The Effects of Hyperinsulinemia on Cochlear Functions

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Abstract

Context: Hyperinsulinemia is the most common metabolic change associated with cochleovestibular diseases. Aim: We aimed to investigate the auditory functions in hyperinsulinemic individuals. Settings and Design: A total of 164 patients were included in this case-control study. While 76 patients with insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR] of ≥2.5) constituted the case group, 88 patients with HOMA-IR values of <2.5 constituted the control group of the study. Material and Methods: The 75 g oral glucose tolerance test, blood biochemistry tests, hormonal analysis, audiological assessment, electrocochleography (EcochG), and transient evoked otoacoustic emissions (TEOAE) testing were performed. Statistical Analysis: One-way analysis of variance and Kruskal–Wallis analysis of variance were used for the comparison of the metabolic and ear parameters in the normal glucose tolerance (NGT), impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) groups. The chi-square test was used to compare nominal variables. Spearman and Pearson correlation coefficients were used for the correlation analyses of continuous variables. Results: The pure tone audiometry at 0.5, 1, 2, and 4 kHz was better in the case group than in the control group. A positive correlation was found between HbA1c and right ear 0.5, 1, 4, and 8 kHz threshold values and left ear 2, 4, 6, and 8 kHz threshold values. A negative correlation was found between HbA1c and speech discrimination scores. The right ear 1.00 and 2.83 kHz TEOAE measurements in the individuals with NGT were found higher than those in patients with IGT, and the 1.42 kHz TEOAE measurements and reproducibility were found higher than those in patients with IFG. The left ear 1.00 and 1.42 kHz TEOAE measurements of the IGT patients were found lower than those of IFG and NGT patients. Conclusion: We showed that hearing was worsening in hyperinsulinemic patients and prediabetic conditions were related to hearing function impairment.

Keywords: Audiometry, Cochlea, HbA1c, hyperinsulinemia, prediabetes

INTRODUCTION

Insulin resistance (IR) is generally defined as a decreased response to normal insulin concentrations. In clinical practice, it is considered as a low glucose response at a certain insulin concentration (endogenous or exogenous).¹² Significant long-term results of IR are the development of type 2 diabetes mellitus (type 2 DM), cardiovascular diseases, obesity, and several malignancies related to IR (colon, breast, endometrial cancers, etc.)³ Hyperinsulinemia and hyperglycemia are the metabolic changes with the highest positive predictive value (96%) in cochleovestibular diseases.⁶⁷

Four basic extracellular potentials exist in the cochlea, which is situated in the inner ear and responsible for hearing: endolymphatic (endocochlear) potential, cochlear microphonics, summation potential (SP), and compound nerve action potential (AP). The electrocochleography...
(EcochG) test, used for monitoring the cochlea and cochlear nerve, can measure three potentials: cochlear microphonic, SP, and AP.\[^5\]

Pure tone audiometry is the most frequently used testing technique in measuring hearing sensitivity. With this technique, the type of hearing loss and the frequencies of hearing loss varying between 250 and 8000 Hz can be determined routinely. There are three types of hearing loss: sensorineural, conductive, and mixed, as a combination of the first two. The impairment of the mechanisms involved in the formation of endolymph or endolymphatic potential due to aging or metabolic causes may result in hearing loss and this is called metabolic hypoacusis.\[^5\]

Otoacoustic emission is defined as the acoustic energy produced by the outer hair cells with active movement in the organ of Corti. Otoacoustic emissions may be recorded spontaneously or evoked.\[^7\] It has been determined that there is a decrease in the otoacoustic emission measurements of type 2 diabetics with hyperinsulinemia.

In this study, we aimed to investigate the effects of hyperinsulinemia, which is the early stage of type 2 diabetes, on inner ear functions using pure tone audiometry, transient evoked otoacoustic emission (TEOAE), and EcochG tests.

**MATERIALS AND METHODS**

This research was designed as a prospective case-control, single-blind clinical study. Among the patients who had been admitted to the outpatient clinics of the Department of Endocrinology and Metabolism of the Başkent University Faculty of Medicine between May 2015 and March 2016, 76 consecutive patients between 18 and 64 years of age with IR [homeostasis model assessment of insulin resistance (HOMA-IR) value of ≥2.5] were enrolled in the case group, and 88 patients with HOMA-IR of <2.5 constituted the control group.

HOMA-IR was calculated using the following formula: [fasting plasma glucose (mg/dL) × fasting insulin level (μU/mL)]/405. Levels of ≥2.5 indicate IR.\[^8-10\]

The patients were grouped as having normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and DM with regard to their responses to the oral glucose tolerance test (OGTT). IFG was defined as fasting blood glucose (FBG) levels between 100 and 125 mg/dL, and IGT was defined as blood glucose levels between 140 and 199 mg/dL 2 hours after administering 75 g of oral glucose.\[^8\] Patients who had levels of HbA1c of ≥6.5% or in the 75 g OGTT, patients with FBG levels of ≥126 mg/dL, and those with second-hour plasma glucose levels of ≥200 mg/dL after confirmation with repeat testing were diagnosed with DM.\[^9\]

Patients with a history of hypertension, thyroid dysfunction, DM, chronic kidney disease, autoimmune or organic hearing loss, Meniere disease, neurodegenerative disorder, history of ear surgery, anatomic ear disorders, noise exposure, hematological or solid organ malignancy, or use of metformin or any other drugs with the potential to influence IR in the last 6 months were not included in the study.

Height, body weight, waist circumference, and right and left arm blood pressure measurements were performed via standard methods by the same physician and recorded. The body mass indices were calculated by dividing body weight (kg) by the square of height (m). Blood pressure was measured with a wall-mounted mercury sphygmomanometer device while the patients were in a sitting position after 30 minutes of resting. Blood pressure measurements were carried out on both arms with 10 minutes between the two measurements. Patients with average blood pressure of 140/90 mmHg or higher were excluded from the study.

**Biochemical examination**

Blood samples were collected from all patients between 08:00 and 10:00 after 8 to 12 hours of fasting. FBG, fasting serum insulin, HbA1c, creatinine, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, thyroid-stimulating hormone (TSH), and free thyroxin (sT4) levels were measured. The patients then consumed 75 g of oral glucose solution and blood samples were taken 30, 60, and 120 minutes later for plasma glucose and insulin levels.

Glucose, creatinine, direct LDL, ultra HDL, and triglyceride kits were processed with the Abbott Architect c8000 device and free T4, TSH, and insulin kits were processed with the Abbott Architect i2000 device. The HbA1c kit was processed immunoturbidimetrically with the Abbott Architect c4000 device (Abbott®, Wiesbaden, Germany).

**Audiological assessment**

Pure tone audiometry, EcochG, and TEOAE tests were performed for all of the patients.

Pure tone air conduction (TDH-39P) and bone conduction audiometry at 125, 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz were tested for all patients, as well as speech audiometry (AC 40, Interacoustics, Assens, Denmark). The speech recognition thresholds of the patients and speech discrimination test scores were assessed. The pure tone averages of 500, 1000, and 2000 Hz frequencies were calculated. Patients diagnosed with conductive hearing loss were excluded from the study.

The otocoustic emission measurements were elicited by presenting nondirectional stimulus at 1.00, 1.42, 2.00, 2.83, and 4.00 kHz (Titan IMP440, Interacoustics, Assens, Denmark).
Among the otoacoustic emission measurements, those with reproducibility rates above 70 were considered significant. The signal-to-noise ratio (SNR) values for both ears were included in the assessment.

EcochG (Audera, GSI, Eden Prairie, MN, USA) measurements were elicited by presenting a 95 dB nHL click stimulus with an external auditory canal electrode (gold tip trode electrode, 10 mm, Sanibel Supply, Assens, Denmark). Patients with SP, or AP ratios of $\geq 0.50$, were considered to have cochlear hydrops, while individuals with ratios of $< 0.50$ were considered normal.

**Statistical analysis**

In the descriptive statistics for the continuous data, the mean, standard deviation, median, and minimum and maximum values were presented, and percentage values were presented for discrete data.

For the comparison of data obtained via measurements between case and control groups, the conformity of the data to normal distribution was tested using the $t$ test and the Mann–Whitney U test. One-way analysis of variance and Kruskal–Wallis analysis of variance were used for the comparison of the metabolic and ear parameters in the NGT, IFG, and IGT groups. The chi-square test was used to compare nominal variables. Spearman and Pearson correlation coefficients were used for the correlation analyses of continuous variables.

For the assessment of differences among nominal variables (sex, glucose, 60th minute glucose, and NGT/IFG/IGT), the $t$ test, Mann–Whitney U test, Kruskal–Wallis analysis of variance, and one-way analysis of variance were used. SPSS 11.5 software (SPSS Inc., Chicago, IL, USA) was used for the calculations and $P < 0.05$ was considered as the limit for statistical significance.

**RESULTS**

A total of 185 patients were initially included in the study. Twenty-one patients were excluded (11 patients were diagnosed with DM, five patients had conductive hearing loss, five patients were lost to follow up for audiologic examination), 76 patients (46.3%) with HOMA-IR levels equal to or higher than 2.5 constituted the case group, and 88 patients (53.7%) with HOMA-IR levels below 2.5 constituted the control group.

There were 39 women in the case group and 56 women in the control group. The sex distributions of the case and control groups were similar ($P = 0.11$). It was found that 96.1% of the individuals in the case group and 98.9% of the control group were younger than 60 years. The mean age was $38.51 \pm 10.28$ years for the case group and $38.81 \pm 9.40$ for the control group ($P > 0.05$). Furthermore, 87.5% of the individuals in the control group and 81.7% in the case group were younger than 50 years. Ages of 50% of the individuals in the control group and 59.3% in the case group were under 40 years (Figure 1).

The mean waist circumference, body mass index, HbA1c, LDL, and triglyceride levels were determined to be higher in the case group compared to the control group, and the mean HDL level was lower [Table 1].

The number of patients with first-hour post-glucose load plasma glucose level of $\geq 155$ mg/dL was higher in the case group than the control group [Table 1].

A statistically significant difference was found between hearing levels in the groups for the right ear at 500, 1000, 2000, and 4000 Hz and for the left ear at 500, 1000, 2000, 4000, and 8000 Hz (for the right ear $P < 0.001$, $P = 0.002$, $P = 0.001$, and $P = 0.006$, respectively, and for the left ear $P < 0.001$, $P = 0.003$, $P = 0.001$, $P < 0.001$, and $P = 0.044$, respectively). Hearing levels (dBHL) were found lower in the case group than the control group. However, there was no
In all patients, a positive correlation was detected between HbA1c levels and hearing levels for the right ear at 500, 1000, 2000, 6000, and 8000 Hz; thus, any suspicion of presbycusis was eliminated.[11]

Table 1: Comparison of the biochemical parameters of the case and control groups

|                      | Case                | Control              | P       |
|----------------------|---------------------|----------------------|---------|
|                      | Mean ± SD/N (%)     | Mean ± SD/N (%)      |         |
| Waist circumference (cm) | 99.69 ± 10.81     | 90.30 ± 12.74        | <0.001  |
| BMI (kg/m²)          | 32.95 ± 5.05       | 29.02 ± 5.11         | <0.001  |
| HOMA-IR              | 3.76 ± 1.26        | 1.73 ± 0.46          | <0.001  |
| HbA1c (%)            | 5.42 ± 0.35        | 5.23 ± 0.29          | <0.001  |
| HDL (mg/dL)          | 44.03 ± 9.78       | 49.62 ± 13.08        | 0.004   |
| LDL (mg/dL)          | 129.63 ± 35.74     | 124.69 ± 35.33       | 0.248   |
| Triglyceride (mg/dL) | 154.76 ± 87.35     | 103.36 ± 56.18       | <0.001  |
| NGT                  | 52.6               | 7.9                  | 0.01    |
| IFG                  | 28.9               | 19.3                 | 0.01    |
| IGT                  | 6.6                | 4.5                  | 0.01    |
| 60th minute glucose  |                     |                      |         |
| <155 mg/dL           | 53.9               | 77.3                 | 0.002   |
| ≥155 mg/dL           | 46.1               | 22.7                 | 0.002   |

BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; NGT, normal glucose tolerance; SD, standard deviation.

The left ear 250 and 4000 Hz audiometry threshold values of patients with NGT were detected to be significantly lower than those of the patients with IFG and IGT (P < 0.05), whereas the 2000, 6000, and 8000 Hz threshold values were significantly lower than those of the patients with IGT (P < 0.05) [Figure 2]. The left ear speech discrimination scores of the patients with NGT were lower than the scores of the patients with IGT (P < 0.05).

**DISCUSSION**

In our study, it was shown that the hearing levels at 0.5 to 8 kHz frequencies among patients with NGT were lower than the levels of patients with IFG and IGT. Similarly, it was found that the NGT group scored better in the TEOAE testing than the prediabetes groups did (IFG and IGT). Moreover, these differences were also present when the parameters were considered separately for both ears and for both groups of patients.

In our study, no significant difference between the case and control groups could be attributed to sex distribution or average age, and a homogeneous distribution was obtained. Only four patients (three from the case group and one from the control group) included in the study were older than 60 years. In order to determine whether these four patients had age-related presbycusis, the pure tone averages for both ears of those patients were compared to the ISO (International Organization for Standardization) 7029 standard values for the age range of 60-64 years and they were found to be below the median values; thus, any suspicion of presbycusis was eliminated.[11] Horikawa et al.[12] showed that the prevalence of hearing loss is 2.1 times higher in diabetic individuals than nondiabetics. It is known that aging plays a role in the development of both DM and hearing impairment. The possibility of aging affecting hearing functions should not be overlooked. However, their review supported the idea that diabetes-
related hearing loss is independent of aging. Our study was conducted with a relatively young to middle-aged group and showed that hearing function impairments developed in prediabetic individuals independently of aging.

The results of another review indicated that type 2 DM had a substantial relation with hearing loss. However, the contribution of DM to moderate and severe hearing loss could not be clarified. This is an important issue since mild hearing loss does not require any aggressive clinical treatment, contrary to moderate and severe hearing loss. However, the mild hearing loss observed in diabetes might easily deteriorate due to external factors such as noise exposure. If prediabetes is effective in the loss of hearing functions, it should be determined, the required precautions should be taken, and hearing functions should be checked periodically.

Fowler et al. showed in a study of monkeys that hearing functions were reduced in hyperinsulinemia, which is a prediabetic stage. In our study, the auditory brainstem response (BERA) test was not conducted. Audiological assessment was performed at 250 and 500 Hz and 1, 2, 4, 6, and 8 kHz frequencies; speech discrimination tests were administered for auditory perception; and TEOAE testing was conducted for assessing outer hair cell functions. It was found that hyperinsulinemia particularly affected the pure tone audiometry results, and the SNR values in TEOAE for the right and left ears showed similarity between the case and control groups. However, when the TEOAE measurements were examined in three separate groups with regard to glycemic level among the hyperinsulinemic group as NGT, IFG, and IGT, it was observed that the cochlear outer hair cell function loss was significantly higher in individuals with dysglycemic conditions accompanying hyperinsulinemia.

Angeli et al. investigated the effect of acute hyperinsulinemia on the cochlea in sheep and showed with EcochG that cochlear functions were inhibited in hyperinsulinemia. In another study examining the effects of acute hyperinsulinemia in sheep with distortion product otoacoustic emission (DPOAE) testing, it was demonstrated that hyperinsulinemia was effective in cellular electrophysiology even in the acute phase, even though it had not been long enough to cause endolymphatic hydrops. In our study, on the other hand, the cochlear functions were investigated in subjects with prediabetic conditions and hyperinsulinemia together with NGT. The case and control groups were compared in both an intragroup and an intergroup manner, but no difference was found in the electrocochleographic examination for both right and left ears. The hearing function impairment observed at frequencies above 1500 Hz in hyperinsulinemia was supported with pure tone audiometry in our study.

In the present study, the HbA1c value and pure tone audiometry thresholds were compared to examine any possible effect of chronic hyperinsulinemia on cochlear functions. Positive correlations were found between HbA1c and the measurements at 500, 1000, 4000, and 8000 Hz for the right ear and the measurements at 2000, 4000, 6000, and 8000 Hz for the left ear. It was shown that the thresholds at 4000, 6000, and 8000 Hz in pure tone audiometry for both right and left ears had increased significantly in individuals with HbA1c of ≥5.7%. When these data and the International Expert Committee classification on HbA1c are taken as a basis, it can be argued that the increase is more significant in hearing thresholds in pure tone audiometry in individuals with high potential for diabetes development. Similar to our results, in a study by Kang et al., an increased risk of hearing loss was shown in the group with moderate and high HbA1c levels compared to the group with low HbA1c levels using pure tone audiometry. In 2008, Hirose claimed that high concentrations of glucose in the endolymph, through
diffusion related to the elevated plasma glucose levels, would cause cochlear impairment. Contrary to our study, they reported HbA1c to be the parameter showing the weakest correlation with hearing thresholds.

In the study of Hong and Kang\[20\] on mice, although there was hearing nerve dysfunction related to hyperglycemia, it was found that there was also functional impairment in central auditory pathways and cochlear outer hair cells due to IR-induced hyperinsulinemia in type 2 DM. In our study, TEOAE testing was conducted to test the outer hair cell functions. However, BERA and central auditory pathway assessments were not conducted separately. Instead, the sensorial and neural pathways were assessed together using pure tone audiometry. Speech discrimination scores were used in the suprasegmental assessment of hearing. In particular, the comparisons on the basis of HbA1c levels demonstrated that the speech discrimination scores for both ears were significantly lower in the case group than the control group. Accordingly, it may be interpreted that the chronic effects of dysglycemic conditions may affect the central auditory processing and perception negatively. This needs to be proved with studies using objective central pathway assessment tests.

When all patients were grouped as NGT, IFG, and IGT and their EcochG-SP/AP measurements were considered, no differences were detected for either the right or the left ear. Similarly, there was no difference among NGT, IFG, and IGT groups with regard to the <0.50 and ≥0.50 limit values of the EcochG-SP/AP ratio for the left and right ears. It is known that EcochG measurements using external auditory canal electrodes do not yield reliable results. The EcochG method has low sensitivity in SP/AP ratio assessment and especially high specificity in cochlear hydrops diagnosis.\[21\] The contribution of EcochG is probably limited in indicating metabolic cochlear disease, unless cochlear hydrops has developed, and based on our findings, we believe that it is not beneficial to use it as a cochlear imaging test in hyperinsulinemia, one of the early diabetic stages. In our study, the chronic effects of hyperglycemia and hyperinsulinemia on the cochlea were presented. It was shown by Ryu et al.\[22\] that hyperglycemia could have an effect on the recovery of sudden idiopathic hearing loss. In this study, with a design similar to ours, the comparative assessment of individuals with impaired glucose disturbances such as prediabetic conditions and diabetes revealed significantly better treatment responses in the normoglycemic group.\[22\]

In a study by Horner\[23\] of induced hydrops in guinea pigs, effects on outer hair cells were seen at the apical turn of the cochlea and caused separation in neural connections, but the outer hair cells at the basal turn of the cochlea were intact. This could be explained by the cochlea protecting its basal turn, where more medial fibers end. The results of that study show similarities to the results of our study, and the elevated impairment especially in the medium frequencies in the audiological assessment in our study could be explained by this mechanism.

The female predominance of our study population may imply that the study represented men less. Due to the limited number of participants (n = 164), the validation of the findings of our study with larger populations would contribute to the generalizability of the data obtained. The balanced age distribution in the case and control groups, the exclusion of patients with hypertension, and the enrollment of a generally younger population enabled us to remove possible confounders and thus probably increased the reliability of the results.

Although the sensorial cell and cochlear neuron loss observed at the basal coil of the cochlea due to age-related hearing loss lowers the reliability of studies with older diabetic patients, age-related presbycusis was eliminated in our study by including patients based on the international standards for presbycusis thresholds. Therefore, we think that the reliability of pure tone audiometry is high in our study.

The euglycemic insulin clamp technique, the gold standard method for calculating IR, was not used in the present study due to difficulties in practicability. This might have influenced the sensitivity and authenticity of the results obtained.

Administration of EcochG as the only electrophysiological assessment limits the possibility of supporting our study with more objective data. The EcochG test plays an important role in the differential diagnosis of endolymphatic hydrops and metabolic ear diseases, and the difference found between the case group and the control group in our study supported this fact. However, the EcochG test could not provide sufficient information as it is not certain whether metabolic exposure could cause hydrops or not.

Although high-frequency audiometry was not performed in our study, significant findings were obtained in the 1.125 to 8 kHz range in hyperinsulinemic and especially dysglycemic individuals. Also, since acoustic trauma exposure, especially exposure over 4 kHz, would decrease the strength of the study, patients with unilateral hearing loss and with noise exposure history were excluded and this risk was reduced substantially.

Although the audiological assessments were conducted under optimal conditions for all patients, the administration of the TEOAE and EcochG measurements in a room without sound isolation decreased the reliability of these tests. The TEOAE testing was preferred instead of DPOAE in our study since it is a practice in clinical studies.

**CONCLUSION**

Our study shows that prediabetic conditions (IFG and IGT) are associated with hearing function impairment before hearing loss occurs.

In dysglycemic conditions, the TEOAE, pure tone audiometry, and speech discrimination scores yield
significant findings, and they can be used clinically for hearing screening in prediabetic patient groups.

Strategies intended to reduce hyperinsulinemia and to prevent diabetes may help to ameliorate hearing dysfunctions, and it is seen that further studies in this respect are required.

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This study was approved with Decision No. 15/18 dated 08/05/2015 by the Başkent University Faculty of Medicine’s Clinical Research Ethics Committee (Project No: KA15/124).

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent
Oral and written informed consent was obtained from all individual participants included in the study.

Data Availability Statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflicts of interest
There are no conflicts of interest.

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