetic cochleopathy? *J Diabetes Complicat*. 2002;16:338-343.
24. Frisina ST, Mapes F, Kim S, Frisina DR, Frisina RD. Characterization of hearing loss in aged type II diabetics. *Hear Res*. 2006;211:103-113.
25. Ren J, Zhao P, Chen L, Xu A, Brown SN, Xiao X. Hearing loss in middle-aged subjects with type 2 diabetes mellitus. *Arch Med Res*. 2009;40:18-23.
26. Eren E, Harman E, Arslanoğlu S, Önal K, Katlmiş H. Does hyperandrogenism affect the otoacoustic emissions and medial olivocochlear reflex in female adults?*Otol Neurotol*. 2013;34:784-789.
27. Wu HP, Guo YL, Cheng TJ, Hsu CJ. Chronological changes in compromised olivocochlear activity and the effect of insulin in diabetic Wistar rats. *Hear Res*. 2010;270:173-178.