

Comparing the Cochlear Spiral Modiolar Artery in Type-1 and Type-2 Diabetes Mellitus: A Human Temporal Bone Study

Shin Kariya^{a,b}, Sebahattin Cureoglu^{a,c*}, Hisaki Fukushima^d, Norimasa Morita^d,
Muzeyyen Y. Baylan^c, Yukihide Maeda^b, Kazunori Nishizaki^b, and Michael M. Paparella^{a,e}

^aInternational Hearing Foundation, Minneapolis, Minnesota 55454, USA, ^bDepartment of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan, ^cDepartment of Otolaryngology-Head & Neck Surgery, University of Minnesota, Minneapolis, Minnesota 55455, USA, and ^dDepartment of Otolaryngology, Kawasaki Medical School, Kurashiki, Okayama 701-0192, Japan, and ^ePaparella Ear Head & Neck Institute, Minneapolis, Minnesota 55454, USA.

This study examined whether pathological findings were present in cochlear vessels for patients with diabetes mellitus. Twenty-six temporal bones from 13 patients with type 1 diabetes mellitus and 40 temporal bones from 20 patients with type 2 diabetes mellitus were examined. Type 2 diabetic temporal bones were divided into 2 groups according to diabetic management (22 temporal bones with insulin therapy, and 18 with oral hypoglycemic drugs). Age-matched normal control temporal bones were also selected. The vessel wall thickness in the cochlear spiral modiolar artery was measured under a light microscope, and the vessel wall ratio (vessel wall thickness/outer diameter of the vessel \times 100) was calculated. The vessel wall thickness and vessel wall ratio in type 1 diabetes mellitus were significantly greater than in normal controls. Type 2 diabetic patients with insulin therapy showed significantly greater vessel wall thickness and vessel wall ratios than controls. In type 2 diabetes mellitus, the vessel wall thickness and vessel wall ratio were greater in patients treated with insulin therapy than in those treated with oral hypoglycemic agents. Type 2 diabetic patients with insulin therapy showed an increased vessel wall thickness and vessel wall ratio compared to patients with type 1 diabetes mellitus. In conclusion, the cochlea in patients with diabetes mellitus shows circulatory disturbance compared to age-matched normal controls.

Key words: diabetes mellitus, temporal bone, cochlear spiral modiolar artery, hearing loss

Hearing loss is a common complication in patients with diabetes mellitus, and hearing thresholds in diabetic patients are progressively increased compared with normal subjects [1, 2]. Both type 1 diabetes mellitus (insulin-dependent diabetes mellitus) and type 2 diabetes mellitus (non-insulin-dependent diabe-

tes mellitus) appear to be associated with hearing impairment [3-5]. As some diabetic patients with mild hearing loss may not complain of a hearing disorder, adding routine audiometry to the annual test for patients with diabetes mellitus has been recommended for physicians by the American Diabetes Association [6, 7]. However, the etiology and nature of the hearing loss associated with diabetes mellitus remains controversial [8].

Diabetes mellitus is strongly associated with accel-

erated atherogenesis [9]. Increased vessel wall thickness has been reported in human temporal bones with diabetes mellitus, and periodic acid-Schiff (PAS) - positive material has been detected in the vascular walls of the cochlea in diabetic patients [10-12]. Although angiopathy and/or neuropathy in the cochlea might be considered important in relation to hearing disorders in diabetic patients, the vascular status of the inner ear in diabetic patients is not fully understood [13-15]. In addition, differences in cochlear vessels between type 1 and type 2 diabetes mellitus do not appear to have been reported. The purpose of the present human temporal bone study was to clarify vascular findings in cochlear vessels for both type 1 and type 2 diabetic patients, and to compare findings between the types of diabetes mellitus.

Materials and Methods

Samples. This study examined 26 temporal bones from 13 patients with type 1 diabetes mellitus (6 men, 7 women; mean age \pm standard deviation (SD), 37.1 ± 13.1 years; range, 18-68 years; mean duration of diabetes, 21.1 ± 11.1 years; range, 6-36 years) and 40 temporal bones from 20 patients with type 2 diabetes mellitus. Temporal bones from patients with type 2 diabetes mellitus were divided into 2 groups according to the method of diabetes management: 11 patients (22 temporal bones) with insulin therapy (7 men, 4 women; mean age, $54.6 \pm$

7.6 years; range, 44-68 years; mean duration of diabetes mellitus, 6.4 ± 5.3 years; range, 0.5-16 years) and 9 patients (18 temporal bones) with oral hypoglycemic drugs (8 men, 1 woman; mean age, 56.9 ± 8.6 years; range, 45-68 years; mean duration of diabetes, 6.5 ± 3.1 years; range, 3-10 years).

The control group for type 1 diabetes mellitus (Control 1) comprised 16 normal temporal bones (7 on right side and 9 on left side) from 11 age-matched subjects (6 men, 5 women; mean age, 39.6 ± 19.0 years; range, 12-66 years), and the control group for type 2 diabetes mellitus (Control 2) comprised 11 normal temporal bones (5 on right side and 6 on left side) from 8 age-matched subjects (4 men, 4 women; mean age, 55.9 ± 10.6 years; range, 40-67 years).

Temporal bones from patients with a history of head trauma, systemic autoimmune disorders, ototoxic drug use, or otological diseases such as otosclerosis and otitis media were excluded from this study, as these factors can affect the cochlea. Temporal bones from patients >70 years old were also excluded. The characteristics of the patients with diabetes mellitus and those of normal controls are shown in Table 1.

Temporal bone samples were obtained from the temporal bone collection of the University of Minnesota. All temporal bones had been previously removed at autopsy, fixed in formalin solution, decalcified, and embedded in celloidin. Each temporal bone was serially sectioned in the horizontal plane at a

Table 1 Characteristics of the patients with diabetes mellitus and the controls

	Type 1 DM	Control 1	P value (1)	Type 2 DM (Insulin therapy)	Type 2 DM (Oral hypoglycemic drug)	Control 2	P value (2)
Number of patients	13	11		11	9	8	
Age (mean \pm SD, year)	37.1 ± 13.1	39.6 ± 19.0	0.676	54.6 ± 7.6	56.9 ± 8.6	55.9 ± 10.6	0.773
Sex: Male/Female	6/7	6/5	0.682	7/4	8/1	4/4	0.212
Duration of DM (mean \pm SD, year)	21.1 ± 11.1			6.4 ± 5.3	6.5 ± 3.1		
Height (mean \pm SD, cm)	166.4 ± 12.5	167.3 ± 9.1	0.961	160.4 ± 5.8	173.8 ± 6.0	167.0 ± 8.4	0.019
Weight (mean \pm SD, kg)	57.3 ± 16.2	77.8 ± 30.9	0.072	79.0 ± 18.8	74.8 ± 10.9	77.4 ± 32.3	0.919
BMI (mean \pm SD)	20.8 ± 5.2	28.1 ± 11.5	0.024	31.7 ± 6.1	24.2 ± 2.1	28.7 ± 13.3	0.066
Blood Sugar (mean \pm SD, mg/dl)	312 ± 138.5	106.8 ± 21.0	<0.001	240.9 ± 109.7	231.7 ± 86.3	109.7 ± 21.9	0.001
BUN (mean \pm SD, mg/dl)	50.0 ± 40.1	19.9 ± 10.5	0.059	34.2 ± 33.2	43.6 ± 18.6	22.9 ± 10.3	0.083
Cre (mean \pm SD, mg/dl)	4.5 ± 4.1	1.0 ± 0.8	0.003	1.5 ± 1.2	4.7 ± 5.3	1.0 ± 0.5	0.023
Number of patients with							
Hemodialysis	8 (61.5%)	0	<0.001	3 (27.3%)	3 (33.3%)	0	0.120
Diabetic Retinopathy	9 (69.2%)	0	<0.001	2 (18.2%)	0	0	0.227
Diabetic Neuropathy	8 (61.5%)	0	<0.001	1 (9.1%)	0	0	0.564
Diabetic Cardiomyopathy	3 (23.1%)	0	0.047	3 (27.3%)	2 (22.2%)	0	0.185
Myocardial Infarction	5 (38.5%)	5 (45.5%)	0.737	4 (36.4%)	4 (44.4%)	4 (50.0%)	0.843
Hypertension	6 (46.2%)	2 (18.2%)	0.154	3 (27.3%)	3 (33.3%)	2 (25.0%)	0.931
Renal transplantation	3 (23.1%)	0	0.063	0	0	0	

BMI, body mass index; BUN, blood urea nitrogen; Cre, serum creatinine.

P value (1): Mann-Whitney's U-test or chi-square test is used to compare between Type 1 DM and Control 1.

P value (2): Kruskal-Wallis test or chi-square test is used to compare between groups (Type 2 DM with insulin, Type 2 DM with oral drug, and Control 2).

thickness of $20\mu\text{m}$. Every 10th section was stained with hematoxylin and eosin (HE), mounted on a glass slide, and evaluated under a light microscope.

The study was approved by the Institutional Review Board (Midwest Center of the National Temporal Bone Hearing and Pathology Resource Registry; Study number, 0206M26181).

Measurement of cochlear vessels. The mid-modiolar section of the cochlea was selected in each temporal bone. Vessel wall measurements were performed in perpendicular cross-sections of the spiral modiolar artery. The vessel that was most perpendicularly sectioned was chosen in each subject. Images were acquired using a digital camera connected to a personal computer. The calibrated image was obtained at a magnification of $\times 600$. Vessel walls were measured using Image-Pro Plus version 3.0 image analysis software (Media Cybernetics, Silver Springs, MD, USA) and calculated with reference to the methods described by Robison [16].

The vessel wall area (VWA) and vessel wall length (VWL) per vessel cross-section were determined using the following formulae:

$$\text{VWA} = T - L_u$$

$\text{VWL} = (\text{outer length of lines delimiting VWA} + \text{inner length of lines delimiting VWA})/2$, where T is the total cross-sectional area of each vessel and L_u is the luminal area. Vessel wall thickness in each vessel is expressed as VWA/VWL .

The vessel wall ratio was determined with the following formula:

$\text{Vessel wall ratio (\%)} = \text{vessel wall thickness}/\text{outer diameter of the vessel} \times 100$

Statistical analysis. Results are presented as means \pm standard deviation (SD). Statistical evaluations were performed using the Kruskal-Wallis test, the Tukey-Kramer test, and the chi-square test for comparing data among 3 or more groups. Mann-Whitney's U test was used for comparison between 2 groups. A correlation analysis was performed by using Spearman's correlation coefficient by rank test. Significant differences were established at a level of $p < 0.05$.

Results

Vessel wall thickness. Vessel walls of the spiral modiolar artery were thick in patients with

diabetes mellitus (Fig. 1). Vessel wall thicknesses of the spiral modiolar artery are shown in Fig. 2. The mean vessel wall thickness was $6.02 \pm 1.70\mu\text{m}$ in type 1 diabetes mellitus, $3.55 \pm 0.72\mu\text{m}$ in Control 1, $6.97 \pm 1.88\mu\text{m}$ in type 2 diabetes mellitus with insulin therapy, $5.08 \pm 1.41\mu\text{m}$ in type 2 diabetes mellitus with oral hypoglycemic agents, and $3.77 \pm 0.81\mu\text{m}$ in Control 2. A statistically significant difference was observed between groups ($p < 0.001$, Kruskal-Wallis test). The vessel wall thickness was significantly higher in type 1 diabetes mellitus than in normal Control 1 ($p < 0.001$, Tukey-Kramer test). Type 2 diabetes mellitus with insulin therapy also showed a significantly greater vessel wall thickness than Control 2 ($p < 0.001$, Tukey-Kramer test). No significant difference in vessel wall thickness was seen between Control 1 and Control 2. The vessel wall thickness in type 2 diabetes mellitus with insulin therapy tended to be higher, although not significantly, than in type 1 diabetes mellitus or in type 2 diabetes mellitus with oral hypoglycemic agents.

In some normal cases, the same individual contributed both ears to the sample population. Vessel wall thicknesses in right temporal bones both in patients with diabetes mellitus and in controls are shown in Fig. 3. The mean vessel wall thickness was $6.01 \pm 1.43\mu\text{m}$ in type 1 diabetes mellitus, $3.42 \pm 0.82\mu\text{m}$ in Control 1, $6.21 \pm 1.78\mu\text{m}$ in type 2 diabetes mellitus with insulin therapy, $4.77 \pm 1.59\mu\text{m}$ in type 2 diabetes

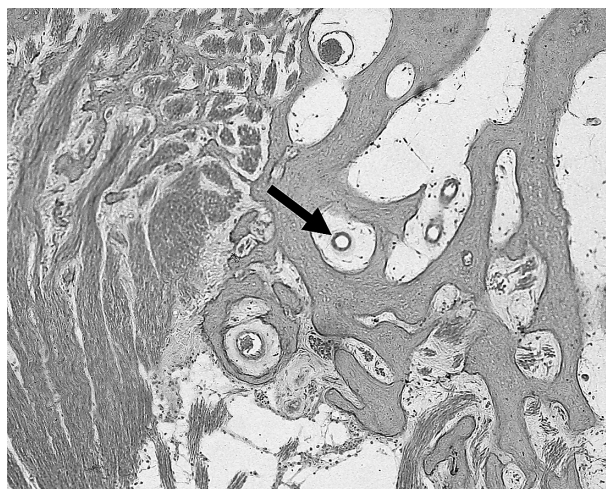


Fig. 1 Vessels in the midmodiolar section of the left cochlea in type 2 diabetes mellitus with insulin therapy (65 years old, male). The vessel wall thickness of the spiral modiolar artery (arrow) is increased.

mellitus with oral hypoglycemic agents, and $3.37 \pm 0.96 \mu\text{m}$ in Control 2. A statistically significant difference was observed between groups ($p < 0.001$, Kruskal-Wallis test). The vessel wall thickness in the

right temporal bone was significantly higher in type 1 diabetes mellitus than in normal Control 1 ($p < 0.01$, Tukey-Kramer test). Type 2 diabetes mellitus with insulin therapy also showed a significantly greater vessel wall thickness than Control 2 ($p < 0.05$, Tukey-Kramer test).

Vessel wall thicknesses in the left temporal bones both in patients with diabetes mellitus and in controls are shown in Fig. 4. The mean vessel wall thickness was $6.02 \pm 1.98 \mu\text{m}$ in type 1 diabetes mellitus, $3.65 \pm 0.66 \mu\text{m}$ in Control 1, $7.80 \pm 1.70 \mu\text{m}$ in type 2 diabetes mellitus with insulin therapy, $5.39 \pm 1.24 \mu\text{m}$ in type 2 diabetes mellitus with oral hypoglycemic agents, and $4.10 \pm 0.54 \mu\text{m}$ in Control 2. A statistically significant difference was observed between groups ($p < 0.001$, Kruskal-Wallis test). The vessel wall thickness in the left temporal bone was significantly higher in type 1 diabetes mellitus than in normal Control 1 ($p < 0.05$, Tukey-Kramer test). Type 2 diabetes mellitus with insulin therapy also showed a significantly greater vessel wall thickness than Control 2 ($p < 0.01$, Tukey-Kramer test).

Vessel wall ratio. The vessel wall ratios of the spiral modiolar artery are shown in Fig. 5. The mean vessel wall ratio was $9.37 \pm 2.50\%$ in type 1 diabetes mellitus, $5.80 \pm 1.40\%$ in Control 1, $12.5 \pm 3.74\%$ in

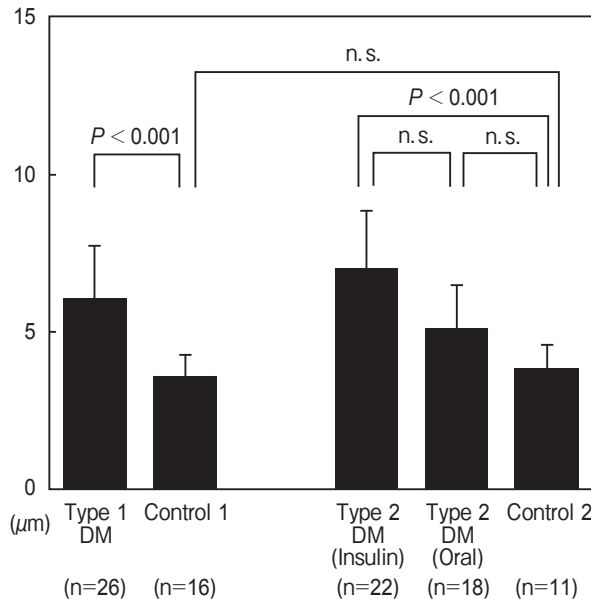


Fig. 2 Vessel wall thickness (means ± SD) in the spiral modiolar artery in temporal bones, combining those on the right and left sides. (n.s., not significant; Tukey-Kramer test)

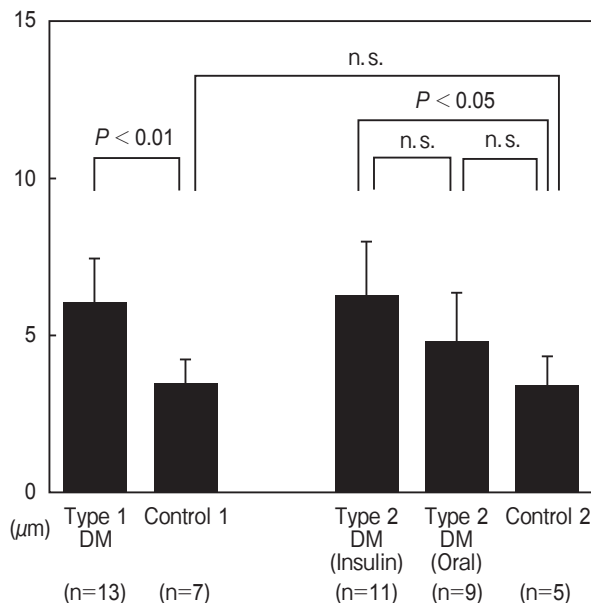


Fig. 3 Vessel wall thickness (means ± SD) in the spiral modiolar artery in right temporal bones. (n.s., not significant; Tukey-Kramer test)

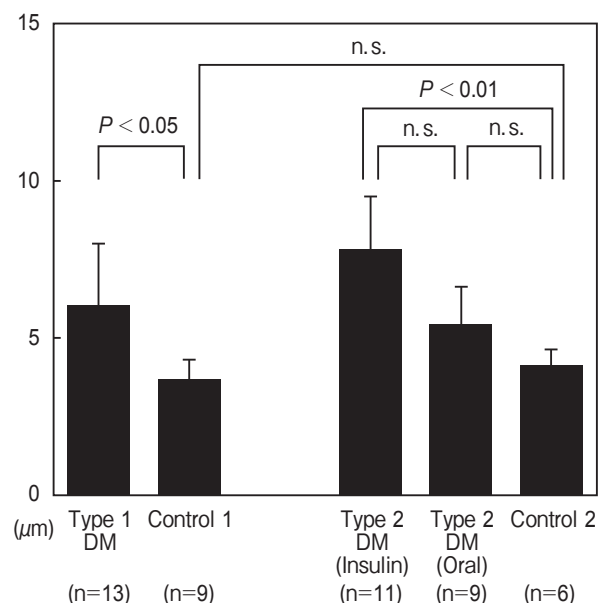


Fig. 4 Vessel wall thickness (means ± SD) in the spiral modiolar artery in left temporal bones. (n.s., not significant; Tukey-Kramer test)

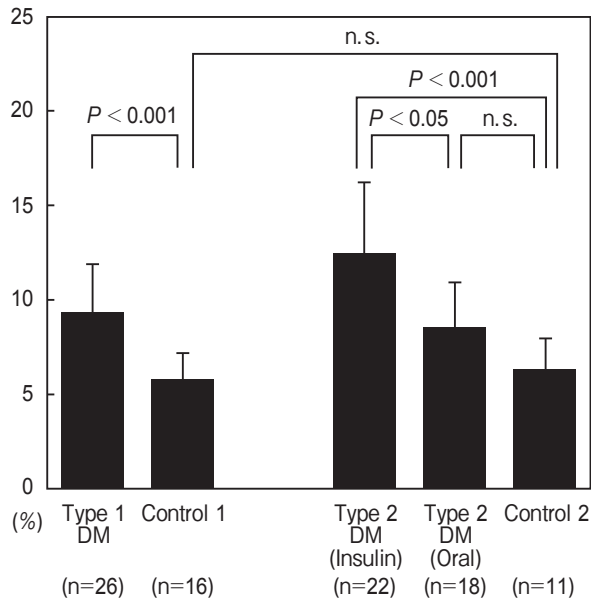


Fig. 5 Vessel wall ratio (means \pm SD) in the spiral modiolar artery in temporal bones, combining those on the right and left sides. (n.s., not significant; Tukey-Kramer test)

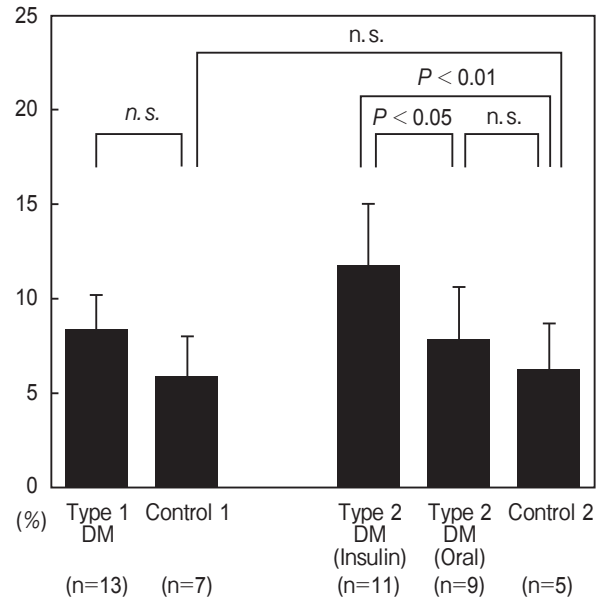


Fig. 6 Vessel wall ratio (means \pm SD) in the spiral modiolar artery in right temporal bones. (n.s., not significant; Tukey-Kramer test)

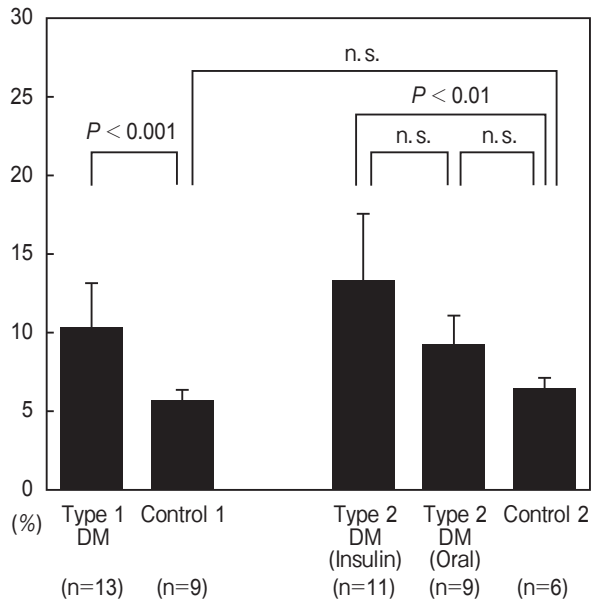


Fig. 7 Vessel wall ratio (means \pm SD) in the spiral modiolar artery in left temporal bones. (n.s., not significant; Tukey-Kramer test)

type 2 diabetes mellitus with insulin therapy, $8.56 \pm 2.38\%$ in type 2 diabetes mellitus with oral hypoglycemic agents, and $6.37 \pm 1.59\%$ in Control 2. A statistically significant difference was observed between

groups ($p < 0.001$, Kruskal-Wallis test). The vessel wall ratio was significantly greater in type 1 diabetes mellitus than in normal Control 1 ($p < 0.001$, Tukey-Kramer test). The vessel wall ratio was significantly greater in type 2 diabetes mellitus with insulin therapy than in type 2 diabetes mellitus with oral hypoglycemic agents ($p < 0.05$, Tukey-Kramer test) or in normal Control 2 ($p < 0.001$, Tukey-Kramer test). The vessel wall ratio in type 2 diabetes mellitus with oral hypoglycemic agents was greater than that in normal Control 2, but the difference did not reach statistical significance. The vessel wall ratio was higher in type 2 diabetes mellitus with insulin therapy than in type 1 diabetes mellitus. No significant difference in vessel wall ratio was seen between Control 1 and Control 2.

The vessel wall ratios in right temporal bones both in patients with diabetes mellitus and in controls are shown in Fig. 6. The mean vessel wall ratio was $8.38 \pm 1.81\%$ in type 1 diabetes mellitus, $5.91 \pm 2.08\%$ in Control 1, $11.75 \pm 3.26\%$ in type 2 diabetes mellitus with insulin therapy, $7.85 \pm 2.78\%$ in type 2 diabetes mellitus with oral hypoglycemic agents, and $6.26 \pm 2.41\%$ in Control 2. A statistically significant difference was observed between groups ($p < 0.001$, Kruskal-Wallis test). The vessel wall ratio in the right temporal bone was higher in type 1 diabetes

mellitus than in normal Control 1. Type 2 diabetes mellitus with insulin therapy showed a significantly greater vessel wall ratio than type 2 diabetes mellitus with oral hypoglycemic agents ($p < 0.05$, Tukey-Kramer test) or Control 2 ($p < 0.01$, Tukey-Kramer test).

Vessel wall ratios in left temporal bones both in patients with diabetes mellitus and in controls are shown in Fig. 7. The mean vessel wall ratio was $10.36 \pm 2.76\%$ in type 1 diabetes mellitus, $5.71 \pm 0.66\%$ in Control 1, $13.31 \pm 4.24\%$ in type 2 diabetes mellitus with insulin therapy, $9.27 \pm 1.81\%$ in type 2 diabetes mellitus with oral hypoglycemic agents, and $6.47 \pm 0.65\%$ in Control 2. A statistically significant difference was observed between groups ($p < 0.001$, Kruskal-Wallis test). The vessel wall ratio in the left temporal bone was significantly higher in type 1 diabetes mellitus than in normal Control 1 ($p < 0.001$, Tukey-Kramer test). Type 2 diabetes mellitus with insulin therapy showed significantly greater vessel wall thickness than Control 2 ($p < 0.01$, Tukey-Kramer test).

Relation with systemic indicators. Body mass index (BMI) was significantly correlated with vessel wall ratio in type 2 diabetes mellitus with insulin therapy ($p < 0.05$, Spearman's correlation coefficient by rank test) and in type 2 diabetes mellitus

with oral hypoglycemic agents ($p < 0.05$, Spearman's correlation coefficient by rank test). The vessel wall thicknesses in diabetes cases and the vessel wall ratio in type 1 diabetes mellitus tended to correlate with body mass index. Blood sugar, blood urea nitrogen, and serum creatinine were not significantly correlated with the vessel wall thickness or vessel wall ratio in diabetes cases.

The vessel wall thickness and vessel wall ratios in diabetic patients with or without related complications (hemodialysis, diabetic retinopathy, diabetic neuropathy, diabetic cardiomyopathy, myocardial infarction, and hypertension) are shown in Table 2. In type 2 diabetes mellitus with insulin therapy, the vessel wall thickness and vessel wall ratio were greater in patients with related complications than in those without complications, especially in diabetic retinopathy ($p < 0.05$, Mann-Whitney's U test).

Right side and left side correlation. A statistically significant correlation was detected between the right and left temporal bones both in the vessel wall thickness and vessel wall ratio in type 1 diabetes mellitus (Vessel wall thickness, $p < 0.05$; vessel wall ratio, $p < 0.01$; Spearman's correlation coefficient by rank test). Right and left temporal bones tended to correlate both in the vessel wall thickness and the vessel wall ratio in type 2 diabetes mellitus. Control

Table 2 Vessel wall thickness and vessel wall ratio in diabetic patients with or without related complications

		Type 1 DM		Type 2 DM (Insulin)		Type 2 DM (Oral)	
		Thickness (μm)	Ratio (%)	Thickness (μm)	Ratio (%)	Thickness (μm)	Ratio (%)
Hemodialysis	+	6.10 ± 1.88	9.61 ± 2.56	7.24 ± 2.64	12.67 ± 3.45	5.68 ± 1.85	7.37 ± 1.03
	-	5.88 ± 1.44	8.98 ± 2.47	6.86 ± 1.59	12.42 ± 3.97	4.72 ± 1.02	9.28 ± 2.70
Diabetic retinopathy	+	5.75 ± 1.52	8.75 ± 1.65	7.83 ± 0.42	$15.38 \pm 2.73^{**}$	-	-
	-	6.60 ± 2.02	10.77 ± 3.53	6.77 ± 2.04	11.82 ± 3.68	5.08 ± 1.41	8.56 ± 2.38
Diabetic neuropathy	+	5.90 ± 1.55	8.98 ± 1.60	7.68 ± 0.48	15.79 ± 4.62	-	-
	-	6.20 ± 1.97	10.00 ± 3.52	6.89 ± 1.97	12.15 ± 3.61	5.08 ± 1.41	8.56 ± 2.38
Diabetic cardiomyopathy	+	5.37 ± 1.16	7.86 ± 1.16	8.03 ± 2.33	13.73 ± 3.45	5.20 ± 1.11	8.31 ± 2.39
	-	6.21 ± 1.81	9.82 ± 2.63	6.54 ± 1.57	12.00 ± 3.85	5.04 ± 1.54	8.65 ± 2.47
Myocardial infarction	+	5.65 ± 1.21	8.41 ± 1.42	7.94 ± 1.98	14.25 ± 3.53	4.76 ± 1.40	7.94 ± 2.54
	-	6.25 ± 1.94	9.97 ± 2.86	6.37 ± 1.61	11.42 ± 3.58	5.33 ± 1.45	9.05 ± 2.27
Hypertension	+	5.99 ± 1.52	9.11 ± 1.56	8.84 ± 3.20	16.19 ± 3.85	4.88 ± 1.36	9.03 ± 1.49
	-	6.04 ± 1.89	9.59 ± 3.13	6.77 ± 1.72	12.11 ± 3.62	5.15 ± 1.48	8.41 ± 2.65

Values are presented as mean \pm SD.

******, $p < 0.05$, Mann-Whitney's U test.

1 showed significant correlation between right and left temporal bones in the vessel wall thickness ($p < 0.001$, Spearman's correlation coefficient by rank test) and vessel wall ratio ($p < 0.001$, Spearman's correlation coefficient by rank test). Because only 3 cases contributed both ears in Control 2, statistical analysis was not performed.

Discussion

A relationship between hearing loss and diabetes mellitus has been suggested for several decades. A recent study examined 5,140 participants to determine relative risk for sensorineural hearing loss in a community-based random sample of patients who reported a history of diabetes mellitus, and concluded that patients with diabetes mellitus are at increased risk for hearing loss [17]. Another large population-based study recruited 3,572 participants, including 344 type 2 diabetic patients, and showed a modest association between type 2 diabetes mellitus and hearing loss [3]. Agrawal *et al.* have reported that a history of diabetes is associated with significantly increased odds of hearing loss in a national cross-sectional survey (adjusted odds ratios, 2.0; 95% confidence interval, 1.2–3.2), with diabetic patients showing significantly poorer hearing levels at 0.5, 1, 3, 4, 6, and 8 kHz in audiometry compared with those without diabetes [18]. These studies have clearly demonstrated diabetes mellitus to be one of the risk factors for sensorineural hearing loss.

The mechanism of sensorineural hearing loss induced by diabetes mellitus remains a source of debate. Multiple factors, including nonenzymatic glycation related to the hyperactivity of free oxygen radicals, might result in functional impairment of outer hair cells of the cochlea [4]. The cochlea is supplied by the spiral modiolar artery and the cochlear branch of the vestibulo-cochlear artery, which are terminal branches of the inner ear artery [19]. Circulatory disturbance induced by microvascular problems has also been suggested as one of the principal factors underlying sensorineural hearing loss in patients with diabetes mellitus [11, 20–22]. The present study clearly shows that the cochlear vessel wall is significantly thicker in both type 1 and type 2 diabetic patients when compared with age-matched normal controls. In addition, although there was no

significant difference in vessel walls between young control subjects and elderly control subjects, patients who managed type 2 diabetes by using insulin therapy displayed thicker vessel walls than other diabetic patients. Our findings revealed that the cochlear microcirculation in patients with diabetes mellitus is affected, especially in type 2 diabetic patients receiving insulin therapy.

Carotid intima-media thickness as measured by ultrasound examination is a useful non-invasive assessment of cardiovascular disease in diabetic patients [23]. Recent studies have shown that carotid intima-media thickness is associated with the extent of atherosclerosis and end-organ damage, and that increased carotid intima-media thickness is related to hearing disorder in general adult population samples [24, 25]. Thickened cochlear vessel walls in the diabetic patients observed in this study might be related to cochlear dysfunction, including sensorineural hearing loss, in patients with diabetes mellitus.

Multiple factors might affect vascular disorders in patients with diabetes mellitus. Endothelial dysfunction is one of the principal factors closely associated with the development of atherosclerosis in both type 1 and type 2 diabetes mellitus [26, 27]. Abnormal production of various mediators in the endothelium, including nitric oxide, prostanoids, endothelin, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), adhesion molecules, and inflammatory cytokines, results in endothelial dysfunction *per se* and atherosclerosis [28]. Type 2 diabetes mellitus is initially characterized by insulin resistance, and the progression of insulin resistance parallels the development of endothelial dysfunction and atherosclerosis [29]. Our findings show that cochlear vessel wall thickness in type 2 diabetic patients with insulin therapy is greater than that in type 2 diabetic patients with oral hypoglycemic agents. Patients managed by insulin might be at a more severe stage of type 2 diabetes mellitus, and differences in vessel wall thickness between those treated with insulin and those with oral hypoglycemic agents observed in this study might reflect the progression of insulin resistance.

Conversely, endothelial impairment does not fully explain the development of angiopathy in patients with type 1 diabetes mellitus, and genetic factors such as angiotensin II type 1 receptor gene polymorphism

influence vascular disorders in patients with type 1 diabetes mellitus [29, 30]. Our findings show that cochlear vessel wall thickness is smaller in type 1 diabetic patients than in type 2 diabetic patients with insulin therapy. Factors other than endothelial dysfunction may therefore need to be present for atherosclerosis to develop in type 1 diabetes mellitus. Kanters *et al.* have examined hyperlipidemic patients with type 1 or type 2 diabetes mellitus, and reported that the thickness of the carotid intima is greater in those with type 2 diabetes than in those with type 1 [31]. Although they did not divide type 2 diabetic patients according to management, our results do not contradict their findings.

Due to the limited number of subjects with available audiograms, the relationship between hearing level and vessel wall thickness in the cochlea was unclear in this study. A positive correlation between the severity of hearing loss and the progression of diabetes mellitus has been reported, but audiological findings in various conditions of diabetic patients remain controversial [2, 32–34]. As significant differences were observed in this study in terms of vessel wall thickness in the cochlea between subtypes of diabetes mellitus, further studies are needed to clarify the pathophysiology of the inner ear in patients with diabetes mellitus.

Conclusion. The thickness of the cochlear vessel wall in diabetic patients was increased, especially in patients with type 2 diabetes managed by insulin therapy. Our findings suggest that cochlear microcirculation might be affected in patients with diabetes mellitus. Administration of vasodilators, corticosteroids, vitamin B12, and hyperbaric oxygen therapy results in a better recovery rate from idiopathic sudden deafness in patients with diabetes mellitus than in those without diabetes mellitus [21]. The vessel wall findings in this study may indicate that the cochlea is under an ischemic state in patients with diabetes mellitus, and that pharmacotherapies known to improve microcirculation in the cochlea might be worth considering for the management of inner ear disturbances, including tinnitus and sensorineural hearing loss.

Acknowledgments. The authors would like to thank Carolyn Sutherland for her technical support. This work was supported by NIDCD 3U24DC008559-03S109, the International Hearing Foundation,

the Starkey Foundation, and the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References

1. Friedman SA, Schulman RH and Weiss S: Hearing and diabetic neuropathy. *Arch Intern Med* (1975) 135: 573–576.
2. Kakarlapudi V, Sawyer R and Staecker H: The effect of diabetes on sensorineural hearing loss. *Otol Neurotol* (2003) 24: 382–386.
3. Dalton DS, Cruickshanks KJ, Klein R, Klein BE and Wiley TL: Association of NIDDM and hearing loss. *Diabetes Care* (1998) 21: 1540–1544.
4. Lisowska G, Namyslowski G, Morawski K and Strojek K: Early identification of hearing impairment in patients with type 1 diabetes mellitus. *Otol Neurotol* (2001) 22: 316–320.
5. Pessin AB, Martins RH, Pimenta Wde P, Simões AC, Marsiglia A and Amaral AV: Auditory evaluation in patients with type 1 diabetes. *Ann Otol Rhinol Laryngol* (2008) 117: 366–370.
6. Hirose K: Hearing loss and diabetes: You might not know what you are missing. *Ann Intern Med* (2008) 149: 54–55.
7. American Diabetes Association: Standards of medical care in diabetes--2008. *Diabetes Care* (2008) 31 Suppl 1: S12–S4.
8. Erdem T, Ozturan O, Miman MC, Ozturk C and Karatas E: Exploration of the early auditory effects of hyperlipoproteinemia and diabetes mellitus using otoacoustic emissions. *Eur Arch Otorhinolaryngol* (2003) 260: 62–66.
9. Sobel BE and Schneider DJ: Cardiovascular complications in diabetes mellitus. *Curr Opin Pharmacol* (2005) 5: 143–148.
10. Kariya S, Cureoglu S, Morita N, Nomiya S, Nomiya R, Schachern PA, Nishizaki K and Paparella MM: Vascular findings in the facial nerve canal in human temporal bones with diabetes mellitus. *Otol Neurotol* (2009) 30: 402–407.
11. Jorgensen MB: The inner ear in diabetes mellitus. *Histological studies. Arch Otolaryngol* (1961) 74: 373–381.
12. Kovar M: The inner ear in diabetes mellitus. *ORL J Otorhinolaryngol Relat Spec* (1973) 35: 42–51.
13. Maia CA and Campos CA: Diabetes mellitus as etiological factor of hearing loss. *Braz J Otorhinolaryngol* (2005) 71: 208–214.
14. Fukushima H, Cureoglu S, Schachern PA, Kusunoki T, Oktay MF, Fukushima N, Paparella MM and Harada T: Cochlear changes in patients with type 1 diabetes mellitus. *Otolaryngol Head Neck Surg* (2005) 133: 100–106.
15. Fukushima H, Cureoglu S, Schachern PA, Paparella MM, Harada T and Oktay MF: Effects of type 2 diabetes mellitus on cochlear structure in humans. *Arch Otolaryngol Head Neck Surg* (2006) 132: 934–938.
16. Robison WG Jr, Kador PF and Kinoshita JH: Retinal capillaries. Basement membrane thickening by galactosemia prevented with aldose reductase inhibitor. *Science* (1983) 221: 1177–1179.
17. Bainbridge KE, Hoffman HJ and 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.
18. Agrawal Y, Platz EA and Niparko JK: Risk Factors for Hearing Loss in US Adults. Data From the National Health and Nutrition Examination Survey, 1999 to 2002. *Otol Neurotol* (2009) 30: 139–145.
19. Nakashima T, Naganawa S, Sone M, Tominaga M, Hayashi H, Yamamoto H, Liu X and Nuttall AL: Disorders of cochlear blood flow. *Brain Res Brain Res Rev* (2003) 43: 17–28.

20. Weng SF, Chen YS, Hsu CJ and Tseng FY: Clinical features of sudden sensorineural hearing loss in diabetic patients. *Laryngoscope* (2005) 115: 1676–1680.
21. Orita S, Fukushima K, Orita Y and Nishizaki K: Sudden hearing impairment combined with diabetes mellitus or hyperlipidemia. *Eur Arch Otorhinolaryngol* (2007) 264: 359–362.
22. Makishima K and Tanaka K: Pathological changes of the inner ear and central auditory pathway in diabetics. *Ann Otol Rhinol Laryngol* (1971) 80: 218–228.
23. Lehmann ED, Riley WA, Clarkson P and Gosling RG: Non-invasive assessment of cardiovascular disease in diabetes mellitus. *Lancet* (1997) 350 Suppl 1: S114–19.
24. Poredos P: Intima-media thickness. Indicator of cardiovascular risk and measure of the extent of atherosclerosis. *Vasc Med* (2004) 9: 46–54.
25. John U, Baumeister SE, Kessler C and Völzke H: Associations of carotid intima-media thickness, tobacco smoking and overweight with hearing disorder in a general population sample. *Atherosclerosis* (2007) 195: e144–149.
26. Jansson PA: Endothelial dysfunction in insulin resistance and type 2 diabetes. *J Intern Med* (2007) 262: 173–183.
27. Hartge MM, Unger T and Kintscher U: The endothelium and vascular inflammation in diabetes. *Diab Vasc Dis Res* (2007) 4: 84–88.
28. Stehouwer CD, Lambert J, Donker AJ and van Hinsbergh VW: Endothelial dysfunction and pathogenesis of diabetic angiopathy. *Cardiovasc Res* (1997) 34: 55–68.
29. Hadi HA and Suwaidi JA: Endothelial dysfunction in diabetes mellitus. *Vasc Health Risk Manag* (2007) 3: 853–876.
30. Schalkwijk CG and Stehouwer CD: Vascular complications in diabetes mellitus. The role of endothelial dysfunction. *Clin Sci (Lond)* (2005) 109: 143–159.
31. Kanters SD, Algra A and Banga JD: Carotid intima-media thickness in hyperlipidemic type I and type II diabetic patients. *Diabetes Care* (1997) 20: 276–280.
32. Celik O, Yalçin S, Celebi H and Oztürk A: Hearing loss in insulin-dependent diabetes mellitus. *Auris Nasus Larynx* (1996) 23: 127–132.
33. Axelsson A, Sigroth K and Vertes D: Hearing in diabetics. *Acta Otolaryngol Suppl* (1978) 356: 1–23.
34. Wackym PA and Linthicum FH Jr: Diabetes mellitus and hearing loss. Clinical and histopathologic relationships. *Am J Otol* (1986) 7: 176–182.