Potential Mediators of Diabetes-Related Hearing Impairment in the U.S. Population

National Health and Nutrition Examination Survey 1999–2004

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OBJECTIVE — We examined potential mediators of the reported association between diabetes and hearing impairment.

RESEARCH DESIGN AND METHODS — Data come from 1,508 participants, aged 40–69 years, who completed audiometric testing during 1999–2004 in the National Health and Nutrition Examination Survey (NHANES). We defined hearing impairment as the pure-tone average >25 decibels hearing level of pure-tone thresholds at low/mid (500, 1,000, and 2,000 Hz) and high (3,000, 4,000, 6,000, and 8,000 Hz) frequencies. Using logistic regression, we examined whether controlling for vascular or neuropathic conditions, cardiovascular risk factors, glycemia, or inflammation diminished the association between diabetes and hearing impairment.

RESULTS — Diabetes was associated with a 100% increased odds of low/mid-frequency hearing impairment (odds ratio 2.03 [95% CI 1.32–3.10]) and a 67% increased odds of high-frequency hearing impairment (1.67 [1.14–2.44]) in preliminary models after controlling for age, sex, race/ethnicity, education, smoking, and occupational noise exposure. Adjusting for peripheral neuropathy attenuated the association with low/mid-frequency hearing impairment (1.70 [1.02–2.82]). Adjusting for albuminuria and C-reactive protein attenuated the association with high-frequency hearing impairment (1.54 [1.02–2.32] and 1.50 [1.01–2.23], respectively). Diabetes was not associated with high-frequency hearing impairment after controlling for A1C (1.09 [0.60–1.99]) but remained associated with low/mid-frequency impairment. We found no evidence suggesting that our observed relationship between diabetes and hearing impairment is due to hypertension or dyslipidemia.

CONCLUSIONS — Mechanisms related to neuropathic or microvascular factors, inflammation, or hyperglycemia may be mediating the association of diabetes and hearing impairment.

Diabetes Care 33:811–816, 2010

Diabetes is associated with hearing impairment in population-based studies (1,2). Diabetes-related hearing impairment has been described as sensorineural in origin, implying that the lesion may be cochlear or of the eighth cranial nerve, but evidence favoring a specific mechanism is insufficient and contradictory (3). One possibility is that microvascular changes, which often lead to nephropathy and retinopathy, also affect the cochlear vasculature. Thickened basilar membranes and capillaries of the stria vascularis and atherosclerotic narrowing of the internal auditory artery were found among autopsied people who had diabetes but not in people without diabetes (4,5). Diabetes is also associated with neuropathic and peripheral artery complications that contribute to diabetic foot ulcers (6). Atrophy of the spiral ganglion and demyelination of the eighth cranial nerve among autopsied diabetic patients suggest a neurological etiology to diabetes-related hearing impairment (5). Regardless of whether the primary lesion is angiopathic or neuropathic, hyperglycemia may contribute (7).

Cardiovascular disease, hypertension, and other cardiovascular risk factors are associated with hearing impairment (8–10). Because people with diabetes have a greater risk of these conditions than those without diabetes (11,12), the relationship between diabetes and hearing impairment may be attributable to a greater prevalence or severity of cardiovascular factors.

Establishing effective interventions to disrupt the pathogenesis of diabetes-related hearing impairment will depend on understanding the mechanisms. This investigation studies potential mediators of the relationship between diabetes and hearing impairment. Specifically, we examine whether the presence of vascular or neuropathic conditions, cardiovascular risk factors, glycemia, or a marker of inflammation explain the association between diabetes and hearing impairment.

RESEARCH DESIGN AND METHODS

— Data come from the National Health and Nutrition Examination Survey (NHANES) collected during 1999–2004, which used a complex, multistage, probability sample designed to be representative of the civilian, noninstitutionalized U.S. population (13). Of 3,192 study participants aged 40–69 years who were randomly assigned to audiometric testing, 2,847 (89.2%) completed the audiometric examination. One-half of the sampled subjects (n = 1,425) was also randomly assigned to attend the examination during the morning session after an overnight fast. Of those, 1,321 subjects (92.7%) could be classified as to whether they had diabetes either by reporting a diagnosis (n = 175) or by having valid plasma glucose measures after fasting 8–24 h (n = 1,146). Another 187 subjects who reported diagnosed diabetes and whose audiometric examination occurred in the afternoon or evening were

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Received 30 June 2009 and accepted 13 January 2010. Published ahead of print at http://care.diabetesjournals.org on 22 January 2010. DOI: 10.2337/dc09-1193.

added to the sample, yielding an analytical sample of 1,508.

Pure-tone audiometry signals were presented to each ear at varying intensities until the threshold at which the participant was just able to perceive the tone was identified. Higher thresholds indicate greater hearing impairment. Pure-tone air conduction hearing thresholds in decibels hearing level (dB HL) were obtained for each ear at 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz by trained audiometric technicians using audiometric equipment and methods that have been described (1,13).

Participants were classified as having low/mid-frequency hearing impairment if the average of pure-tone thresholds (hereafter referred to as pure tone average) measured at 500, 1,000, and 2,000 Hz in the worse ear exceeded 25 dB HL. High-frequency hearing impairment was defined as the pure-tone average measured at 3,000, 4,000, 6,000, and 8,000 Hz in the worse ear exceeding 25 dB HL. The pure-tone average in the worse ear was used to classify participants as having impairment in at least one ear. We identified 14 participants with at least one audiometric nonresponse (tone not perceived). Given that the average of these participants' available pure-tone thresholds exceeded 25 dB HL, we classified these participants as impaired at the frequency range within which the audiometric nonresponse occurred.

During in-home interviews, demographic characteristics and a medical history were obtained (13). We defined coronary heart disease as a positive response to any of three questions asking whether a doctor had told them they have coronary heart disease, angina, or had had a heart attack. Of participants who reported smoking at least 100 cigarettes in their lifetime, those who answered affirmatively to "do you smoke now?" were classified as current smokers. Occupational noise exposure was defined as a history of loud noise at work that required speaking in a loud voice.

Anthropometric and clinical measures were obtained during physical examinations that included a blood draw and urine collection (13). Participants were identified as having diabetes from a valid fasting plasma glucose of ≥126 mg/dl or a positive response to the question, "Other than during pregnancy (for women), have you ever been told by a doctor that you have diabetes?" BMI was computed from measured weight (kg) divided by square of the measured height (m) and categorized with cut points of <25, 25–29.9, and ≥30 kg/m^2. We defined central adiposity as a waist measurement of ≥102 cm for men and ≥88 cm for women. We defined hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or participant report of a diagnosis or current antihypertensive medication use. Peripheral arterial disease and arterial stiffness were derived from the ankle-brachial index in either the right or left ankle. We defined peripheral arterial disease as an ankle-brachial index <0.9 and arterial stiffness as an ankle-brachial index >1.4. Peripheral neuropathy was defined as having at least one insensate area of six metatarsal sites tested (three on each foot) using a standard 10-g monofilament test.

Urinary albumin was determined from a solid-phase fluorescent immunoassay, and urinary creatinine was analyzed using the Jaffe kinetic rate reaction. Albuminuria was defined as a ratio of urinary albumin to urinary creatinine ≥30 mg/g. As a marker of inflammation, C-reactive protein (mg/dl) was quantified in serum by latex-enhanced nephelometry using a Behring Nephelometer (Dade Behring, Somerville, NJ) and categorized into tertiles due to skewness. Total cholesterol and HDL were measured enzymatically. High cholesterol was defined as total cholesterol ≥240 mg/dl, a positive response to when asked if a health professional had ever told the participant he or she has high cholesterol, or participant report of current use of lipid-lowering medications. Low HDL was defined as HDL <40 mg/dl. A1C was assessed by Boronate affinity high-performance liquid chromatography using Primus CLC330 and Primus CLC385 (Primus, Kansas City, MO), and values were standardized to the method of the Diabetes Control and Complications Trial, yielding interassay coefficients of variation <3.0% (13).

Data analysis

Statistical differences in the distribution of covariates, including sociodemographic characteristics, noise exposure, peripheral neuropathy, glycosylated hemoglobin, and vascular factors, were examined using a *t* test (for continuous characteristics) or χ^2 test (for categorical characteristics). For the *t* test, values for A1C were transformed by taking their inverse to meet the assumption of normality. We used logistic regression to establish preliminary odds ratios for the association of diabetes with hearing impairment at low/mid and at high frequencies, adjusted for age, sex, race/ethnicity, education, smoking, and occupational noise exposure. All covariates, whether conceptualized as potential mediators or confounders, were regressed on diabetes status while adjusting for age, sex, race/ethnicity, education, and smoking (14). Covariates were also tested for an association with low/mid- and high-frequency hearing impairment (without controlling for diabetes). Significant associations of these factors with diabetes and with hearing impairment were interpreted as evidence consistent with a mechanistic pathway operating through these variables (15), with the caveat that our cross-sectional study design does not permit distinction between biological mediators and confounders, which have no causal role. We then examined whether further statistical adjustment for a given covariate would diminish the preliminary odds ratios of diabetes with hearing impairment. Thus, if the odds ratio for the association of diabetes and hearing impairment decreased after adjusting for a potential mediator, we interpreted this observation as evidence of partial mediation or partial confounding by this factor. Finally, parsimonious models were developed to estimate associations between diabetes and hearing impairment simultaneously adjusting for all significant covariates. Age and A1C were treated as continuous variables in all regression models. Tests of quadratic terms for each suggested no significant curvilinear relationship with hearing impairment. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and SUDAAN version 10.0.0 (Research Triangle Institute, Research Triangle Park, NC), incorporating 6-year sample weights. For those in the fasting sample, fasting weights were doubled to account for the one-half of the fasting sample for whom audiometric measures were unavailable. For subjects with diagnosed diabetes, audiometric weights were used.

RESULTS — Characteristics of the U.S. population aged 40–69 years are presented in Table 1, stratified by low/mid- and high-frequency hearing impairment. People with hearing impairment were, on average, 6 years older than those without hearing impairment, and a lesser proportion was non-Hispanic black. Six-

Table 1—*Characteristics of the U.S. population aged 40–69 years by hearing impairment status at low/mid and high frequencies, NHANES 1999–2004* (n = *1,508*)

	Low/mid frequency	Low/mid frequency		High frequency	High frequency	
	Impaired (n = 297)*	Not impaired (n = 1,211)		Impaired (n = 879)†	Not impaired (n = 629)	
	Means or % ± SE	Means or % ± SE	P	Means or % ± SE	Means or % ± SE	P
Age (years) (mean)	57.7 ± 0.6	51.5 ± 0.3	<0.001	55.4 ± 0.4	49.2 ± 0.4	<0.001
Race/ethnicity (%)			<0.001			<0.001
Non-Hispanic white	80.8 ± 3.5	76.3 ± 1.7		81.2 ± 2.1	72.3 ± 2.0	
Non-Hispanic black	4.8 ± 1.2	10.4 ± 1.0		6.1 ± 0.8	13.3 ± 1.4	
Mexican American	3.9 ± 0.8	5.3 ± 0.8		4.8 ± 0.8	5.3 ± 0.9	
Other, including multiracial	10.6 ± 2.8	8.1 ± 1.4		7.9 ± 1.7	9.1 ± 1.7	
Male sex (%)	46.3 ± 3.8	46.4 ± 1.8	0.96	60.8 ± 2.3	29.9 ± 2.4	<0.001
Education (%)			0.016			0.002
Less than high school	28.2 ± 3.8	15.7 ± 1.1		21.4 ± 1.7	13.5 ± 1.4	
High school	23.0 ± 3.2	25.1 ± 1.6		26.2 ± 1.4	23.1 ± 2.3	
More than high school	48.8 ± 4.2	59.2 ± 1.6		52.4 ± 2.1	63.4 ± 2.4	
Occupational noise exposure (%)	35.2 ± 4.2	33.2 ± 2.2	0.67	42.0 ± 2.9	23.8 ± 2.2	<0.001
Diabetes (%)‡	23.1 ± 3.6	11.6 ± 0.9	0.003	16.1 ± 1.6	9.2 ± 1.2	<0.001
Coronary heart disease (%)‡	10.4 ± 2.3	6.2 ± 0.9	0.09	9.7 ± 1.2	3.6 ± 0.9	<0.001
BMI status (%)‡			0.28			0.004
<25 kg/m^2	24.7 ± 4.7	30.0 ± 1.6		23.4 ± 2.0	34.2 ± 2.3	
25–30 kg/m^2	31.9 ± 5.3	36.7 ± 1.7		39.4 ± 2.6	33.2 ± 2.3	
>30 kg/m^2	43.4 ± 5.8	33.3 ± 2.3		37.2 ± 2.7	32.7 ± 2.6	
Central adiposity (%)‡	62.8 ± 4.8	56.4 ± 2.2	0.32	58.4 ± 2.5	57.5 ± 2.4	0.76
Peripheral neuropathy (%)‡	15.2 ± 3.6	7.7 ± 0.9	0.07	11.9 ± 1.3	5.5 ± 1.4	0.003
Albuminuria (%)‡	10.0 ± 2.1	7.5 ± 0.9	0.23	8.2 ± 0.93	6.8 ± 1.1	0.41
Peripheral arterial disease (%)‡	2.7 ± 1.0	2.8 ± 0.5	0.49	3.8 ± 0.9	2.0 ± 0.7	0.27
Arterial stiffness (%)‡	0.9 ± 0.6	1.6 ± 0.5	0.50	1.4 ± 0.5	1.5 ± 0.7	0.84
Hypertension (%)‡	46.3 ± 5.5	41.8 ± 1.9	0.32	43.8 ± 2.8	41.4 ± 2.9	0.64
High cholesterol (%)‡	54.3 ± 7.8	54.3 ± 2.4	0.94	59.7 ± 3.8	51.2 ± 3.0	0.11
Low HDL (%)‡	27.0 ± 4.7	17.0 ± 1.6	0.01	22.2 ± 2.3	12.6 ± 1.5	<0.001
A1C (%) (mean)‡§	5.8 ± 0.11	5.6 ± 0.03	0.01	5.7 ± 0.04	5.5 ± 0.03	<0.001
CRP (%)‡			<0.001			0.13
Lowest tertile	19.3 ± 4.0	35.5 ± 1.7		30.9 ± 2.5	35.3 ± 2.2	
Middle tertile	39.6 ± 5.7	32.5 ± 1.7		32.2 ± 1.8	33.9 ± 2.3	
Highest tertile	41.1 ± 4.6	32.0 ± 1.6		37.0 ± 2.5	30.8 ± 2.1	
Currently smokes (%)‡	29.5 ± 3.6	24.0 ± 1.7	0.69	31.0 ± 2.2	19.9 ± 2.2	<0.001

*$PTA_{(500, 1,000, 2,000\ Hz)}$ >25 dB in the worse ear. †$PTA_{(3,000, 4,000, 6,000, 8,000\ Hz)}$ >25 dB in the worse ear. ‡Age adjusted to the 2000 U.S. census. §*P* value calculated for difference in inverse-transformed A1C.

ty-one percent of adults with high-frequency hearing impairment were male, which was over twice the proportion among those without hearing impairment. We found no difference in low/mid-frequency hearing impairment by sex. Adults with hearing impairment had significantly less education. Over 40% of those with high-frequency hearing impairment reported occupational noise exposure, compared with 24% of those without high-frequency hearing impairment. The lack of a difference in occupational noise exposure between those with and without low/mid-frequency impairment was expected because the frequencies over which the pure-tone average was calculated excluded those most susceptible to injury from noise. Age-adjusted prevalence of diabetes among the hearing impaired was twice that of those not impaired in the low/mid-frequency range and 75% greater than those not impaired in the high-frequency range.

Age-adjusted prevalence estimates of potential confounders or mediators of the association between diabetes and hearing impairment at low/mid- and high-frequency ranges are also presented in Table 1. Coronary heart disease was more prevalent among those with hearing impairment in both frequency ranges, but the difference was not significant in the lower frequency range (P = 0.09). Compared with the nonimpaired subjects, adults with high-frequency hearing impairment were more likely to be overweight or obese, but we observed no difference in the prevalence of central adiposity by hearing impairment status. Adults with high-frequency hearing impairment had a greater prevalence of peripheral neuropathy than those who were unimpaired; the difference was marginally significant at low/mid-frequency. Prevalence of albuminuria, peripheral arterial disease, hypertension, and high cholesterol did not differ by hearing impairment status. The proportion of adults with low HDL was higher among the hearing impaired at both frequency

Table 2—*Multivariable-adjusted* prevalence odds ratios (95% CI) for the association between diabetes and low/mid- and high-frequency hearing impairment in U.S. adults aged 40–69 years, by frequency range, NHANES 1999–2004* (n = *1,508*)

	Low/mid frequency	High frequency
Preliminary model	2.03 (1.32–3.10)	1.67 (1.14–2.44)
+Peripheral neuropathy	1.70 (1.02–2.82)	1.73 (1.15–2.61)
+Albuminuria	2.01 (1.29–3.12)	1.54 (1.02–2.32)
+BMI status	1.85 (1.20–2.84)	1.59 (1.07–2.37)
+Low HDL	1.97 (1.24–3.12)	1.63 (1.08–2.46)
+CRP	1.98 (1.26–3.10)	1.50 (1.01–2.23)
+A1C	1.90 (1.11–3.24)	1.09 (0.60–1.99)

Data are odds ratio (95% CI). *Adjusted for age, sex, race/ethnicity, education, smoking, and occupational noise exposure.

ranges. Adults with hearing impairment had a mean A1C that was significantly higher by 0.2%. C-reactive protein (CRP) was shifted to higher levels among adults with hearing impairment compared with those without impairment, but the distributions were significantly different only at the high-frequency range. The proportion of current smokers was higher among subjects with high-frequency hearing impairment than among those without.

A series of models that tested whether anthropometric, neuropathic, vascular, inflammatory, and glycemic factors may be mediating the association between diabetes and hearing impairment is presented in Table 2. In our preliminary model, diabetes was associated with twice the odds of low/mid-frequency hearing impairment (odds ratio 2.03 [95% CI 1.32–3.10]) and a 67% increased odds of high-frequency hearing impairment (1.67 [1.14–2.44]) while adjusting for age, sex, race/ethnicity, education, smoking, and occupational noise exposure.

Hypertension, high total cholesterol, central adiposity, peripheral arterial disease, arterial stiffness, and coronary heart disease were not associated with either low/mid-frequency or high-frequency hearing impairment (data not shown). Thus, these factors were not considered as potential confounders or mediators of its relationship with diabetes.

When added as an explanatory factor of the low/mid-frequency hearing impairment association with diabetes, peripheral neuropathy diminished the preliminary odds ratio to 1.70 (95% CI 1.02–2.82). Controlling for peripheral neuropathy did not attenuate the association of diabetes with high-frequency hearing impairment. Conversely, adjusting for albuminuria did not diminish the odds ratio for diabetes with low/mid-frequency hearing impairment but did lower the odds ratio for the association with high-frequency hearing impairment to 1.54 (1.02–2.32). The diminished association of diabetes with low/mid-frequency hearing impairment while controlling for BMI (1.85 [1.20–2.84]) should be interpreted with caution because BMI was not associated with low/mid-frequency hearing impairment in preliminary analyses; thus, it did not meet our established criteria for being considered a potential mediator or confounder. BMI was associated with high-frequency hearing impairment in preliminary analyses, and controlling for its effect attenuated the association of diabetes with high-frequency impairment (1.59 [1.07–2.37]). Low HDL did not appreciably attenuate the association of diabetes with hearing impairment in either frequency range.

Controlling for CRP did not appreciably diminish the association of diabetes with low/mid-frequency hearing impairment but did reduce the odds ratio for high-frequency hearing impairment to 1.50 (95% CI 1.01–2.23). Adjusting for A1C resulted in a slightly attenuated odds ratio of 1.90 (1.11–3.24) for the low/mid-frequency hearing impairment association and, for high-frequency hearing impairment, diminished the association so that diabetes was no longer significantly associated (1.09 [0.60–1.99]). In fully adjusted models, diabetes remained significantly associated with a 98% increased odds of low/mid-frequency hearing impairment (1.98 [1.26–3.10]) and a 50% increased odds (1.50 [1.01–2.23]) of high-frequency hearing impairment after controlling for age, sex, race/ethnicity, education, smoking, occupational noise exposure, and CRP (Table 3).

CONCLUSIONS — Diabetes-related hearing loss may be sensorineural, whereby a cochlear or neural lesion impedes the transmission of auditory signals to the brain. We hypothesized a biological model in which diabetes contributes to hearing impairment through a vascular or neuropathic mechanism, with either related to hyperglycemia. We tested this hypothesis by evaluating the extent to which controlling for A1C and markers of vascular, neurologic, and inflammatory pathology explained the greater prevalence of hearing impairment among subjects with diabetes (1).

Diabetic neuropathy is a heterogeneous disorder that affects sensory and motor nerves and those responsible for autonomic functions (16). Using monofilament testing on the sole of the foot, a common screening test for diabetic peripheral neuropathy, we found some evidence that peripheral neuropathy is mediating the association with low/mid- but not high-frequency hearing impairment. Using one or more insensate sites to classify insensate foot yields moderately high sensitivity and specificity (~80%) (17), but the degree of false-positivity may differ by diabetes status. The full effect of a possible mediator (or confounder) may not be detected if a variable

Table 3—*Independent associations* between diabetes and CRP as a potential mediator and low/mid- and high-frequency hearing impairment among the U.S. population aged 40–69 years, NHANES 1999–2004* (n = *1,508*)

	Low/mid frequency	High frequency
Diabetes	1.98 (1.26–3.10)	1.50 (1.01–2.23)
CRP tertile		
Lowest	Referent	Referent
Middle	1.74 (1.02–2.96)	1.16 (0.84–1.60)
Highest	1.89 (1.21–2.95)	2.12 (1.47–3.05)

Data are odds ratio (95% CI). *Adjusted for age, race, sex, education, smoking, and occupational noise exposure.

is subject to misclassification. Alternatively, our measure may be a poor proxy for neuropathy of the cochlea.

Histopathological evidence of the inner ear suggests that angiopathic mechanisms plays a role in diabetes-related hearing impairment (5). We used albuminuria as a proxy for cochlear vasculopathy because there is increasing recognition of pathological mechanisms that may be shared by the renal and otological systems (18). We found a modest effect of controlling for albuminuria, which reduced the association of diabetes with high-frequency hearing impairment (odds ratio 1.67–1.54) but did not affect the association for low/mid-frequency impairment. Previous epidemiological evidence of an association between nephropathy (defined as renal transplant, dialysis, gross proteinuria [≥100 mg/dl], or creatinine ≥1.6 mg/dl) and hearing impairment among subjects with diabetes suggests that the relationship may only be observable with more severe kidney dysfunction (2).

We found no evidence that any vascular component to diabetes-related hearing loss is mediated through or confounded by high cholesterol, low HDL, hypertension, or history of cardiovascular events. These results are consistent with studies by Helzner et al. (19) and Torre et al. (20), although Torre et al. and Gates et al. (8) identified an association of cardiovascular disease with cochlear impairment among women, a result we did not replicate. Comparisons should be made cautiously, however, because methodological differences of the previous studies include sampling older individuals, excluding mild cases of hearing impairment, assessing preclinical hearing impairment, and not adjusting for diabetes. The low overall prevalence of peripheral vascular disease and arterial stiffness (3 and 1.5%, respectively) in our relatively young sample may have limited our ability to detect any effect of these macrovascular conditions. Of all cardiovascular disease risk factors that we examined, only BMI attenuated the preliminary associations. Our fully adjusted models do not include BMI, so obesity may be a marker for an inflammatory process that promotes atherosclerosis or neuropathy (6,21).

Our results showing CRP may mediate the association of diabetes with high-frequency hearing impairment suggest the role of an inflammatory mechanism. Inflammatory diseases resulting in sensorineural hearing loss have been described in clinical studies (22,23), but to our knowledge, this inflammatory marker has not been correlated with diabetes-related hearing impairment in population-based studies. CRP correlates with cardiovascular risk factors such as obesity, HDL, hypertension, and smoking, which might implicate an atherosclerotic mechanism, so it is unclear why our results do not suggest a role of other vascular measures (24).

Glycemia may be a factor in diabetes-related hearing impairment. In our analysis, controlling for A1C diminished the odds ratio for diabetes with low/mid-frequency hearing impairment slightly from 2.03 to 1.90 but attenuated the association with high-frequency hearing impairment to a nonsignificant level. Because most of the variance in A1C is explained by diabetes, interpreting the role of A1C as a mediator may be overstating the case. Glycated hemoglobin has not been associated with hearing impairment, both in a general population and among people with diabetes (2). However, we previously demonstrated a gradient in hearing impairment prevalence by glycemic status (comparing persons with diabetes, impaired fasting glucose, and normal glucose metabolism), implicating hyperglycemia as a possible mediator of diabetes-related hearing impairment (1).

These cross-sectional data limit our ability to distinguish between factors acting as mediators and those operating as confounders, because statistical adjustment for either will diminish the preliminary association. When we derived models adjusting for all independently associated potential mediators or confounders, there remained a 98% increased odds of low/mid-frequency hearing impairment and a 50% increased odds of high-frequency hearing impairment associated with diabetes that was left unexplained. This evidence may indicate that the measures available in these survey data do not adequately represent the neuropathic and microvascular mechanisms we hypothesized and highlights the difficulty in studying the pathology of the inner ear using noninvasive measures. Alternatively, there may exist unexplored biological mechanisms including glucose sensitivity, insulin resistance, temporal bone pathology, more frequent ear infections, or genetic factors that predispose to hearing loss and cosegregate with other genetic factors that predispose to diabetes.

In summary, we find that factors related to neuropathy, microangiopathy, inflammation, and glycemia explain part of the association between diabetes and hearing impairment. Additional studies are necessary to delineate temporal relationships among diabetes, potential mediators, and hearing impairment.

Acknowledgments— This work was financially supported by the National Institute of Diabetes and Digestive and Kidney Diseases (HHSN267200700001G).

No potential conflicts of interest relevant to this article were reported.

Preliminary results of this report were published in abstract form at the 68th Scientific Sessions of the American Diabetes Association, San Francisco, California, 6–10 June 2008.

We thank Laura Fang and Danita Byrd-Holt for programming support and Keith Rust for statistical support.

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