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Severity of hearing impairment is positively associated with urine albumin excretion rate in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: To identify risk factors for hearing impairment among patients with type 2 diabetes mellitus.

Methods and Materials: A total of 68 patients with type 2 diabetes were enrolled between March and September of 2011. Pure-tone auditory tests were carried out for each patient at the following speech frequencies: 250; 500; 1,000; 2,000; 4,000 and 8,000 Hz. Participants were classified as having hearing impairment if the average of the pure-tone thresholds measured at 500, 1000 and 2000 Hz in either ear exceeded 25 dBHL. Demographic, anthropometric, clinical, and laboratory parameters and diabetes-associated complications were analyzed.

Results: Patients were divided into those with (n = 32) and without (n = 36) hearing impairment. Hearing impaired participants had a higher urine albumin-to-creatinine ratio than those without (223.1 vs 56.5 mg/g, respectively). After adjustment for age, sex and other risk factors, the urine albumin-to-creatinine ratio remained significantly associated with hearing impairment (odds ratio 9.07, 95% confidence interval 1.73–47.43, P = 0.009). There were no significant differences in oxidative stress between the two groups.

Conclusions: The present study showed increased albuminuria was positively associated with the severity of hearing impairment among patients with type 2 diabetes. Screening for hearing impairment in diabetic patients who develop albuminuria might provide early detection of hearing impairment.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that can lead to vascular and neurological degeneration. Hearing function depends on the health of small blood vessels and nerves that are affected by high blood sugar levels. Additionally, hyperglycemia could activate oxidative stress that could also affect hearing function. Thus, patients with type 2 diabetes might be more likely to experience hearing problems than healthy individuals[1]. Some studies have reported that diabetes patients have greater high-frequency hearing loss than those without diabetes[2–5], whereas others showed the same observation for low frequency hearing[6]. The most convincing of these reports is a recent study of 5,742 participants in the National Health and Nutrition Examination survey by Bainbridge *et al.*[7], who found that patients with diabetes showed greater hearing loss than non-diabetes patients.

Differences between type 2 diabetic patients with vs those without hearing loss have not been established. Furthermore, the association between oxidative stress and auditory system had not been clearly elucidated. Thus, the aim of the present study was to identify factors related to hearing impairment among type 2 diabetes patients. Additionally, we sought to examine the association between oxidative stress and hearing impairment.

METHODS

Study Population

The study enrolled 68 type 2 diabetes patients who attended the metabolism outpatient clinic at Kaohsiung Chang Gung

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Memorial Hospital between March and September 2011. Demographic and anthropometric variables, laboratory data and diabetes-related complications were recorded. Diagnosis of type 2 diabetes was based on the World Health Organization criteria[8]. The Human Research Ethics Committee of Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, approved this study. Informed consent was obtained from each patient.

Clinical and Serum Biochemical Analyses

Anthropometric measures were assessed by trained observers. Weight and height were measured with the participants wearing light clothing and no shoes. Waist circumference was assessed at the mid-point between the lowest rib and the iliac crest[9]. The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m)[9].

Venous blood samples were collected for measurements of fasting glucose, glycosylated hemoglobin (HbA_{1c}), serum total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, creatinine, insulin and high-sensitivity C-reactive protein (hs-CRP). hs-CRP was measured by the cardiophase high-sensitivity nephelometric method (Dade Behring, Marburg, Germany) using a Behring Nephelometer II Analyzer. The lowest hs-CRP detection limit was <0.15 mg/L. In our laboratory, mean intra-assay coefficients of variance were <3.5%. Creatinine concentrations in serum and urine were determined by the Jaffe method utilizing a Wako Creatinine-Test (Wako Pure Chemicals, Osaka, Japan).

The concentration of 8-hydroxydeoxyguanosine (8-OH-dG) was determined by using a competitive enzyme-linked immunosorbent assay (ELISA) kit (high sensitive 8-OHdG Check; Japan Institute for the Control of Aging, Shizuoka, Japan) according to the manufacturer's instructions.

Assessment of Albuminuria and Renal Function

Albumin excretion rate (AER) was determined by measuring the urine albumin-to-creatinine ratio (UACR) in spot urine. The abbreviated Modification of Diet in Renal Disease (MDRD) Study Group equation was used to calculate the estimated glomerular filtration rate (eGFR): eGFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × 0.742 (if female)[10]. Urine albumin concentrations were determined by immunonephelometry (Dade-Behring, Marburg, Germany).

Assessment of Hearing Impairment

Pure-tone air- and bone-conduction auditory tests were carried out for each ear using a clinical audiometer with insert earphones at the following speech frequencies: 250; 500; 1,000; 2,000; 4,000; and 8,000 Hz. Participants were classified as having hearing impairment if the average of the pure-tone thresholds (PTA) measured at 500, 1,000 and 2,000 Hz exceeded 25 dBHL in either ear.

Statistical Analysis

Continuous data are expressed as means with standard deviations, and categorical data are expressed as numbers and percentages. An independent *t*-test was used for comparing continuous variables, and the χ^2-test was used for comparing categorical variables between patients with and without hearing impairment. A *P*-value of <0.05 was considered to be statistically significant. A linear regression analysis was carried out to analyze the association between hearing loss level and metabolic parameters. Logistic regression analysis was applied to examine whether hearing loss was associated with UACR levels. Three separate logistic regression models were applied: an unadjusted model; a model adjusted for age and sex (model 1); and a model adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, Hs-CRP, HbA_{1c}, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride and eGFR (model 2). Results of the linear regression analyses are expressed as an odds ratio (OR) with a 95% confidence interval (CI). All statistical analyses were carried out using SPSS version 17 (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 68 participants in the study, 32 (47.1%) had hearing impairment and 36 (52.9%) did not. Table 1 summarizes the demographic, anthropometric, and clinical and laboratory parameters of the participants stratified by hearing status. Participants with impaired hearing had a higher UACR level than those without (223.1 vs 56.5 mg/g, respectively). No significant intergroup differences were found with regard to age, sex, BMI, hypertension, HbA_{1c}, lipid profiles and serum hs-CRP.

As shown in Table 2, logistic regression analysis using an unadjusted model determined that every increment of log UACR was associated with an increased odds of having hearing impairment (OR 3.32, 95% CI 1.30–7.56, $P = 0.001$). After adjusting for age and sex (model 1), the association between log UACR and the presence of hearing loss remained significant (OR 3.26, 95% CI 1.31–8.12, $P = 0.011$). In model 2, the OR was 9.07 (95% CI 1.73–47.43, $P = 0.009$) after further adjustment for BMI, serum creatinine, eGFR, HbA_{1c}, lipid profile, hs-CRP and blood pressure.

When the level of hearing loss (dB) was analyzed as a continuous variable, it was positively correlated with UACR and serum creatinine, but negatively correlated with eGFR in a simple linear regression analysis, and after control for age and sex (Table 3). The levels of 8-OH-dG were not correlated with level of hearing loss (dB).

DISCUSSION

Several prior studies concluded that type 2 diabetic patients have worse hearing by comparison with healthy individuals[7,11,12]. However, the difference in hearing impairment among type 2 diabetic patients has not been well delineated. The present report is one of a limited number of studies to compare differences between type 2 diabetic patients with hearing

Table 1 | Characteristics of patients with and without hearing impairment

n	No hearing impairment 36	Hearing impairment 32	*P*-value
Sex (male/female)	21/25	18/14	1.00
Age (years)	60.3 ± 10.2	63.8 ± 8.3	0.12
Diabetes duration (years)	5.8 ± 5.5	7.7 ± 5.6	0.17
BMI (kg/m^2)	26.6 ± 3.2	26.4 ± 4.4	0.84
Waist circumference (cm)	91.4 ± 7.4	91.2 ± 11.2	0.91
UACR (mg/g)	56.5 ± 144.6	223.1 ± 446.6	0.038
Log UACR	1.32 ± 0.51	1.74 ± 0.71	0.006
HbA_{1c} (%)	7.0 ± 0.7	7.4 ± 1.2	0.11
Blood lipid profile (mg/dL)			
Total cholesterol	164.0 ± 38.1	166.8 ± 34.3	0.75
HDL cholesterol	51.8 ± 11.8	56.6 ± 14.0	0.13
LDL cholesterol	92.5 ± 34.7	93.5 ± 31.3	0.90
Triglyceride	145.7 ± 84.6	147.2 ± 82.1	0.94
Serum creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.4	0.07
eGFR (mL/min per 1.73 m^2)	85.2 ± 18.2	75.7 ± 24.1	0.07
hsCRP (mg/L)	2.3 ± 2.3	2.5 ± 3.2	0.70
Systolic blood pressure (mmHg)	139 ± 18	143 ± 23	0.45
Diastolic blood pressure (mmHg)	73 ± 15	77 ± 12	0.20
Metabolic syndrome (%)	44.4	53.1	0.63
Hypertension (%)	45.5	57.1	0.47
8-OH-dG (ng/mL)	2.04 ± 0.37	2.03 ± 0.38	0.891

Data are presented as *n*, mean ± standard deviation or %. 8-OH-dG, 8-hydroxydeoxyguanosine; BMI, body pass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; UACR, albumin-to-creatinine ratio.

Table 2 | Logistic regression of log albumin-to-creatinine ratio and the presence of hearing impairment in patients with type 2 diabetes

Regression models	Odds ratio	*P*-value
Unadjusted model	3.32 (1.30–7.56)	0.011
Model 1	3.26 (1.31–8.12)	0.011
Adjusted for age and sex		
Model 2	9.07 (1.73–47.43)	0.009
Adjusted for age, sex, BMI, systolic BP, diastolic BP, hs-CRP, HbA_{1c}, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, creatinine and eGFR		

BMI, body mass index; BP, blood pressure; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Table 3 | Linear regression analysis of the association between metabolic parameters and severity of hearing loss (dB)

	Standard regression coefficient	*P*-value	Standard regression coefficient*	*P*-value
UACR	0.501	<0.001	0.496	<0.001
HbA_{1c}	0.075	0.542	0.083	0.493
Diabetes duration	0.246	0.050	0.235	0.059
Serum creatinine	0.353	0.003	0.361	0.003
eGFR	–0.365	0.002	–0.328	0.006
8-OH-dG	–0.149	0.225	–0.118	0.342

*Values were adjusted for age and sex. 8-OH-dG, 8-hydroxydeoxyguanosine; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; UACR, urinary albumin-to-creatinine ratio.

impairment and those without. The main finding of the present study was that hearing loss in patients with type 2 diabetes is positively associated with UACR, even after adjustment for age, sex and other confounding factors. Indeed, the prevalence of hearing impairment was up to 47.1% in patients with type 2 diabetes mellitus in the present study. In concert with our finding, Chen *et al.*[13] reported the prevalence of hearing impairment among adults without diabetes aged 25–69 years did not show a significant change from 1971 to 2004 (46.4–48.5%). Furthermore, another study showed that approximately 59% of patients with non-insulin dependent diabetes mellitus (NIDDM) had hearing impairment[11].

As the cochlea is highly microvascular and considered vulnerable to the effects of hyperglycemia, the hearing loss associated with diabetes is theorized to be attributed to microangiopathy. Some authors have reported that hearing impairment was associated with vessel wall thickening or atrophy of the stria vascularis[14,15]. Other studies have shown basement membrane thickening consistent with diabetic microangiopathy in insulin-dependent diabetic rats, but not in non-diabetic rats[16]. Additionally, others have found that diabetic sensorineural hearing loss results from microangiopathic changes in the endolymphatic sac and/or basilar membrane vessels[17]. Hearing impairment has also been associated with chronic kidney disease or diabetic nephropathy. For instance, Dalton *et al.*[11] reported that individuals with type 2 diabetes and nephropathy were more likely to have hearing loss than those with diabetes, but free of nephropathy (OR 2.28, 95% CI 1.04–5.00). Finally, Kakarlapudi *et al.*[18] found that creatinine levels were associated with the severity of hearing loss in a very large cohort of chart reviews of diabetic patients.

Diabetic nephropathy, the major microvascular complication of diabetes, is characterized by a global involvement of glomeruli, which contains various types of renal cells, the vasculature and tubulointerstitium. Increased urinary albumin excretion is an important early clinical manifestation of diabetic nephropathy[19,20]. The positive association between the presence of hearing loss and increased UACR in the present study provides

further support for microangiopathy as the possible cause of hearing loss in type 2 diabetes.

Diabetes results in increased oxidative stress. Research over the past few decades has shown that elevated oxidative stress plays an important role in the pathogenesis of diabetic complications[21–23]. Although oxidative stress was seldom considered a potential cause of hearing loss in type 2 diabetic patients, Aladag *et al.*[24] reported that oxidative stress might play an important role in hearing impairment in patients with type 2 diabetes. Specifically, higher levels of serum protein oxidation products, nitric oxide and enzymatic anti-oxidant activity were found in a group of 63 patients with type 2 diabetes compared with a control group of 37 participants. 8-OH-dG has often been used as a biomarker of oxidative deoxyribonucleic acid damage in relation to diabetes mellitus[25,26]. In the current study, however, hearing impairment was not associated with 8-OH-dG among patients with type 2 diabetes. There are some possible explanations for this difference. First, this different result could be as a result of the different marker of oxidative stress we used. It is possible that hearing impairment is related to some oxidative stress markers. Second, the formation of free radicals is related to the presence of high glucose levels. In the present study, however, the level of HbA_{1c} was not different between patients with or without hearing impairment. Third, the difference in blood glucose variability might be the possible reason, as glucose fluctuations showed a more specific triggering effect on oxidative stress[27]. Further studies are required to improve our understanding of the exact role of oxidative stress in this process and possible ways to prevent it.

The evidence that duration of diabetes is associated with the likelihood of hearing impairment is inconclusive. Some studies showed that the duration of diabetes is a risk factor for the incidence of hearing impairment in patients with diabetes[6,28], but other studies showed that the duration of diabetes had little effect on it[11,29]. In the present study, although it did not reach statistical significance, patients with hearing impairment had longer duration of diabetes than those without. In addition, the association between the duration of diabetes and severity of hearing loss bordered on a statistically significant value ($P = 0.05$) under linear regression analysis. Thus, further large-scaled studies are required to discover the role of the duration of diabetes on the impairment of hearing loss.

There was no association between glycemic control, as assessed by HbA_{1c} levels, and hearing loss in the present study, which is consistent with some previous reports[11,30]. It is unlikely that a single HbA_{1c} measurement concurrent with the hearing evaluation would be associated with hearing loss, because this outcome represents the average glucose control over the preceding 2–3 months. Accordingly, more longitudinal studies are necessary to evaluate the long-term effects of glycemic control on hearing impairment in type 2 diabetic patients.

The present study had a number of limitations that warrant mention. First, we did not collect individual histories of noise exposure. The difference in individual noise exposure could confound the association between diabetes and hearing loss. Second, as this was a cross-sectional study, we could not establish a cause-effect relationship. Further longitudinal studies are necessary to confirm the association between hearing loss and albuminuria in type 2 diabetic patients. Nevertheless, the findings of the present study might still serve as a reference for clinicians to assess the relationship between hearing impairment and albuminuria in patients with type 2 diabetes. Awareness of the elevated risk of developing hearing impairment for diabetic patients with elevated albuminuria would prompt the early detection of hearing impairment.

In conclusion, the present results suggest that increased UACR, but not oxidative stress, was correlated with hearing loss in patients with type 2 diabetes mellitus. Additionally, the severity of hearing loss was associated with worsening renal function and increasing UACR.

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