Early Indices of Reduced Cochlear Function in Young Adults with Type-1 Diabetes Revealed by DPOAE Fine Structure

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Abstract

Background: The relationship between type-1 diabetes mellitus (DM) and cochlear dysfunction remains inconclusive.

Purpose: The purpose of this study was to examine otoacoustic emissions (OAEs) in normal-hearing young adults with type-1 DM as compared with matched controls and identify potential covariates influencing OAE findings.

Research Design: Cross-sectional study.

Study Sample: N = 40 young adults aged 18–28 years including individuals with type-1 DM (n = 20) and age–gender matched controls (n = 20) with normal hearing sensitivity.

Data Collection and Analysis: Measures of pure-tone threshold sensitivity and OAEs, including distortion product otoacoustic emissions (DPOAEs), transient evoked OAEs, and DPOAE fine structure, were compared between groups. Covariates such as noise exposure and DM-related factors (e.g., duration of disease, glycated hemoglobin levels) were considered. Statistical analysis included analysis of variance and linear regression.

Results: Measures of hearing sensitivity and auditory function in both groups were comparable for all assays, except DPOAE fine structure. A reduced number of fine structure peaks and component amplitudes were found in the type-1 diabetes DM group with the primary difference in the reflection component.

Conclusions: The results indicate that reduced cochlear function in young adults with type-1 DM can be revealed using DPOAE fine structure, suggesting potential clinical applications of DPOAE fine structure in early identification of cochlear pathology. Potential factors underlying these findings are discussed.

Key Words: diabetes, fine structure, noise, otoacoustic emission

Abbreviations: ANOVA = analysis of variance; DM = diabetes mellitus; DPOAE = distortion product otoacoustic emission; LSF = least squares fit; MEMR = middle ear muscle reflex; MOCR = medial oliviocochlear reflex; NCV = nerve conduction velocity; OAE = otoacoustic emission; RMS = root mean square; SEM = standard error of the mean; SOAE = spontaneous otoacoustic emission; SPL = sound pressure level; TEOAE = transient evoked otoacoustic emission

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INTRODUCTION

The relationship between diabetes mellitus (DM) and hearing loss has been studied and debated for more than a century. Previous studies have been inconclusive and even contradictory regarding the influence of diabetes on auditory function, as reviewed by Maia and Campos (2005). DM is suggested to contribute to dysfunction of the auditory pathway through numerous mechanisms, with cochlear microangiopathy and diabetic neuropathy considered primary factors (Maia and Campos, 2005; Austin et al, 2009; Konrad-Martin et al, 2010). The past few decades have seen an unprecedented increase in DM throughout the world (Wild et al, 2004; Menke et al, 2014), which raises concern for increased risk for auditory pathology. The aim of the present study is to further explore potential effects of type-1 DM on cochlear function and specifically through the measurement of distortion product otoacoustic emission (DPOAE) fine structure.

OAE and Diabetes

OAE, sounds generated by a healthy inner ear, provide a sensitive assay of cochlear function. Several groups have examined the influence of type-1 DM/insulin-dependent DM on OAEs in adult and pediatric populations. Di Leo et al (1997) and Di Nardo et al (1998) examined DPOAEs (Level: $L_1 = L_2 = 70$ dB sound pressure level [SPL], $f_2/f_1 = 1.22$) and transient evoked OAEs (TEOAE) (80 dB peak SPL clicks) in adults (mean age = 28 years), with type-1 DM and normal pure-tone thresholds compared with matched controls. Di Leo et al (1997) found reduced TEOAE amplitudes in participants with type-1 DM diabetes and comorbidity of reduced nerve conduction velocity (NCV) but not in those with normal NCV. On the other hand, Di Nardo et al (1998) found reduced DPOAE amplitudes in patients with and without reduced NCV. The researchers attributed the changes in OAE amplitudes to microvascular compromise, despite not including measurements for the presence of microangiopathy. Lisowska et al (2001) also reported reduced DPOAE ($L_1 = L_2$, 35–70 dB SPL, $f_2/f_1 = 1.22$) amplitudes in normal hearing adults (aged 21–42 years) with type-1 DM compared with matched controls. In contradiction to the suggested mechanism proposed by the previous studies, they reported no relationship to the presence of microangiopathy (as measured by ophthalmoscopy and 24-hour albumin excretion rate). The authors suggested that the impairment was related to early metabolic complications, including nonenzymatic glycation related to excess free radical activity. Ottaviani et al (2002) evaluated TEOAEs (75–90 dB peak SPL clicks) and DPOAEs ($L_1 = L_2 = 70$ dB SPL, $f_2/f_1 = 1.22$) in normal-hearing adults (mean age = 31 years) with type-1 DM. Amplitudes were significantly reduced compared with matched controls for both types of OAE responses. These findings demonstrate changes in OAE amplitudes in adult populations despite hearing sensitivity within normal limits.

Findings in children and teenagers have been less conclusive. TEOAEs (80, 70, and 60 dB peak SPL clicks) measured in children from the age of 6 to 16 years revealed no significant difference in TEOAE amplitude when compared with matched controls (Namyslowski et al, 2001). Similar findings were described by Ugur et al (2009), who found no difference in TEOAE (75–85 peak SPL clicks) or DPOAE ($L_1 = L_2 = 70$, $f_2/f_1 = 1.22$) amplitudes in normal-hearing children (aged 6–16 years) with type-1 DM compared with matched controls. In addition, they found no difference in spontaneous OAEs (SOAEs). More recently, ALDajani et al (2015) examined DPOAEs ($L_1 = 65$ dB SPL, $L_2 = 55$ dB SPL, $f_2/f_1 = 1.22$) in children (aged 4–14 years) with type-1 DM and normal hearing sensitivity compared with matched controls. They found no difference in DPOAE amplitudes, except at 1000 Hz (lower in type-1 participants) and found no relationship to diabetes control or duration of disease. By contrast, Abd El Dayem et al (2014) found significantly lower TEOAE amplitudes at 1000, 1500, and 4000 Hz in children with type-1 DM; however, the children in that study with DM also had elevated pure-tone thresholds compared with controls.

In summary, studies that have focused on type-1 DM and OAEs have contradictory findings. Reduced amplitude in TEOAEs and DPOAEs in adults were reported by several studies (Di Nardo et al, 1998; Lisowska et al, 2001; Ottaviani et al, 2002) whereas one reported no difference without the presence of reduced NCV (Di Leo et al, 1997). Studies limited to children and teenagers with type-1 DM have demonstrated no significant differences in TEOAE, DPOAE, or SOAEs compared with matched controls (Namyslowski et al, 2001; Ugur et al, 2009), except for one study at one DPOAE frequency (ALDajani et al, 2015) and another that examined TEOAEs in children with elevated pure-tone thresholds (Abd El Dayem et al, 2014).

OAE Theory and Sensitivity to Pathology

Recently there has been an emerging interest in understanding the cochlear sources of OAEs, methods for increasing OAE sensitivity to cochlear dysfunction, and implications for pathology on relative source contributions. The current prevailing theory suggests that OAEs arise by ≥2 different mechanisms: nonlinear distortion and linear reflection. This so-called "two-source theory" of OAE generation states that the nonlinear distortion source stems from localized distortion induced by the response of the basilar membrane near the peak

overlap of the traveling waves evoked by the primaries. By contrast, the reflection source stems from linear reflection of the energy from preexisting small irregularities in cochlear mechanics near the frequency of the emission (Talmadge et al, 1998; Shera and Guinan, 1999; Talmadge et al, 1999). Although all evoked OAEs are theoretically mixtures of nonlinear distortion and linear reflection sources, experimental evidence based on differential phase characteristics suggests that low-level TEOAEs predominantly arise from linear reflection sources whereas DPOAE are mostly dominated by the nonlinear distortion source. Excellent reviews on these sources are available to the interested reader (Kemp, 1986; Shera, 2004; Johnson, 2010).

When DPOAEs are obtained with very small frequency steps, they show quasiperiodic peaks and valleys in amplitude referred to as *fine structure* (He and Schmiedt, 1993). The DPOAE fine structure measured in the external ear canal is representative of the mixture and interaction of the two source components as described previously. Because DPOAE components are generated by different mechanisms that arise from different cochlear regions, the two components are potentially differentially sensitive to changes in cochlear function. Selective reduction of the more vulnerable reflection component can modify the variability of the DPOAE with frequency without leading to a reduction of overall level (Rao and Long, 2011).

Numerous investigators (Hall and Lutman, 1999; Lucertini et al, 2002; Shupak et al, 2007; Sisto et al, 2007) have suggested that OAEs may provide sensitive early indices of cochlear damage, sometimes referred to as "subclinical" damage, meaning reduced OAE responses despite normal audiometric pure-tone sensitivity. Furthermore, fine structure changes have been suggested to provide an early indication of damage before changes in DPOAE level alone. Mauermann et al (1999) examined variable audiometric configurations of cochlear hearing loss and suggested that if hearing loss occurred in the frequency region of the distortion product ($2f_1 - f_2$), but the region of the primaries (f_1, f_2) was normal, the fine structure would be diminished but overall level of the response preserved. However, when $2f_1 - f_2$ fell in a region of normal threshold sensitivity the fine structure was preserved as long as the distortion product was generated, even with mild damage to the region of the primaries. Reuter and Hammershøi (2006) examined fine structure in a temporary threshold shift experiment and did not find a systematic change in the overall fine structure. Wagner et al (2008) found a decrease in the number of fine structure with increasing hearing loss. Yet, neither Reuter and Hammershøi (2006) nor Wagner et al (2008) examined differential effects on source contributions by separating the source components. Rao and Long (2011) examined changes in the DPOAE fine structure and separated components before and after the consumption of aspirin. Low-level stimuli resulted in the reduction of both components with the reflection component showing more vulnerability, whereas higher level stimuli showed reduction in only the reflection component. On the other hand, Abdala and Dhar (2012) found reduction in the distortion component with age from newborn to older adults, with smaller drops in the reflection component.

The purpose of the study reported here is to examine measures of cochlear function in young adults with type-1 DM and normal hearing sensitivity compared with age–gender matched control participants. The first aim tests the hypothesis that young adults with type-1 DM have reduced cochlear function compared with matched controls. The second aim tests the hypothesis that covariates (e.g., glycated hemoglobin levels) are related to reduced cochlear function.

MATERIALS AND METHODS

Participants

Participants were recruited over the period of January 2010 through August 2010, from the Vanderbilt Eskind Diabetes Clinic, Vanderbilt University Medical Center, and via internet postings on the Vanderbilt Kennedy Center and the Vanderbilt Diabetes Research clinical studies websites. Inclusion criteria required participants to be aged 18–28 years, have normal to near-normal hearing (≤30 dB HL at 250–8000 Hz, no air-bone gap >10 dB [all participants had thresholds ≤25 dB HL]), normal middle ear function (static compliance >0.3 ml, normal ear canal volume, and middle ear pressure ± 100 daPa; ASHA, 1997), nonsmoker, no use of aspirin (within 48 hours), and no significant exposure to other ototoxic drugs.

A power analysis was performed to determine the required sample size. The analysis was based on the effect size from a study that evaluated TEOAEs and DPOAEs in adults with type-1 DM compared with controls (Ottaviani et al, 2002). To obtain a power of $\beta = 0.80$ a sample size of ~16 participants was indicated per group. Based on this information, a sample size of 20 participants per group was planned for a total n = 40. Approval was obtained from the Vanderbilt University Institutional Review Board and all participants provided informed consent using Institutional Review Board–approved materials and procedures.

The study sample consisted of 20 participants with type-1 diabetes (referred to as type-1 DM group) and 20 age–gender matched controls (referred to as control group). Participants with type-1 DM were primarily recruited from the Vanderbilt Eskind Diabetes Clinic. Control participants, recruited using the multiple

methods indicated, were subsequently matched to the type-1 DM participants for age (within one year) and gender. Control participants were not tested to rule out diabetes or prediabetes. Eighteen of the participants were male and 22 were female.

History

Comprehensive medical history including diabetes and otologic variables and a noise exposure history were obtained through interviewer-administered questionnaires. Questions concerning DM included age of onset, duration, method of treatment, average glycated hemoglobin (i.e., average of past five measures), and quality of DM management (self-reported and based on glycated hemoglobin measures). Noise exposure was estimated from reported noise exposure for nine noisy activities and used to calculate LAeq8760h. In brief, "L" represents sound pressure in dB SPL, "A" represents the use of an A-weighted frequency response, "eq" represents a 3-dB exchange rate for calculation of the time/level relationship, and "8,760" represents the total duration of the noise exposure in hours over one year. Further details on methods for noise estimation and other variables can be found in Spankovich et al (2017) and in a publically available dissertation (Spankovich, 2010).

Measurements

All testing was performed in both the right and left ears of the participants. An otoscopic examination was completed to rule out the presence of occluding cerumen and/or visible pathology. Testing was performed in a quiet laboratory space (middle-ear measures) and double-walled sound-attenuating room (behavioral thresholds, OAEs) while the participant was seated in a comfortable chair. A closed-captioned movie was viewable through a sound-treated window on a monitor in the adjoining room. Participants were instructed to sit quietly and try to minimize physiological noise (i.e., heavy breathing, movement, etc.). All OAEs (excluding DPOAE fine structure) were recorded and analyzed with the Intelligent Hearing Systems (Miami, FL) Smart TrOAE and Smart DPOAE and the Etymotic Research (Elk Grove Village, IL) ER10D probe and ER3A insert earphones. Test stimuli were calibrated using a Brüel and Kjaer Pulse (software version 11.0) system (Naerum, Denmark).

Middle Ear Assessment

Tympanometry and middle ear muscle reflex (MEMR) thresholds for tones were measured to rule out middle ear dysfunction and provide a measure of lower brainstem function, respectively. Both ipsilateral and contralateral MEMR thresholds (500–4000 Hz) were measured in 5-dB steps on a Grason Stadler GSI TympStar (Grason-Stadler Inc., Eden Prairie, MN). Tympanometry was compared with normative values (ASHA, 1997). All included participants met normative criteria and had present reflexes.

Behavioral Pure-Tone Thresholds

Pure-tone thresholds were tested with a Grason Stadler GSI 61 audiometer (Grason-Stadler Inc.) using Etymotic ER3A insert earphones (Etymotic Research), a RadioEar B71 bone conduction stimulator (New Eagle, PA), and a Sennheiser HDA 200 extended high frequency (10000–16000 Hz) headphones (Wedemark, Germany).

The audiometer and transducers were calibrated by a certified engineer (e3 Med-Acoustics, Atlanta, GA) to meet American National Standards Institute (ANSI S3.6-1989, 1996, 2004 and 3.43-1992) standards. Air conduction thresholds were measured at octave and interoctave frequencies from 250 through 16000 Hz and bone conduction at octaves from 250 to 4000 Hz, in 5-dB steps using a standard method of limits technique.

TEOAEs

TEOAEs were obtained with 80-dB peak SPL clicks (nonlinear stimulus protocol) and 65-dB peak SPL clicks (linear stimulus protocol). The nonlinear protocol provides a method to control for stimulus artifact and is a stimulus paradigm used in clinical protocols. The use of the term "nonlinear" can be confusing but refers in this instance to a change in the stimulus polarity and intensity (i.e., stimulus sets of three 80-dB peak SPL positive polarity clicks and one 90-dB peak SPL inverse polarity click). The duration of each click was 75 μsec; 1,024 stimuli were presented at a rate of 19.30 clicks/second and averaged. The linear protocol used a 75-μsec click, but was presented at two different rates, 19.30 and two clicks/second at 65 dB peak SPL. The TEOAE recorded at two clicks/second was extracted from data collected in a quiet ("without suppressor") condition during the assessment of the medial oliviocochlear reflex (MOCR) via TEOAE suppression based on (Berlin et al, 1995). The slower rate used in the TEOAE suppression model allows for the forward masking paradigm used for the MOCR approach to allow suppression measures in ipsilateral and bilateral conditions. Our MOCR data are not described here but in brief did not show significant differences between groups. To control for potential stimulus artifact occurring early in the response with the linear protocol (65 dB peak SPL at the two rates), the Kresge EchoMaster Program (version 4.0, Louisiana State University, New Orleans, LA; Wen et al, 1993) was used to quantify emission amplitude in an 8- to 18-ms time window. This software provides a root mean square (RMS) value in any selectable time interval.

DPOAEs

A DPOAE test was performed using f_2 tone frequencies of 500–8000 Hz, four frequencies per octave, f_2/f_1 ratio of 1.22, and intensity levels of $L_1 = 65$, $L_2 = 55$ dB SPL.

DPOAE Fine Structure

Custom programs for Macintosh computers developed by C. L. Talmadge PhD were used to generate stimuli and record the ear canal signals (RecordAppX). Two ER2 (Etymotic Research) tube phones were connected to a two-port ER10B+ low-noise microphone, which was inserted in the ear canal using a disposable tip. The stimuli were conditioned, preamplified and filtered (Stanford SR650, 300–10000 Hz) before being digitized by a MOTU 828 (24 bit, 44,100 samples/second) under computer control.

Stimuli were initially calibrated using the Knowles Electronics Manikin for Acoustic Research and a Brüel & Kjaer Pulse (software version 11.0) system to estimate level at the eardrum. In addition, at the start and end of each session, white noise was played through each tube phone in turn, recorded and analyzed using a fast Fourier transform to evaluate probe fit for consistency and to ensure that levels near 1000 Hz approximated the required stimulus level for each output.

Tone pairs were presented using an up-, down-frequency sweeping paradigm (Long et al, 2008), an f_2/f_1 ratio of 1.22, f_2 range from 1000 to 11314 Hz (seven second sweep, ~2 seconds per octave), and stimulus levels $L_2 = 35, 50, 65$ and $L_1 = 39$ dB SPL + $0.4 \times L_2$. These intensities were based on the so-called "scissors" paradigm that was developed to ensure that the region of maximum overlap stays fixed when stimulus level is changed to optimize the level of the distortion source (Kummer et al, 1998). Previous work has suggested the scissor paradigm may be more sensitive to cochlear dysfunction than the commonly used $L_2 = L_1$-10 dB SPL primary levels and evoke larger responses at lower levels (Johnson and Baranowski, 2012). Sweeps were obtained for each L_2 stimulus level and averaged to increase the signal-to-noise ratio between the measured DPOAE fine structure and background noise. The number of sweeps obtained at each level depended on the primary level, with the lowest level requiring more sweeps to ensure a good signal-to-noise ratio ($L_2 = 35$, N = 60) than higher presentation levels ($L_2 = 50$, N = 36; $L_2 = 65$, N = 24). Testing was performed in both ears and at the three different levels in one session.

Spectrograms of the individual sweeps were visually inspected and sweeps contaminated by noise (e.g., body movement and coughing) were eliminated before averaging at each level. The remaining sweeps with identical stimulus conditions (i.e., sweep direction and stimulus intensity) were averaged to reduce the noise floor and subtracted to estimate the noise floor. Up- and down-frequency sweeps were analyzed independently and compared as a cross-check measure. The remaining data analyses were restricted to the up-sweep data. The up-sweep and down-sweep data provide comparable fine structure outcomes (Long et al, 2008).

The level and phase of the total DPOAE fine structure and its components were extracted using a least squares fit (LSF) procedure (Long and Talmadge, 1997). Overlapping Hann-windowed segments of data were analyzed with the LSF procedure. The bandwidth of the filter was determined by the size of the analysis window. The band-pass filter used in the LSF analysis changes center frequency as the DPOAE frequency changes, allowing the total amplitude and phase to be estimated as a function of frequency. A wideband LSF analysis was used to estimate the total DPOAE fine structure (5,512 analysis points, 8 Hz filter).

MATLAB-based analysis software (NIPR) was used to separate the nonlinear distortion and linear reflection sources from the resulting composite DPOAE fine structure. NIPR uses an inverse fast Fourier transform–based algorithm to convert the frequency domain complex–valued DPOAE fine structure amplitude to the time domain, where a time window filter is applied to separate the sources based on their phase lag. Additional procedural details on LSF and NIPR are available in Withnell et al (2003) and Long et al (2008).

Three primary measures were extracted from the data: (1) the fine structure frequency count (i.e., number of peaks); (2) DPOAE fine structure amplitude in 1/3 octave bands (dB SPL) for the composite, separated nonlinear distortion, and linear reflection components; and (3) the slope of the phase for the separated nonlinear distortion and linear reflection sources. Fine structure features (i.e., number of peaks) were extracted with a custom automatic MATLAB-based algorithm using criteria set forth by Dhar and Abdala (2007) and Abdala and Dhar (2010). The minimum criteria for a peak were as follows: (1) the signal-to-noise ratio >6 dB; (2) fine structure depth >2.5 dB, where depth was computed as 20 $\log_{10}$ (P_{max}/P_{av_min}), where P_{max} was the DPOAE fine structure amplitude at a maximum and P_{av_min} was the average DPOAE fine structure amplitude of the preceding and following minima; and (3) spacing ratio (f/Δf) <25, where f was the geometric mean between two adjacent minima frequencies and Δf was the frequency separation between them. The total number of fine structure peaks was counted in the frequency range 1000–10000 Hz (referenced to f_2) to limit the influence of noise usually noted <1000 Hz. The RMS power averaging in 1/3 octave bands of the raw sound pressure values was used to smooth the data across frequency and to average DPOAE fine structure

amplitude for the composite and separated nonlinear distortion and linear reflection components (individual participant difference in fine structure limit averaging of data). The slope of the phase for the separated nonlinear distortion and linear reflection sources were calculated by using the Excel slope function.

Statistical Analysis

All 40 participants (20 type-1 DM and 20 controls) were included in the analyses, with the exception of fine structure (n = 32). The sample size was reduced for fine structure because of excessive artifact that limited use of data for eight participants. The eight participants without fine structure data were split evenly between type-1 DM (n = 4) and control participants (n = 4), five were female and three were male. The data (i.e., pure-tone thresholds, OAEs) were first entered into Excel spreadsheets and subsequently transferred to SPSS (version 24; IBM, Armonk, NY) for statistical analyses. Paired t test and analysis of variance (ANOVA) were performed to compare data from the separate ears. No significant group differences were found between ears for outcomes in which both ears were included in the analysis (i.e., pure-tone thresholds, OAEs); therefore, left and right ear data were averaged. The ear-averaged data were compared between groups using the full sample of n = 40 and excluding the eight participants omitted from the DPOAE fine structure data. DPOAE fine structure data were limited to the ear with the lowest artifact and stronger response (defined here as higher fine structure peak count). ANOVAs were performed to compare means between groups. For all OAE measures, estimates of the noise floor were compared to determine if groups had comparable noise floors. Spearman correlations and linear regressions were performed to determine relationships of auditory outcomes (i.e., pure-tone thresholds and OAEs) with covariates (i.e., gender, age, noise history, diabetes duration, average glycated hemoglobin, self-reported quality of DM management, number of complications). Estimates of effect size were derived from partial eta squared (partial η^2). A significance criterion of $p < 0.05$ was selected for all tests.

RESULTS

The mean age was 22.9 years (control group) and 22.6 years (type-1 DM group) (standard error of the mean [SEM] ± 0.59 control group, ± 0.63 type-1 group). Participants were college graduates or currently attending either college or high school. No significant medical histories associated with hearing loss were reported. A few participants reported regular use of aspirin (one control group, two type-1 DM group) but not within 48 hours of the testing sessions and, therefore, were not excluded. No differences were observed between groups in regards to middle ear findings including peak static compliance, pressure, or MEMR thresholds (data not shown). MEMR amplitude was not recorded.

Behavioral Pure-Tone Thresholds

No significant differences between groups in pure-tone thresholds were found for frequencies from 250 to 16000 Hz or for pure-tone averages for low, high, and extended frequencies. Figure 1 shows the thresholds for type-1 DM and control groups for the left and right ears for the full sample. Error bars are provided but difficult to observe because of overlapping data.

Cochlear Function—OAEs

TEOAE

Two TEOAE stimulus levels were used. The 80 dB peak SPL data were analyzed for overall TEOAE amplitude and amplitude at 1/2-octave frequency bands, 1000, 1500, 2000, 3000, and 4000 Hz. Only the overall TEOAE amplitude was compared for data evoked by the 65-dB peak SPL click (for both rates). This limitation was because of the need to window the response to the 65-dB peak SPL (linear protocol) stimuli to reduce interference from stimulus artifact. No significant differences between groups were seen for either the 80-dB or 65 dB-peak SPL stimulus noise floor [$F_{(1, 38)} = 0.99$; $p > 0.05$ and $F_{(1, 38)} = 0.88$; $p > 0.05$, respectively] or at specific frequency bands between groups for average responses or stratified by ear (band data are reported in Spankovich et al, 2017). Figure 2 shows the

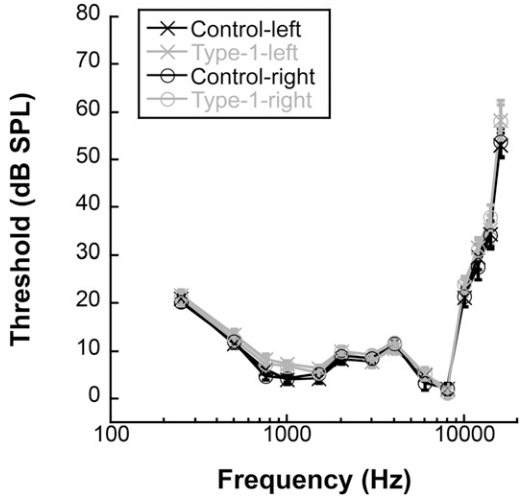

Figure 1. Pure-tone thresholds (dB SPL) by ear and group. comparison of thresholds showed no significant difference ($p > 0.05$) in hearing sensitivity between groups from 250 to 16000 Hz.

mean overall TEOAE amplitude for both groups for responses to the 80-dB peak SPL clicks (left bars) [$F_{(1, 38)} = 1.77$, $p > 0.05$], to the 65-dB peak SPL clicks at 19.30 clicks/second (center bars) [$F_{(1, 38)} = 3.51$; $p > 0.05$], and 65-dB peak SPL clicks at two clicks/second (right bars) [$F_{(1, 38)} = 2.95$; $p > 0.05$]. Although not statistically significant, the amplitude generally is lower for the type-1 DM group.

DPOAE

Similar to the TEOAE data, no statistically significant differences were present for noise floor levels between groups. Likewise, no significant differences in DPOAE amplitudes between groups were observed for average DPOAE response or stratified by ear. The average DPOAE responses for each group are shown in Figure 3. A supplemental table shows the mean differences and statistical results (Supplemental Table S1, supplemental to the online version of this article).

DPOAE Fine Structure

The number of fine structure peaks is presented in Figure 4. A main effect of the decrease in the number of fine structure peaks was found with the increase in stimulus level [$F_{(1, 30)} = 6.982, p < 0.05$]. The number of fine structure peaks was not significantly different between groups at 35 dB SPL but was significantly higher in the control group at 50 dB SPL [$F_{(1, 30)} = 4.229$, $p < 0.05$] and 65 dB SPL [$F_{(1, 30)} = 4.946$, $p < 0.05$]. In other words, the number of fine structure peaks differed between groups at higher levels, but both groups demonstrated a decrease in the number of fine structure peaks with increase in level.

Figure 5 shows the DPOAE fine structure amplitude for each 1/3 octave frequency band (as a function of the f_2 frequency) at each stimulus level. The DPOAE fine structure amplitude of the composite DPOAE (a, left column), the separated distortion source (b, middle column), and reflection source (c, right column) are provided for the three intensities (L_2 = 65 dB SPL, top row; L_2 = 50 dB SPL, middle row; and L_2 = 35 dB SPL, bottom row). We performed an ANOVA at each level and for each component across frequency to determine the main effect of type-1 DM. For the composite DPOAE, type-1 DM did not have a significant main effect on the observed differences at any level, 35 dB SPL [$F_{(1, 30)} = 1.50, p > 0.05$], 50 dB SPL [$F_{(1, 30)} = 0.50, p > 0.05$], or 65 dB SPL [$F_{(1, 30)} = 0.01$, $p > 0.05$]. The distortion source also lacked a main effect related to type-1 DM at 35 dB SPL [$F_{(1, 30)} = 1.21$, $p > 0.05$], 50 dB SPL [$F_{(1, 30)} = 0.333$, $p > 0.05$] or 65 dB SPL [$F_{(1, 30)} = 0.01$, $p > 0.05$]. Type-1 DM did have a significant main effect on the differences in reflection source amplitude at 35 dB SPL [$F_{(1, 30)} = 6.16, p < 0.05$], 50 dB SPL [$F_{(1, 30)} = 5.64$, $p < 0.05$], and 65 dB SPL [$F_{(1, 30)} = 5.87, p < 0.05$]. Pairwise comparisons are shown in Table 1. Most significant differences between groups were for the reflection source, where significant differences were seen at numerous frequencies (primarily in the 1800–4000 Hz spectrum) and stimulus levels, all in favor of greater amplitude in the control group. In general, differences in RMS amplitude approaching 5 dB SPL or greater

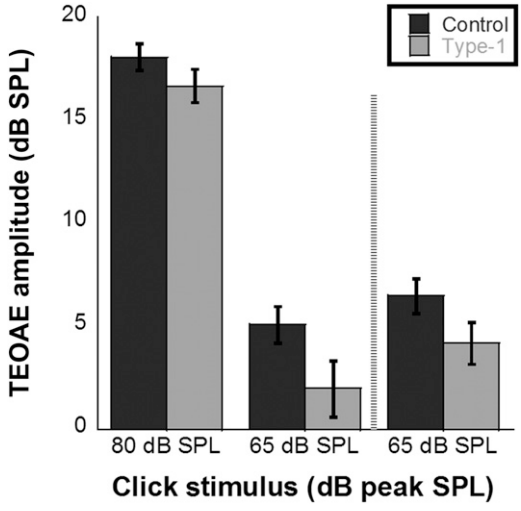

Figure 2. TEOAE amplitude by level and group. Comparison of TEOAE levels (mean and SEM for the control group [black] and type-1 group [gray]). A trend for slightly reduced amplitudes was present at each level tested in the type-1 group. There was no statistically significant difference ($p > 0.05$) between groups for TEOAE amplitudes at the 80-dB peak SPL (nonlinear protocol) or 65-dB peak SPL (linear protocol) at the 19.30 clicks/second rate as shown *left of the divide*. The *right of the divide* shows the TEOAE amplitude using the linear protocol at the slower stimulus rate (two clicks/second) used in the MOCR measurement paradigm. No significant difference was indicated ($p > 0.05$).

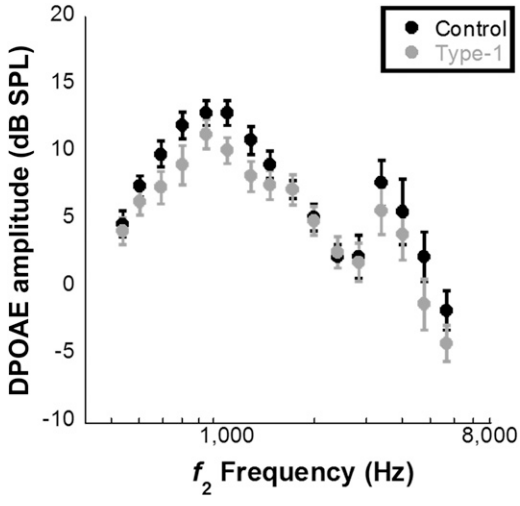

Figure 3. DPOAE amplitude by f_2. Comparison of DPOAE amplitudes (mean and SEM for the control group [black] and type-1 group [gray]). There were no significant differences between groups, $p > 0.05$ at any frequency.

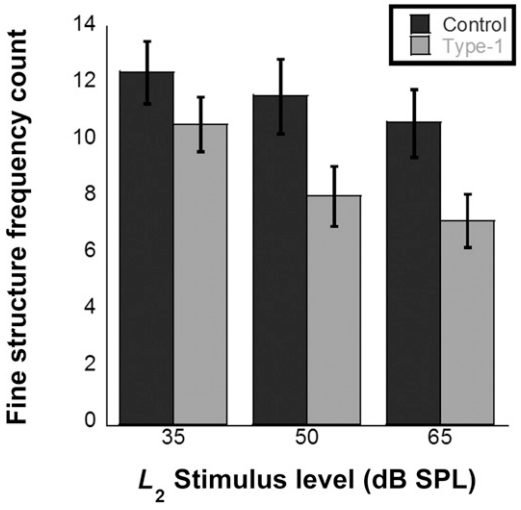

Figure 4. Fine structure peak count. The number of fine structure peaks at each L_2 level tested (mean and SEM for the control group [black] and type-1 group [gray], significance denoted by asterisk *). The results indicate a statistically significant higher number of fine structure maxima and minima in the control group, at $L_2 = 50$ and 65 dB SPL. The change in fine structure count from $L_2 = 35$ to $L_2 = 65$ (reduction with increase in L_2) was similar across groups, that is, there was reduction in fine structure with increase in level seen in both groups.

were statistically significant. The effect sizes of the observed significant differences are provided in Table 2. Overall, type-1 DM accounted for an estimated 12–40% of the variance in DPOAE RMS amplitude. The largest estimated effect of type-1 DM was for the 35 dB SPL stimulus level for the reflection component at 2919 Hz.

In addition to the DPOAE fine structure amplitude at the three stimulus levels, we examined the growth of the response (i.e., change in amplitude) with increase in stimulus level. Table 3 summarizes the findings, limited to statistically significant relationships. In each case, the largest growth in the DPOAE fine structure amplitude was seen in the type-1 group (i.e., less compression). The growth in amplitude also can be seen in Figure 5 for the composite and separated sources.

No significant differences were found between groups for phase slope for either source or at any stimulus level. In addition, no significant differences between groups were found for change in slope with increase in level for either source (distortion [$F_{(1, 30)} = 0.080$, $p > 0.05$]; reflection [$F_{(1, 30)} = 0.028$, $p > 0.05$]).

Covariates

The mean glycated hemoglobin (i.e., average of past 5 hemoglobin A1c [HbA1c] values per participant) was 7.75% (SEM = 0.36) and mean diabetes duration 8.85 years (SEM = 1.45); no participants reported a history of neuropathy, nephropathy, or retinopathy. No significant correlations were found for age- or diabetes-related covariates (i.e., diabetes duration, average glycated hemoglobin, reported control, and number of complications reported) with pure-tone thresholds or OAEs, including fine structure variables. Both the type-1 DM and control groups reported comparable histories of noise exposure. The average LAeq8670h (estimated noise exposure over the previous year) was 73.5 (SEM ± 1.18) and 74.6 (SEM ± 1.02) for control and type-1 DM groups, respectively [$F_{(1, 38)} = 0.54$, $p > 0.05$]; both groups reported on average moderate noise exposure and reported similar numbers of temporary threshold shifts. Correlation and multivariate linear regressions were performed to assess relationships between noise history, type-1 DM, and DPOAE fine structure outcomes; no clear relationship was demonstrated. But, the reflection component RMS amplitude at 9260 Hz was significantly negatively associated with LAeq8760h [$F_{(1, 31)} = 4.42$, $p < 0.05$] when gender-adjusted; that is, amplitude was lower with higher reported noise exposure history. However, the noise floor level >8000 Hz may have confounded this finding.

Excluded Participants

Eight participants were excluded from the DPOAE fine structure data because of noise artifact. It is plausible that differences observed in the fine structure data may be reflective of sample disparities. The demographics for the reduced group were comparable, four were from the control group and four from the type-1 DM group. Five of the excluded participants were male and three were female. Nonetheless, the matched nature of the age and gender for the control and type-1 DM group was well conserved. The average age of the smaller group was 22.6 years for both controls and type-1 DM group participants (SEM ± 0.66 control group, ± 0.71 type-1 group); this was comparable with full sample mean age of 22.9 years (control group) and 22.6 years (type-1 DM group) (SEM ± 0.59 control group, ± 0.63 type-1 group). Next, we analyzed the pure-tone thresholds, TEOAEs, and DPOAEs limited to the 32 participants with corresponding fine structure data. Findings were analogous to the full sample findings. For pure-tone threshold averages: low frequency [$F_{(1, 24)} = 1.75$, $p > 0.05$], high frequency [$F_{(1, 24)} = 0.001$, $p > 0.05$], and ultrahigh frequency [$F_{(1, 24)} = 0.974$, $p > 0.05$], no significant differences were observed between groups. TEOAEs did not show statistically significant differences using the 80-dB peak SPL nonlinear stimulus [$F_{(1, 24)} = 0.853$, $p > 0.05$] or the 65-dB peak SPL linear stimuli at either rate of 19.30 clicks/second [$F_{(1, 24)} = 2.96$, $p > 0.05$] or two clicks/second [$F_{(1, 24)} = 3.57$; $p > 0.05$]. Finally, DPOAE amplitudes did not show any significant differences at any tested frequency between groups; a supplemental table is available to the

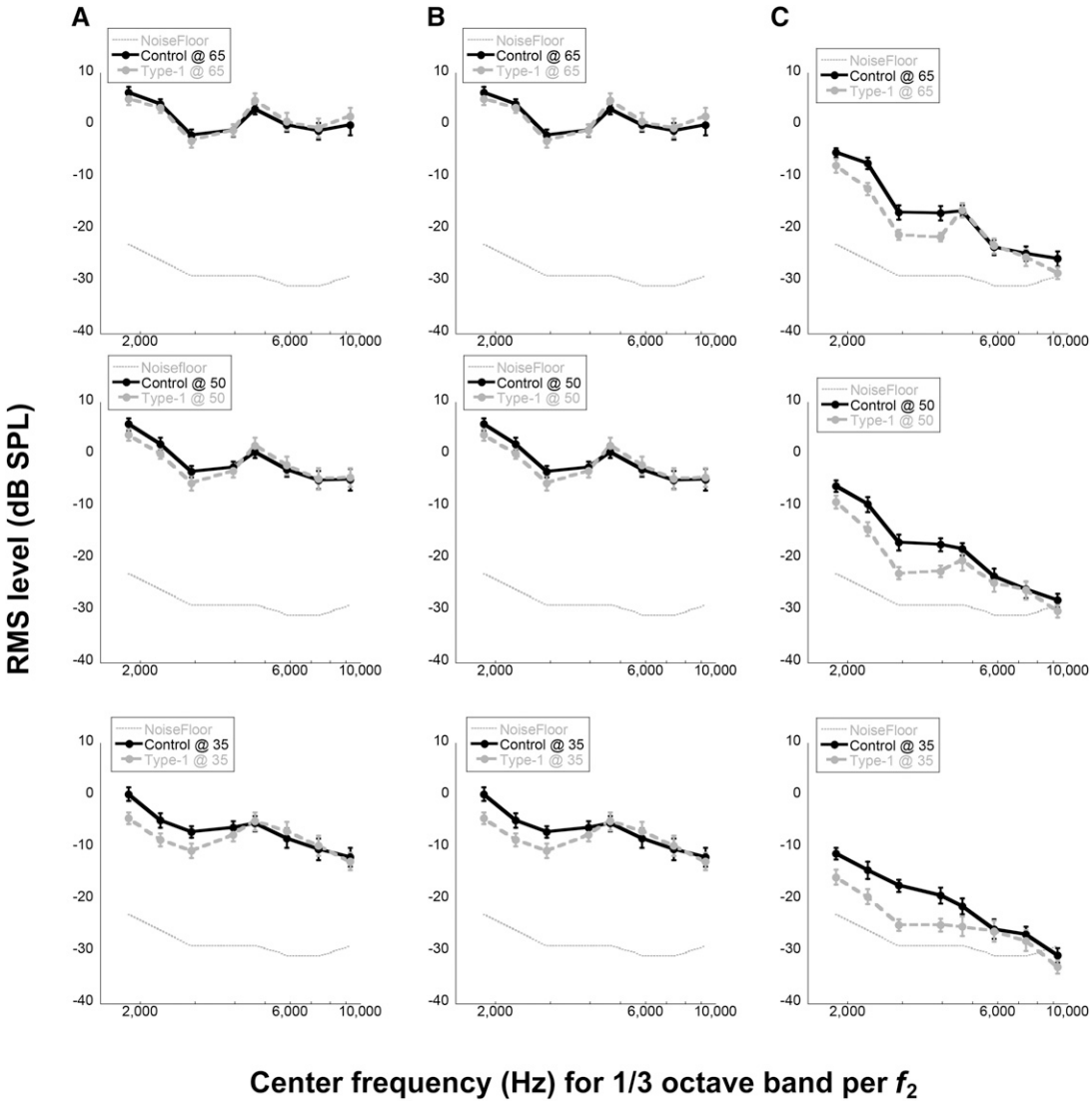

Figure 5. DPOAE fine structure RMS amplitude. The RMS amplitude (y-axis) for each group (mean and SEM for the control group [black] and type-1 group [gray], the gray dotted line is the average noise floor) at the three different L_2 levels tested across the center frequency in 1/3rd octave bands for f_2 (x-axis) is shown in three columns (A–C). The left column (A) illustrates the RMS amplitude for the composite DPOAE, the center column (B) shows the separated nonlinear distortion source, and the right column (C) displays the separated linear reflection source. The top row shows the responses at 65 dB SPL, middle row at 50 dB SPL, and bottom at 35 dB SPL. The amplitudes for the first two columns (A and B) across levels are very similar as the distortion source dominates the composite response; however, the separated reflection source (C) is not only visually different but shows greater differences between groups.

interested reader as Supplemental Table S2, supplemental to the online version of this article (n = 32).

DISCUSSION

Although the relationship of diabetes to hearing loss remains under debate regarding cause and effect, as a whole, the literature supports an influence of DM on susceptibility to hearing loss. Although no significant differences were seen for behavioral thresholds or TEOAEs and DPOAEs obtained with commonly used clinical protocols (similar to Namyslowski et al, 2001; Ugur et al, 2009), we did find significant differences in mean DPOAE fine structure measures in participants with type-1 DM compared with controls. The lack of differences in common clinical OAE protocols was likely related to the relatively good quality of DM management among our participants and lack of comorbidities as seen in other studies of type-1 DM (Di Leo et al, 1997; Lisowska et al, 2001). All participants were matched by age and gender between groups and there was no indication of difference in noise exposure history in the groups to explain differences; in other words, both groups had comparable LAeq8670h.

Consistent with the literature, the number of fine structure peaks was the greatest at the lowest stimulus

Table 1. Mean Amplitude (dB SPL) Differences in DPOAE Fine Structure between Groups (Control—Type-1 DM)

Frequency (Hz) (f_2-1/3 Octave Band)	L_2 Level (dB SPL)		
	35	50	65
Composite response			
1159 Hz	3.250 (1.65; −0.11, 6.61)	2.170 (1.34; −0.56, 4.90)	1.231 (1.39; −1.62, 4.10)
1462 Hz	2.632 (1.59; −0.62, 5.88)	2.284 (1.39; −0.55, 5.12)	1.407 (1.39; −1.42, 4.23)
1840 Hz	4.611 (1.74; 1.05, 8.17)*	2.031 (1.62; −1.28, 5.35)	1.248 (1.59; −2.01, 4.51)
2318 Hz	3.780 (1.90; −0.10, 7.66)	1.849 (1.56; −1.35, 5.05)	0.757 (1.34; −1.97; 3.49)
2919 Hz	3.627 (1.76; 0.02, 7.23)*	2.187 (1.79; −1.48, 5.85)	1.147 (1.65; −2.22, 4.51)
3960 Hz	1.332 (1.81; −2.35; 5.02)	0.691 (1.69; −2.75, 4.13)	0.034 (1.63; −3.35, 3.28)
4633 Hz	0.407 (2.27; −5.04, 4.23)	1.206 (1.86; −5.00, 2.59)	1.647 (1.69; −5.09, 1.79)
5836 Hz	1.326 (2.51; −6.45, 3.79)	0.869 (2.18; −5.32, 3.58)	0.732 (1.95; −4.70, 3.24)
7352 Hz	0.778 (2.79, −6.49, 4.93)	0.242 (2.67; −5.68, 5.20)	0.563 (2.40; −5.47, 4.34)
9260 Hz	0.819 (2.49; −4.25, 5.89)	0.373 (2.73; −5.95, 5.20)	1.747 (2.55; −6.95, 3.45)
Generator component			
1159 Hz	2.776 (1.72; −0.74, 6.30)	1.686 (1.45; −1.30, 4.65)	0.390 (1.65; −2.99, 3.77)
1462 Hz	2.977 (1.67; −0.43, 6.38)	2.010 (1.56; −1.19, 5.21)	1.024 (1.55; −2.13, 4.18)
1840 Hz	4.771 (1.83; 1.03, 8.51)*	2.373 (1.64; −0.99, 5.74)	1.397 (1.59; −1.87, 4.66)
2318 Hz	3.482 (1.89; −0.38, 7.34)	1.581 (1.55; −1.60, 4.76)	0.398 (1.35; −2.36, 3.16)
2919 Hz	3.308 (1.87; −0.51, 7.12)	2.076 (1.84; −1.67, 5.82)	1.048 (1.68; −2.39, 4.48)
3960 Hz	0.597 (1.92; −3.31, 4.51)	0.268 (1.75; −3.31, 3.84)	0.340 (1.63; −3.75, 3.08)
4633 Hz	0.648 (2.29; −5.33, 4.04)	1.381 (1.87; −5.20, 2.44)	1.761 (1.68; −1.67, 5.20)
5836 Hz	1.282 (2.71; −6.82, 4.26)	0.848 (2.25; −5.45, 3.75)	0.762 (1.95; −4.83, 3.30)
7352 Hz	0.716 (2.86; −6.55, 5.11)	0.377 (2.74; −5.97, 5.21)	0.631 (2.45; −5.65, 4.39)
9260 Hz	0.940 (2.66; −4.49, 6.37)	0.305 (2.85; −6.13, 5.52)	1.664 (2.49; −6.76, 3.43)
Reflection component			
1159 Hz	3.764 (1.33; 1.06, 6.47)*	3.471 (1.10; 1.24, 5.70)*	1.77 (1.33; −0.94, 4.50)
1462 Hz	3.056 (1.76; −0.54, 6.65)	3.574 (1.30; 0.92, 6.23)*	3.216 (1.39; −0.38, 6.05)
1840 Hz	4.576 (1.83; 0.84, 8.32)*	3.042 (1.64; −0.312, 6.39)	2.490 (1.60; −0.79, 5.77)
2318 Hz	5.119 (2.24; 0.54, 9.69)*	4.792 (2.01; 0.69, 8.89)*	4.923 (1.62; 1.61, 8.23)**
2919 Hz	7.636 (1.69; 4.18, 11.08)**	5.943 (1.99; 1.87, 10.01)**	4.262 (1.77; 0.63, 7.89)*
3960 Hz	5.656 (2.03; 1.51, 9.81)**	5.057 (1.72; 1.55, 8.56)**	4.550 (1.67; 1.15, 7.95)**
4633 Hz	3.797 (2.43; −1.17, 8.76)	2.128 (2.27; −2.52, 6.77)	0.140 (1.76; −3.45, 3.73)
5836 Hz	0.404 (2.77; −6.06, 5.26)	1.129 (2.27; −3.49, 5.75)	0.293 (2.05; −4.49, 3.91)
7352 Hz	1.196 (2.53; −3.97, 6.36)	0.150 (2.37; −4.70, 4.99)	0.760 (2.12; −3.56, 5.08)
9260 Hz	2.143 (1.94, −1.83, 6.11)	2.069 (1.85; −1.72; 5.85)	2.763 (1.87; −1.05, 6.58)

Notes: *$p < 0.05 > 0.01$; **$p < 0.01$. Standard error and confidence intervals provided in parentheses.

level and diminished with increase in stimulus level (Kemp, 1979; Engdahl and Kemp, 1996; Heitmann et al, 1996; Kummer et al, 1998) in both groups. However, the type-1 DM group demonstrated a less finer structure (Figure 4) and larger differences in fine structure peaks with increasing level compared with controls. As the stimulus level was increased the DPOAE fine structure diminished or became smoother for both groups. The more substantial difference in the number of fine structure peaks at the two higher stimulus levels may be a result of reduced linear reflection contributions in the type-1 DM group and lower saturation level. The linear reflection source's characteristic phase properties are critical to the fine structure peaks as the phase rotation for the distortion source is minimal. Thus, the interaction and resulting fine structure peak count is highly dependent on the strength of the linear reflection; hence, the larger number of fine structure peaks at the lowest stimulus level where the reflection source dominates (Talmadge et al, 1999; Abdala et al, 2011; Rao and Long, 2011).

The DPOAE fine structure amplitude data were significantly diminished in the type-1 DM group, particularly for the separated linear reflection component (Figure 5). Previous research in humans has suggested that higher level stimulus–evoked DPOAE amplitudes are less susceptible to changes with cochlear damage (Engdahl and Kemp, 1996). Diminished low-level stimulus–evoked responses with the preservation of higher level stimulus–evoked responses correlates with a potential loss of nonlinearity to the system.

The reduced linear reflection source with minimal differences in composite and nonlinear distortion source is consistent with the literature (Mauermann et al, 1999), suggesting greater sensitivity of the reflection source and predominantly reflection-based OAEs, such as SOAEs, stimulus frequency OAEs, and TEOAEs (Engdahl and Kemp, 1996; Kummer et al,

Table 2. Effect Size (η^2) for Differences in DPOAE Fine Structure Mean Amplitude (dB SPL) between Groups

	L_2 Level (dB SPL)		
Frequency (Hz) (f_2-1/3 Octave Band)	35	50	65
Composite			
1840 Hz	0.19	NS	NS
2919 Hz	0.12	NS	NS
Generator component			
1840 Hz	0.19	NS	NS
Reflection component			
1159 Hz	0.21	0.25	NS
1462 Hz	0.19	0.20	0.15
1840 Hz	0.17	0.10	NS
2318 Hz	0.15	0.16	0.24
2919 Hz	0.41	0.23	0.16
3960 Hz	0.21	0.22	0.19

Note: η^2 = Partial eta squared. NS = not significant.

1998; Kemp, 2002; Sisto et al, 2007) to cochlear pathology. In support of this suggestion, the data in Figure 2 show a larger separation in TEOAE amplitude between groups with lower level stimuli with a 3.1-dB difference at 65 dB SPL, whereas only a 1.3-dB difference at 80 dB SPL. However, source susceptibility may be dependent on the nature of the pathology as reviewed in the introduction. It is plausible that type-1 diabetes may create a metabolic disturbance in the cochlea perhaps related to cochlear microangiopathy, reducing the driving force and the gain of the cochlear amplifier. Stimulus frequency OAEs, low-level TEOAE, and low-level DPOAE fine structure reflection components and sensitivity to DM-related cochlear dysfunction should be considered for future study given the primary deficits in reflection source–based responses.

Our covariate findings revealed limited variability attributed to the influence of age- and diabetes-related variables (i.e., duration, HbA1c, control, etc.) on auditory function. This finding is not surprising given the young age of the sample (18–28 years) and the lack of reported poor DM management or DM-related complications (no participants reported neuropathy, retinopathy, or nephropathy). Reported noise exposure was similar between groups; however, animal studies (Raynor et al, 1995; Smith et al, 1995; McQueen et al, 1999; Wu et al, 2009) have indicated increased susceptibility to noise-induced hearing loss in rodents with "DM." Our recent work did not demonstrate a relationship between noise history and TEOAE, DPOAE, or auditory brainstem response (ABR) outcomes (Spankovich et al, 2017). The lack of ABR differences in Spankovich et al (2017) compared with DPOAE fine structure differences here may be explained by earlier effects of microangiopathy and DM on cochlear function versus neural function but this suggestion is debatable (Maia and Campos, 2005). It also remains possible that exacerbated susceptibility to noise induced pathology may contribute to the reduced amplitudes and peak count observed given the significant differences in the 2000–4000 Hz spectrum. Although based on the metrics of noise history used in this study, there was no clear statistical finding that noise exposure history was a significant factor driving the observed differences. Further research is needed to understand relationships between type-1 DM and mechanisms for reduced fine structure findings, including differential susceptibility to noise-induced cochlear pathology.

The study was not without limitations. First, control participants were not tested to rule out DM or pre-DM. It is possible that control participants may have undiagnosed DM, but this was unlikely. Second, noise artifact limited the number of participants with DPOAE fine structure data. Nonetheless, the same relationships were demonstrated when analyses were limited to participants with DPOAE fine structure data. Third, the large number of comparisons increases risk for type II error; though, the consistent difference in reflection component findings supports our conclusion.

From a clinical standpoint, the sensitivity of DPOAE fine structure and capability to separate sources support the potential clinical value of evaluating DPOAE fine structure for identifying early indications of reduced cochlear function and cochlear pathology. Application of DPOAE fine structure in clinical audiological diagnostic evaluation has been impeded by the time demands of the traditional fixed-frequency stimulation method. The

Table 3. Amplitudes of the Composite DPOAE Fine Structure and Each of the Components with Change in L_2 (Amplitude at L_2, 65—Amplitude at L_2, 35)

Change in Fine Structure Amplitude		Control	Type-1 DM	Control SEM	Type-1 DM SEM	*F*
1840 Hz	Composite	6.16	9.50	0.66	0.75	11.46
	Distortion	6.29	9.66	0.71	0.65	12.04
2318 Hz	Composite	8.93	11.95	0.69	0.94	6.87
	Distortion	9.31	12.39	0.65	0.95	7.51
2919 Hz	Composite	5.15	7.63	0.68	0.76	5.92
	Distortion	5.58	7.83	0.69	0.77	4.76
	Reflection	0.63	3.99	0.68	0.83	9.98
4633 Hz	Reflection	4.95	8.88	1.07	1.25	5.78

Notes: The table is limited to statistically significant findings ($p < 0.05$). Early indices of reduced cochlear function.

reduced time demands of the sweep-frequency method developed by Long et al (2008) and findings presented here demonstrate the potential of clinical applications of DPOAE fine structure in identifying early indications of reduced cochlear function. Further studies are needed to determine the best parameters for acquiring data (e.g., sweep time per octave and levels) and analyzing outcomes (e.g., separating sources, how to count fine structure, amplitude, etc.) to determine function and establish normative data. The ability to measure fine structure and separate the distortion and reflection components in one rapid test is appealing and prompts speculation of numerous applications, including newborn hearing screening, ototoxicity/noise monitoring, and advanced diagnostics, to differentiate pathology based on source (i.e., distortion and reflection source) analysis.

CONCLUSION

In summary, we report reduced cochlear function, as measured by DPOAE fine structure in participants with type-1 DM, despite the lack of statistical differences with commonly used TEOAE and DPOAE clinical parameters. Differences were observed between groups in reduced fine structure peak count for higher level stimuli, smaller amplitude with lower-level stimuli (particularly in the reflection source), and altered growth of the responses. We also demonstrate potential for DPOAE fine structure clinical applications in early identification of reduced cochlear function. Future studies will be needed to further explore the best test parameters and analysis methods for clinical application.

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