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Vascular and Neuroepithelial Histopathology of the Sacculle in Humans with Diabetes Mellitus

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Abstract

Hypothesis—This study aimed to determine if there are quantitative differences in the neuroepithelium and microvasculature of the sacculle between subjects with and without diabetes mellitus (DM).

Background—Histopathologic changes that may underlie the association between DM and vestibular dysfunction have not been characterized in humans.

Methods—Human temporal bones (HTBs) from 39 subjects with DM (n=16 type I DM (T1DM), n=23 type II DM (T2DM)) were compared to 40 group age-matched controls. Vessel wall thickness was measured from the saccular arteriole. Type I and type II vestibular hair cell (VHC) counts were performed on perpendicularly oriented saccular maculae using differential interference contrast microscopy (T1DM: 5 HTB/3 subjects; T2DM: 9HTB/8 subjects; controls: 25 HTB/20 subjects).

Results—The mean density of type I VHCs was 16 to 17% lower in the DM groups compared to controls (T1DM 52.21 [4.26], T2DM 53.3[5.34], control 63.14 [2.49] cells/mm², $p=0.02$). There were no differences between T1DM, T2DM, and control groups in type II VHC density (T1DM 40.89 [5.17], T2DM 40.44 [6.93], control 42.80 [1.79] cells/mm², $p=0.92$) or in mean vessel wall thickness (T1DM 2.23[0.62], T2DM 2.18 [0.53], control 2.00 [0.53] μ m, $p=0.26$).

Conclusion—Neuroepithelial pathology, manifested as lower density of type I VHCs, was observed in the sacculles of subjects with DM. Saccular microangiopathy, expressed as alterations in arteriole thickness, was not observed. These findings are consistent with histologic observations in animals with experimentally induced diabetes. DM may have a selective and deleterious effect on human vestibular sensory epithelia.

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Keywords

temporal bone; saccule; vestibular; labyrinth; diabetes mellitus; histopathology; otopathology; human

Introduction

The worldwide incidence and prevalence of diabetes mellitus (DM) are increasing at epidemic rates (1, 2). In multiple organ systems, the chronically high glucose concentrations that characterize the disease cause capillaries and small arterioles to accumulate basement membrane material that thickens vessel walls and alters vascular permeability (3). Known as diabetic microangiopathy, this hyperglycemia-induced microvascular pathology results in the most commonly recognized diabetes complications: retinopathy, nephropathy, and peripheral neuropathy (3).

Diabetes may also result in pathology and dysfunction of the inner ear. DM is epidemiologically associated with sensorineural hearing loss (4-6). The cochleae of humans and animals with DM manifest corresponding microangiopathic and neuroepithelial changes, including capillary basement membrane thickening in the stria vascularis, thickening and occlusion of cochlear arterioles and arteries, and variable degrees of cochlear hair cell and spiral ganglion cell loss (7, 8). Adults with DM are also at increased risk of vestibular dysfunction and falls, independent of the presence of peripheral neuropathy and retinopathy (9, 10). When comparing vestibular test results to those of controls, subjects with DM have more dysfunction of the otolith organs, superior and lateral semicircular canals, and/or their corresponding vestibular nerve afferents (11-13). However, any corresponding vestibular end organ pathology in humans with DM remains uncharacterized.

A series of light and electron microscopic investigations of pathologic changes in the saccule was carried out in rats with drug-induced diabetes (14-16). Unlike controls of the same age, saccules from rats with longer durations of diabetes had scattered type I vestibular hair cell degeneration but neither group had type II vestibular hair cell degeneration (14). Diabetic rat saccules also had greater capillary lumen diameters and capillary density. However, there was no evidence of saccular capillary basement membrane thickening even though the kidneys of the same animals manifested clear evidence of concurrent microangiopathy in the form of glomerular basement membrane thickening (15).

This human temporal bone study aimed to quantitatively compare the vestibular neuroepithelium and microvasculature of the saccule between subjects with and without DM. Based on observations in the rat model (14), we hypothesized that there would be differential loss of type I vestibular hair cells compared to type II vestibular hair cells in the saccules of subjects with DM. Despite the findings in the rat model (15), we also hypothesized that saccule arteriolar wall thickness, a surrogate for microangiopathy, would be greater among subjects with DM because of the consistent observations of vascular basement membrane thickening and increased arteriole thickness in other human labyrinthine vessels.

Materials and Methods

Subjects and specimens

This study examined temporal bones from 39 patients with DM (15 women, 24 men; ages (mean [standard deviation] 57 [17] years (range 18-91 years)). There were 16 subjects with type I DM (T1DM) (48 [20] years; range 18-91 years) and 23 subjects with type II DM (T2DM) (63 [12] years; range 45-86 years). The control group was composed of 40 group age-matched normal temporal bones from subjects without DM (16 women, 24 men, mean age 56 [20], range 18-95 years). Temporal bones from subjects known to have the following conditions that might affect the vestibular system were excluded from this study: head trauma, systemic autoimmune disorders, ototoxic drug use, and any defined otologic disease (e.g., Meniere's disease, otosclerosis, active otitis media).

Temporal bones were obtained from the collection at the University of Minnesota (Minneapolis, MN). All of the temporal bones had been removed at autopsy, fixed in formalin solution, decalcified, and embedded in celloidin. Each bone was serially sectioned in the horizontal plane at a thickness of 20 μ m. Every 10th section was stained with hematoxylin and eosin (HE) and mounted on a glass slide for light microscopy. The study was approved by the Institutional Review Board of the University of Minnesota (0206M26181).

Sacculle vessel wall thickness measurements

Morphometric measurements were made on the perpendicular cross section of the most prominent straight arteriole underlying the saccular macula in one temporal bone from each subject. The saccular arteriole branch from the saccular artery, which is a branch of the posterior (or inferior) vestibular artery (17). Images were acquired with a digital camera connected to a personal computer. The calibrated image of the vessel was obtained at a magnification of $\times 600$. The length and cross sectional areas of the cut surfaces of the vessel were measured using Image-Pro Plus version 3.0 image analysis software (Media Cybernetics, Silver Springs, MD, USA). As described by Robinson (18), vessel wall thickness was characterized as the ratio between the vessel wall area (VWA) and the vessel wall length (VWL). VWA is calculated by subtracting the cross sectional area of the vessel lumen from the total cross sectional area of the vessel. VWL is the difference between the lengths of the lines delimiting the outer border and the inner border of the VWA.

Vestibular Hair Cell Density

Quantitative assessment of the saccular hair cells was performed (19). Assessment was restricted to specimens with minimal to mild postmortem neuroepithelial autolysis and in which the plane of section was perpendicular to the surface of the sensory epithelium. For each suitable sacculle, the 3 consecutive middle sections of the macula were selected for counting. Using differential interference contrast microscopy at $\times 1008$ magnification (Plan-Apochromat, Carl Zeiss Microscopy, LLC, Thornwood, NY, USA), the cuticular plate and stereociliary bundles of the saccular vestibular hair cells were visualized and types I and II vestibular hair cells were distinguished morphologically. Counts of hair cells with visible nuclei were performed over viewable surface areas of 0.006 mm². The results were

expressed in terms of cell density, the number of hair cells per 0.01 mm² surface area. Surface area was determined by multiplying the thickness of the section (20 µm) by the length of the sensory epithelium where the count was made. The raw hair cell counts were corrected for double counting of nuclei split between 2 sections using the formula of Abercrombie [$H_i = h_i \times t/(t + d)$ where H_i = corrected density of hair cells, h_i = raw density, t = thickness of section (20 µm), and d = mean value of nuclear diameters in 250 vestibular hair cells], which results in correction factors of 0.82 for type I hair cells and 0.87 for type II hair cells (19).

Statistical Analysis

Results are presented as mean [standard deviation (SD)]. Statistical comparisons were performed using one-way ANOVA for vessel wall thickness and with the Kruskal Wallis H-Test, followed by a post-hoc Mann Whitney test when differences were identified, for age and vestibular hair cell density. A p value less than 0.05 was considered statistically significant.

In some cases, the same individual contributed both ears to the sample population for vestibular hair cell counts (but not for vessel wall measurements).

Results

There was no difference in the mean age at death between the age-matched DM (n=39) and control (n=40) groups undergoing morphologic assessment and vessel wall thickness measurements (control 56 [SD 20], T1DM 48[20], T2DM 63 [12] years, $p=0.054$). There were no qualitative differences in saccule morphology between subjects with and without DM. In all specimens, maculae were of normal shape, otoconial membranes were identified, and neither hydrops nor collapse of the saccular membrane were present. A representative light micrograph of the right temporal bone from a 56-year-old woman with T2DM is shown in Figure 1, illustrating the location of the saccular macula and arteriole within the vestibule.

The mean vessel wall thickness of the saccular arteriole did not differ between subjects with T1DM, T2DM, and controls ($p=0.26$) (Table 1). Using the observed mean [SD] of the control group for the calculation, the study had 80% power to detect a difference in thickness of 0.45 µm (23%).

Saccular epithelia suitable for quantitative vestibular hair cell analysis were present in 14 temporal bones from 11 subjects with DM (3 with T1DM [5 temporal bones], 8 with T2DM [9 temporal bones]) and in 25 temporal bones from 20 control subjects (Figure 2). There was no significant difference in the mean age at death between the groups undergoing hair cell counts (control: 55 [21], T1DM: 41 [13], T2DM: 62 [12] years, $p=0.15$). The mean type I hair cell density was 17% lower in the T1DM and 16% lower in T2DM groups compared to controls ($p=0.015$) (Table 1). While type I hair cell density differed between T1DM and controls ($p=0.04$) and between T2DM and controls ($p=0.02$), there was no difference between T1DM and T2DM groups ($p=0.74$). There was no difference in type II hair cell density between the T1DM, T2DM, and control groups ($p=0.72$) (Table 1).

Discussion

In this study, we sought histologic evidence of peripheral vestibular pathology among subjects with diabetes. We observed that the density of type I vestibular hair cells was 16 to 17% lower among the saccules of diabetic subjects, compared to normal controls, and did not differ by diabetes type. There were no differences in type II vestibular hair cell density. We also observed no difference between groups in saccular arteriole vessel wall thickness and thus found no light microscopic evidence of saccular arteriole microangiopathy.

Our findings of a differential loss of type I vs. type II vestibular hair cells in the absence of vestibular diabetic microangiopathy are consistent with observations in a diabetic rat model (14, 15). Specifically, Myers and colleagues observed scattered abnormal appearing type I vestibular hair cells in the saccules of rats with long durations of diabetes (9-12 months) that were not present in controls. Electron micrograph examination indicated that the abnormal appearing type I hair cells were degenerating, based on their shrunken size, granular osmophilic cytoplasm, poorly preserved cytoplasmic organelles, and nuclear chromatin clumping (14). Individual nerve fibers continued to innervate both degenerating and normal-appearing hair cells, suggesting that the cell death did not result from neuropathy (14, 16). Using the same model, Meyers observed that there were no differences between diabetic rats and controls in the mean wall thickness of capillaries underlying the saccule when examined by light microscopy or in the capillary basal lamina thickness measured by electron microscopy (15).

One potential explanation for differential hair cell loss in the absence of microangiopathy is inter-cell type variation in glucose uptake and handling. Cells that cannot sufficiently limit glucose influx in the setting of hyperglycemia appear to be particularly vulnerable to glucose toxicity and injury (3). Glucose uptake is regulated in most tissues by the level of expression of glucose transporters on cellular surfaces (20). Multiple glucose transporter isoforms exist, each having distinct kinetic properties, regulation, and expression patterns (20). Various tissues in the cochlea (e.g., organ of Corti vs. stria vascularis) differ in their expression of glucose transporter isoforms and these disparities have been proposed as mechanisms for cochlear subsite-specific hyperglycemic pathology (7). Glucose transporter isoforms in vestibular neuroepithelial cells are not well characterized, but there is evidence that the saccule is a site of insulin signaling and that glucose handling may differ between cell types. Specifically, in surgical explants of human saccules, the insulin-sensitive glucose transporter (GLUT4) was detected in the saccular vestibular hair cells and supporting cells while the insulin receptor was expressed only in the vestibular hair cells (21). The vestibular hair cell types were not distinguished in the study, but type I and II vestibular hair cells are known to differ in passive membrane and electrical filtering properties (22) as well as in their uptake and/or retention of substances such as gentamicin (23). Thus, it is theoretically possible that the hair cell types differ in glucose handling as well, leading to differential susceptibility to hyperglycemia. Further elucidation of the glucose transporters and insulin signaling pathways in the vestibular sensory neuroepithelia may shed more light on the underlying mechanism of our findings.

The apparent absence of saccular arteriole microangiopathy among subjects with DM is also intriguing, particularly because it conflicts with findings in other human inner ear sub-sites (7, 8, 24). When cochlear and facial nerve pathology was characterized in the temporal bones of a majority of the same diabetic subjects examined in the present study, the mean wall thicknesses of the cochlear spiral modiolar artery and of the small vessels within each segment of the facial nerve canal were 70 to 200% greater among the subjects with DM than normal controls (8, 24). The present study of the sacculus was sufficiently powered to detect a difference in vessel wall thickness of 23% (0.45 μ m) or greater. Thus, our results suggest that the saccular arteriole may not experience the same amount of diabetic angiopathic change as other inner ear sub-sites. Saccular microangiopathy was also absent in rats with drug induced diabetes who had significant microangiopathic glomerular basement membrane thickening in their kidneys (15). Taken together, these findings are consistent with either a differential susceptibility of the saccular vasculature to diabetes and/or may reflect a chronological order effect, with cochlear and facial nerve vessel damage preceding vestibular.

Although tests of saccular function were not available for the subjects of this investigation, our finding of type I vestibular hair cell loss is consistent with studies of vestibular function among diabetics. While the exact roles of type I vs. type II vestibular hair cells in sensory processing remain undetermined, the cervical vestibular evoked myogenic potential (cVEMP) response, a test of saccular and inferior vestibular nerve function, appears to be more dependent on the presence of functioning type I than type II vestibular hair cells in the saccular maculae of guinea pigs (25). Thus, sufficient selective type I hair cell loss would be expected to affect cVEMP responses (although the degree of loss necessary to produce overt dysfunction is unknown). Indeed, a recent study comparing vestibular test results from a sample of adults over 50 years of age with at least a 10 year duration of T2DM to matched controls found that the cVEMP response was absent in 32% of DM ears compared to 12% of control ears ($p=0.02$) and that the cVEMP peak-to-peak amplitude was decreased among those with T2DM (13). Similarly, sand rats with diet-induced hyperglycemia had reduced amplitudes and prolonged latencies of the linear vestibular evoked potential (VsEP), which is an objective correlate of otolith end organ dysfunction (26). Some (11, 12), but not all (13, 27), human studies also found delayed latencies of the cVEMP response among those with DM. However, our study was not designed to identify the histopathologic correlates of cVEMP latency differences, as they are more likely to result from retrolabyrinthine neural pathology (28).

This study has several limitations. Specimens were preserved in a manner suitable only for light microscopic evaluation, precluding ultrastructural examination of the hair cells, capillary basement membrane, and myelin sheaths. Vestibular hair cell counts could only be performed in sensory organs containing perpendicularly sectioned regions and that have minimal post-mortem autolysis. This limited our quantitative analysis to the sacculus. Archival human temporal bone studies also have inherently limited sample sizes and that precluded accurate subgroup analysis of our heterogeneous sample (e.g., by treatment modality). Full medical and vestibular histories and electrophysiologic testing were not available for most subjects, impeding our ability to correlate the findings with symptoms or signs or to control for potential confounders, comorbidity, duration or severity of disease,

and treatment modalities. Accordingly, while the results support an association between diabetes and our histopathological observations, direct causation cannot be inferred. Finally, the degree to which saccular hair cell density correlates with vestibular symptoms is unknown. Thus, we cannot assess if the observed difference in type I hair cell density would be sufficient to produce vestibular symptoms in diabetic patients or contribute to diabetes-related fall risk.

Conclusions

Diabetes is associated with saccular neuroepithelial pathology, manifested as a lower density of type I vestibular hair cells. The saccular microvasculature may be less susceptible to the effects of diabetes than other inner ear sites, as no evidence of microangiopathy was observed. Our findings are consistent with histologic observations in an animal model with experimentally induced diabetes, supporting the use of this model in future investigations. Additional characterization of cellular glucose uptake and handling may shed further light on the selective and deleterious effects of diabetes on human vestibular sensory epithelia.

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Figure 1.

(A) Light micrograph of the right temporal bone from a 56-year-old woman with type II diabetes mellitus (hematoxylin and eosin stain). Magnified view of boxed area in (A) shown in (B). The straight arteriole of the saccule supplies the macula from the saccular artery, a branch of the posterior (inferior) vestibular artery (17). There were no qualitative light microscopic differences between the diabetes and control groups. The boxed area in B corresponds to Figure 2B.

Figure 2.

Differential interference photomicrographs of the saccular macula from (A) a 60 year-old-man without diabetes and (B) the 56 year old woman with type II diabetes mellitus from Figure 1. Hair cells (HC) are located apically in the neuroepithelium and are distinguished from supporting cells by the presence of a stereocilia bundle and cuticular plate. Type I HCs are flask shaped, with rounded bases, narrow apical necks and spherical nuclei. Type II HCs are cylindrical with ovoid nuclei (19). Thin arrows: Type I Vestibular Hair Cells; Thick arrows: Type II Vestibular Hair Cell; Arrow heads: Supporting Cells.

Quantitative comparison of saccular maculae between subjects with and without diabetes: arteriole thickness and vestibular hair cell density

Table 1

	Control			T1DM			T2DM		
	N	Mean (SD)		N	Mean (SD)		N	Mean (SD)	p-value
Vessel Wall Thickness (μm)	40	2.00 (0.54)		16	2.23 (0.62)		23	2.18 (0.53)	0.26
Hair Cell Density (<i>cells/0.01 mm²</i>)	25		5				9		
Type I VHC		63.14 (12.44)			52.21 (4.26)			53.3 (5.34)	0.02
Type II VHC		42.80 (8.97)			40.89 (5.17)			40.44 (6.93)	0.92

T1DM: Type I DM, T2DM: Type II DM, VHC: Vestibular hair cell, SD: standard deviation.