EARLY INDICES OF AUDITORY PATHOLOGY IN

YOUNG ADULTS WITH TYPE-1 DIABETES

By

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To my family and friends, never stop being a student ;)

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Nobody has been more important to me in the pursuit of this endeavor than my family. I would like to thank my mother and father, whose love and encouragement has allowed me to pursue my growing collection of degrees. My brother, for his support and free hair cuts over the years. My dog dean, for his unconditional love and waking me up every morning at 7 am. However, most importantly I wish to thank my beautiful and loving fiancé, Keyla, for her patience and immeasurable support and belief in me. As you wish!

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COMMONLY USED ABBREVIATIONS

ABR   Auditory Brainstem Response
ANOVA   Analysis of Variance
DPOAE   Distortion Product Otoacoustic Emission
f   Frequency
Hz   Hertz
MEMR   Middle Ear Muscle Reflexes
NRHL   Noise Related Hearing Loss
OAE   Otoacoustic Emission
PTA   Pure Tone Average
PTAL   Pure Tone Average Low Frequency
PTAH   Pure Tone Average High Frequency
PTAE   Pure Tone Average Extended High Frequency
RMS   Root Mean Squared
SPL   Sound Pressure Level
SEM   Standard Error of the Mean
TEOAE   Transient Evoked Otoacoustic Emission

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CHAPTER I

INTRODUCTION

The relationship between diabetes and hearing loss has been postulated since case

studies reported by Jorado (1857) and Edgar (1915). Subsequent research has attempted

to delineate the pathophysiology, clinical manifestation, and covariates involved. Yet,

the relationship between diabetes and hearing loss still remains a matter of controversy.

The root of this controversy generally can be traced to study design, specifically

population variables and methodology of assessing hearing. These factors will be

addressed in discussions that follow. Taylor and Irwin (1978), Fowler and Jones (1999),

and Maia and Campos (2005) provide excellent reviews of the literature for their

respective eras.

The proposed pathological mechanisms contributing to hearing loss in persons

with type-1 diabetes include: localized microangiopathy in the inner ear, neuronal

degeneration, and compromised stress response and metabolic function (all with potential

underlying genetic influences). These pathological changes and metabolic disturbances

may contribute to cochlear, retrocochlear, and combined hearing disorders. However, the

underlying cellular and molecular mechanisms contributing to hearing loss remain vague.

A review of proposed mechanisms underlying type-1 diabetes and hearing loss is

provided as an appendix (see Appendix A).

Rationale

The rationale for this dissertation was to address the lack of a comprehensive study of auditory function in young adults with type-1 diabetes with consideration of variables that may exacerbate their risk for hearing loss (e.g., noise exposure). The need for this study was based on two prominent features of a thorough literature review.

First, the literature review demonstrated inconsistent and contradictory findings for all auditory function outcomes commonly used in the clinic. The sources of these inconsistencies are primarily related to study design problems, specifically population variables (no use of matched controls) and methodologies for assessing hearing (lacked sensitive metrics or had inappropriate methods) (see chapter specific literature reviews). Thus, we sought to perform a comprehensive study, utilizing the most sensitive metrics available (using evidence-based methods), and incorporating an age- sex-matched control group.

Second, recent epidemiological findings reported by Bainbridge et al. (2008) and others have demonstrated reduced auditory function in participants with diabetes, particularly at younger ages (< 40 years of age). They also reported the differences in auditory function compared to controls diminished with age. This finding was attributed to competing factors associated with presbycusis in the control group that narrowed the gap between groups and masked the contribution from diabetes. The demonstration of hearing loss in this younger diabetes group questions the hypothesized influence of diabetes related complications (e.g., neuropathy and micronangiopathy) that interact with the aging process and result in accelerated age-related hearing loss. While this may be a factor, we hypothesized that the early onset of hearing loss demonstrated in these

epidemiological studies might be related to exacerbated risk for noise related hearing loss (NRHL).

To appropriately address these questions we have selected a young adult age group (18 to 28 years of age). This age group was selected for the following reasons: (a) the age range limits the confounds associated with aging and hearing loss (presbycusis), (b) they are young enough for potential early intervention of exacerbating effects of covariates (e.g., noise exposure), (c) the group tends to have relatively high noise exposure, and (d) are old enough to sit quietly for testing.

In addition, we implemented the most sensitive metrics of auditory function available to examine hearing sensitivity, cochlear function, and neural function. The objectives were to determine if type-1 diabetes is associated with changes in auditory function and the sensitivity of our methods in identifying early signs of auditory pathology.

Purpose

The primary goal of this dissertation research is to perform an in-depth examination of auditory function (cochlear and peripheral neural [efferent and afferent]) in young adults with type-1 diabetes (referred to as experimental group) as compared to age- and gender-matched control participants (referred to as control group). Secondary objectives include: (a) evaluating covariates associated with auditory function and diabetes, with an exploration of increased susceptibility to noise-related pathology in persons with type-1 diabetes and (b) assessing the application of auditory function measures performed to identify early signs of sensorineural pathology.

Specific Aims

Specific Aim 1. Characterize auditory function in young adults with type-1 diabetes using physiologic methods sensitive to subtle changes in cochlear and neural function in comparison to a matched control group. Previous studies relating auditory function in patients with diabetes have shown mixed results with some studies noting differences and others not. These differences are likely related to sensitivity of the measures used (discussed further in chapter specific literature reviews). Underlying Hypothesis: The experimental group will demonstrate comparable basic audiological outcomes (e.g., pure-tone thresholds 250-8000 Hz), but demonstrate significantly poorer function compared to the control group on more sensitive measures of cochlear function and peripheral auditory neural integrity (e.g., otoacoustic emissions). Expected Findings: The experimental group is expected to have normal pure-tone thresholds, but significantly reduced or abnormal cochlear hair cell responses and significantly altered peripheral auditory neural function.

Specific Aim 2. Determine relationships and influence of covariates (age, sex, diabetes related variable) on auditory function in the experimental group. Underlying Hypothesis: Age, sex, and diabetes related variables (duration, HbA1c, control, and complications) influence auditory function. Expected Findings: We do not expect an interaction of age with auditory function due to the young age of our sample. However, we do expect sex-related differences in auditory function, particularly in cochlear and afferent neural function in both the control and experimental groups. We expect analyses of diabetes related variables in relation to auditory test outcomes will show significantly worse performance on pure tone testing, cochlear, and neural function in experimental

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participants with "poorer" maintained diabetes compared to participants with "better" maintained diabetes and the matched-control group participants.

Specific Aim 3. We will explore the effects of noise exposure history on auditory function in our experimental and control group. Risk for noise-related auditory damage will be estimated via retrospective questionnaires. Underlying Hypothesis: Diabetes is associated with susceptibility to noise-related hearing loss. Expected Findings: The experimental group is expected to demonstrate elevated pure-tone thresholds at frequencies associated with noise related hearing loss (3000-16000 Hz) and reduced cochlear hair cell and efferent neural function, factors which have been associated with noise-related hearing loss (NRHL) in general population studies. Control and experimental groups with greater noise exposure are expected to have worse outcome measures. However, the effect is expected to be greater in the experimental group.

Due to the large scope of this study an alternative format was chosen to enhance readability. The various outcomes assessed and analyzed are divided into chapters that each includes sections on Literature Review, Methods, Results, and Discussion. Chapter III addresses the Basic Audiological Test Battery; we then move to subsequent chapters that address Cochlear Function, followed by Efferent and Afferent Auditory Neural Function, consideration of Covariates, and Noise Exposure. Each of these chapters consists of a separate literature review, purpose, methods, results, and discussion corresponding to the respective research questions. The sectional discussions are complemented with an Integrating Discussion (Chapter IX) and proposed Future Directions (Chapter X).

CHAPTER II

OVERVIEW OF METHODS AND

PARTICIPANT CHARACTERISTICS

Overview of Methods

The scope of this study includes measures of hearing sensitivity (pure-tone

thresholds 250-16000 Hz), middle ear function (tympanometry and middle-ear muscle

reflexes), cochlear mechanics (otoacoustic emissions), and peripheral auditory afferent

and efferent neural function (auditory brainstem responses and otoacoustic emission

suppression, respectively). In addition, retrospective medical and noise exposure histories

were obtained. Participants were recruited from the Vanderbilt University campus,

Vanderbilt Eskind Diabetes Clinic, and the Vanderbilt Kennedy Center subject

recruitment website.

Participant Inclusion Criteria

Participant inclusion criteria included ages 18-28 years, normal to near-normal

hearing ($\leq$ 35 dB HL at 250-8000 Hz, no air-bone gap > 10 dB HL), normal middle ear

function (static compliance > .3 ml, normal ear canal volume, and middle ear pressure ±

100 daPa; ASHA, 1990), non-smoker, and no use of aspirin (within 48 hrs) or significant

exposure to other ototoxic drugs.

Power Analysis

A power analysis was performed to determine the required sample size. The analysis was based on the effect size data from two similar studies that evaluated otoacoustic emissions (TEOAE & DPOAE) in young adults with type-1 diabetes compared to controls (Ottaviani et al., 2002) and auditory brainstem response (ABR) latency in children with type-1 diabetes compared to controls (Durmus et al., 2004). To obtain a power of $\beta = 0.80$ a sample size of approximately 16-18 participants was indicated per group. Based on this information, a sample size of 20 participants per group was planned for a total n = 40.

General Sample Characteristics

The study sample consisted of 20 experimental participants with type-1 diabetes (referred to as experimental group) and 20 age-gender matched controls (referred to as control group). Participants with type-1 diabetes were enlisted first and then controls were matched for age (within 1 year) and for sex. Two additional control subjects were tested, but excluded due to air-bone gaps > 10 dB HL. Eighteen of the participants were male and 22 were female. The mean age was 22.9 years (control group) and 22.6 years (experimental group) (standard error of the mean (SEM) ± 0.59 control, ± 0.63 type-1). Thirty-seven of the participants were White/Caucasian, while two were Black/African American (1 control group, 1 experimental group) and one was Asian (control group). All participants reported average to above average socioeconomic status (SES) except

one (control group) who reported lower than average SES (see question 9 in Appendix C). Participants were college graduates or currently attending college or high school. No significant medical histories associated with hearing loss were reported. Several participants reported regular use of aspirin (2 experimental, 1 control), but not within 48 hours of the testing sessions and were therefore not excluded.

Experimental Group Specific Characteristics

The experimental group consisted primarily of patients from the Vanderbilt University Eskind Diabetes Clinic. The age of diagnosis of type-1 diabetes ranged from 3 to 24 years (mean 13.8, SEM ± 1.25). The duration of diabetes ranged from 1 to 21 years (mean 8.85 ± SEM 1.45). Sixty percent of the experimental group treated their diabetes with a pump device, while the other 40% used shots. No experimental subjects reported nephropathy, retinopathy, or neuropathy associated with their diabetes. Table 2-1 presents the frequency of other co-morbidities. Very few complications were reported in this sample.

Table 2-1. Frequency of Diabetes Related Complications

Diabetes Related Complication	Frequency
High Blood Pressure	2
High Cholesterol	2
Hypertension	1
Hypotension	3
Other Cardiovascular Disease	0
Addison Disease	0
Celiac Disease	1
Coma	3
Rheumatoid Arthritis	0

Glycated hemoglobin (HbA1c) levels (5 previous levels over approximately the past 15 months) were obtained from each experimental participant's medical records. The HbA1c levels ranged from 5.54 to 12.0 %, (mean 7.75%, SEM ± 0.36). Further details on the experimental group including severity/control will be explored in the Chapters VI and VII (Covariates and Noise Exposure, respectively), including potential influence on auditory function.

Research Approval and Recruitment

Approval was obtained from the Vanderbilt Institutional Review Board (VIRB) to conduct this study. All participants provided informed consent using VIRB approved materials and procedures. Participants were advised they could withdraw from the study at any time; none withdrew.

CHAPTER III

BASIC AUDIOLOGICAL BATTERY

Literature Review

In the context of this dissertation, basic audiological battery will refer to pure tone thresholds and immittance testing. The introduction of pure tone audiometry allowed researchers a common measure to characterize changes in auditory sensitivity associated with diabetes. The typical pattern of hearing loss described in the early literature was a progressive, bilateral sensorineural hearing loss (SNHL), affecting the high frequencies (Jorgensen and Buch, 1961; Taylor and Irwin 1978; Kurien et al., 1989). However, exceptions have been reported, including acute (Jorgensen and Buch, 1961), unilateral (Jorgensen and Buch, 1961), and low to mid frequency loss (Jorgensen and Buch, 1961; Tay et al., 1995). Other studies have demonstrated pure tone threshold changes with diabetes across low, mid, and high frequencies (Ferrer et al., 1991; Cullen and Cinnamond, 1993). On the other hand, many studies have demonstrated no relationship between pure tone thresholds and diagnosis of diabetes (Axelsson and Fagerberg, 1968; Gibbin and Davis, 1981; Osterhammel and Christau, 1980; Seiger et al., 1983). Unfortunately, most of these studies did not discriminate between types of diabetes (according to modern criteria), included both young and old participants, and generally lacked matched controls.

Studies specifically on type-1 diabetes demonstrated conflicting results. Osterhammel and Christau (1980) and Sieger et al (1983) each demonstrated normal pure

tone thresholds, while Ferrer et al. (1991) reported elevated pure tone thresholds across all frequencies tested (250-8000 Hz). All of these studies were performed in younger populations under 40 years of age. More recent studies incorporating otoacousitc emissions (OAE) and auditory brainstem responses (ABR) have tended to control for pure tone thresholds, requiring "normal" thresholds for participation.

In addition to the above case and case-control studies, several epidemiological studies have examined pure tone thresholds as an outcome for assessing the relationship between diabetes and hearing loss. The Framingham Heart Study examined audiometric data and found no association between diabetes and hearing loss for pure tone averages (PTA) (Gates et al., 1993). Data from the Beaver Dam Aging Study (PTAs) revealed only a weak association. A five-year prospective study of diabetes and hearing loss was performed in the veteran population. Vaughan et al. (2005) analyzed PTAs including extended high frequencies and found that diabetic patients under the age of 60 years were at risk for greater hearing loss at frequencies greater than 10000 Hz. These findings were supported by a recent study by Austin et al. (2009). They compared medical records from a Veteran Affairs database. Diabetes was classified as insulin dependent (IDDM) and non-insulin dependent (NIDDM). Slight differences were seen for IDDM and NIDDM, but overall diabetes was associated with an increased risk of elevated PTAs particularly in adults under 50 years of age. An NIH sponsored study by Bainbridge et al. (2008) found evidence from PTAs of over 5000 participants that diabetes was an independent risk factor for hearing loss. Finally, Agrawal et al. (2009) examined adults aged 20 to 60 years of age who participated in the National Health and Nutrition

Examination Survey. They also demonstrated diabetes as an independent risk factor for hearing loss.

The studies discussed above have focused primarily on the existence of sensorineural hearing loss with limited consideration of middle or external ear pathology (conductive), with most controlling for conductive hearing loss. In the early 1980s and 1990s consideration of potential effects on middle ear function were initiated. Most studies indicated no effect of diabetes on tympanometry (Osterhammel and Christau, 1980; Seiger et al., 1983) or middle ear muscle reflexes (Seiger et al., 1983). However, two studies by Virtaniemi et al. (1993, 1994) demonstrated diminished tympanogram amplitudes and middle ear muscle responses (respectively) despite absence of conductive hearing loss. Stiffening of the middle ear system was proposed as the underlying mechanism for both findings related to changes in vascular supply to middle ear structures. No neural mechanism was proposed related to diminished MEMR.

Purpose and Hypothesis

The purpose of the basic audiological battery portion of this study was to rule out presence of conductive pathology and determine overall hearing threshold sensitivity. In addition, extended high frequency pure tone thresholds (10000-16000 Hz) were obtained. Several studies have indicated that extended high frequency thresholds may reveal early signs of hearing loss prior to changes in the traditional frequency range tested in clinical evaluation (250-8000 Hz) (Fausti et al., 1993; Knight et al., 2007; Somma et al., 2008) including two diabetes studies (Vaughan et al., 2005; Austin et al., 2009). We hypothesized that each group would demonstrate similar pure-tone thresholds at

frequencies 250-8000 Hz. We expect the experimental group to show poorer extended

high frequency thresholds. However, we did not expect any difference for immittance or

MEMRs.

Methods

    <u>Procedures and Data Analysis</u>. All testing was performed in both the right and

left ears of the participants. An otoscopic exam was completed to rule out presence of

occluding cerumen. Pure-tone thresholds were tested with a Grason Stadler GSI 61

audiometer (Eden Prairie, MN) using Etymotic ER3A insert earphones (Elk Grove

Village, IL), a RadioEar B71 bone conduction stimulator (New Eagle, PA), and

Sennheiser HDA 200 extended high frequency (10000-16000 Hz) headphones

(Wedemark, Germany). All testing was completed in a double-walled sound treated

room.

    The audiometer and transducers were calibrated by a certified Med-Acoustics

engineer (Atlanta, GA) prior to the initiation of the study to American National Standards

Institute (ANSI S3.6-1989, 1996, 2004 and 3.43). In brief, the transducer sound pressure

level (SPL) was measured in a coupler (dependent on transducer type) using asound level

meter (Quest OB-300, Oconomowoc, WI), while the audiometer was set at 70 dB HL (55

dB HL at 16000 Hz). This was performed for each frequency from 125-16000 Hz

(ER3A, 125-8000 Hz and Sennheiser HDA 200, 8000-16000 Hz).   A biological check

was performed before testing each participant.

    Air-conduction thresholds were measured at octave and inter-octave frequencies

from 250-16000 Hz and bone conduction in octave steps from 250-4000 Hz, in 5-dB

steps using a standard method of limits technique (Hughson and Westlake, 1944).

Participants were excused if an air-bone gap > 10 dB HL was indicated and

recommendations for follow-up with a health care professional were made. Pure tone

averages (PTA) for low (PTAL; 250-1500 Hz), high (PTAH; 2000-8000 Hz), and

extended-high frequencies (PTAE; 10000-16000 Hz) were calculated and compared

between ears and groups.

Middle ear testing, 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. Testing was performed in a quiet lab

space while the participant was seated in a comfortable chair. Both ipsilateral and

contralateral MEMR thresholds (500-4000 Hz) were measured in 5 dB steps on a Grason

Stadler GSI TympStar (Eden Prairie, MN). The equipment was checked in a 2 cc coupler

prior to testing participants. Tympanometry was compared to normative values (ASHA,

1990). All subjects met normative criteria. MEMRs (500-4000 Hz) were compared

between ears and groups.

Statistical Analysis

All 40 participants (20 control, 20 experimental) were included in the analysis.

The data from the audiological battery (pure-tones, immittance, MEMR) were first

entered into Excel spreadsheets and subsequently transferred to SPSS (version 18) for

statistical analyses. The first step in the statistical analysis was to compare results in the

left versus right ears to determine if an ear difference existed and if ear data could be

averaged for further analyses. Analyses of Variance (ANOVA) were performed on the

three PTAs (PTAL, PTAH, and PTAE) and MEMR (500, 1000, 2000, and 4000 Hz), to compare data from the separate ears. A significance criterion of $p < .05$ was selected. No significant differences were seen between ears, therefore, left and right ear data were averaged. Second, the ear-averaged data were compared between groups. ANOVAs were performed to compare mean PTAs and MEMRs between groups.

Results

All participants had thresholds within normal ranges (< 20 dB HL) for frequencies with normative data (250-8000 Hz) and no air-bone gap greater than 10 dB. No significant differences were found between groups for PTAs (PTAL, PTAH, and PTAE) or MEMR (500, 1000, 2000, and 4000 Hz). Thus our hypothesis was confirmed, except for the extended high frequency thresholds (PTAE). Figure 1 displays the average SPL in dB (SPLogram) for each group. The SPL was determined by converting dB HL to dB SPL using the appropriate references for each type of transducer (ER3A and Sennheiser HDA200) available in the GSI 61 clinical audiometer manual based on the ANSI standards listed above.   The further analyses were performed to explore covariates; these findings are discussed in the two sections in Chapters VI and VII titled "Covariates" and "Noise Exposure", respectively.
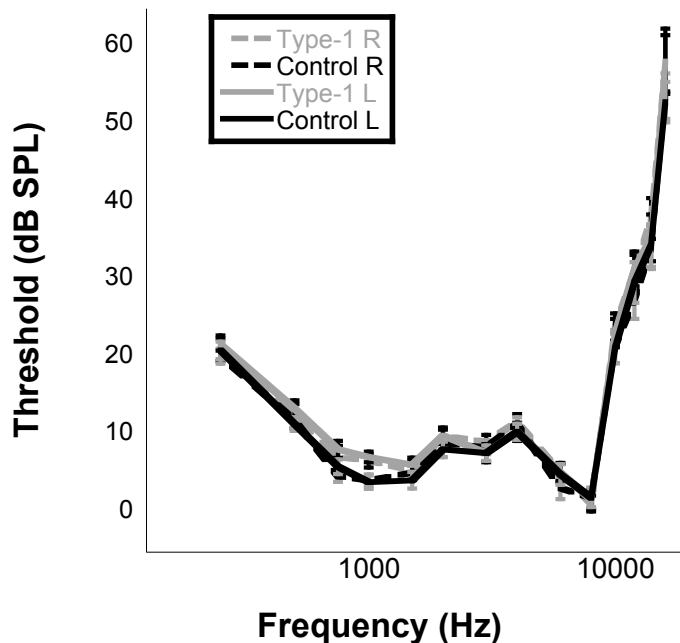
Figure 3-1. Average Sound Pressure Level Thresholds. The average thresholds in the left (solid) and right (dash) ears in the control (black) and experimental group (type-1, in grey) are displayed. No significant differences were seen between ears or between groups at any threshold or PTA (PTAL, PTAH, and PTAE). Mean and SEM data are shown.

Discussion

The basic audiological analysis of pure tone thresholds and middle ear function

demonstrated normal hearing and no significant ear effect or difference between the

control and experimental groups. These findings are consistent with case-control studies

performed in younger diabetes subjects (< 40 years of age) and matched-control samples

(Osterhammel and Christau, 1980; Sieger et al., 1983). We did expect a difference for

PTAE (extended high frequencies), but did not find one. Several studies have indicated

that extended high frequency testing can demonstrate early signs of cochlear damage

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(Fausti et al., 1993; Knight et al., 2007; Somma et al., 2008). Two studies (Vaughan et al., 2005; Austin et al., 2009) found poorer pure tone thresholds in adults with diabetes in frequencies above 10000 Hz. However, the age of the population was much older in both studies (veterans, ~25-80 years of age) and both were population based epidemiological studies with larger sample sizes (n > 300). Therefore, their results may not be captured in a case-control study design. A threshold method with greater sensitivity (e.g., three interval forced choice) may have uncovered differences, but was excluded due to time demand and preference for commonly used clinical methods.

Nonetheless, the majority of previous studies that examined pure tone thresholds lacked an appropriate matched control population and/or did not consider type of diabetes. These factors likely underlie the contradictory findings in the literature. Based on these findings, the clinical diagnosis would be consistent with normal auditory sensitivity for each of our groups.

CHAPTER IV

COCHLEAR FUNCTION

Literature Review

The existence of otoacoustic emissions (OAE), first proposed by Gold (1948) and demonstrated experimentally by Kemp (1978), provided a glimpse into the mechanics of the cochlea not previously possible. Otoacoustic emissions represent measurable sounds produced as a by-product of cochlear function. These emissions are usually measured with a sensitive microphone placed in the external ear canal of the subject. As the theoretical, physical, and physiological understanding of sources contributing to OAEs continue to develop, earlier indications of cochlear pathology become possible, potentially allowing intervention and prevention of subjective pathology (e.g., pure tone thresholds).

Sources and Types of OAEs. The primary sources of OAEs are dependent on the evoking stimuli. The proposed mechanics include a non-linear distortion source (non-linear referring to compressive growth with increase in stimulus level) and coherent-reflection source (both involving a backward travelling wave on the basilar membrane), fast wave compression (fluid compression), and multiple interactions not fully understood and debated (Shera, 2004; Ren et al., 2006). Excellent reviews are available for the interested reader (Shera, 2004; Shera and Guinan, 2008; Johnson, 2010).

Four primary categories of OAEs exist, spontaneous otoacoustic emissions (SOAE), stimulus frequency otoacoustic emissions (SFOAE), transient evoked

otoacoustic emissions (TEOAE), and distortion product otoacoustic emissions (DPOAE).

SOAEs represent the simplest form of an OAE, as they do not require an evoking

stimulus. SOAEs are theoretically generated by repeated coherent-reflections (from

existing perturbations) of a travelling wave back and forth on the basilar membrane

(Shera, 2004). These reflections become "in phase" and result in a measurable SOAE

(Boul and Lineton, 2010). SFOAEs are evoked by a single tone and believed to be due

primarily to the coherent-reflection source similar to SOAEs, but acquired by an evoking

stimulus (Shera, 2004). TEOAEs (typically evoked with a click stimulus) have been

demonstrated primarily to have a coherent-reflection source (Kalluri and Shera, 2001),

but also have been shown to have a non-linear distortion portion (Yates and Withnell,

1999). For TEOAEs, the 80 dB peak SPL "nonlinear" mode represents the traditional

screening protocol. The term "nonlinear" refers to a change in the stimulus polarity

(three 80 dB peak SPL positive polarity clicks and one 90 dB peak SPL negative polarity

click). This should not be confused with the nonlinear distortion source (too be

explained).

DPOAEs are evoked using two simultaneous pure-tones at slightly different

frequencies (f_1, f_2; with $f_2 > f_1$) and variable intensities. The abbreviation f_1 denotes the

lower frequency in the pair and f_2, the higher frequency. Similarly, L_1 represents the

intensity level of the lower frequency tone and L_2, the intensity of the higher frequency.

The f_2/f_1 represents the ratio of the frequencies of the two tones, with a ratio in the range

of 1.20 to 1.22 typically used in humans as these ratios yield the higher DPOAEs. The

largest distortion product in humans is the cubic distortion product, noted as $2f_1 - f_2$.

DPOAEs include contributions from both the coherent-reflection and the non-linear distortion sources (two-source model, not to be confused with the "nonlinear" click mode for TEOAEs), but at different locations along the basilar membrane. The distortion source component arises from nonlinear interaction of two relatively high-level stimuli at a location near the f_2 place where the DPOAE is generated, while the reflection component is generated near the $2f_1$-f_2 (typically the largest DPOAE) characteristic place from a relatively low-level stimulation. Both sources contribute to the DPOAE measured in the ear canal (Shera and Guinan, 1999). Figure 4-1 provides an overview of the two-source OAE model.
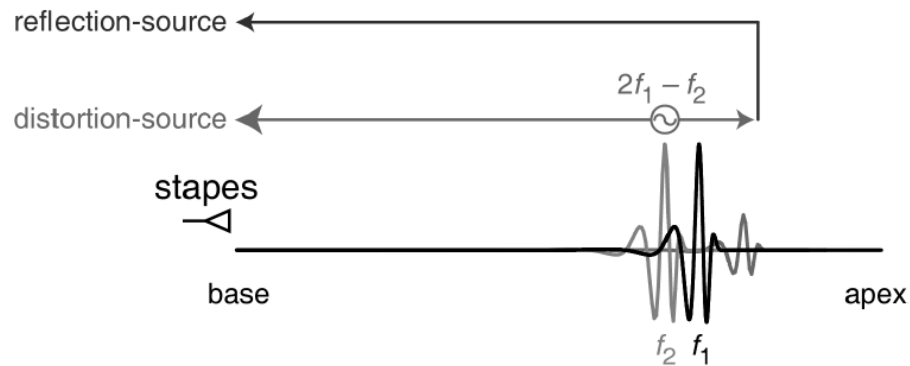
Figure 4-1. Two-Source DPOAE Model. In this simplified schematic two primary tones have been presented (bottom tracing marked f_1 and f_2) in the ear canal, the overlap region of these two tones produces a non-linear response (represented by the line titled distortion source with the circle) that travels both back to the middle ear (to stapes) and toward the apical portion of the cochlea. The wave traveling to the apex reaches a region of maximum excitement ($2f_1$-f_2, the small wave to the far right in the bottom tracing) and results in the formation of another traveling wave back to the middle ear (top line titled reflection source). This figure is from Shera (2009).

One important feature of the two-source model of DPOAEs is the relative phase change with varied stimulus frequency. As stimulus frequency is varied, the phase of the

response arising from the reflection source changes rapidly, while the phase of the response arising from the distortion source changes slowly. This relationship is based on a theoretical relationship between the stimulus and the source first proposed by Kemp and Brown (1983).

The coherent-reflection source is created by a place-fixed pre-existing perturbation (cell to cell force interactions in a normal cochlea) that scatters the incoming stimulus. Since the source (pre-existing perturbation) is fixed in place, as the stimulus frequency changes so does the phase lag. On the other hand, the non-linear distortion source is not due to a pre-existing perturbation, but is actually induced by the stimuli. Therefore, the source is fixed to the wave induced by the stimulus, so the source of the response moves with the wave of the stimulus resulting in zero phase lag. (Shera, 2004). Figure 4-2 illustrates the phase-source relationship.
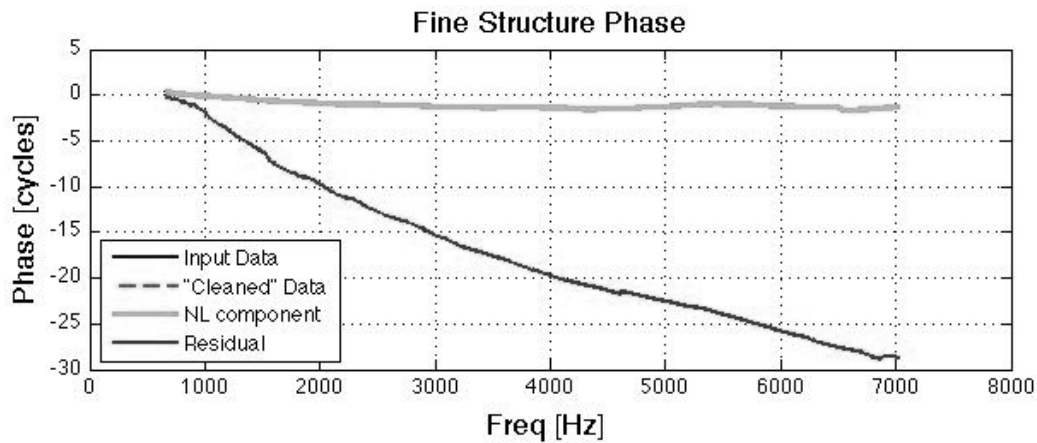
Figure 4-2. Phase-source Relationship. This figure depicts the change in phase with frequency for the two components. In this figure the reflection component is the darker line (residual) and the distortion component is the lighter line (NL component). As frequency increases minimal change in the phase occurs for the distortion component, but the reflection component phase lag increases. This change in phase is based on the two-source model discussed above. The remaining data in the figure box are hidden by the NL component line (lighter line).

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Fine Structure in Otoacoustic Emissions. The interaction of these two sources, as in DPOAEs, can result in constructive and destructive interference. When the two components are in phase, the magnitude of the overall response is greater than the distortion component alone; when out of phase, the magnitude is lower than the distortion component. As a consequence, DPOAEs show quasi-periodic peaks and valleys in amplitude when the response is measured in small frequency steps, referred to a fine structure (Johnson, 2010). When DPOAEs are measured at larger frequency steps the investigator cannot be sure where a particular DPOAE falls within the fine structure (i.e., at a peak or valley) and may incorrectly infer a dip in the response as representing a pathology rather than as a normal dip at that region in the fine structure (Long et al., 2008). Figure 4-3 provides an example of DPOAE fine structure.
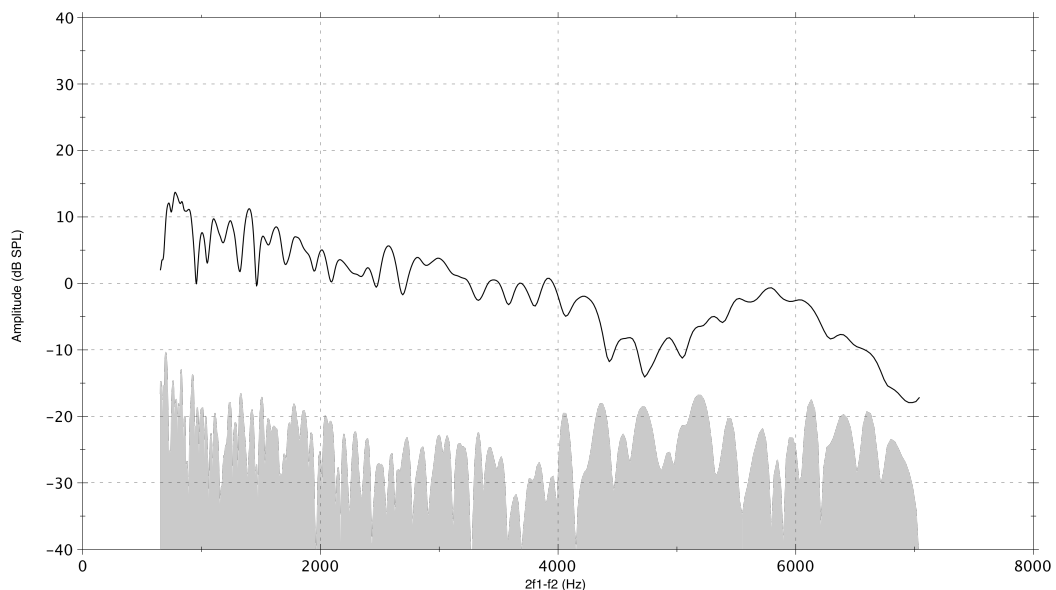
Figure 4-3. Fine Structure. The figure shows the DPOAE fine structure (thin black line) and noise floor (grey fill). The number of fine structures is created by the constructive and destructive relationship between the non-linear distortion and coherent-reflection sources.

This interaction of the reflection and distortion components has led to a series of studies seeking to separate and quantify these two sources from the existing fine structure. The two primary methods for separating fine structure components have been (1) a suppressor stimulus, to eliminate the reflection source and (2) a time-windowing approach, separating components based on their phase relationship. The suppressor approach was limited due to loss of the reflection source from the measure, artifact of the suppressor stimulus on the response, and potential to diminish not only the reflection source, but the generator source as well (Johnson, 2010). The time-windowing approach has been limited by the time demand to record DPOAEs at many closely spaced frequencies.

In 2008, Long et al. introduced a frequency sweep approach not dependent on performing small distinct frequency steps with fixed primaries. The primary tones were swept in frequency while maintaining a constant ratio. The responses generated from this paradigm have been demonstrated to be consistent with fine structure seen with small frequency steps with fixed primaries, and to provide a much more time efficient measure. Further details on the sweeping primary paradigm are available in Long et al. (2008).

Sensitivity to Pathology. Numerous studies have demonstrated that OAEs (all types) show susceptibility to cochlear pathology, with change in pure tone thresholds and even prior to changes in pure tone thresholds. For example, Attias et al. (1995) found reduced TEOAE (80 dB peak SPL "nonlinear" clicks) responses in military personnel with significant noise exposure, but normal pure tone thresholds. Similar findings using TEOAEs and DPOAEs were reported by Lucertini et al. (2002) and Sisto et al. (2007).

Sisto et al. (2007) provide a comprehensive review of the literature for the interested reader.

Kummer et al. (1998) demonstrated changes in DPOAE amplitudes with change in stimulus levels. The growth of DPOAEs is compressive in normal hearing participants (saturating at moderate levels). In other words, as stimulus intensity increases the growth of the DPOAE amplitude reaches a point of maximal excitement; this is related to the compressive non-linear nature of the DPOAE response. Kummer et al. (1998) showed that participants with cochlear impairment demonstrated reductions in DPOAEs at low stimulus levels, but less reduction at higher stimulus levels, such that the growth of the DPOAE became linear.

The contribution of two sources (as in DPOAEs) arising from different properties for the length of the basilar membrane may introduce variability into responses where cochlear health is not constant. For example, Mauermann et al. (1999) showed that the contribution of the reflection-source component is absent whenever hearing loss occurs at the DPOAE $2f_1$-f_2 place, while the contribution from sources more related to the non-linear distortion may be observed even in cases of mild hearing loss. However, with a mild sloping high frequency hearing loss, if the more apically located $2f_1$-f_2 region is preserved the reflection component may be preserved as well (Johnson, 2010). Thus the effect of hearing loss on cochlear fine structure and its sources may be dependent on the specific pathology associated with the loss (Abdala and Dhar, 2010).

Diabetes and OAE Responses. Several groups have examined the influence of diabetes on OAE responses. Di Leo et al. (1997) and Di Nardo (1998) examined DPOAEs (Level: L_1=L_2=70 dB SPL, f_2/f_1=1.22) and TEOAEs (80 dB peak SPL

"nonlinear" clicks; a description of nonlinear clicks is provided in the methods section of this chapter) in young adults with insulin dependent diabetes mellitus (IDDM) and normal pure-tone thresholds compared to matched-controls. They found reduced TEOAE amplitudes in diabetic participants with reduced nerve conduction velocity (NCV), but not in diabetic participants with normal NCV. DPOAE amplitudes were reduced in both patients with NCV and without reduced NCV. The researchers contributed the changes in OAE amplitudes to microvascular compromise, despite measurement for presence of microangiopathy.

Reduced DPOAE ($L_1=L_2$, 35-70 dB SPL, $f_2/f_1=1.22$) findings were also reported in normal hearing young adults with type-1 diabetes (Lisowska et al., 2001). Despite the fact that these researchers evaluated numerous stimulus levels, growth of DPOAE amplitudes was not discussed, but significant differences were seen at each level. In contradiction to the suggested mechanism proposed by the previous studies, they reported no relationship to the presence of microangiopathy (evaluated by opthalmoscopy and 24 hour albumin excretion rate), finding altered responses in both patients with microangiopathy and without. The authors suggested that the impairment was related to early metabolic complications, including nonenzymatic glycation related to excess free radical activity, but not directly due to microangiopathy. In 2002 Ottaviani et al. evaluated TEOAEs (to 75-90 dB peak SPL "nonlinear" clicks) and DPOAEs ($L_1=L_2=70$ dB SPL, $f_2/f_1=1.22$) in normal hearing young adults with type-1 diabetes. Significantly reduced amplitudes were seen compared to controls (not matched) for both types of OAE responses.

In contrast, Namyslowski et al. (2001) examined TEOAEs (80, 70, and 60 dB peak SPL, "nonlinear" mode) in children from 6 to 16 years of age. No significant difference in TEOAE amplitude was seen compared to controls at any level. Ugur et al. (2009) found comparable results to the previous study with no difference in TEOAE (75-85 peak SPL, "nonlinear" click) or DPOAE ($L_1=L_2=70$, $f_2/f_1=1.22$) amplitudes in children with type-1 diabetes compared to age-matched controls. In addition, they found no difference in SOAEs. No previous studies have examined DPOAE fine structure in a population with diabetes.

Purpose and Hypothesis

We included an assessment of cochlear function incorporating OAEs to identify signs of damage that may have not been observed in pure-tone threshold assessment. Numerous studies reviewed have demonstrated the ability of OAEs to identify early signs of cochlear pathology prior to changes in thresholds. The purpose of this study section was to perform a comprehensive assessment of cochlear function using OAEs. Procedures incorporated commonly used clinical protocols (as described in the literature review) and novel research protocols, (e.g., sweeping primary tones DPOAE paradigm developed by Long et al., 2008) that allow collection of data needed for separate quantification of reflection and distortion components of cochlear responses. The primary objective was to compare cochlear responses between groups. The secondary objective was to explore the utility of these measures in identifying early signs of cochlear pathology prior to changes in pure tone thresholds. Further discussion of this secondary objective is presented in Chapter IX.

We hypothesized that OAE amplitudes would be diminished in the experimental group compared to the control group and that the most prominent differences would be seen in the DPOAE fine structure outcomes. Further analyses of the influence of Covariates and Noise Exposure will be described in subsequent chapters.

Methods

All cochlear function testing was performed in a double-walled sound treated room, while the participant was seated in a comfortable chair. A closed-captioned movie was viewable through the window (sound treated) of the room on a monitor located in the adjoining room. Participants were instructed to sit quietly and try to minimize physiological noise (heavy breathing, movement, etc).

TEOAE Procedures. TEOAEs were recorded with the Intelligent Hearing Systems (IHS) SmartTrOAE (Miami, FL) and the Etymotic Research (ER) 10D probe microphone (Elk Grove Village, IL). The IHS system was calibrated using the Brüel and Kjaer Pulse (software version 11.0). TEOAE responses were obtained with 65 dB peak SPL "linear" clicks and 80 dB peak SPL "nonlinear" clicks in the right and left ears with the 10D probe inserted in the ear canal using an ER10D foam tip. The 80 dB peak SPL "nonlinear" mode represents the traditional clinical screening protocol. The "nonlinear" in this instance refers to a change in the stimulus polarity (three 80 dB peak SPL positive polarity clicks and one 90 dB peak SPL negative polarity click). The duration of each click was 75 usec and 1024 stimuli were presented and averaged at each level.

The advantage of the "nonlinear" mode is that artifacts can easily be reduced since they add linearly, while the actual OAEs based on their inherent nonlinear growth

(nonlinear in this case referring to compressed growth with increase in stimulus level), do not add in a linear manner. Though the "nonlinear" mode is preferred at higher intensities, at lower intensities (i.e. 65 dB peak SPL) stimuli with a constant polarity (so-called "linear") can be used. To control for potential stimulus artifact occurring early in the response, the Kresge EchoMaster Program (version 4.0; Wen et al., 1993) was used to quantify emission amplitude in an 8- to 18-ms time window (see later discussion).

Basic DPOAE Procedures. A screening DPOAE was performed using f_2 tone frequencies of 500-8000 Hz, 4 frequencies per octave, f_2/f_1 ratio of 1.22, and intensity levels of L_1=65, L_2=55 dB SPL. The same calibrated IHS system (but the SmartOAE program) and probe were used as in TEOAE recordings; responses were measured in both ears.

DPOAE Fine Structure Procedures. A custom designed DPOAE fine structure system (NIPR, C. Tallmadge) interfaced with a Stanford Research Systems low-noise amplifier and an Etymotic Research ER10B low-noise probe microphone was used to measure DPOAE fine structure. Stimuli were calibrated using the Kemar (Knowles Electronics Manikin for Acoustic Research) and the Brüel and Kjaer Pulse system to estimate the level at the eardrum. 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 Transfer (FFT) to evaluate the probe fit and ensure that levels near 1000 Hz approximate the required stimulus level for each output.

Custom programs for a Macintosh computer (MAC OS) developed by C Talmadge were used to generate the stimuli and record the ear canal signals. Two ER2 (Etymotic Research, Elk Grove Village, IL) tube phones were connected to a two-port

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ER10B low-noise microphone, which was inserted in the ear canal using an ER10A

disposable tip. Before being digitized by the MOTU (Cambridge, MA) 828 (24 bit,

44100 samples/sec), the signal from the microphone was conditioned, pre-amplified and

filtered (300-10,000) by a Stanford (Sunnyvale, CA) SR650 low-noise amplifier under

computer control.

Tone pairs were presented using an up-, down-sweeping paradigm (Long et al.,

2008), an f_2/f_1 ratio of 1.22, f_2 range from 1000-11314 Hz (7 second sweep,

approximately 2 seconds per octave), and intensity levels L_2 =35, 50, 65 and L_1 = 39 dB

SPL + 0.4 x L_2.   These intensities were based on the so-called "scissors" paradigm that

theoretically accounts for the different compression of an f_2/f_1 ratio of 1.22 at the DPOAE

overlap region (distortion source) (Kummer et al., 2000). Sweeps were obtained for each

primary level and averaged to increase the signal-to-noise ratio between the measured

DPOAE and background noise. The number of sweeps obtained at each level depended

on the primary level, with the lowest level requiring more sweeps (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.

Data Analysis

TEOAE and Basic DPOAE. TEOAE data and noise levels for the 80 dB peak

SPL nonlinear clicks in the 1000-4000 Hz range were transferred to an Excel database

(dB Response and dB Noise). TEOAE 65 dB peak SPL linear click data were first

analyzed using the Kresge EchoMaster software in an 8-18 ms window to minimize

contributions of stimulus artifact to the data being analyzed. In the case of the 65 dB SPL

level, use of the window approach excludes ability to examine frequency specific data. Therefore, the overall root mean squared (RMS) amplitude and noise level were collected and transferred to an Excel database.

In addition, the basic DPOAE ($2f_1$-f_2) amplitude and noise floor data were entered into an Excel database. The TEOAE and DPOAE data were then transferred to an SPSS database for statistical analysis. All 40 participants were included in the analysis.

DPOAE fine structure. Spectrograms of the individual sweeps were visually inspected and noisy sweeps were eliminated before averaging at each level. The remaining sweeps with identical stimulus conditions (sweep direction and stimulus intensity) were averaged to reduce the noise floor and subtracted to estimate the noise floor. Up- and down-sweeps were analyzed independently and compared as a cross-check. 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)

A least-squares fit (LSF) procedure was used to extract the level of the DPOAE generator component for each averaged sound file using overlapping analysis windows. This yielded estimates at every 2 Hz around 1000 Hz and every 6 Hz above 4000 Hz (Long et al., 2008). Software developed by Dr. C. Talmadge based on the program NIPR was used to separate the nonlinear distortion and linear reflection components. NIPR is a MATLAB-based analysis program that uses an Inverse Fast Fourier Transfer (IFFT)-based algorithm to convert the frequency domain complex-valued DPOAE amplitude to the time-domain, where a time window filter is applied to separate the components based on their phase lag. Additional procedural details on LSF and NIPR are available in Long et al. (2008).

Three primary outcomes were extracted from the data: (1) the overall fine structure frequency count, (2) RMS levels in 1/3 octave bands (dB SPL) and (3) the slope of the phase for the nonlinear distortion and linear reflection components. Fine structure features (peak count) were extracted with a custom automatic algorithm in MATLAB based on the criteria set forth by Dhar and Abdala (2007) and Abdala and Dhar (2010). The RMS amplitude was calculated using a program developed by C Talmadge, while the slope of the phase was calculated by using the slope function to the raw data in Excel.

In brief, the signal to noise ratio was > 6 dB, fine structure maxima > 2.5 dB, where depth was computed as $20 \log_{10} (P_{max}/P_{av\_min})$, where P_{max} was the DPOAE level at a maximum and P_{av_min} was the average DPOAE level of the preceding and following minima; and spacing ratio < 25 (f/Δf), 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 were counted in the frequency range 1000-6000 Hz to limit influence of noise and to maintain consistency with the procedures of Abdala and Dhar (2010). In addition, the change in each outcome with increase in level was calculated by taking the difference for each outcome (Fine structure count at 35 dB SPL – 65 dB SPL; RMS levels at 65 dB SPL- 35 dB SPL; Phase slope at 35 dB SPL – 65 dB SPL). These data were entered into an Excel database and later transferred to an SPSS database for statistical analysis. Eight participants were excluded due to high noise and artifact in the response (3 control and 5 experimental) for an n = 32. The better ear (least noisy) for each participant was used in the statistical analysis.

Statistical Analysis

TEOAE and Basic DPOAE. Statistical analyses were performed using SPSS

(version 18.0). Data were compared between ears and groups using analysis of variance

(ANOVA) and p < .05 as the criterion for significance. First, TEOAE (overall 80 dB and

65 dB peak SPL and at 1000, 1500, 2000, 3000, and 4000 Hz at 80 only) and DPOAE

(over f2 range) data were compared across ears. No significant differences were

indicated and individual ear data were averaged. Next, TEOAE and DPOAE noise levels

were compared between the control and experimental groups (this was done for

individual ear data). Finally, the TEOAE and DPOAE amplitudes averaged across both

ears were compared between groups. Data were excluded if cross-correlations were less

than 70%.

DPOAE Fine Structure. Statistical analysis was performed using SPSS (version

18.0). Data were compared between groups using analysis of variance (ANOVA) and p <

.05 as the criterion for significance. Number of fine structure at each stimulus level,

RMS level (1/3 octave bands 1000-6000 Hz at each stimulus level), and slope of the

phase (overall, distortion component, and reflection component) were compared between

the control and experimental groups. In addition, the difference at the highest and lowest

level for each of the above outcomes was computed and compared between groups

(change with stimulus level).

Results

TEOAE. Both groups showed similar noise floors for all outcomes. We

examined two TEOAE intensity levels, the clinical commonly used level of 80 dB peak

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SPL and a lower level of 65 dB peak SPL. The 80 dB data were analyzed for overall

level and at 5 frequencies, 1000, 1500, 2000, 3000, and 4000 Hz. Data at 65 dB were

only compared for the overall level. This was limited due to the need to window the

response to the 65 dB peak SPL stimuli in order to diminish the stimulus contribution

(explained above).

No significant differences were seen between groups for either the 80 dB or 65 dB

peak SPL stimulus noise floor, the overall TEOAE response, or at specific frequencies

between groups. However, a trend was present for slightly lower responses in the

experimental group compared to the control group. Figure 4-4 shows the mean overall

TEOAE amplitude for responses to the 65 dB peak SPL "linear" clicks and to the 80 dB

peak SPL "nonlinear" clicks. Note the trend of lower amplitude for the experimental

group, particularly for the 65 dB peak SPL linear clicks stimulus.
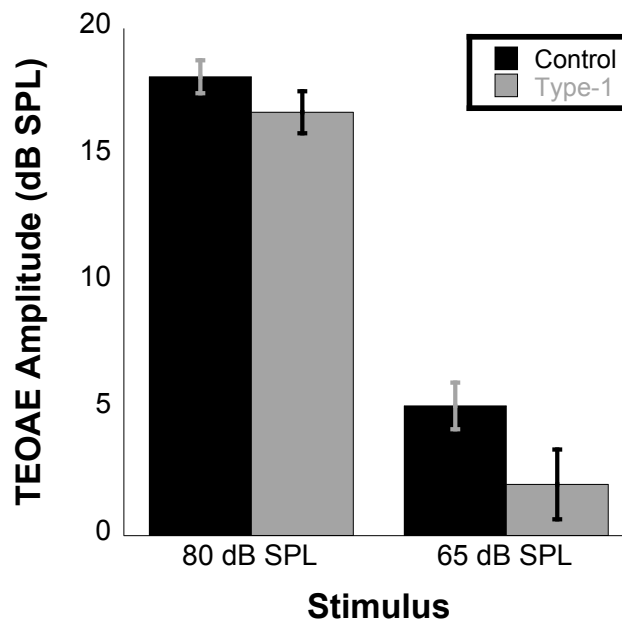
Figure 4-4. TEOAE Amplitude by Level and Group. No significant difference was found between groups (p < .05) for responses at 80 dB peak SPL or 65 dB peak SPL. However, a trend for slightly reduced amplitudes was present at each level tested in the experimental (type-1) group. Mean and SEM are shown.

Basic DPOAE. As reported for the TEOAE data, no significant differences were present for noise levels between groups. Likewise, no significant differences in DPOAE amplitudes between groups were indicated. The average DPOAE responses for each group are illustrated in Figure 4-5.
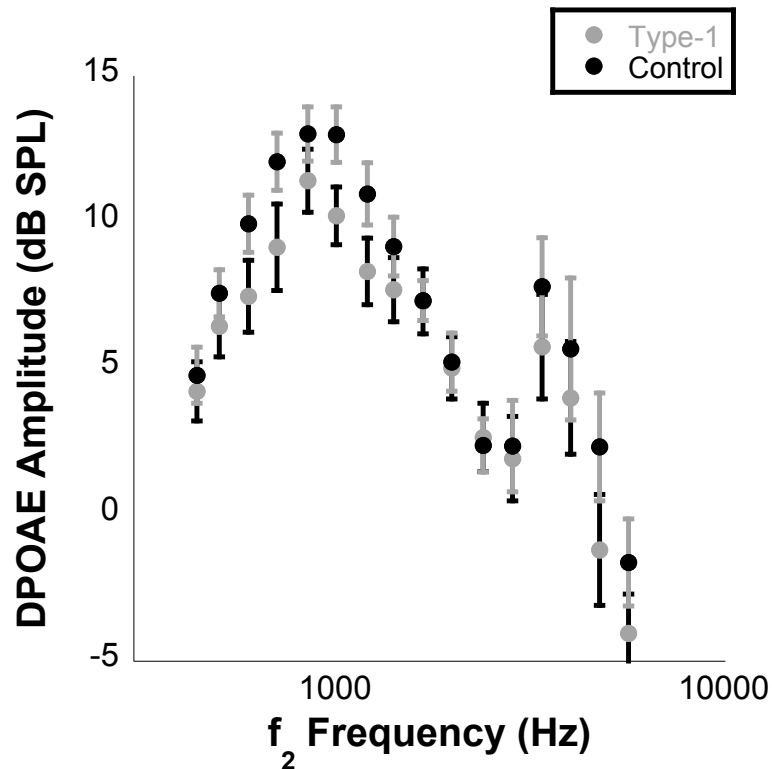
Figure 4-5. DPOAE Amplitude by f_2. Comparison of DPOAE responses demonstrated no significant difference between groups (p < .05). However, the type-1 diabetes subjects showed a trend for lower level responses.   Mean and SEM are shown.

DPOAE Fine Structure. The fine structure count (number of peaks) is presented in Figure 4-6. A main effect of decrease in fine structure count was found with increase in stimulus level (F=6.982, p < .05). However, the change in fine structure count with increase in level was similar between groups (F=1.165, p >.05). The fine structure count was not significantly different between groups at 35 dB SPL (F=1.498, p > .05), but were significantly higher in the control group at 50 dB SPL (F=4.229, p <.05) and 65 dB SPL (F=4.946, p<.05).
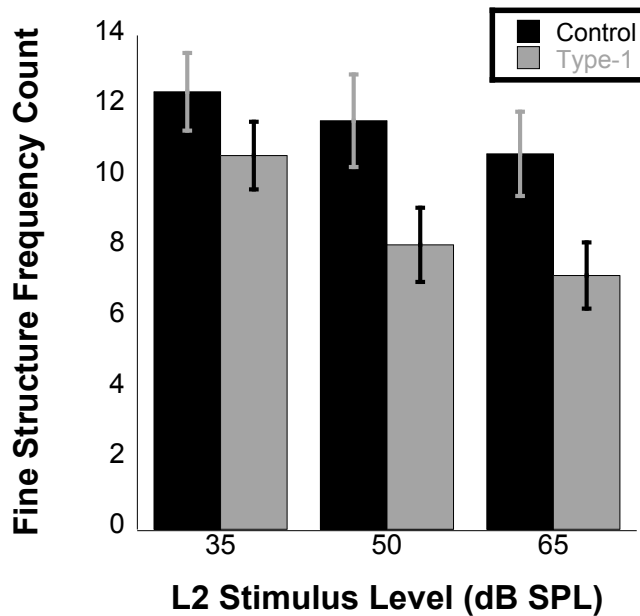
Figure 4-6. Fine Structure Count. The number of fine structure components at each L_2 level tested is provided. The results indicate a higher number of fine structure components in the control group, that were statistically significant at L_2 = 50 and 65 dB SPL. The change in fine structure count from L_2 = 35 to L_2 = 65 was similar between groups. Data for the control group are in black, and experimental (type-1) in grey. Mean and SEM are shown.

The RMS level for each frequency band and level is summarized for each group in Figure 4-7. The overall fine structure RMS (a, top left) and the separated distortion component (b, top right) and reflection component (c, bottom center) are presented. The only significant finding for (a, top left) was at the lowest level (L2 =35 dB SPL) and frequency (1176 Hz), where the control RMS is significantly greater than type-1 (F=6.987, p < .05). Similar, the (b, top right) distortion component RMS was significantly higher in the control group at 35 dB SPL, 1176 Hz (F=6.790, p < .05), while no other frequency band showed a significant difference. The majority of the significant findings were for the (c, bottom center) reflection component, where significant

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differences were seen at several frequencies and levels, all in favor of greater RMS in the

control group. The significant reflection component RMS findings are summarized in

Table 4-1.
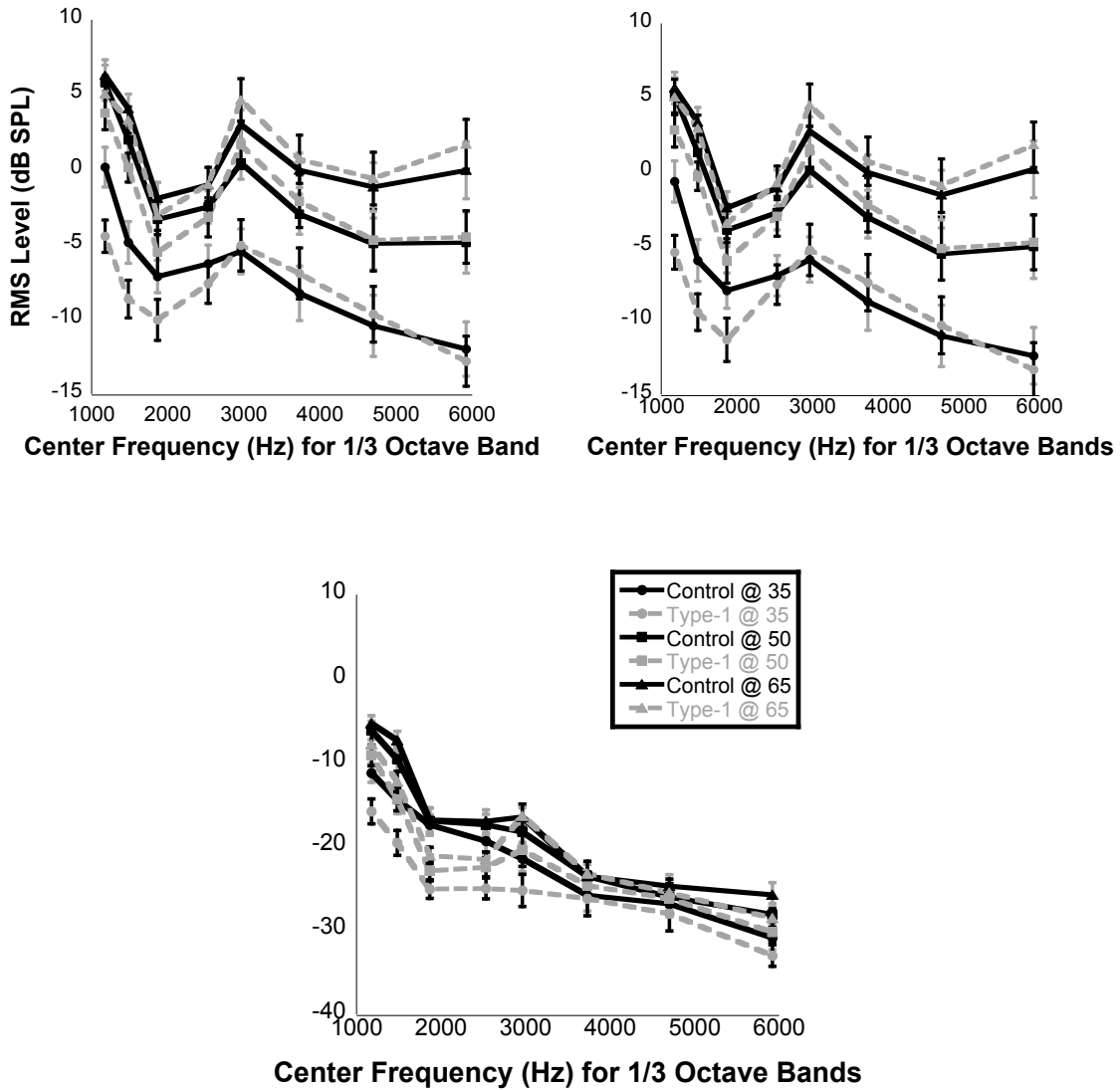
Figure 4-7. RMS Amplitude. The figure presents the RMS for each group at the
three different L2 levels tested across the center frequency of 2f1-f2. Top left illustrates
the RMS for the overall fine structure, top right the distortion component, and bottom
center the reflection component. The RMS amplitudes for the two top figures are very
similar as the distortion component provides the primary RMS amplitude source to the
both responses. However, the separated reflection component (bottom center) is
diminished in the type-1 diabetes group. Mean and SEM are shown.

Table 4-1. Significant Reflection Component RMS findings. The mean data and
SEM are provided graphically in the previous figure.

Reflection Component	F
35 dB @ 1176 Hz	6.243
35 dB @ 1482 Hz	5.128
50 dB @ 1482 Hz	5.692
65 dB @ 1482 Hz	9.217
35 dB @ 1866 Hz	20.439
50 dB @ 1866 Hz	8.898
65 dB @ 1866 Hz	5.756
35 dB @ 2531 Hz	7.748
50 dB @ 2531 Hz	8.674
65 dB @ 2531 Hz	7.470

In addition to the RMS amplitude, we examined growth of the response, again for

overall fine structure RMS and each component. Table 4-2 summarizes the significant

findings. In each case the largest growth with increase in level was seen in the type-1

diabetes group (i.e., less compression).

Table 4-2. Fine Structure with Change in L2 Level. The growth of RMS
amplitude was significantly greater in the type-1 diabetes group. The diminished
response at the lowest stimulus level (L2=35 dB SPL), but comparable high-level
response makes the response growth larger in the type-1 diabetes group.

Change in Fine Structure	Control	Type-1	Control SEM	Type-1 SEM	F
1176 Hz Fine RMS	6.163	9.499	.659	.748	11.459
1176 Hz Distortion RMS	6.293	9.666	.710	.651	12.024
1482 Hz Fine RMS	8.933	11.956	.691	.946	6.877
1482 Hz Distortion RMS	9.309	12.393	.647	.948	7.513
1866 Hz Fine RMS	5.149	7.629	.679	.764	5.922
1866 Hz Distortion RMS	5.575	7.835	.688	.778	4.765
1866 Hz Reflection RMS	.6258	3.990	.684	.831	9.985
2962 Hz Refection RMS	4.948	8.884	1.07	1.25	5.781

A comparison of the slope of the phase for each component is provided in Figure

4-8. The slope of the distortion component did not significantly change with increase in

stimulus level (F=3.492, p > .05), but remained around zero. On the other hand, the slope

of reflection component decreased significantly with increase in stimulus level

(F=24.022, p < .05). No significant differences were found between groups for phase

slope for either component or any level. In addition, no significant differences between

groups were found for change in slope with increase in level for either component

(distortion [F=.080, p > .05]; reflection [F=.028, p > .05]) .
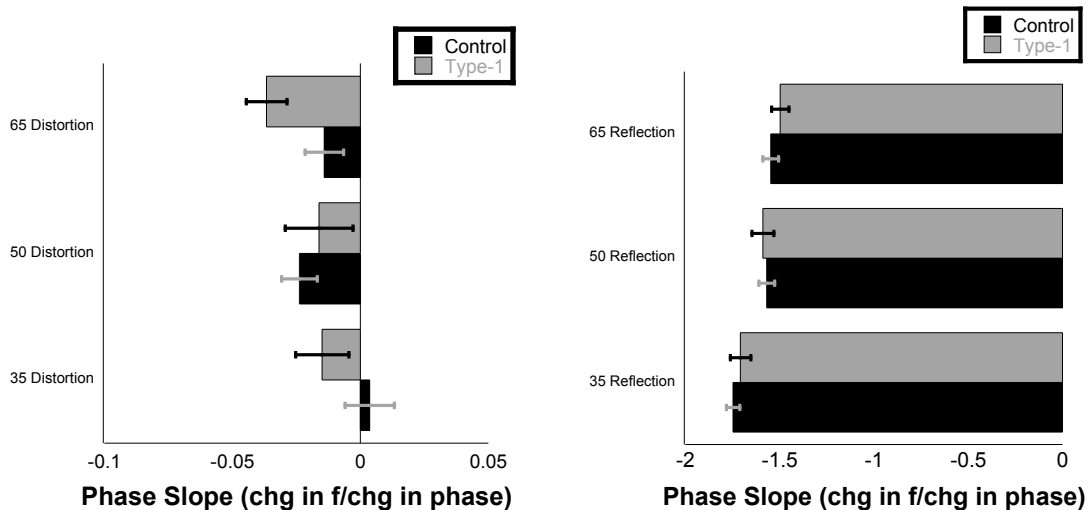
Figure 4-8. Slope of the Phase. The individual components are separated and the
slope of the phase was calculated, where slope = Δ phase/Δ frequency. The slope
is much higher in the reflection component (right panel), as the phase changes
greatly with frequency. However, phase change in the distortion component (left
panel) is minimal. The increase in stimulus level reduces the contribution of the
reflection component, which is a lower-level evoked response. However, the
increase in diminishes mixing of the two-sources and the distortion component
moves around zero. The group comparison for each level-component
combination and change with increase in L2 was not significant. Mean and SEM
are shown.

Discussion

Our previous review of the literature highlighted the inconsistencies among studies regarding the relationship between OAE responses and diabetes. The previous studies that have focused on younger groups and involved matched controls found similar responses between experimental participants and controls (Di Leo et al., 1997; Di Nardo et al., 1998; Namyslowski et al., 2001; Ugur et al., 2009). However, our results are in contradiction to the reduced OAE amplitudes reported by Lisowska et al. (2001) and Ottaviani et al. (2002). While our basic TEOAE and DPOAE responses revealed no significant differences, an obvious trend for reduced amplitudes in experimental participants was observed.

Fine structure findings revealed reduced frequency of fine structure components in the type-1 diabetes group. Dhar and Abdala (2007) demonstrated reduced fine structure components in adults compared to newborns (both with normal pure-tone thresholds), but contributed the difference to maturational changes in the cochlea and middle ear. Wagner et al. (2008) found reduced fine structure number (count) with increasing hearing loss. This loss suggested diminished interaction between the two-source components.

The RMS amplitude values were greater in the control group, with the reflection component showing the majority of the reduced amplitude in the type-1 diabetes group. Mauermann et al. (1999) demonstrated that the reflection component was more sensitive to pathology. This finding suggests that the reduced reflection in the type-1 diabetes group may be related to early signs of cochlear pathology or general reduced function.

On the other hand, no significant difference between groups in overall phase slope was found. The overall phase slope for the entire frequency range may not be sensitive to early cochlear pathology, particularly if the damage is localized. In addition, no difference in change in fine structure frequency count or change in phase with stimulus intensity (L_2) was found. The change in fine structure count and phase slope of the components is in line with the primary source contributing to the fine structure with change in stimulus intensity, L_2. Basically, as you increase the stimulus intensity the contribution from the low-level reflection component diminishes, hence the decrease in the fine structure count and the slope of the phase. Both groups had similar change in the response with increased stimulus intensity; the lack of a difference may be due to the non-localized nature of the data analysis. Our analysis of the fine structure count was inclusive of the frequency range (f_2 =1000-6000 Hz) and we calculated the slope of the phase for the entire response (f_2 = 1000-11314 Hz). A future analysis of more discrete frequency bands may provide more details.

The RMS level growth response was greater in the type-1 diabetes participants. This may seem like a contradiction, but is consistent with Kummer et al. (1998). They suggested that cochlear pathology resulted in loss of non-linearity. In other words, reduction in of the DPOAE response was greatest at low levels, but smallest at the highest stimulus levels such that the growth becomes linearized, therefore, the larger growth in response in the type-1diabetes group. On the other hand the control group had stronger low-level responses and saturated at higher levels, resulting in less growth in comparison, consistent with compression.

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The count of fine structure components was shown to decrease with increase in stimulus. The higher number of fine structure in the control group is consistent with their larger RMS amplitude from the reflection source, as the phase characteristic (rapid change with frequency) of the reflection component contributes greatly to the fine structure (and the trend for larger TEOAE and DPOAE responses in controls) (Johnson, 2010). The distortion component provides the primary contribution at higher stimulus intensities; hence the decrease in fine structure components with increased stimulus level and the phase slope remaining around zero.

In summary, the commonly used clinical protocol OAE (TEOAE and DPOAE) methods did not demonstrate a significant difference in OAE responses between the control and type-1 diabetes group. This finding is not surprising as both groups had similar pure-tone thresholds and normal middle ear function. Nonetheless, the type-1 diabetes group did show a trend for reduced OAEs. This may be due to early indices of cochlear pathology or general reduced function.

The DPOAE fine structure data did show a significant difference in fine frequency count, RMS levels (in particular the reflection component), and RMS growth. The reduced number of fine structure, lower RMS, and increased RMS growth are consistent with expected changes with reduced cochlear function (Mauermann et al., 1999).

Our findings support the use of DPOAE fine structure in identifying early signs of cochlear pathology. Also, our method to collect DPOAE fine structure provides an efficient method to enable DPOAE fine structure measurements in clinical populations not previously feasible due to the time demands of previous methods (Long et al., 2008).

We will give further consideration to influence of Covariates and Noise Exposure in their respective Chapters VI and VII.

CHAPTER V

EFFERENT AND AFFERENT AUDITORY FUNCTION

Literature Review of Efferent Function

Efferent auditory function refers to the top-down influence of the central auditory system on peripheral auditory function, both sensory and neural. Efferent function has been suggested to have roles in protection from acoustic trauma, understanding of speech in noise, and localization (Guinan, 2006). This review focuses on peripheral portions of this feedback system, specifically the medial olivocochlear (MOC) pathway.

The MOC pathway was first described in detail by Rasmussen in 1946. Axons of the MOC project dorsomedially from the superior olivary complex to Rosenthal's canal, where they travel through the osseous spiral lamina and enter the Organ of Corti. MOC fibers synapse at the base of the outer hair cell (OHC) body and can directly influence OHC activity. The MOC system has been implicated in detection of signals in noise, protection from noise damage, selective attention, and OHC gain control.

Non-invasive assays using OAE responses and auditory brainstem responses (ABR) have allowed examination of MOC efferent function in humans. Briefly, a contralateral (opposite to test ear) or forward masked suppressor stimulus (same ear) is introduced while the effect on the test stimulus is measured. Only limited work has explored neural responses (ABR) as a tool to measure efferent suppression in humans (Folsom and Owsley, 1987; Polyakov et al., 1998). The primary assay in humans uses

OAEs. The interested reader is referred to Guinan (2006) for an excellent review of efferent auditory function and methods of OAE suppression.

All types of OAEs can be used to obtain efferent responses. The most common characteristic is a decrease in amplitude; thus the term suppression is often used. Berlin et al. (1993) presented a method of evaluating suppression with TEOAEs acquired with "linear" click stimuli. TEOAEs were selected due to their wide availability and potential ease for clinical application. The linear mode was chosen, as a large portion of the suppression effect is linear (Guinan, 2006). In short, efferent suppression of TEOAEs is recorded by introducing a suppressor stimulus into the ipsilateral (same), contralateral (opposite), or both ears. A forward masking paradigm is introduced where the suppressor stimulus is presented prior to the emission-evoking stimulus and the measured emission is compared to conditions without the suppressor stimulus. Further details are available in Hood et al. (1999).

Diabetes and OAE Suppression. Only two studies have examined OAE suppression in a diabetes population, both in children. Namyslowski et al. (2001) reported reduced contralateral suppression of TEOAEs, recorded at 80, 70, and 60 dB peak SPL nonlinear clicks, in children with diabetes, aged 6- to 16 years, compared to controls, with no differences between groups for TEOAE amplitude. The limitation of the study was the use of nonlinear clicks and pure tone stimuli as the suppressor; noise has been demonstrated to provide a stronger suppressing effect (Berlin et al., 1993). Recently, similar results of contralateral suppression (white noise) of TEOAEs (75-85 dB peaks SPL nonlinear clicks) were reported in children with type-1 diabetes (Ugur et al. 2009).   However, the findings are tempered by the use of a nonlinear stimulus and high

intensity of stimulus that may elicit a MEMR and artificially create a reduced emission due to a stiffened middle ear. Neural pathology affecting efferent neural function was suggested.

Purpose and Hypothesis

The purpose of evaluating efferent function was to determine if efferent reflex characteristics, and thus a component of neural integrity, are altered in the experimental group compared to the control group. Since reduced efferent strength is believed to have implications for susceptibility to hearing loss (Guinan, 2006), we included a measure to address the effect of type-1 diabetes on peripheral auditory efferent function using OAE suppression. In addition, no studies have examined ipsilateral or bilateral OAE suppression in subjects with diabetes (contralateral suppression is the least robust assay of efferent responses; bilateral suppression amplitude is significantly greater; Berlin et al., 1995).

Methods

Procedures. TEOAE suppression was measured using the IHS SmartTroae system (Miami, FL). Testing was performed in a double-walled sound treated room, while the participant was seated in a comfortable chair. A closed-captioned movie was viewable through a window (sound treated) on a monitor in the adjoining room. Participants were instructed to sit quietly and try to minimize physiological noise (heavy breathing, movement, etc.). TEOAE and suppressor stimuli were presented via two ER 10D probes inserted in each ear canal using an ER10D foam tip. The ear with the

greatest amplitude for 65 dB peak SPL linear clicks (discussed in the previous section) was used as the test ear.

Effects of binaural and contralateral suppressor stimuli on TEOAEs were assessed using a forward-masking paradigm (Berlin et al., 1995). Broad-band noise (60 dB SPL, 400 ms duration) preceded click stimuli (75 μsec; 65 dB peak SPL linear click) by 10-msec (Berlin et al., 1995). Averages (400) without the suppressor were interleaved with conditions acquired with one of the suppressors (binaural and contralateral). At least two runs of each condition were measured. Stimulus stability was assessed to assure data quality for calculation of MOC reflex strength. Responses were accepted when both stimulus stability in all conditions and OAE reproducibility in the without suppressor condition exceeded 70%. There were approximately 2 noise-click pairs per second and 400 sweeps were included in each average response. Therefore, the click rate is much slower than the rate for the TEOAEs obtained at 80 and 65 dB peak SPL that were discussed in the previous chapter.

Data Analysis

The Kresge EchoMaster software was used to analyze the suppression data in a time window of 8-18 msec, the time period with the greatest effect (Collet et al. 1990; Berlin et al. 1993). This analysis program allows detailed comparisons of RMS amplitude, cross-correlations of the responses, and analysis of time delays (check of individual runs and phase consistency). The two most similar responses for each condition (least amplitude and phase difference and highest cross-correlation) were averaged. The average response for the suppressor conditions (bilateral and contralateral)

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were subsequently subtracted from the without condition to determine amount of suppression. Data with low cross-correlations (>70%) were excluded from the statistical analysis.

All 40 participants were tested, but fifteen participant's (12 experimental and 3 controls) data could not be included in the suppression analysis due to low-level TEOAE amplitudes in the without condition, leaving 8 matched pairs. However, as an exploratory analysis we examined the response level in the without condition between groups. At least two runs of the without condition were collected in all 40 participants. The two without conditions with the least amplitude difference and highest cross-correlation (phase and amplitude) were averaged and compared between groups. The without condition uses a similar 65 dB SPL "linear" click as previously discussed in Chapter IV, but at a much slower rate, ~2 clicks per second. This slower rate is reflective of the noise-click paradigm for the suppression conditions.

Statistical Analysis

Statistical analysis was performed using SPSS (version 18.0). Data were compared between ears and groups using analysis of variance (ANOVA) with $p < .05$ as the criterion for significance. First, noise amplitudes in the response were compared to determine if groups had comparable noise floors. Next, the without suppressor TEOAE condition (65 dB peak SPL nonlinear click, ~2/sec) amplitude was compared between groups. Finally, the level of contralateral and binaural suppression was compared between groups.

Results

Comparisons between groups for the without suppressor condition (collected on all 40 participants) revealed no significant difference for TEOAE amplitude or noise level ($F = 2.529$, $p > .05$; $F = 1.505$, $p > .05$). However, as seen with the previous OAE results, the experimental group had slightly lower amplitudes in the without condition. Despite the lack of a significant difference in amplitude, 12 of the experimental participants' without suppressor responses were too low (< 3 dB SPL) to perform suppression, while only 3 controls had levels too low (< 3 dB SPL). Nonetheless, for participants with large enough without condition amplitude response ($n = 16$, 8 matched pairs) no significant difference was found for bilateral ($F = .219$, $p > .05$) or contralateral conditions ($F = .069$, $p > .05$); see Figure 3-10.
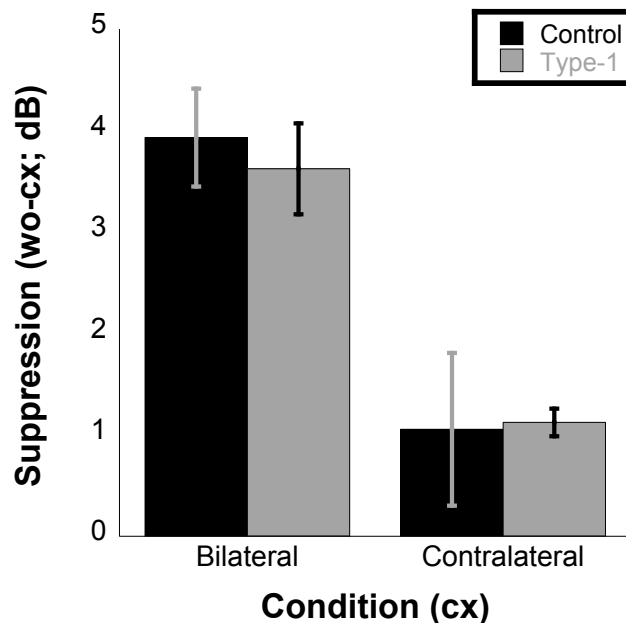
Figure 5-1. TEOAE Suppression Comparison. No significant group effect was seen for TEOAE suppression. Bilateral results are left and contralateral right. Mean and SEM are shown.

Discussion

The lack of a significant difference between groups for the without amplitude condition is consistent with the findings at 65 dB peak SPL previously discussed. The without suppressor condition amplitudes were examined due to the high number of type-1 diabetes subjects that did not meet the criteria for inclusion in the suppression analysis. While no significant difference existed between groups for TEOAE suppression, the experimental subjects were 4 times more likely to have responses too low in the without condition (< 3 dB SPL) to effectively measure suppression. The influence of covariates on this measure and potential interaction in reducing amplitude in participants will be discussed in a future chapter. Both groups demonstrated bilateral and contralateral suppression levels comparable to those reported in the literature (Berlin et al., 1995)

While the two other studies to examine OAE suppression in a diabetes population (both in children) found reduced suppression (Namyslowski et al., 2001; Ugur et al., 2009) we found no difference in TEOAE suppression. However, both of these previous studies used higher stimulus levels and nonlinear clicks that may have confounded their findings. Also the absence of a difference may be related to lack of diabetes related complications among the experimental group (no participants reported any neurological deficits) and/or the reduced sample size available due to low level responses.

Literature Review of Afferent Function

Auditory brainstem response (ABR) testing can be used to objectively record neural activity of the auditory pathway at the VIIIth nerve and brainstem level. By means of ABR, it is possible to assess the integrity of neural brainstem generators. The origin of

wave I is the distal cochlear nerve, the wave II is of proximal cochlear nerve origin, and

wave III is of lower brainstem origin, while the sources of waves IV and V are primarily

in the mid/high brainstem. The generated waveforms beyond wave I have multiple

generator inputs. An excellent history and recent review of the ABR is available to the

interested reader in Moeller (2006). In Figure 5-2 an example of ABR waveforms is

illustrated.
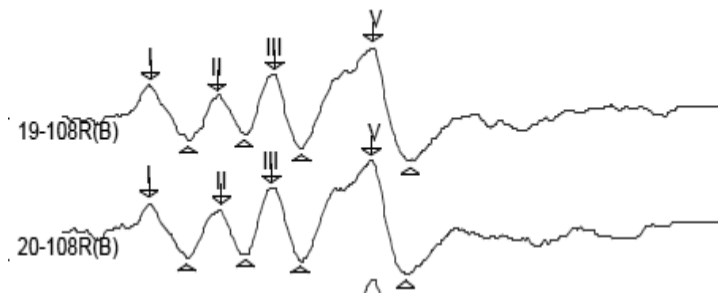
Figure 5-2. ABR waveform. The waves provided correspond to auditory evoked
brainstem responses. Waves I, II, III, and V are marked as selected during data
analysis.

The ABR is used clinically in a number of capacities from determining hearing

status in newborns to identifying auditory neural pathologies (e.g., vestibular

schwanomma). The primary outcomes are amplitude and latency, particularly for wave I

and wave V and the interwave latency between wave I-V. Reduced growth of ABR

amplitude (with increase in stimulus level) can be seen even in the presence of normal

ABR threshold and has been associated with noise-related pathology of the primary

auditory afferent fibers (Kujawa and Liberman, 2006).

ABR rate changes may also contribute to identification of early signs of neural

brainstem pathology (Gerling and Finitzo-Hieber, 1983; Don et al. 1977). Neuro-

physiological mechanisms considered to be responsible for amplitude and latency shift

with increased rate include reduced cochlear receptor function, decrease in synaptic activity, and compromised refractory period. The normal effect of increased stimulus level is increased response amplitude up to a level of saturation. The normal effects of increased rate include reduced amplitude, but minimal change in latency of wave I; and for wave V, minimal change in amplitude, but increase in latency (Don et al., 1977; Burkard et al., 2007).

ABR and Diabetes. Goldsher et al. (1986) examined ABRs in participants (15-55 years of age) with insulin dependent diabetes mellitus (IDDM), with and without peripheral neuropathy, compared to age-matched controls. ABRs were recorded at two rates (10/sec and 55/sec) with 75 dB HL clicks. The participants with neuropathy demonstrated prolonged peaks and greater abnormality at the higher rate compared to controls particularly for later waves (III and V). Those without neuropathy resembled controls in all respects. Parving et al. (1990) reported prolonged wave V with long-term IDDM and presence of microangiopathy. Donald et al. (1981) reported the dominant effects of diabetes on wave V findings. The lack of wave I findings in these studies suggests minimal involvement of the distal VIIIth nerve (histological work in humans and animals supports minimal VIIIth nerve effects of diabetes, see Appendix A).

Al-azzai and Mirza (2004) found impaired neural conduction time in both type 1 and 2 diabetic adults compared to controls, but no difference between types of diabetics or duration of disease. However, Bayazit et al. (2000) found that the likelihood of encountering a diabetic complication in adults increases as ABR results become abnormal. Vaughan et al. (2007) explored ABR differences in veterans with and without diabetes (the type of diabetes was not discussed) and found prolonged wave III and V

latencies, but no association with diabetes related clinical characteristics (retinopathy, nephropathy, HbA1c, glucose, insulin use, and duration). Virtaniemi et al. (1995) found that short-term improvement in metabolic control in diabetic adults had no effect on ABR findings.

ABR disturbances (prolonged latency) have also been described in children with IDDM when compared to normative values (Niedzielska et al., 1998). ABR findings have revealed prolonged absolute latencies in adolescent and young adult subjects with diabetes compared to age-matched controls, primarily affecting wave V (Durmus et al., 2004).

In summary, contradictory findings have been reported on the influence of diabetes on ABR latency and amplitude. The lack of consensus is amplified by the inconsistent findings regarding influence of diabetes related variables. For example, Goldscher et al. (1986) found abnormal ABR characteristics in participants with diabetes, but only in those with neuropathy. Other studies have found no relationship to presence of neuropathy (Vaughan et al., 2007). The predominant effects reported in the literature were prolonged latency and reduced amplitude in later waves (III and V), while wave I (corresponding to the distal VIIIth nerve) was spared.

Purpose and Hypothesis

The ABR enables evaluation of the auditory nerve and brainstem pathways to determine presence of afferent neural dysfunction. ABR testing was performed to assess afferent auditory function in experimental participants compared to controls. We examined ABR responses to determine the influence of diabetes on peripheral auditory

neural function.   In addition to absolute wave amplitude and latency, we incorporate rate effects and growth functions in an attempt to identify early indices of neural damage. We did not anticipate significant difference in absolute wave latency or amplitude, but hypothesized reduced amplitude growth with increased stimulus level (ABR growth function) and reduced amplitude and prolonged latency with increased rate (Rate effects). The rationale was based on the ability of these suprathreshold metrics (ABR growth function and Rate effect) to identify early signs of neural pathology despite normal thresholds (Gerling and Finitzo-Hieber, 1983; Kujawa and Liberman, 2006).

Methods

Procedures. The IHS smartEP system was used to measure ABR responses. Recordings were made in a double-walled sound treated room with the participant seated in a reclining chair. Stimuli were calibrated with the Brüel and Kjaer Pulse system.

We recorded ABRs using monaurally presented 100 μsec click stimuli (50, 65, and 80 dB nHL at 27.7/sec and 77.7/sec, and 2048 sweeps) and standard ABR recording procedures (with the exception of increased sweeps/average). The stimulus levels chosen fall in the range where the low intensity (50 dB nHL) is above threshold, but would demonstration of a change in amplitude with an increase to the highest level (80 dB nHL). The rates selected were based on the findings of Don et al. (1977) that demonstrated minimal changes in ABR latency at rates below 30 clicks/sec or beyond 70 clicks/sec, but large changes from 30 to 70 clicks/sec.

At least two runs were performed at each level and for each rate to replicate the response and rule out artifact (non-repeating peaks). A rarefaction polarity was used to

determine amplitude and latency. In addition, a condensation polarity was also used to

rule out artifact, to differentiate cochlear microphonic from neural components, and to

determine presence of dys-synchrony (if dys-synchrony was observed we would expect

the rarefaction and condensation responses to be out of phase). The electrode setup

consisted of a two-channel electrode montage, ipsilateral (Cz-stimulus ear lobe) and

midline (Cz-Oz) channels (to maximize wave V response amplitude). The electrode

impedance was checked at the beginning and end of each ABR session to ensure that

impedance was less than 5 kΩ and less than 2 kΩ between electrodes. The default band-

pass filter of 100 (high pass) and 3000 Hz (low pass) was implemented.

Data Analysis

The peaks for wave I, III, and V (only wave I and V were analyzed) were selected

to determine response peak-to-peak (positive to negative) amplitude and latency. If the

peak latency and amplitude were inconsistent (absent peak, different latency) the data

were excluded. If the two responses replicated the average amplitude and latency of each

peak was calculated and then averaged. Two independent reviewers examined the

responses with comparable findings.

Statistical Analysis

Statistical analyses were performed using SPSS (version 18.0). Data were

compared between ears and groups using analysis of variance (ANOVA) and $p < .05$ as

the criterion for significance. Prior to group comparisons, we considered the effect of

rate and level on wave I and V amplitude and latency.

Next, absolute amplitude, latency, and wave I-V inter-wave latency were examined between groups. Additionally, change in absolute amplitudes and latencies related to increase in rate and level were considered. Rate induced changes in amplitudes were measured by calculating the difference between amplitude for wave I and V (amplitude at 27.7 clicks/sec – amplitude at 77.7/sec). Rate induced change in wave I and V latency were calculated by taking the difference between latency at 77.7 clicks/sec – 27.7 clicks/sec for each respective wave. Rate induced change in the inter-wave latency were also examined between groups. Finally, change in amplitude and latency due to increase in stimulus level were compared between groups (80 dB nHL – 65 dB nHL for wave I; 80 dB nHL – 50 dB nHL for wave V).

Results

Prior to examining group differences we explored some basic characteristics of the responses. First, wave I and V absolute amplitudes at rates 27.7 clicks/sec and 77.7 clicks/sec were compared at 80 dB nHL. Wave I showed significant decrease in amplitude with an increase in rate ($p < .05$). Wave V amplitude did not show a significant change with increase in rate. Next, we considered change in wave I and V absolute latency with increase in rate. Wave V, but not wave I demonstrated significant increases in latency with increase in rate. In addition there was a significant increase in the inter-wave I-V latency. The change in inter-wave latency was related to the four times larger change in wave V latency compared to that of wave I. Figure 5-3 illustrates the change in latency and amplitude with change in rate.
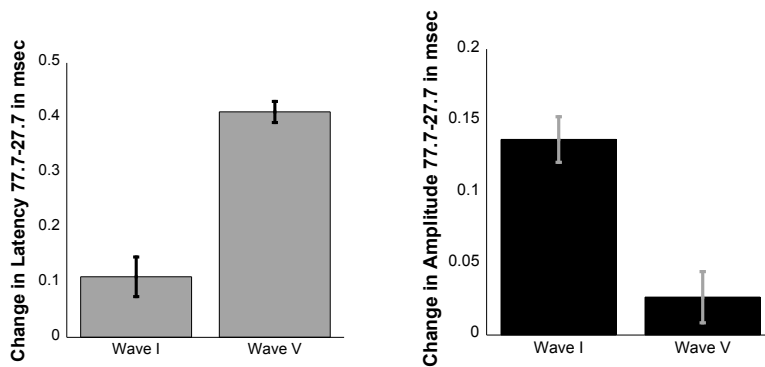
Figure 5-3. ABR Latency and Amplitude Rate Effects. We depict the change in latency (grey) and amplitude (black) with change in rate for wave I and V. It is clear that there is a greater change in latency for wave V and greater change in amplitude with wave I. This finding is consistent with known rate effects in the literature (reviewed by Burkard et al., 2007). Mean and SEM are shown.

The expected changes in latency and amplitude were observed related to level and rate effects. However, we found no significant difference between the experimental and control group for the following: absolute latency and amplitude, interwave I-V latency, change in amplitude and latency with increased rate, or change in amplitude and latency with increased level. In summary, both groups displayed similar ABR findings for both wave I and wave V. See tables in Appendix B.

Discussion

Our study demonstrated no significant difference for ABR responses between the experimental group and controls. Our findings are consistent with those reported in the literature in subjects without impaired neural function (Goldsher et al., 1986; Parving et al., 1990). While we did not expect differences in absolute wave amplitude and latency, our hypothesized rate and growth function effects were also absent. This is likely related to the lack of diabetes related complications associated with neural dysfunction in our

sample; no participants reported history of neuropathy, retinopathy or nephropathy. While it is possible that type-1 diabetes can lead to impaired auditory neural function, the primary findings in histopathological studies support a dominantly cochlear pathology (see Appendix A).

CHAPTER VI

COVARIATES

Literature Review

   A number of covariates have been proposed to influence the relationship between diabetes and hearing loss. These include: sex, age, noise exposure (explored in the next section), and diabetes variables (cardiovascular health, duration of diabetes, severity of diabetes, method of treatment, neuropathy, nephropathy, and retinopathy). Reports exist that both support and challenge most of these covariates.

   Sex. The influence of sex on susceptibility to hearing loss has been revisited many times over the years. The common finding is that males generally have greater susceptibility to age-related hearing loss (Glorig and Nixon, 1960; Gates et al., 1990) and noise induced hearing loss (reviewed in Henderson et al., 1990). However, a gender reversal has also been noted, where females have greater loss at frequencies below 1000 Hz, while males have greater loss above 1000 Hz (Jerger et al., 1993). It is unclear whether these are inherent biological differences or merely a reflection of differences in lifestyle. Indeed, Rosen et al. (1962) explored thresholds in a population relatively free of any noise exposure and found that males and females showed no differences in high frequency thresholds.

   Despite the audiometric contradiction, studies of TEOAEs and DPOAEs routinely show diminished responses in males compared to females. This finding is seen both in newborns (limiting confounds of noise exposure), adults, and animal models.

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Interestingly, TEOAEs show greater reduction than seen in DPOAEs. This difference has been attributed to external/middle ear difference and/or modulation by some biological factor, such as androgens (McFadden, 1999) or efferent function (Velenovsky and Glattke, 2002) on the linear reflection mechanism, while the nonlinear distortion mechanism is relatively unaffected (McFadden et al., 2009). Only one study has examined the influence of sex on DPOAE fine structure. The results demonstrated no difference in frequency of fine structure, but larger depth and spacing in females (Dhar and Abdala, 2007). ABR findings have also suggested shorter latencies in females compared to males, even after control for differences in head size. A shortened and stiffer cochlea in females has been proposed to explain this difference (Edwards et al., 1983; Don et al., 1993).

Sex differences in type-1 diabetes factors are believed to be fairly minimal. Most studies have reported equivocal metabolic control, though some studies have found higher HbA1c levels in young females compared to males, and an influence of endocrine changes has been speculated (Hochhauser et al., 2008). Nonetheless, the understanding of physiological differences between the sexes and their influence on diabetes is limited.

The effect of sex on auditory function in persons with diabetes also remains unclear. Tayor and Irwin (1978) reported significantly poorer thresholds in females with diabetes compared to males. Dietzel et al. (1964) found the opposite results, while Cullen et al. (1993) reported that males displayed elevated thresholds. Axelsson and Fagerberg (1968), Ray et al. (1995) and El-Tabal et al. (2003) found no sex effect. Ottaviani et al. (2002) reported that females had significantly higher TEOAE amplitudes compared to males in both control and experimental participants. However, they did not

describe the relationship in any detail. ABR findings have shown that males with diabetes have prolonged latency compared to females with diabetes, but not significantly different than male controls, which may or may not have been correlated with cochlear or head/brain size difference (Pudar et al., 2009).

Age. It is well known that hearing loss increases with age. However, findings regarding the influence of age on the relationship between diabetes and hearing loss has been mixed. Many early studies found greater loss in older adults with diabetes, however most of these studies did not have age-matched controls nor control for other covariates such as noise exposure, ototoxic drugs, etc (Fowler and Jones, 1999). Kurien et al. (1989) reported significantly elevated high frequency thresholds in all age groups. A significant correlation of pure tone thresholds with diabetes and age was demonstrated by Ferrer et al. (1991). El-Tabal et al. (2003) showed no relationship between diabetes and age for participants less than 40 years of age.

Recent large scale epidemiological studies have suggested that diabetes is related to an early onset of hearing loss, showing elevated pure tone thresholds at younger ages compared to controls (Vaughan et al., 2005; Bainbridge et al., 2008; Austin et al., 2009). The diminished difference with age was attributed to competing causes that accumulate over a lifetime and narrow the gap. This provides a partial explanation for why previous studies that looked at the relationship between diabetes and hearing loss in older adults have found contradictory findings. Another reason is that metrics were limited to pure-tone thresholds and not inclusive of other sensitive metrics like OAEs and extended high frequencies testing.

Diabetes Variables. The influence of diabetes related covariates also have contradictory findings. Tay et al. (1995) demonstrated elevated hearing thresholds with longer duration of diabetes, but no relationship with retinopathy. On the other hand, Cullen et al. (1993) found no relationship of hearing thresholds with duration, insulin dosage or family history. Another study of participants with type-1 diabetes found a relationship with duration of disease and retinopathy, but not with neuropathy, HbA1c, or hypoglycemic episodes (Ferrer et al., 1991).

Di Leo et al. (1997) and Di Nardo (1998) found reduced TEOAE amplitudes in diabetic participants with reduced nerve conduction velocity (NCV), but not in diabetic participants with normal NCV. DPOAEs were reduced in both patients with NCV and without NCV. No associations were for duration of diabetes, HbA1c values (single measure at time of testing) with either TEOAEs or DPOAEs. These researchers contributed the changes in OAE amplitudes to microvascular compromise, despite no measurement for presence of microangiopathy. Lisowska et al. (2001) found similar results with DPOAEs in normal hearing young adults with type-1 diabetes. They reported no relationship to the presence of microangiopathy (evaluated by opthalmoscopy and 24 hour albumin excretion rate), finding altered responses in both patients with miroangiopathy and without. Ottaviani et al. (2002) found significant differences between persons with type-1 diabetes compared to controls (not matched) for both TEOAE and DPOAE amplitudes, but no relationship was demonstrated with duration of disease, HbA1c, mean daily insulin dose, micoralbuminuria, and presence of neuropathy. This is the first study to examine DPOAE fine structure and type-1 diabetes.

Goldsher et al. (1986) described prolonged ABR latency in IDDM patients with neuropathy, but not in IDDM patients without neuropathy. Bayazit et al. (2000) reported an increase in diabetic complications with abnormal ABR results. A study in children (8-21 years) found no significant differences between diabetes and control groups or a relationship with control (maintenance of diabetes) or presence of neurological or vascular complications (Sieger et al., 1983).

Purpose and Hypothesis

The literature review described highly variable findings related to the influence of sex, age, and diabetes factors on auditory function. The purpose of the covariate analysis was to determine the influence of these covariates on the outcome measures. We do not expect an age effect, simply due to the use of a younger population. There may be some inherent sex differences, particularly in OAEs and ABR responses (as described in the literature review). We also consider the influence of diabetes factors in potentially exacerbating or mitigating findings. We hypothesized that "poorer" maintained diabetes would demonstrate poorer outcomes, while "better" maintained diabetes participants would have similar function as the control participants.

Methods

Procedures and Analyses. The individual procedures for each auditory function measure were described previously in their respective sections. Data on sex, age, and diabetes variables (duration, average HbA1c, episodes of poor control, self-control rating, physicians-control rating, number of complications/co-morbidities) were obtained

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through an interviewer-administered questionnaire (see Appendix C for full questionnaire). The questions included were based on those asked in the SEARCH study (SEARCH, 2007) and suggested by an expert in diabetes (William Russell, MD). The participant's previous five glycated hemoglobin levels (HbA1c) were acquired (with consented permission) from the participant's health care provider. We were unable to access HbA1c findings for one of the experimental participants.

In addition to examining these independent covariates, the experimental group was separated into two additional groups by ranking degree of "control" of diabetes. The degree of "control" was determined with consideration of HbA1c levels, episodes of poor control, self and physician rating (as rated by the participant, asked "how would your doctor rate your diabetes control"), and presence of complications. Participants' "control" was categorized as "poorer control" based on the sum of these criteria: average HbA1c > 7.5%, self or physician rating was < good (fair or poor), participant reported episodes of poor control, and if they reported diabetes related complications (see Table 1 in Chapter II). The experimental participants were then ranked, those with the greatest frequency of these criteria were placed in the group "poorer control", while the participants with the lowest frequency were considered to have "better control". Figure 6-1 shows the separation of better and poorer control compared to Average HbA1c levels. The overlap region is related to contribution of other factors such as self-control rating, reported poor control, and number of diabetes related complications. Sex of the participant was not a determining factor in determining "control".
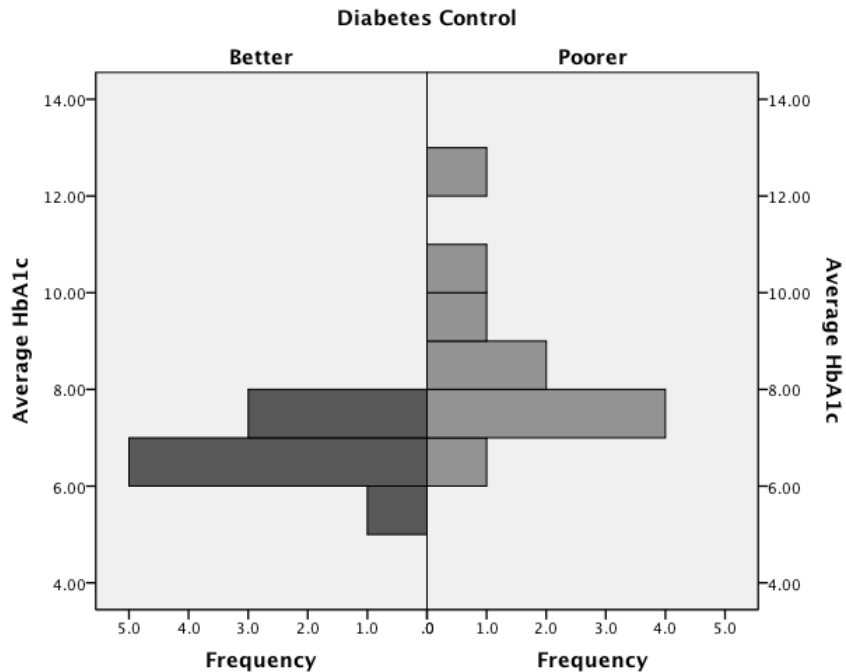
Figure 6-1. Derived Diabetes Control by HbA1c. This figure shows the separation of type-1 participants into levels of control compared to Hba1c. The overlap reflects weighting from self and doctor-control rating, reported poor control, and number of diabetes related complications. Note that data were not available for one participant.

The statistical analysis started with Spearman rho correlations; comparing the auditory function measures with age and the diabetes related covariates (independent variables listed above and the derived "control" of diabetes). The sexes were compared in regards to age, auditory function measures and diabetes variables using ANOVA and chi-square. All statistical analyses included the significance criteria, $p < .05$.

Results

No significant correlations were found for age or diabetes related covariates with any auditory function outcome. No significant difference was observed between males

and females in terms of age, pure tone thresholds (PTAL, PTAH, PTAE), or amount of

TEOAE suppression (bilateral or contralateral). Significant differences were present for

the without condition (65 dB peak SPL clicks presented at the slower rate). Significant

findings were also found for TEAOE amplitudes at both 80 dB peak SPL and 65 dB peak

SPL (regular rate). In addition, DPOAE findings were significantly different between the

sexes. In all instances of significant findings females demonstrated greater OAE

amplitudes than males.

DPOAE fine structure results also revealed significant differences between sexes

related to RMS level; however, the number of fine structure components (count) and

phase slopes were not different. Also, change in RMS, fine structure count, and phase

slopes with increase in stimulus intensity (L_2) were not significantly different between

sexes. Finally, a number of ABR amplitude and latency differences were indicated.

Again, females demonstrated greater amplitudes and shorter latencies in all instances.

Tables 6-1 (OAEs), 6-2 (ABR), and Figure 6-2 (Fine Structure) provide a summary of the

significant sex differences for auditory function outcomes determined by ANOVA at p <

.05.

Table 6-1. ANOVA for Otoacoustic Emission Amplitudes and Sex. The significant correlations between OAE response amplitudes (dB SPL) and sex (M = male, F = female) at $p < 0.05$ are provided. In all instances the direction is for greater amplitude and smaller latency in females.

OAE Measures	Mean M	Mean F	SEM M	SEM F	F
TEOAE 65 dB 19.3/sec	.5878	6.0032	1.31	.831	13.037
TEOAE 80 dB 19.3/sec	15.6275	18.8559	.853	.496	11.656
1000 Hz	-8.9781	-5.1677	1.18	.765	7.824
1500 Hz	-13.5744	-8.1136	1.39	.824	12.368
2000 Hz	-19.2600	-14.4764	1.09	.999	10.365
3000 Hz	-21.1800	-16.3155	1.19	1.18	8.271
4000 Hz	-22.5997	-17.2752	.869	.967	16.068
TEOAE 65 dB ~2/sec	3.3645	7.0167	1.13	.649	8.566
DPOAE 592	6.9167	10.2727	1.23	.923	4.941
DPOAE 701	8.3611	12.4545	1.57	.871	5.695
DPOAE 841	10.4722	13.7273	1.01	.881	5.931
DPOAE 997	9.5278	13.4318	1.18	.630	9.425
DPOAE 1199	7.1944	11.8636	1.17	.827	11.179
DPOAE 1401	6.8611	9.8864	1.19	.827	4.616
DPOAE 1666	5.5556	8.9545	.888	.769	8.449
DPOAE 1977	2.6111	4.40105	1.04	.712	14.778
DPOAE 2382	.3056	4.3636	1.17	.724	9.314
DPOAE 2834	-2.1667	5.2955	1.81	.808	16.128
DPOAE 3379	2.4722	9.9773	1.81	1.33	11.557
DPOAE 4002	.5833	7.8636	2.23	1.90	6.263
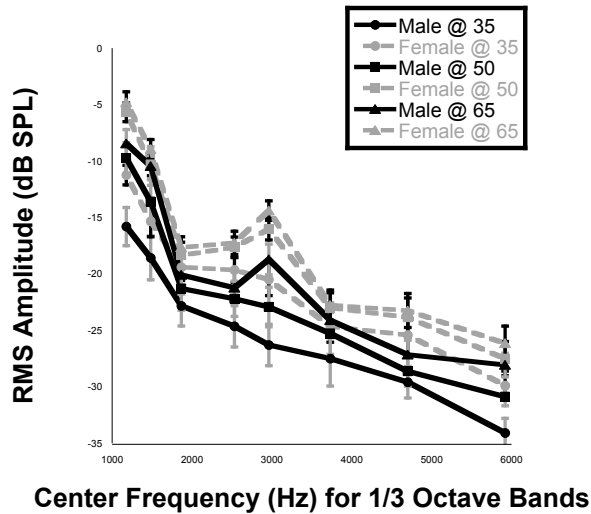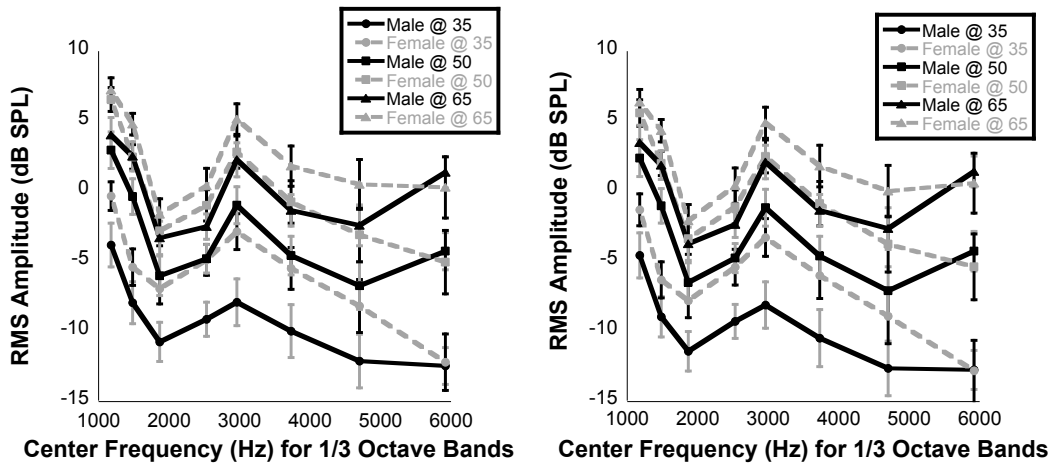
Figure 6-2. Fine Structure RMS Amplitudes by Sex. The figure presents the RMS for each group at the three different L2 levels tested across the center frequency of 2f1-f2. The top left illustrates the RMS for the overall fine structure, the top right the distortion component, and the bottom center the reflection component. The RMS for top right, top left, and bottom center are reduced in males. However, the growth of RMS is not significantly different. This indicates that the non-linear function is conserved in both males and females overall. Mean and SEM are shown.

Table 6-2. ANOVA for ABR and Sex. The significant ANOVA findings between ABR latency (msec) and amplitude (µv) and sex at p < 0.05 are provided. In all instances the direction is for greater amplitude and smaller latency in females.

ABR Outcomes	Mean M	Mean F	SEM M	SEM F	F-test
Wave I lat @ 108 27.7	1.7389	1.6601	.032	.020	4.561
Wave V lat @ 108 27.7	5.9853	5.7365	.043	.039	18.031
Wave V lat @ 93 dB 27.7	6.4072	6.1160	.053	.041	19.347
Wave V lat @ 78 dB 27.7	7.080	6.5917	.084	.055	25.030
Wave I lat @ 108 dB 77.7	1.9125	1.6949	.075	.036	7.599
Wave V lat @ 108 dB 77.7	6.3961	6.1504	.057	.047	11.193
Wave V lat @ 93 dB 77.7	6.9201	6.5904	.075	.049	13.994
Wave V lat @ 78 dB 77.7	7.5888	7.0918	.084	.054	25.564
Wave I lat Δ in rate @ 108	.2114	.0379	.070	.027	6.295
Wave I-V lat @ 108 dB 27.7	4.2464	4.0764	.049	.048	6.029
Wave I amp @ 108 27.7	.2456	.3422	.017	.022	11.535
Wave V amp @ 108 27.7	.3549	.4798	.026	.033	8.365
Wave I amp @ 108 dB 77.7	.1258	.2253	.014	.033	6.593
Wave V amp @ 93 dB 77.7	.2951	.3681	.019	.017	8.153
Wave V amp Δ in rate @ 108	-.0171	.0658	.024	.023	6.061
Wave V amp growth @ 27.7	.0617	.1680	.028	.024	8.235

Despite the observed difference in auditory function between males and females, no significant findings related to sex were indicated for diabetes variables. Both males and females demonstrated similar HbA1c levels, frequency of complications, and control (reported and derived). Table 6-3 and Figure 6-3 summarize the male and female diabetes related variables, no significant differences were seen at p < .05.

Table 6-3. Male vs. Female Diabetes Control. No significant difference in diabetes related variables was found using ANOVA, p < .05.

Diabetes Variables	Mean M	Mean F	SEM M	SEM F
HbA1c	7.12	8.33	.284	.589
Duration (years)	8.44	9.18	2.21	2.03
Complications Frequency	.778	.455	.132	-.097
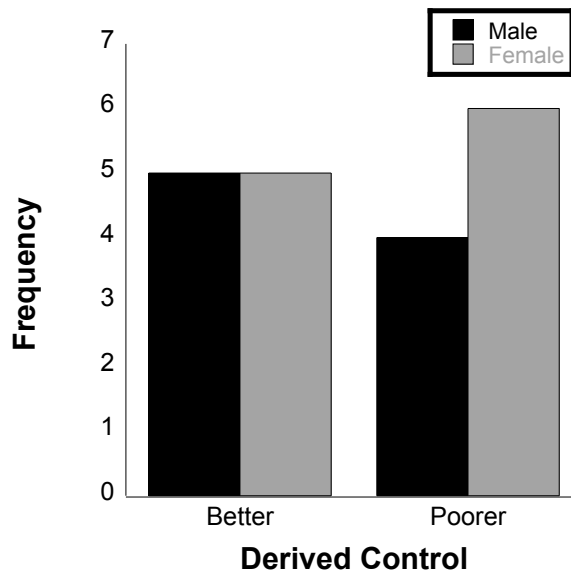
Figure 6-3. Control by Sex. Both males and females showed similar frequency of "better" and "poorer" control status. Chi-square between sexes was not significant, p < .05.

Discussion

The influence of covariates related to age and diabetes characteristics were

minimal. This is not surprising given the young age of the sample and lack of significant

auditory function findings between type-1 diabetes and controls. Most diabetes related

complications increase in incidence with increasing duration of disease (Sieger et al.,

1983), the younger age and minimal report of complications may have precluded

identification of a relationship with our diabetes related variables. This is in line with

early findings of Rosen and Davis (1971); they found no correlation between severity of

microangiopathy and degree of hearing loss in participants with diabetes below the age

25 years.

While, no sex differences were found for the basic audiological findings (PTA and immittance results), differences were revealed for TEOAEs, DPOAEs, and ABR latency and amplitudes. These findings are consistent with the reviewed literature, where females demonstrated stronger OAEs and ABR responses compared to males. Potential explanations for these differences include genetic predisposition, biomolecular function (e.g., influence of androgens during development), cochlear characteristics (e.g., size and stiffness), lifestyle influence, and level of noise exposure (see Chapter VII titled Noise Exposure).

Previous work has demonstrated influence of diabetes-related complications and characteristics (HcA1c, duration, control, etc.) on pure tone thresholds, OAEs, and ABR findings. However, we did not find any significant trends or influence of these covariates on our findings. This may be partially explained by the lack of diabetes-related complications, young age of the participants in this study, higher average socioeconomic status, care being provided by a top rated medical center, and good control among our sample.

Finally, we did not find any significant differences between males and females in regards to diabetes characteristics. Males and females demonstrated similar duration, HbA1c levels, frequency of complications, and reported/derived control.

CHAPTER VII

NOISE EXPOSURE

Literature Review

The literature on noise exposure or acoustic overexposure is immense. Noise
exposure in this study refers to exposure to all sources of "loud" sounds including
occupational and recreational sources. The literature supports occupational sources as the
primary factor contributing to noise-related hearing loss (NRHL). However, much recent
work has found greater influence of recreational sources in directly causing NRHL or
exacerbating the effects of occupational noise exposure by diminishing recovery time.
Maassen et al. (2001) provide an excellent review on influence and interaction of
recreational noise sources.

The literature on the susceptibility of persons with diabetes to NRHL is minimal.
In this review we consider the influence of covariates (analyzed in the previous section)
on susceptibility to NRHL (sex, age, and diabetes) and the ability of our outcomes to
identify early signs of noise-related damage. In Appendix A we speculate on underlying
mechanisms that may contribute to exacerbated risk of NRHL in the diabetes population.

Sex. It is generally accepted that males develop greater high frequency hearing
loss than females with age. A common factor believed to contribute to this difference is
greater exposure to damaging levels of sound. Indeed, several studies have demonstrated
that males tend to have higher and more frequent exposure to loud sounds from both
recreational, occupational, and military sources (Serra et al., 2005; Helfer et al., 2010).

While frequency of encounter with noisy sources has traditionally been higher in men, the exact influence of sex is less known. Boettcher (2002) found no indication that sex exacerbated risk of NRHL in the gerbil. Willott (2009) examined the influence of sex and gonadal hormones on susceptibility to NRHL in C57BL/6J mice. The results indicated that ovarian hormones increased risk of low-frequency hearing loss in females. This difference might be explained by changes in hormones with maternal response to pups; these high frequency demands may diminish the importance of low frequency hearing and allocate less protection to this region. McFadden et al. (1999, 2000) reported that female chinchillas incurred more high frequency NRHL than males, but the opposite was true at low frequencies. However, human studies of higher levels of estrogen and/or progesterone have demonstrated protective effects in reducing susceptibility to hearing loss (Kilicdag et al., 2004; review by Hultcrantz et al., 2006).

Human research has also demonstrated higher low frequency thresholds in females compared to males, while males have greater high frequency thresholds than females (Moscicki et al., 1985; Jerger et al., 1993). In general, experimental studies of TTS in humans have found that males exhibit more TTS than females from low-frequency exposures (below 2000 Hz), whereas females exhibit more TTS than males from high-frequency exposures (above 2000 Hz) (as reviewed by McFadden et al., 1999; Ward, 1966).

Data regarding sex effect on NRHL in humans varies. Several studies suggest that males may be more susceptible than females, whereas others do not support such a conclusion (as reviewed by Boettcher, 2002 and Henderson et al., 1993). Again, the contribution of physiological differences vs. environmental contributions to differential

susceptibility remains unclear. However, efferent function has been demonstrated to be stronger in women than in men (as reviewed by Velenovsky and Glattke, 2002) and along with hormonal differences may reflect differences in susceptibility. Even if similar noise exposures exist between men and women, there are other health and lifestyle differences between men and women that can play a role (e.g., disease, diet, etc.).

Age. The effect of age on susceptibility to hearing loss in general also has received a great deal of attention with contradictory findings. However, it does seem that noise exposure increases dramatically from childhood to young adult ages (Maassen et al., 2001; Biassoni et al., 2005). Greater independence contributes to increased opportunity for exposure to both recreational (e.g., concerts, bars, clubs, car stereo) and occupational sources.

The study of influence of exposure age on susceptibility to NRHL also reveals contradictory findings. Boettcher (2002) examined the influence of age on susceptibility to acoustic trauma in gerbils. Animals were exposed as either young adults (6-8 months) or near the end of the average lifespan (34-38 months). The degree of NRHL was similar for each group, suggesting no difference for susceptibility to hearing loss. Fraenkel et al. (2003) found no difference in threshold shift for young and old rats with ABR and OAEs. Sun et al. (1994) reported that aged chinchillas incurred similar amounts of hair cell loss from noise as younger chinchillas, while McFadden et al. (1997) reported that older chinchillas had more hair cell loss, but similar thresholds. Miller et al. (1998) exposed young and aged CBA/J mice with similar pre-exposure thresholds to noise and reported that aged animals were more susceptible to thresholds shifts and hair cell loss. Meanwhile, studies in guinea pigs and cats have indicated that young animals are more

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susceptible to noise induced damage (Jauhiainen et al., 1972; Price, 1976). More recently, Kujawa and Liberman (2006) demonstrated that animals exposed earlier in life had greater threshold shifts when measured at 2 weeks post exposure and greater degrees of neural degeneration with age. Other earlier animal studies have reported a sensitive period of noise susceptibility early in age (Bock and Seifter, 1978; Lenoir et al., 1979; Henry, 1984 as reviewed by Henderson et al., 1993).

Few studies have examined differential susceptibility to NIHL due to age in humans, particularly incorporating both children and adults. Those that have also revealed contradictory results with some suggesting increased susceptibility in younger participants, some reporting increased risk in older participants, and others no difference (as reviewed by Siervogel et al., 1982; Hetu et al., 1977). First, the physiological difference in susceptibility would be difficult to estimate based on age alone without consideration of noise history and other factors. Older participants have had a lifetime for potential exposure to noxious noise stimuli, which would be less in younger participants. However, studies have shown that efferent function strength may affect susceptibility to NIHL, matures over time in newborns, and diminishes with older age (Moore et al., 1999; Zhu et al., 2007). These relative changes in efferent function suggest increased risk for NRHL in the youngest and oldest age groups.

Second, we must also consider the environmental element. To accurately, examine the differential susceptibility to hearing loss, the noise exposure would have to be similar (as well as other history). It is more likely that young adults and adults of working age will be exposed to occupational noise that has been associated with increased risk of hearing loss than children, who likely are limited to recreational sources

of noise exposure. Recreational sources of noise have been indicated as having a variable amount of influence on NRHL, however firearms use has consistently demonstrated increased risk (Neitzel et al., 2004; Clark, 1991).

The question remains if the age of humans physiologically influences risk for NRHL. If one could take a child and adult with low noise exposure history, control genetic and other risk factors (smoking, medical health, lifestyle, etc.), and then expose them to a noise to look at TTS, it might be possible to get a glimpse at physiological susceptibility. This author was unable to find such a study with these stringent constraints; however, a study by Hetu et al. (1977) found no difference between 12 year olds and adults for TTS after exposure to a broad-band noise.

Diabetes. Very few epidemiological studies have examined diabetes and susceptibility to NRHL. Most human studies have excluded or controlled for noise exposure, while a few have considered it as an independent factor contributing to variance in auditory function (e.g., Dalton et al., 1998). Vaughan et al. (2005) performed a 5-year prospective study of diabetes and hearing loss. Pure tone threshold testing revealed an interaction between noise, age, and diabetes. However, the high level of noise exposure among all controls and diabetes groups limited the ability to draw conclusions on differences in susceptibility to NRHL.

Two human clinical studies have specifically examined diabetes (type not indicated) as a risk factor for NRHL. Both studies were performed in adults with occupational noise exposure. Hodgson et al. (1987) found no evidence of poorer hearing thresholds in participants with diabetes than control participants with similar noise exposure levels. However, Ishii et al. (2003) studied NIDDM and noise exposure and

found that persons with NIDDM were more likely to develop severe NRHL than those without NIDDM.

Controlled animal experiments have demonstrated a more significant loss of outer hair cells (OHCs) in noise exposed rats with diabetes compared to noise exposed controls, but without consideration of molecular mechanisms and relationship to glucose metabolism (Smith et al., 1995; Raynor et al., 1995). McQueen et al. (1999) found significant basement membrane thickening of the cochlea (microangiopathy) in rats with NIDDM, however only in the combination with obesity and/or exposure to noise. Wu et al. (2009) found that rats with diabetes demonstrated impaired recovery from a noise induced temporary TTS, and that recovery was improved to control levels with insulin treatment. An expanded review is provided in Appendix A.

Outcome measures. The traditional clinical indication of NRHL is a "notched" audiogram. A noise-notch typically means thresholds at 3000, 4000, and/or 6000 Hz that are substantially worse than thresholds at lower and higher frequencies. This is related to the resonant frequency of the external and middle ear, which gives greatest emphasis to frequencies around 2700 Hz and the half octave shift of the inner ear region of maximal excitement (Rosowksi, 1991; Cody and Johnstone, 1981).

In contrast the audiogram of pure age-related hearing loss is typically down-sloping with progressively worsening threshold in the higher frequencies (as reviewed by Rabinowitz et al., 2006). The noise-notch is not an absolute evidence of noise damage; other factors can also contribute to notched audiograms. However, notches present in younger subjects may provide good evidence of noise exposure (Gates et al., 2000). Extended high frequency audiometry may also serve as an early predictor of NRHL

(Fausti et al., 1981). This is consistent with animal work showing early signs of acoustic overexposure in the "hook" of the cochlea (extreme base) (Wang et al., 2002).

Otoacoustic emissions may show changes prior to even any change in threshold. The changes can include reduced amplitude and changes in response growth (Attias et al., 1995; Lucertini et al., 2002; Sisto et al., 2007). Strength of efferent suppression may have a role in protection from NRHL, however the direct influence of loud sound on the efferent system itself is unknown. Kujawa and Liberman (2006) demonstrated that mice exposed to moderate levels of noise exposure experienced changes in suprathreshold ABR amplitude (reduced growth related to primary loss of afferent neural fibers of the auditory nerve) despite normal ABR thresholds. The loss was further confirmed with histological analyses.

In summary, a number of factors may influence susceptibility to NRHL. The relationship between NRHL and diabetes has received limited study in both human and animal populations, but the findings thus far indicate some elevated susceptibility to damage. In this section we consider the relationship between diabetes and noise exposure history.

Purpose and Hypothesis

The purpose of this section of the study was to examine the interaction between noise exposure history and type-1 diabetes. To uncover the relationship we have performed an in-depth retrospective history of noise exposure and include the most sensitive auditory function metrics available (discussed in their respective sections). Based on previous work we hypothesize that persons in the experimental group with

higher noise exposure will have greater damage compared to those with lower noise exposure and more so than controls. In addition, we will determine if noise exposure is an independent factor contributing to greater degree of hearing loss in persons with diabetes. Exacerbated susceptibility to NRHL may help explain the recent epidemiological findings for early onset of hearing loss in younger persons with diabetes. For the interested reader a biomolecular basis of our hypothesis is reviewed and presented in appendix A.

Methods

Procedures. Noise exposure history and other noise exposure information were obtained through interviewer-administered questionnaires to estimate frequency, duration and subjective level of daily noise exposure from recreational and occupational sources. Noise exposure estimates were used to classify each participant into categories of "higher" or "lower" exposure to dangerous levels of noise.

Responses to three questionnaires were selected to examine noise exposure. These particular questionnaires were chosen to account for recent- and life-long exposure to potentially damaging sources and levels of sound. These type of questionnaires have been the most commonly used to examine noise exposure in younger populations incorporating recreational sources. The first questionnaire was a modified version of a noise exposure history used by Seixas et al. (2004) with components from a history developed by Neitzel et al. (2004a, 2004b). We will subsequently refer to these items as the noise exposure history (NEH). The second questionnaire was a General Noise History (GNH) based on the work of Jukitulppo et al. (1997; 2006). The GNH provided

a retrospective estimate of noise exposure during an average week over the past few months, with consideration of frequency, duration, use of hearing protection, and subjective loudness (using a five-item Likert scale). The third questionnaire was the Adolescents' Habits and Hearing Protection Use (AHH) (Olsen-Widen and Erlandsson, 2004; Holmes et al., 2007). The AHH was presented in a modified form to elucidate an estimate of noise exposure over the participant's lifetime. Approval was received from the authors of these questionnaires for their use in this study. The questionnaires, instructions, and further details are located in Appendix C. Prior to this study, all of the questionnaires were piloted in a group of Ph.D. graduate and high school students to determine wording, variable inclusion, and ease of use.

Data Analysis

The frequency, duration, use of hearing protection and subjective loudness of noise exposure were considered. The GNH and AHH, in addition to the total number of noisy activities and subjective response to level of exposure to loud sounds (NEH) were used to determine the participant's total noise history (TNH). In the GNH, noise exposures with subjective ratings (sr) of ≥ 3.5 were multiplied by the number of days per week (dw) and number of hours per day (hd) and summed, GNH $= \sum$ (sr x dw x hd). For the AHH, the frequency of participation in 14 noisy environments was evaluated. A weighting was applied to frequency of participation (1=never, 2=seldom, 3=sometimes, 4=often) and summed. The participant's were then ranked on their GNH and AHH scores (0 = lowest, 1 = mid level, 2 = highest level). The TNH was calculated as the sum of the GNH and AHH rankings plus the following from the NEH: the total number of

noisy activities performed on a regular basis, musician training, work in a noisy

environment and gun/hunting use (from the NEH). An extra point was added to the

overall TNH for each activity noted on the NEH.

   The NEH revealed few participants were exposed to high levels of noise at work

(n =4). All but one participant reported owning a personal listening device (MP3 player,

iPod, etc.). The average weekly use of personal listening devices is presented in Figure

7-1.
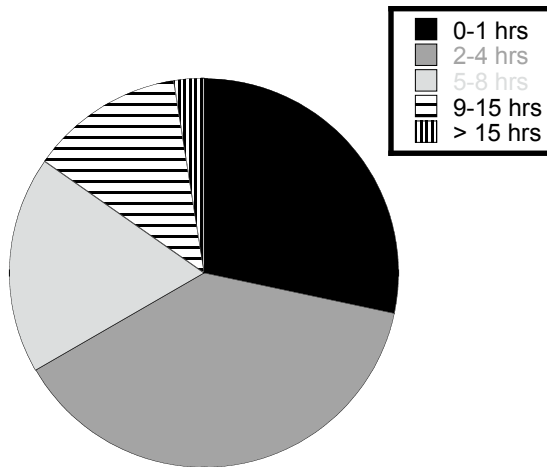
Figure 7-1. Personal Listening Device Weekly Use. The overall average weekly
use in hours for personal listening devices use. The majority of participants used
their device 4 hours or less per week.

   The mean level setting for personal listening devices (based on a loudness scale

corresponding to number of increments on an iPod, ~16 clicks reaches maximum output

level) in quiet was 6.26 (SEM ± .505) and in noise 11.41 (SEM ± .415). Only one

participant reported having continuous tinnitus. Twenty-six participants indicated never

or rarely experiencing a change in hearing when exposed to loud sounds (transient

tinnitus, aural fullness, pain, etc.). Table 7-1 summarizes activities reported that were

performed on a weekly basis at some point in the participant's life.

Table 7-1. Noise Exposure History Noisy Activity Participation. The percentage
of participants that indicated that they partake in a selected activity on a weekly
basis at some time in their life.

Noisy Activity	% Yes
Musician/Music Instrument	60
Carpentry	7.5
Metal Work	5
Chainsaw	2.5
Other Power Tools	12.5
Motorsports (motorcycle, boating, etc.)	12.5
Concert Attendance	20
Bar/Club	75
Gun/Hunting	2.5
Construction Work	0
Factory Work	2
Mechanic Work	0

Finally, participants were asked to report their subjective rating of lifetime

exposure to loud sounds, Figure 7-2 provides a summary.
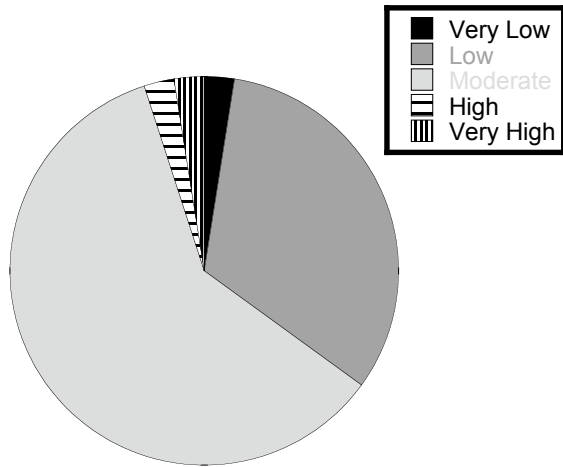
Figure 7-2. Lifetime of Noise Exposure Rating. This figure illustrates the reported lifetime of noise exposure in the sample. The majority of participants reported moderate to low levels of noise exposure.

Figure 7-3 and Tables 7-2 and 7-3 provide summary descriptives for the GNH, and AHH responses.
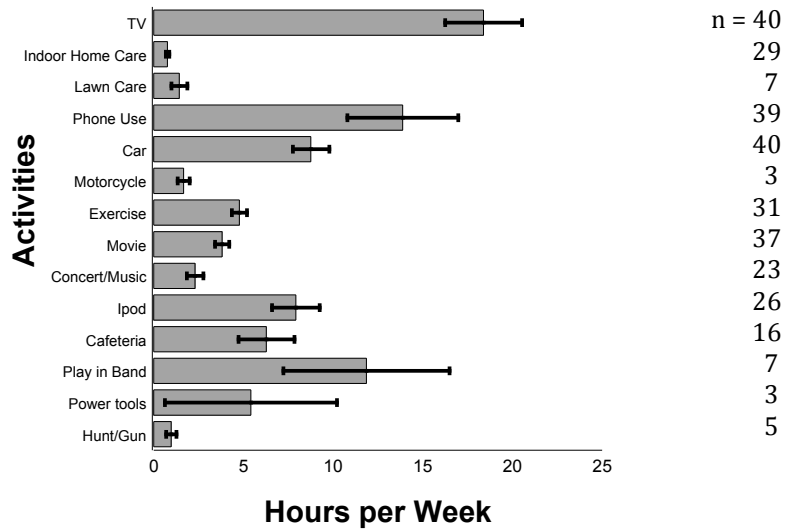
Figure 7-3. General Noise History Activity. This figure illustrates the hours per week of participation in different potentially noisy activities. To the right is the number of participants that reported performing the activity. Few participants reported louder activities such as motorcycle, power tools, playing in a band, hunting/gun shooting. Mean and SEM are shown.

Table 7-2. General Noise History Loudness and Hearing Protection Use. This table provides the mean subjective rating of loudness level (1 = quiet, 2 = somewhat quiet, 3 = noticeable, 4 = loud, 5 = very loud). In addition, the number of participants that reported using a hearing protection device (HPD) while performing the activity. The loudest activities were hunt/gun, concert attendance, and playing in a band. Very few participants reported HPD use except for the hunt/gun activity. No participants reported recent activity in the list of activities at the bottom of the table.

Activities	n	Mean	SEM	HPD
TV	40	2.31	.081	0
Indoor Home Care	29	2.83	.143	0
Lawn Care	7	3.86	.143	2
Phone Use	39	2.19	.057	0
Car	40	2.59	.071	0
Motorcycle	3	3.33	.333	0
Exercise	31	2.55	.138	0
Movie	37	3.11	.095	0
Concert/Music	23	4.00	.141	1
Ipod	26	2.87	.126	0
Cafeteria	16	2.87	.072	0
Play in Band	7	3.43	.414	2
Power Tools	3	3.33	.601	0
Hunt/Gun	5	4.50	.387	4

Pedestrian, Plane, Boating, Construction, Industry/Factory Job, Farm work, Mechanic, Military service, Explosives/fireworks not included due to limited reported participation

Table 7-3. Adolescent Hearing Habit (AHH) Participation and HPD Use. This table provides a summary of frequency of noisy activity reported by the subjects. The Hearing Protection Device (HPD) use is also indicated. Again participants that hunted were more likely to report use of HPD.

Noisy Activity	Never	Seldom	Often	Always	HPD
Fireworks	3	37	0	0	0
Hunting/Gun Use	25	12	3	0	12
Motorcycle	31	7	1	1	1
Lawn Mower	21	10	5	3	4
NASCAR	35	4	1	0	2
Rock Concert	4	20	15	1	5
Disco/Club	8	7	18	7	2
Aerobics Class	19	5	6	10	0
Headphones	2	1	6	31	0
Stereo in Home	4	12	15	9	1
Stereo in Car	2	6	12	20	0
Play in Band	24	4	3	9	5
Power Tools	24	11	4	1	6
Work	21	9	3	7	4

In summary, the noise exposure history descriptive information revealed limited participation in higher noise activities such as hunting/gun use, playing in a band or working in a noisy environment. The difference in reported activities between the GNH and AHH were related to the retrospective timeline associated with each metric. The purpose of the GNH was to determine noisy activity participation on average over the past few weeks, while the modified AHH and NEH were used to determine lifetime of participation in noisy activities.

Statistical Analysis

Spearman rho correlations were performed to determine relationships between descriptive variables and noise exposure. Chi-square and ANOVA were performed to

compare findings for categorical and scale variables, respectively. Data were entered into

SPSS from Excel databases. The NEH, GNH, AHH and TNH results (see Appendix C for

copies of the questionnaires) were compared among groups (experimental and control)

and sexes. The purpose of this analysis was to determine if the experimental and control

group differed in degree of noise exposure and if differences existed between the sexes (p

$< .05$).

Results

 No significant correlations were discovered regarding noise exposure and

presence of type-1 diabetes (including NHE, GNH, and AHH variables and TNH). This

means that both the control and type-1 diabetes groups had similar noise exposure

histories (see Figure 8-1 in Chapter VIII titled Sex, noise, and type-1 diabetes section).

On the other hand, significant correlations for noise exposure were found with sex, with

males demonstrating greater noise exposure in all instances (AHH = -.386, $p < .05$ and

TNH = -.339, $p < .05$). Figure 7-4 shows the mean noise exposure history for males

compared to females. Sex differences were significant for mean TNH (F = 4.921, $p <$

.05) and AHH (F = 6.203, $p < .05$), but not GNH (F = 1.422, $p > .05$).
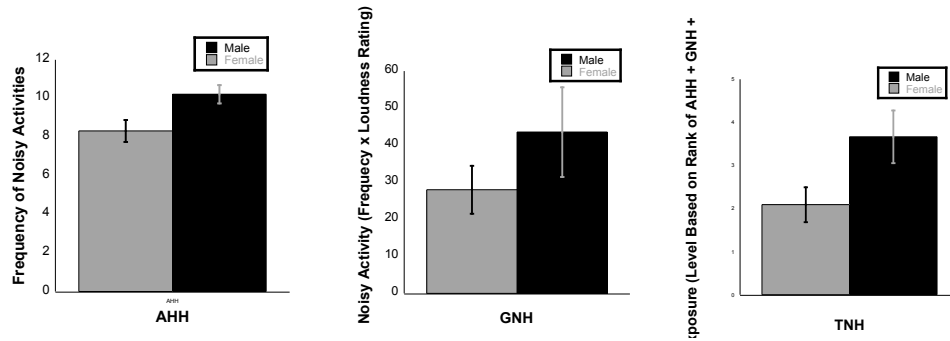
Figure 7-4. Males versus Females Noise History. This figure demonstrates the higher levels of noise exposure reported by males compared to females. The AHH (far left) and TNH (far right) revealed significantly higher noise exposure in males, the variance in the GNH (center) was too large to demonstrate a difference. This supports the notion that the acute noise history metric is much more variable than consideration of longer- term noise exposure history. Mean and SEM are shown.

Experimental and control participants were subsequently rank ordered for TNH

and separated into high and lower noise exposures groups and compared. Figure 7-5

shows the separation of higher and lower noise exposure based on the TNH.
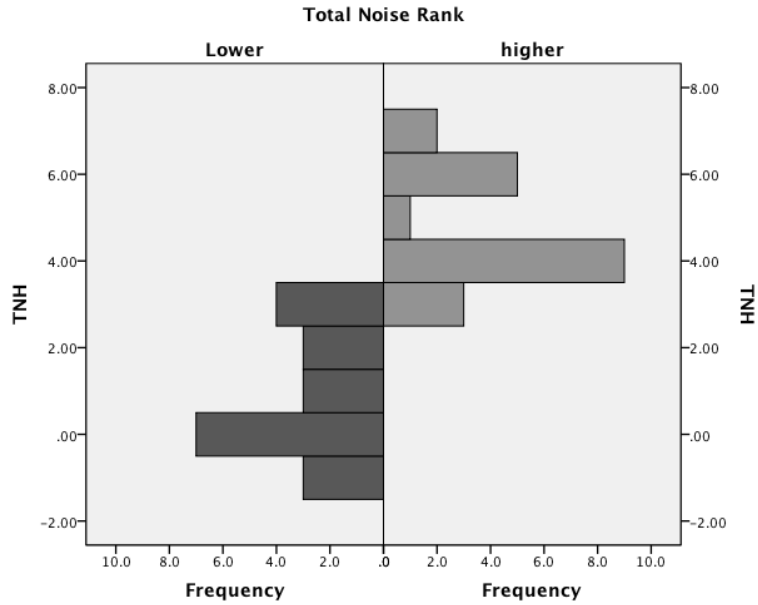
Figure 7-5. Total Noise Rank. The figure depicts the frequency count for separation of participants into higher and lower noise exposure based on TNH rank. Ties were separated on exposure to highest intensity noise sources, e.g., gun/hunting.

Table 7-4 summarizes the significant auditory function findings and level of noise exposure, $p < .05$, the SEM is provided in the parentheses. The primary finding was diminished TEOAE and DPOAE fine structure findings. No PTA or regular DPOAE demonstrated significant differences, while one ABR variable was significant.

Table 7-4. Higher vs. Lower Levels of Total Noise History. This table provides the auditory function outcomes that demonstrated significant differences (p < .05) in noise exposure for higher and lower levels of THN.

Auditory Measure	n	Lower (SEM)	Higher (SEM)	F-test
TEOAE 65 dB 19.3/sec	40	5.30 (1.12)	1.83 (1.19)	4.520
TEOAE 65 dB 2/sec	40	6.89 (.850)	3.86 (.961)	5.592
TEOAE 80 dB	40	18.46 (.742)	16.35 (.698)	4.304
1500 Hz	40	-8.223 (1.11)	-12.912 (1.16)	8.533
4000 Hz	40	-17.83 (1.09)	-21.52 (.962)	6.401
Reflection @ 35 dB, 1176 Hz	32	-11.20 (.834)	-15.05 (1.54)	4.111
Reflection @ 65 dB, 3731 Hz	32	1.71 (1.57)	-.793 (1.15)	6.329
Reflection @ 35 dB, 5920 Hz	32	-29.36 (1.34)	-33.77 (1.22)	5.833
Wave I Lat 108 dB @ 27.7	40	1.65 (.027)	1.74 (.024)	5.207

Next, a 2 X 2 ANOVA examining the interaction of noise exposure (higher and lower TNH) and diabetes was performed in the auditory function measures that demonstrated a significant relationship to noise. The findings are summarized in Table 7-5. The only significant interaction for noise was seen for the $L_2 = 35$ dB SPL reflection component RMS at 1176 Hz, (F = 4.853, p < .05).

Table 7-5. Interaction of Diabetes and TNH. One significant interaction was indicated (*), but the findings for the type-1 group with higher noise exposure show a trend for reduced function (same n as previous table). SEM in parentheses.

Auditory Measure Diabetes x TNH	Control Lower	Type-1 Lower	Control Higher	Type-1 Higher
TEOAE 65 dB 19.3/sec	6.15 (1.15)	4.46 (1.95)	4.08 (1.42)	-.42 (1.69)
TEOAE 65 dB 2/sec	8.13 (.844)	5.65 (1.41)	4.89 (1.42)	2.82 (1.36)
TEOAE 80 dB	18.65 (.902)	18.27 (1.22)	17.56 (.946)	15.14 (.912)
1500 Hz	-7.35 (1.08)	-9.10 (1.97)	-10.97 (1.65)	-14.87 (1.46)
4000 Hz	-19.13 (1.22)	-16.53 (1.79	-20.43 (1.66)	-22.61 (.939)
Reflection @ 35 dB,1176Hz*	-11.62 (1.09)	-10.79 (1.33)	-11.52(1.69)	-19.46 (1.82)
Reflection @ 65 dB,3731Hz	-21.98 (1.93)	-19.47 (1.88)	-24.60 (1.99)	-25.52 (1.54)
Reflection @ 35 dB,5920Hz	-28.46 (2.18)	-32.5 (1.68)	-30.26 (1.80)	-35.35 (1.51)
Wave I Lat 108 dB @ 27.7	1.63 (.050)	1.65 (.044)	1.72 (.039)	1.72 (.034)

Discussion

In the previous sections we found significant differences in auditory function between type-1 diabetes and control groups limited to the most sensitive measure of cochlear function (DPOAE fine structure). In addition, there was limited influence of diabetes related covariates on auditory function. However, we did find an overall sex difference with males demonstrating poorer cochlear and afferent function. On the other hand, no sex effects were seen in relationship to diabetes related variables, indicating similar levels of control and care.

The noise exposure profiles demonstrated rare exposure to occupational sources of noise exposure. The primary sources of noise exposure in this population were related to recreational and leisure activities. However, most of these activities were only performed occasionally. Activities such as bar/club attendance (75%), musical instrument/playing in band (60%), and concert attendance (20%) had the greatest frequency of weekly participation at some period in life. However, very few participated in activities such as gun/hunting (2.5%) and power tools use (12.5%).

The literature provides contradictory evidence to the influence of sporadic recreational noise exposure on susceptibility to hearing loss, most studies indicating a limited influence (Mostafaspour, 1998). The lack of occupational noise exposure in this group may have limited our capacity to explore noise exposure as a variable of influence. In other words, the range of noise exposure may have not been large enough to distinguish higher levels of noise exposure with greater probability of damage from lower levels with diminished probability of damage. However, we were able to show that participants with higher noise exposure had poorer outcomes.

When examining noise exposure, no significant difference in noise exposure histories were found between the experimental and control groups, though males did demonstrate significantly higher levels of noise exposure. This creates a dilemma, since males have higher noise exposure and poorer auditory function it is difficult to separate the influence of noise exposure alone on diabetes and auditory function. For example, males with higher noise exposure make up the majority of the participants in the "high noise" groups, since males have poorer auditory function this may artificially exacerbate the noise findings.

Another limitation of the analyses alluded to already was the variability of noise exposure levels. Only a minority of participants reported work related noise exposure, the majority of the noise exposure reported was related to recreational sources that can be highly variable in level, duration, and questionable in relation to pathological influence. There was not a large range of noise exposure with few participants reporting very high or very low life long levels of noise exposure; most reported moderate exposure (see Figure 7-2). A solution to this limitation would be for future studies to recruit participants with higher levels of similar noise exposure with type-1 diabetes and without. In addition, examining susceptibility to temporary threshold shift may provide some clues to the interaction of noise and type-1 diabetes.

CHAPTER VIII

SEX, NOISE, AND TYPE-1 DIABETES

The finding that male participants have greater noise exposure and reduced auditory function outcomes compared to female participants limits our ability to examine the interaction between noise and type-1 diabetes. We did not have a sample size sufficient to examine noise groups (those with lower and higher TNH) in males and females separately. This would be an appropriate next step to determine the underlying influences. Instead, Tables 8-1 and 8-2 provide summaries of mean responses for males only and females only for the auditory function measures that were shown in the previous chapter to be significantly related to noise exposure. The trend of the data supports poorer performance in the groups Diabetes with High Noise exposure (both males and females) compared to Control groups (High Noise and Low Noise). Note the sample size for each group.

Table 8-1. Summary of Sex, Noise, and Diabetes. This table breaks down the mean amplitude for OAE responses and ABR wave I latency. Males and females with higher noise exposure show a trend for lower amplitude responses in comparison to controls and prolonged wave I latency. The sample size for each is provided in parentheses.

Auditory Measure	Diabetes Low Noise		Diabetes High Noise		Control Low Noise		Control High Noise	
	M (2)	F (8)	M (7)	F (3)	M (4)	F (6)	M (5)	F (5)
TEOAE 65 19/sec	-2.04	6.08	-2.34	4.04	5.39	6.66	1.89	6.27
TEOAE 65 2/sec	1.32	6.74	1.31	6.34	8.70	7.74	2.79	6.99
TEOAE 1500 Hz	-17.21	-7.07	-16.3	-11.6	-7.52	-7.24	-13.6	-8.8
TEOAE 4000 Hz	-25.2	-14.4	-22.7	-22.4	-20.7	-18.4	-23.3	-17.6
Wave I Lat 108 @ 27	1.74	1.63	1.74	1.66	1.56	1.68	1.80	1.64

Table 8-2. Summary of Sex, Noise, and Diabetes for Fine Structure. The table summarizes fine structure findings that were significant for levels of noise exposure. Males with high noise and diabetes have the poorest RMS levels. The sample size is provided in parentheses.

Fine Structure	Diabetes Low Noise		Diabetes High Noise		Control Low Noise		Control High Noise	
	M (1)	F (6)	M (6)	F (2)	M (3)	F (4)	M (5)	F (5)
Reflection @ 35 dB, 1176 Hz	-13.42	-11.31	-21.24	-14.11	-10.77	-10.80	-12.72	-10.33
Reflection @ 65 dB, 3731 Hz	-17.98	-19.72	-26.12	-27.70	-20.62	-22.99	-24.97	-24.24
Reflection @ 35 dB, 5920 Hz	-30.49	-30.23	-35.17	-35.90	-30.32	-27.05	-35.73	-29.28

To further explore this relationship we examined male control versus male experimental participants and female control versus female type-1 diabetes participants separately, excluding further separation into higher and lower noise. Since males (both control and type-1) had higher noise exposure than females (both control and type-1), a

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greater loss in the male experimental group versus the male control group may be related to the higher noise exposure, particularly if the female group comparison did not show the same finding. The first step was to account for noise exposure to determine if the sex-specific controls differed from the experimental subjects. Figure 8-1 shows the average TNH for males and females with type-1 diabetes compared to controls and separated by sex (similar findings were found for the GNH and AHH).
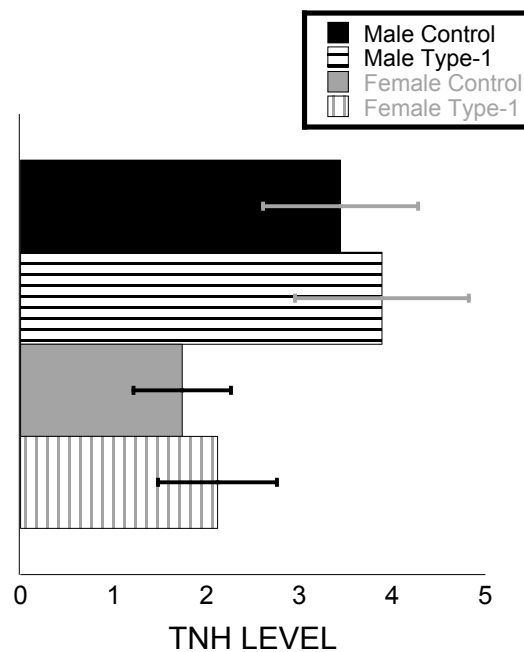
Figure 8-1. Sex-Specific Noise Exposure Levels. Male controls and experimental participants had similar group noise exposure, as did the females, with males being higher and females being lower. Mean and SEM shown.

While males in general have greater noise exposure than females, male control and male type-1 participants did not differ significantly from each other, which holds true for females as well. Table 8-3 summarizes the sex-specific comparison of the noise related outcome measures (from Chapter VII) and presence of diabetes; SEM are provide in parentheses. The asterisk indicates a significant finding.

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Table 8-3. Sex-specific Comparison. This table provides a summary of the findings for outcomes that were significantly related to noise. The asterisk (*) indicates a significant result. (n =40 TEAOE and ABR; n=32 Fine Structure).

Auditory Measure	M Control	M Type-1	F Control	F Type-1
TEOAE 65 dB 19.3/sec	3.45 (1.73)*	-2.27 (1.51)	6.48 (.748)	5.52 (1.52)
TEOAE 65 dB 2/sec	5.42 (1.74)	1.31 (1.15)	7.41 (.600)	6.62 (1.17)
TEOAE 80 dB	16.77 (1.23)	14.49 (1.12)	19.19 (.442)	18.51 (.902)
1500 Hz	-10.66 (2.05)*	-16.49 (1.38)	-7.92 (.825)	-8.30 (1.47)
4000 Hz	-21.95 (1.32)	-23.25 (.869)	-17.99 (1.31)	-16.55 (1.45)
Reflection @ 35 dB, 1176Hz	-11.9 (1.87)*	-20.12 (1.92)	-10.54 (1.35)	-12.02 (1.08)
Reflection @ 65 dB, 3731Hz	-.186 (1.46)	-2.74 (1.74)	-23.69 (1.79)	-21.71 (2.08)
Reflection @ 35 dB, 5920Hz	-33.70 (2.09)	-34.5 (1.61)	-11.23 (2.82)	-13.36 (3.05)
Wave I Lat 108 dB @ 27.7	1.72 (.059)	1.76 (.082)	1.68 (.034)	1.64 (.022)

Interestingly males, who as a group have higher noise exposure, show significant differences between groups, while females, with lower noise exposure as a group, do not. This finding suggests that the interaction of higher noise exposure in males with type-1 diabetes may partially explain the reduced function. On the other hand, females with overall lower noise exposure did not show a difference between groups.

To clarify this question a larger sample size and greater range of noise exposure will be needed. Another potential explanation is related to sex differences in regards to metabolic function and diabetes. Though our type-1 group did not show differences in terms of control, HbA1c, or presence of diabetes related complications, some sex-specific (e.g., related to hormones) interaction with type-1 diabetes may exist that reduces cochlear function in males regardless of noise exposure history (see McFadden et al., 2009 for a review on sex-differences and auditory function).

In summary, the preliminary indication of noise interaction with diabetes demonstrated in Chapter VII may be confounded by the predominant male sex

comprising the high noise groups. Separate sex-specific findings however support either an interaction of sex with diabetes resulting in reduced function, the type-1 diabetes groups showing increased risk for NRHL, or an interaction.

CHAPTER IX

INTEGRATING DISCUSSION

While the very relationship of diabetes to hearing loss remains under debate, as

demonstrated by the contradictory findings reviewed, as a whole, the literature supports

an influence of diabetes on susceptibility to hearing loss. We report no difference

between the type-1 diabetes and control groups using the common clinical methods for

basic audiological measures, cochlear function, peripheral efferent function, and

peripheral afferent function assessment.

However, we did find significant differences in DPOAE fine structure measures.

The reduced RMS amplitudes associated with the reflection component, diminished

number of fine structures (count), and increased RMS amplitude growth was

characteristic of changes related to early signs of cochlear pathology. In an everyday

clinical assessment our groups would not have demonstrated a difference in auditory

function. Therefore, our findings also give support to the potential clinical implications of

DPOAE fine structure and lower level TEOAEs (65 dB peak SPL) in identifying early

signs of cochlear pathology (one of our secondary objectives of this study; see Chapter X

Future Directions).

Our covariate findings revealed limited influence of age and diabetes related

variables (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

control or diabetes related complications (no participants reported neuropathy, retinopathy, or nephropathy).

On the other hand, we did find a strong influence of sex on our outcome measures, primarily reduced OAE amplitudes and prolonged ABR latency and reduced amplitudes of wave I and V in males. However, these sex differences have been reported in numerous studies. Females generally have stronger OAEs (larger amplitudes) and ABRs (shorter latency and larger amplitude). However, these differences may not reflect "better" auditory function, but differences in external/middle ear characteristics and cochlear size. For example, McFadden et al. (2009) demonstrated that OAEs associated with the reflection component (TEOAE, SFOAE, SOAE) were larger, while OAEs primarily representative of the distortion component (DPOAE) were more similar between sexes. It is plausible that length differences of the cochlea (female cochlea's are 8-13% shorter than males) may increase the perturbations that underlie the theoretical source of the reflection component.

The most noteworthy finding related to sex was the results of the sex-specific analysis. When auditory function was examined in the male experimental group versus the male control group, a significant difference was found in a number of the outcome measures, most prominently low-level TEOAEs and DPOAE fine structure. However, comparable findings were not found in the female group comparison.

The difference in sex-specific findings may be related to an interaction between male sex and type-1 diabetes (e.g., biochemical effect of andrognes) or potentially the higher noise exposure demonstrated in our male participants. Noise-related damage is associated with both mechanical and metabolic compromise. Overexposure to noise can

alter cochlear homeostasis resulting in excessive reactive oxygen/nitrogen species, vascular changes, activation of apoptosis-like pathways, excitoxic events, and subsequent cellular damage (Henderson, 2006). Therefore, the pathological effects of noise on the auditory system may be exacerbated by consequences of genetic, autoimmune, and biochemical interactions associated with diabetes.

Recent epidemiological findings have demonstrated poorer pure-tone thresholds in populations with diabetes, particularly in young adulthood, but as age increased threshold findings compared to controls diminished (Vaughan et al., 2005; Bainbridge et al., 2008; Austin et al., 2009). This reduces the likelihood of age and diabetes related complications underlying the earlier onset hearing loss. Therefore we hypothesized that type-1 diabetes may exacerbate susceptibility to noise related hearing loss (NRHL).

Diabetes, specifically hyperglycemia, initiates a complex cascade of biochemical consequences. Three main effects are non-enzymatic glycation, activation of polyol pathway, and generation of reactive oxygen/nitrogen species. Metabolic processes disrupted include: energy production, abnormal accumulation of metabolic by-products, nitric-oxide and glutathione dysregulation, glycation, lipid balance abnormalities, and protein synthesis dysfunction. Above all increased oxidative stress has been implicated in diabetes pathogenesis and co-morbidities associated with diabetes including hearing loss (Liu et al., 2008; Aladag et al., 2009). The cumulative effects of these biochemical changes may contribute to damage of blood vessels and compromised metabolic function. The high-energy demands of the cochlea could be disrupted by these changes, particularly with additional demands created by noise exposure.

The findings of reduced cochlear function, primarily in male participants with type-1 diabetes and higher noise exposure provides preliminary support to our hypothesis of increased risk for NRHL. This finding is timely given the recent indications of increased incidence of noise-related hearing loss in adolescents 12-19 years of age (Shargorodsky et al., 2010). If participants with type-1 diabetes are at increased risk for NRHL, then stronger efforts in prevention may offset the early onset of loss found in epidemiological studies.

CHAPTER X

FUTURE DIRECTIONS

The following steps are recommended for future phases of this work:

1. The demonstration of early indices of reduced cochlear function is compelling

    and suggests that sex, noise, and/or the interaction of sex and noise may influence

    the early onset of hearing loss in the diabetes population reported in recent

    epidemiological studies. In order to fully pursue this question we will need to

    increase our sample size with inclusion of more male and female participants with

    greater noise exposure histories. Therefore, a next step will be to recruit more

    age- and sex-matched participants with occupational sources of steady noise with

    our same inclusion criteria.

2. The findings of this study suggest minimal neural involvement in the reduced

    function found. Therefore, as we continue this study we will limit the auditory

    function measures to the basic audiological battery and otoacoustic emissions

    (TEOAEs, DPOAEs, and DPOAE Fine Structure). This will also focus part of

    our effort identifying early indices of cochlear damage prior to changes in pure-

    tone thresholds or even commonly used clinical OAE testing protocols (DPOAE

    fine structure and low-level TEOAEs).

3. Another important step will be enhancing our data analysis methodology to look at more fine structure features (e.g. spacing, depth, etc.) and frequency specific bands, similar to our 1/3 octave band RMS amplitude analysis. Frequency band analysis may provide more details to location of pathology.

4. A retrospective account of noise exposure is limited, particularly by participant recall error (overestimates and underestimates). Moreover, a passive prospective account (e.g. noise diary) or daily noise exposure may not be representative of the participants "true" life-long noise exposure. Therefore, in addition to the sample adjustments proposed in step 1, we will also seek to examine susceptibility to a temporary threshold shift (TTS). A TTS experiment involves a noise exposure paradigm. The participant is exposed to a sound level that will cause a temporary reduction in thresholds that fully recover. By including a TTS experiment we can explore if persons with diabetes have exacerbated TTS compared to controls and monitor the progression of DPOAE fine structure changes immediately after the insult and as the threshold recovers.

APPENDIX A

MECHANISMS CONTRIBUTING TO HEARING LOSS IN DIABETES

The purpose of this appendix is to provide a brief review of the literature focused on the cellular and molecular pathophysiology of hearing loss related to diabetes. In contrast to the large number of clinical and epidemiological studies of diabetes, very few studies have directly examined the basic pathological interaction between diabetes and hearing loss. The limited understanding of the cellular and molecular pathways contributing to hearing loss in persons with diabetes is related to absence of a proper animal model of diabetes and lack of access to cochlear tissue in humans in vivo.

Human Histological Studies. Human histological studies examining the effects of diabetes and auditory pathology are fairly limited. Recently, Fukushima et al. (2005, 2006) examined histological cochlear changes in adults with type 1 and type 2 diabetes and found significantly greater cochlear microangiopathy, degeneration of the stria vascularis, spiral ligament, and auditory outer hair cells than in age-matched controls. No significant difference was seen in number of spiral ganglion cells. Subjects with a history of noise exposure were excluded. The author's interpretation was that microangiopathy associated with diabetes affected inner ear vasculature and caused degeneration of inner ear structures. These findings suggest a primarily cochlear pathology.

Animal Studies. The most commonly used animal model of diabetes is the streptozocin-treated (STZ) rat. Most studies of diabetes and hearing loss in animals have used this model (Nageris et al., 1998; Liu et al., 2008), including those examining

susceptibility to noise related hearing loss (Smith et al., 1995; Raynor et al., 1995; Wu et al., 2009). However, the problem with this is model is that STZ itself may interfere with hair cell metabolism (Fowler and Jones, 1999). A second model, the mouse strain SHR/N-cp is a rat that develops diabetes at 12 months of age. This model has also been used in auditory function studies (Triana et al., 1991), including noise (McQueen et al., 1999). However, cochlear pathology in the model was demonstrated at 5 months of age, which was 7 months prior to the animal becoming "diabetic". Therefore, the cause may represent a genetic mutation rather than direct effect of diabetes itself. A third model, the NOD strain of mice has also been used to study auditory function, in particular autoimmune effects (Nakae and Tachibana, 1986; Ohlemiller et al., 2008; Vasilyeva et al., 2009).

Vasilyeva et al. (2009) examined the interaction of age and diabetes in two animal models, one representative for type-1 diabetes (STZ) and a second representative of type-2 diabetes (dietary induced). The results demonstrated reduced auditory function in both models, but the ABR thresholds and wave I amplitudes were only significantly altered in the type-2 model.

No animal model of diabetes is perfect and much work is needed in understanding the cellular and molecular influences of diabetes on susceptibility to hearing loss. The primary pathological findings in these studies examining "diabetic" animals are outer hair cell loss (with mostly preserved inner hair cells), pathological changes of the stria vascularis, reduced endocochlear potential (battery that drives cochlea involving k+ recycling involving the stria vascularis), and minimal changes in primary afferent auditory nerve fibers.

Genetic Influence. The genetic relationship between hearing loss and diabetes is complex and inclusive of direct, indirect, and environmental influences. Specific genetic mutations affecting nuclear and mitochondrial genes in both syndromic and non-syndromic manifestations have been related to hearing loss and diabetes (Diniz et al., 2009). These include Wolfram Syndrome, maternally inherited diabetes and deafness (MIDD), and myoclonic epilepsy, lactic acidosis, and stroke-like episodes (MELAS) (Kokotas et al., 2007).

Autoimmune Associations. Autoimmune factors have been associated with both diabetes and hearing loss. However, the precise interaction of autoimmune disease, diabetes, and hearing loss has been elusive. In NOD mice-models of autoimmune effects, the main implications are believed related to strial pathology. In the case of type-1 diabetes, primary damage involves inflammatory infiltration and destruction of organs and connective tissue. By contrast, cochlear pathology in these mice does not show inflammation, but instead immunoglobulins that bind to endothelial cells and capillary basement membranes (Ohlemiller et al., 2008).

Biochemical Hypotheses. Wang and Schacht (1990) examined the role of insulin in the inner ear of the guinea pig. They reported a lack of an effect of insulin on glucose metabolism in the cochlea, but the hormone did increase protein synthesis and lipid metabolism. They proposed a phospholipid-based transmembrane signaling system mediating the effects of insulin on the inner ear.

Diabetes, specifically hyperglycemia, initiates a complex cascade of biochemical consequences. Three main effects are non-enzymatic glycation, activation of the polyol pathway, and generation of reactive oxygen/nitrogen species. Metabolic processes

disrupted include: energy production, abnormal accumulation of metabolic by-products, nitric-oxide and glutathione dysregulation, glycation (advanced glycation end products), lipid balance abnormalities, and protein synthesis dysfunction. Tissue damage associated with diabetes includes: endothelial, neural, extracellular, and collagen compromise (Frisina et al., 2006). Up-regulation of vascular endothelial growth factor (VEGF) and nitric oxide isoforms have been demonstrated in the cochlea of diabetic rats (Liu et al., 2008).

Increased oxidative stress also has been implicated in diabetes pathogenesis and co-morbidities associated with diabetes including hearing loss (Liu et al., 2008; Aladag et al., 2009). Attempts have been made to correlate oxidative stress with glycated hemoglobin (Hb_{A1c}) (Choi et al., 2008; Goodarzi et al., 2008). The cumulative effects of these biochemical changes contribute to damaged blood vessels and compromised metabolic function. The high-energy demands of the cochlea could be disrupted by these changes, particularly with additional demands created by noise exposure.

Noise and Diabetes Interaction. The effects of noise exposure alone on hearing are well documented. Noise-induced damage is related to both mechanical and metabolic compromise. Overexposure to noise can alter cochlear homeostasis resulting in excessive reactive oxygen/nitrogen species, vascular changes (an initial ischemia followed by reprefusion), activation of apoptosis-like pathways (e.g. Bcl-2 family), excitotoxic events (excessive glutamate), and subsequent cellular damage (Henderson, 2006). The pathological effects of noise on the auditory system may be exacerbated by the consequences of genetic, autoimmune, and biochemical interactions associated with diabetes discussed above.

Controlled animal experiments have demonstrated a more significant loss of outer hair cells (OHCs) in noise exposed rats with diabetes (STZ injected) compared to noise exposed controls but without consideration of molecular mechanisms and relationship to glucose metabolism (Smith et al., 1995 and Raynor et al., 1995). McQueen et al. found significant basement membrane thickening of the cochlea (microangiopathy) in rats (SHR/N-cp) with NIDDM, however only in the combination with obesity and/or exposure to noise. Wu et al. (2009) found that rats (STZ injected) with diabetes demonstrated impaired recovery from a noise induced temporary threshold shift, this recovery was improved to control levels with insulin treatment.

Summary. The relationship between diabetes and hearing loss has been debated for over a century. Study methodology limitations and differences have led to highly variable findings. Prominent examples are the interaction between age and diabetes, lack of consideration for type of diabetes, and minimal account for control or severity of diabetes. The cumulative effects of diabetes contribute to damaged blood vessels and compromised metabolic function. The high-energy demands of the cochlea could be disrupted by these changes, particularly with additional demands created by noise exposure. Human studies of diabetes generally have excluded individuals with a history of noise exposure or ignored the potential interaction between noise and diabetes on hearing status. This hypothesized interaction may leave diabetics with high levels of noise-exposure at exacerbated risk for noise-related hearing loss.

Mean and SEM for non-significant data are provided for outcomes comparing control and experimental groups not presented in a table or figure in the manuscript. The order of the presentation of tables follows the outline of the dissertation manuscript.

Pure Tone Threshold Average		PTALOW	PTAHI	PTAE
Control	Mean	4.6250	3.9750	-.1875
	N	20	20	20
	SEM	.66775	.63606	2.00026
Type-1	Mean	6.3250	4.4750	2.8437
	N	20	20	20
	SEM	.70736	.64018	2.23030
Total	Mean	5.4750	4.2250	1.3281
	N	40	40	40
	SEM	.49902	.44720	1.49839

TEOAE Amplitudes		TEOAE	TEOAE 1000 Hz	TEOAE 1500 Hz	TEOAE 2000 HZ	TEOAE 3000 HZ	TEOAE 4000 HZ
Control	Mean	18.1023	-5.6187	-9.1578	-15.7225	-18.0443	-19.7765
	N	20	20	20	20	20	20
	SEM	.64795	.88726	1.04506	.80858	1.43670	1.01532
Type-1	Mean	16.7040	-8.1460	-11.9843	-17.5355	-18.9647	-19.5660
	N	20	20	20	20	20	20
	SEM	.82794	1.12253	1.36437	1.42884	1.16735	1.20555
Total	Mean	17.4031	-6.8824	-10.5710	-16.6290	-18.5045	-19.6713
	N	40	40	40	40	40	40
	SEM	.53083	.73461	.87789	.82319	.91661	.77808

TEOAE Noise		TEOAE	TEOAE 1000 Hz	TEOAE 1500 Hz	TEOAE 2000 Hz	TEOAE 3000 Hz	TEOAE 4000 Hz
Control	Mean	6.9980	-20.6380	-25.0965	-30.9535	-34.3740	-29.5015
	N	20	20	20	20	20	20
	SEM	.79665	.66678	.87658	.46714	1.78879	.26019
Type-1	Mean	8.5385	-19.1790	-24.0310	-30.5780	-35.9840	-29.5245
	N	20	20	20	20	20	20
	SEM	.94376	.87662	.85344	.53922	.87213	.57903
Total	Mean	7.7683	-19.9085	-24.5637	-30.7657	-35.1790	-29.5130
	N	40	40	40	40	40	40
	SEM	.62191	.55600	.60981	.35339	.99062	.31331

TEOAE at 65 dB		Slow rate	Fast rate
Control	Mean	6.510675	5.1153
	N	20	20
	SEM	.8556498	.92081
Type-1	Mean	4.235825	2.0172
	N	20	20
	SEM	1.0103217	1.37498
Total	Mean	5.373250	3.5663
	N	40	40
	SEM	.6783494	.85357

DPOAE Amp 1		dp436	dp498	dp592	dp701	dp841	dp997	dp1119	dp1401	dp1666
Control	Mean	4.775	7.575	9.950	12.07	13.025	13.00	10.975	9.1750	7.3250
	N	20	20	20	20	20	20	20	20	20
	SEM	.9586	.8015	.9759	.9755	.92656	.9514	1.0640	1.0041	.67986
Type-1	Mean	4.525	6.100	7.575	9.150	11.500	10.35	8.5500	7.8750	7.5250
	N	20	20	20	20	20	20	20	20	20
	SEM	.8851	1.142	1.203	1.473	1.0606	.9529	1.1007	1.0716	1.09152
Total	Mean	4.650	6.837	8.762	10.61	12.262	11.67	9.7625	8.5250	7.4250
	N	40	40	40	40	40	40	40	40	40
	SEM	.6443	.6989	.7881	.9032	.70574	.6976	.78016	.73226	.63487

DPOAE Amp 2		dp1977	dp2382	dp2834	dp3379	dp4002	dp4749	dp5636
Control	Mean	5.2250	2.3750	2.3500	7.8000	5.6750	2.3250	-1.6250
	N	20	20	20	20	20	20	20
	SEM	.99173	.90820	1.56319	1.67897	2.42717	1.84044	1.48894
Type-1	Mean	5.1750	2.7000	1.5250	5.4000	3.5000	-1.9000	-4.0250
	N	20	20	20	20	20	20	20
	SEM	1.03826	1.16269	1.55152	1.82259	1.93479	1.91414	1.33696
Total	Mean	5.2000	2.5375	1.9375	6.6000	4.5875	.2125	-2.8250
	N	40	40	40	40	40	40	40
	SEM	.70865	.72862	1.08902	1.23805	1.54182	1.35352	1.00616

DPOAE Noise1		dp436	dp498	dp592	dp701	dp841	dp997	dp1199	dp1401	dp1666
Control	Mean	-2.85	-3.95	-6.55	-7.50	-11.20	-9.85	-12.85	-15.50	-15.80
	N	20	20	20	20	20	20	20	20	20
	SEM	.982	.961	.809	.587	.647	.802	.525	.763	.579
Type-1	Mean	-2.15	-2.75	-5.65	-7.30	-9.45	-11.00	-11.80	-14.65	-16.65
	N	20	20	20	20	20	20	20	20	20
	SEM	1.173	1.289	.765	.798	.716	.775	.942	.689	.604
Total	Mean	-2.50	-3.35	-6.10	-7.40	-10.33	-10.43	-12.33	-15.08	-16.23
	N	40	40	40	40	40	40	40	40	40
	SEM	.757	.799	.554	.489	.497	.558	.539	.512	.418

DPOAE Noise 2		dp1977	dp2382	dp2834	dp3379	dp4002	dp4749	dp5636
Control	Mean	-19.75	-23.50	-24.10	-22.90	-18.35	-15.85	-12.55
	N	20	20	20	20	20	20	20
	SEM	.593	.587	.688	.571	.704	.744	.727
Type-1	Mean	-19.45	-23.85	-25.00	-23.05	-18.40	-14.30	-11.15
	N	20	20	20	20	20	20	20
	SEM	.647	.708	.661	1.053	.400	.543	.838
Total	Mean	-19.60	-23.68	-24.55	-22.98	-18.38	-15.07	-11.85
	N	40	40	40	40	40	40	40
	SEM	.434	.455	.476	.591	.400	.471	.559

OAE Suppression Amp and Noise		AVGWO Amp	AVGWO Noise	AVGBI Amp	AVBBI Noise	AVGCO Amp	AVGCO Noise
No	Mean	8.51863	-2.49800	4.68613	-1.2691	7.49675	-1.2784
	N	8	8	8	8	8	8
	SEM	.984360	.607449	1.07970	.975240	.976926	.96120
Yes	Mean	7.12275	-1.45837	3.49900	.55500	6.00150	-.3245
	N	8	8	8	8	8	8
	SEM	1.47100	.986714	1.28710	1.24589	1.45433	.94501
Total	Mean	7.82069	-1.97819	4.09256	-.35706	6.74912	-.8014
	N	16	16	16	16	16	16
	SEM	.873766	.575575	.825861	.799731	.868027	.66266

OAE Suppression CCX and Suppression		BISUP	BISUP CXX	COSUP	COSUP CCX
Control	Mean	3.8325	.87250	1.02188	.93450
	N	8	8	8	8
	SEM	.50977	.029092	.274670	.017486
Type-1	Mean	3.6236	.73850	1.12112	.88250
	N	8	8	8	8
	SEM	.44821	.043177	.048089	.023418
Total	Mean	3.7281	.80550	1.07150	.90850
	N	16	16	16	16
	SEM	.32899	.030524	.135305	.015632

ABR Amplitude		I10827	V10827	I9327	V9327	V7827	I10877	V10877	V9377	V7877
Control	Mean	.2950	.4248	.1177	.3143	.2918	.1797	.4039	.3407	.3103
	N	20	20	11	19	19	17	18	18	18
	SEM	.01902	.03528	.0108	.02258	.02388	.03593	.02125	.0185	.02748
Type-1	Mean	.3024	.4224	.1457	.3459	.3223	.1805	.4028	.3271	.3020
	N	20	20	11	20	20	16	20	20	20
	SEM	.02610	.03175	.02102	.02118	.01927	.02143	.02470	.0209	.02038
Total	Mean	.2987	.4236	.1317	.3305	.3074	.1801	.4033	.3336	.3059
	N	40	40	22	39	39	33	38	38	38
	SEM	.01595	.02343	.0119	.01546	.01526	.02090	.01623	.0139	.01665

ABR Latency		I10827	V10827	I9327	V9327	V7827	I10877	V10877	V9377	V7877
Control	Mean	1.6958	5.8365	2.129	6.1874	6.7650	1.8203	6.2853	6.7296	7.2779
	N	20	20	11	19	19	17	18	18	18
	SEM	.03212	.05534	.1122	.05728	.08103	.07954	.06209	.07084	.08672
Type-1	Mean	1.6954	5.8604	2.062	6.3103	6.8665	1.7656	6.2501	6.7619	7.3715
	N	20	20	11	20	20	16	20	20	20
	SEM	.02184	.04398	.1051	.05443	.09434	.03047	.05667	.07496	.09250
Total	Mean	1.6956	5.8484	2.095	6.2504	6.8171	1.7938	6.2668	6.7466	7.3272
	N	40	40	22	39	39	33	38	38	38
	SEM	.01917	.03494	.0754	.04020	.06217	.04317	.04142	.05116	.06331

Spearman rho Correlations of Diabetes Control and Auditory Function

PTA Averages		Control	HbA1c
Control	Correlation Coefficient	1.000	.674[**]
	Sig. (2-tailed)	.	.002
	N	20	19
HbA1c	Correlation Coefficient	.674[**]	1.000
	Sig. (2-tailed)	.002	.
	N	19	19
PTALOW	Correlation Coefficient	-.087	-.187
	Sig. (2-tailed)	.715	.443
	N	20	19
PTAHI	Correlation Coefficient	-.261	-.600[**]
	Sig. (2-tailed)	.266	.007
	N	20	19
PTAE	Correlation Coefficient	-.113	-.073
	Sig. (2-tailed)	.635	.766
	N	20	19

Note: the one significant finding for high PTA (2000-8000 Hz). The direction of the relationship shows poorer hearing with better control, the relationship was loss with consideration of total control. This finding is probably a chance finding due to the overall well controlled diabetes among our sample.

TEOAE Amplitude		Control	HbA1c
Control	Correlation Coefficient	1.000	.674[**]
	Sig. (2-tailed)	.	.002
	N	20	19
HbA1c	Correlation Coefficient	.674[**]	1.000
	Sig. (2-tailed)	.002	.
	N	19	19
TEOAE	Correlation Coefficient	-.173	-.178
	Sig. (2-tailed)	.465	.466
	N	20	19
TEOAE 1000 Hz	Correlation Coefficient	-.087	-.082
	Sig. (2-tailed)	.716	.740
	N	20	19
TEOAE 1500 Hz	Correlation Coefficient	-.009	-.107
	Sig. (2-tailed)	.971	.664
	N	20	19
TEOAE 2000 Hz	Correlation Coefficient	.035	.097
	Sig. (2-tailed)	.885	.692
	N	20	19
TEOAE 3000 Hz	Correlation Coefficient	-.416	-.345
	Sig. (2-tailed)	.068	.148
	N	20	19
TEOAE 4000 Hz	Correlation Coefficient	-.295	-.156
	Sig. (2-tailed)	.207	.523
	N	20	19

DPOAE Amplitude 1		Control	HbA1c
Control	Correlation Coefficient	1.000	.674[**]
	Sig. (2-tailed)	.	.002
	N	20	19
HbA1c	Correlation Coefficient	.674[**]	1.000
	Sig. (2-tailed)	.002	.
	N	19	19
dp436	Correlation Coefficient	.009	.220
	Sig. (2-tailed)	.971	.364
	N	20	19
dp498	Correlation Coefficient	-.148	-.101
	Sig. (2-tailed)	.535	.681
	N	20	19
dp592	Correlation Coefficient	-.227	-.293
	Sig. (2-tailed)	.336	.224
	N	20	19
dp701	Correlation Coefficient	-.035	-.177
	Sig. (2-tailed)	.884	.469
	N	20	19
dp841	Correlation Coefficient	.035	-.229
	Sig. (2-tailed)	.884	.345
	N	20	19
dp997	Correlation Coefficient	.061	-.049
	Sig. (2-tailed)	.799	.843
	N	20	19
dp1199	Correlation Coefficient	.139	.161
	Sig. (2-tailed)	.558	.511
	N	20	19
dp1401	Correlation Coefficient	.017	-.087
	Sig. (2-tailed)	.942	.723
	N	20	19
dp1666	Correlation Coefficient	.044	.011
	Sig. (2-tailed)	.855	.964
	N	20	19

DPOAE Amplitude 2		Control	HbA1c
Control	Correlation Coefficient	1.000	.674[**]
	Sig. (2-tailed)	.	.002
	N	20	19
HbA1c	Correlation Coefficient	.674[**]	1.000
	Sig. (2-tailed)	.002	.
	N	19	19
dp1977	Correlation Coefficient	.052	.317
	Sig. (2-tailed)	.827	.186
	N	20	19
dp2382	Correlation Coefficient	-.096	.260
	Sig. (2-tailed)	.688	.283
	N	20	19
dp2834	Correlation Coefficient	-.130	.203
	Sig. (2-tailed)	.584	.404
	N	20	19
dp3379	Correlation Coefficient	-.087	.158
	Sig. (2-tailed)	.716	.518
	N	20	19
dp4002	Correlation Coefficient	.087	.290
	Sig. (2-tailed)	.716	.229
	N	20	19
dp4749	Correlation Coefficient	.052	.030
	Sig. (2-tailed)	.827	.903
	N	20	19
dp5636	Correlation Coefficient	-.235	-.190
	Sig. (2-tailed)	.319	.435
	N	20	19

ABR Latency		Control	HbA1c
Control	Correlation Coefficient	1.000	.674**
	Sig. (2-tailed)	.	.002
	N	20	19
HbA1c	Correlation Coefficient	.674**	1.000
	Sig. (2-tailed)	.002	.
	N	19	19
I10827	Correlation Coefficient	.087	-.270
	Sig. (2-tailed)	.716	.263
	N	20	19
V10827	Correlation Coefficient	.113	-.268
	Sig. (2-tailed)	.636	.267
	N	20	19
I9327	Correlation Coefficient	.520	.261
	Sig. (2-tailed)	.101	.467
	N	11	10
V9327	Correlation Coefficient	-.052	-.149
	Sig. (2-tailed)	.828	.542
	N	20	19
V7827	Correlation Coefficient	.139	-.147
	Sig. (2-tailed)	.560	.547
	N	20	19
I10877	Correlation Coefficient	.054	-.346
	Sig. (2-tailed)	.842	.206
	N	16	15
V10877	Correlation Coefficient	.295	-.133
	Sig. (2-tailed)	.207	.586
	N	20	19
V9377	Correlation Coefficient	.104	.011
	Sig. (2-tailed)	.662	.963
	N	20	19
V7877	Correlation Coefficient	.191	-.046
	Sig. (2-tailed)	.420	.853
	N	20	19

ABR Amplitude		Control	HbA1c
Control	Correlation Coefficient	1.000	.674**
	Sig. (2-tailed)	.	.002
	N	20	19
HbA1c	Correlation Coefficient	.674**	1.000
	Sig. (2-tailed)	.002	.
	N	19	19
I10827	Correlation Coefficient	-.087	.339
	Sig. (2-tailed)	.716	.156
	N	20	19
V10827	Correlation Coefficient	.026	.314
	Sig. (2-tailed)	.913	.191
	N	20	19
I9327	Correlation Coefficient	.000	.236
	Sig. (2-tailed)	1.000	.511
	N	11	10
V9327	Correlation Coefficient	.243	.465
	Sig. (2-tailed)	.302	.055
	N	20	19
V7827	Correlation Coefficient	.295	.509
	Sig. (2-tailed)	.207	.051
	N	20	19
I10877	Correlation Coefficient	-.027	.511
	Sig. (2-tailed)	.921	.052
	N	16	15
V10877	Correlation Coefficient	.035	.312
	Sig. (2-tailed)	.885	.193
	N	20	19
V9377	Correlation Coefficient	.252	.323
	Sig. (2-tailed)	.285	.177
	N	20	19
V7877	Correlation Coefficient	.122	.380
	Sig. (2-tailed)	.609	.109
	N	20	19

Demographics

1. ☐ Male   ☐ Female

2. ☐ White, Non-Hispanic   ☐ Hispanic, Latino, Mexican
   ☐ Asian   ☐ Black, African-American
   ☐ Pacific Islander   ☐ Native American
   ☐ Other (specify)

3. Date of Birth _____ (month, day, year) _____ age

4. What is your approximate weight (lb)? _____

5. What is your approximate height (in)? _____

6. What is your current school grade? _____

7. Where do you attend school? _____
   ☐ Public ☐ Private ☐ Home

8. What is the highest level of school either or your parents/guardians have completed? ☐ Elementary or grade school   ☐ High School
   ☐ Some College or university   ☐ Associate Degree
   ☐ Bachelor's Degree   ☐ Master's Degree
   ☐ Professional or Doctorate Degree

9. How would you consider your family's socioeconomic status?
   ☐ Above Average   ☐ Average   ☐ Below Average

10. Do you have a job? ☐ Yes ☐ No; more than one ☐ Yes ☐ No
    If yes: What type of job? (e.g. waitress) _____
    How many hours do you work per week? _____
    How often are you exposed to high noise at work? High noise meaning louder than a noisy restaurant or loud enough that you have to raise your voice to talk to someone 3 feet or less away.
    ☐ Never or almost never ☐ Less than half the time ☐ Half time
    ☐ More than half the time ☐ Always or almost always
    If yes please fill out a work section for each job individually

General Noise History

1. Please mark into the table how many days per week and how many hours per day you participate in these noisy activities on an average week and for how many years. If less than 1 hr fill in approximate minutes per day with an "m" after, e.g. 30 m. Also estimate the loudness where **1 = quiet, like an empty room; 2 = somewhat quiet, can hear clearly over sound without need for people to raise voice; 3 = noticeable; sound of activity is loud enough to be distracting and difficult to understand others without raising voice; 4 = loud; can barely hear others even with voice raised; 5 = very loud; at the point where cannot hear others at all and may start to be painful. SEE NOISE THERMOMETER FOR REFERNCE.** HPD = Hearing Protection Device. PLD = personal listening device. Indicate if you wore a PLD or HPDs while performing any of the activities (Y or N).

Noisy Activity		Day /wk	Hr/ Day	Yrs	Loudness					PLD	HPD
					1	2	3	4	5		
Home Life	TV/Stereo/vid.game										
	Home care										
	Lawn care										
	Phone conversation										
Travel/ Recreation	Car (drive/ride)										
	Pedestrian busy traffic										
	Bus, Subway										
	Plane										
	Motorcycle, 4 wheeler, dirt bike, motorsport										
	Exercise Workout										
	Boating										
Outing/ Event	Movie, theatre, restaurant, bar										
	Concert, Fair, Party, Sporting Event										
PLD w/phones	Ipod, portable game										
School, Job, and Music	Classroom										
	Cafeteria										
	Gymnasium										
	Play in Band or Music Instrument										
	Sport Practice/game										
	Use power tools										
	Construction job										
	Industry/Factory job										
	Farm work										
	Mechanic										
	Military service										
Other Noisy	Hunting, gun range										
	Explosives/fireworks										
	Write in:										

2. How often do others ask you to turn down your PLD/TV/Stereo volume?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ All the time

3. Compared to your peers rate your PLD/TV/Stereo loudness settings?

☐ Much Lower ☐ Little lower ☐ Same ☐ Little higher
☐ Much higher

4. Do you own an ipod, mp3 player, or other PLD?
☐ Yes ☐ No *If no skip to question 9*

5. How much do you use your ipod, mp3 player, or other PLD during a typical week?

☐ 0-1 hr/wk ☐ 2-4 hr/wk ☐ 5-8 hr/wk ☐ 9-15 hr/wk ☐ >15 hr/wk

6. How long have you owned a PLD type device?
☐ < 6 months ☐ > 6 months to < 1 yr ☐ > 1 yr to < 3 yrs
☐ > 3 yr to < 5 yr ☐ > 5 yr

7. The following bars represent volume levels on a PLD. Fill in what best represents the volume at which you usually listen to your music in quiet?   ↓ (mid)
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ (max)

8. The following bars represent volume levels on a PLD. Fill in what best represents the volume at which you usually listen to your music in noise (e.g. like on a bus)?
                                                    ↓ (mid)
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ (max)

9. Do you have continuous tinnitus (buzzing or ringing) in your ears almost all the time?
☐ Yes   ☐ No

10. How often have you noticed a change in you hearing/ears (muffled, blocked, ringing, pain) when you have been exposed to noise/loud sounds?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

11. In what noise sources have you noticed changes to your hearing and or experienced tinnitus?

☐ None   ☐ School ☐ Work ☐ Home   ☐ Movie ☐ Concert
☐ PLD   ☐ Bar/Club/Restaurant   ☐ Other (specify) _____ _____

12. What percentage of time are you exposed to the 5 noise levels (Q1 and NOISE THERMOMETER) on an average week day/night (total should = 100%)?

1_____ 2_____ 3_____ 4_____ 5_____

13. What percentage of time are you exposed to the 5 noise levels (Q1 and NOISE THERMOMETER) on an average weekend day/night (total should = 100%)?

1_____ 2_____ 3_____ 4_____ 5_____

14. Have you ever done any of the following types of work or activities on a regular basis (weekly)? Check all that apply

☐ Musician   ☐ Carpentry/woodwork   ☐ Metal work
☐ Chainsaw   ☐ Other power tools   ☐ Motorsports
☐ Concerts   ☐ Club/Bar/Restaurant   ☐ Gun/Hunt/Explosive
☐ Construction ☐ Factory/Industry   ☐ Mechanic

15. What is your personal noisy activity?
☐ Very low, almost none ☐ Low, rarely ☐ Moderate, sometimes
☐ High, often ☐ Very high, all the time

Work Related Noise Exposure

1. What best fits your job description from question 9?
☐ Bar/Restaurant/Club   ☐ Movie Theatre   ☐ Retail
☐ Musician   ☐ Construction   ☐ Lawn Service
☐ Mechanic   ☐ Farm   ☐ Military ☐ Other (specify)_____

2. How many hrs per week do you work this job? _____

3. On a scale of 1-5, what is the usual level of your work environment? SEE NOISE THERMOMETER FOR REFERNCE
☐ 1= quiet, like an empty room   ☐ 2 =somewhat quiet, can hear clearly over sound without need for people to raise voice   ☐ 3= noticeable; sound of activity is loud enough to be distracting and difficult to understand others without raising voice ☐ 4= loud; can barely hear others even with voice raised
☐ 5=very loud; at the point where cannot hear others at all and may start to be painful.

4. How variable is the noise level?
☐ Always variable   ☐ Usually variable   ☐ Usually steady
☐ Completely steady

5. What percentage of time are you exposed to the 5 noise levels (Q2 and NOISE THERMOMETER) at work (total should = 100%)?
1_____   2_____   3_____   4_____   5_____

6. Some noises, like a nail gun, are very loud but short in time, how often are you exposed to these kinds of sounds at work?
☐ Never   ☐ Rarely ☐ Sometimes   ☐ Often   ☐ Always

7. How often do you use hearing protection at this job?
☐ Never   ☐ Rarely ☐ Sometimes   ☐ Often   ☐ Always

8. Have you ever received hearing conservation training?
☐ Yes   ☐ No   ☐ Not sure

AHH	How often do you participate in this activity?				How often do you wear ear protection when doing this activity?		
	Never	Seldom	Sometimes	Often	Never	Sometimes	Always
use fireworks							
target practice or hunting with firearms							
ride a moped or motorcycle							
use a power lawn mower							
participate or attend NASCAR, speedway or drag racing events							
attend rock concerts							
attend discos or dances							
attend aerobic classes							
listen to music under headphones							
listen to music from your home stereo system at loud levels							
listen to music from your car stereo system at loud levels							
play in a band/orchestra							
use noisy tools or machines							
work in a noisy environment							

Otologic/Medical History

Hearing History

1. Do you have or feel you have a hearing loss?
☐ Yes   ☐ No   ☐ Not sure
   If no skip to question 8

2. Which ear?
☐ Right   ☐ Left   ☐ Both

3. Is one ear better than the other?
☐ Right   ☐ Left   ☐ Same

4. How long have you had a hearing problem?
☐ < 1 year   ☐ 1-5 years   ☐ 6-10 years   ☐ > 10 years

5. Do you know what caused it? Check all that apply
☐ Since birth   ☐ Related to a disease or syndrome   ☐ Noise
☐ Medication   ☐ Injury or Accident   ☐ other (specify) _____

6. Has this hearing loss been confirmed by a doctor or audiologist?
☐ Yes   ☐ No   ☐ Not sure

7. What type of hearing loss is it?
☐ Sensorineural (inner ear)   ☐ Conductive (external/middle)
☐ Mixed (both)

8. Have you ever had an ear infection?
☐ Yes   ☐ No   ☐ Not sure
When was the last? _____
How many total? _____
Did you have tubes? _____ when? _____

9. Have you ever had an ear surgery other than tubes?
☐ Yes   ☐ No   ☐ Not sure

10. Have you ever had balance /dizziness problems?
☐ Yes   ☐ No   ☐ Not sure; if yes describe _____

11. Have you ever had an ear injury (trauma)?
☐ Yes ☐ No ☐ Not sure

12. Have you ever had a head injury that affected hearing?
☐ Yes ☐ No ☐ Not sure

13. Do you regularly take aspirin?
☐ Yes ☐ No ☐ Not sure

14. Have you ever had any IV antibiotics?
☐ Yes ☐ No ☐ Not sure

15. Have you ever taken any chemotherapeutic agent?
☐ Yes ☐ No ☐ Not sure

16. Have you taken an anti-malarial drug?
☐ Yes ☐ No ☐ Not sure

17. Have you taken any diuretics?
☐ Yes ☐ No ☐ Not sure

18. Do you currently or in the past smoke cigarettes, cigars, other?
☐ Yes ☐ No ☐ Not sure

19. Does someone in your household smoke or smoked while you were growing up?
☐ Yes ☐ No ☐ Not sure

20. Do you currently or in your past consumed alcohol?
☐ Yes ☐ No ☐ Not sure, if yes how often a month_____

21. Does anyone in your family have a hearing loss other than from getting older? ☐ Yes ☐ No ☐ Not sure
a. Relationship _____ b. cause _____ c. age of onset
☐ birth
☐ child ☐ adult d. how much loss ☐ little ☐ lot ☐ deaf
b. Relationship _____ b. cause _____ c. age of onset
☐ birth
☐ child ☐ adult d. how much loss ☐ little ☐ lot ☐ deaf

22. Have you ever had speech/language issues requiring intervention?

☐ Yes ☐ No ☐ Not sure

23. Have you ever been told by a doctor you have any of the following illnesses? Check all that apply

☐ kidney disease ☐ meningitis ☐ mumps
☐ measles ☐ chicken pox ☐ tonsillitis
☐ hyperbillirubinemia ☐ autoimmune ☐ HIV/AIDS
☐ shingles ☐ diphtheria ☐ rheumatic fever
☐ polio ☐ scarlet fever ☐ pneumonia
☐ high cholesterol ☐ heart disease ☐ hypertension
☐ Meniere's disease ☐ otosclerosis ☐ epilepsy
☐ mastoiditis ☐ cancer ☐ Crohn's disease
☐ Cushing Syndrome ☐ cystic fibrosis ☐ obesity/overweight
☐ pancreatitis ☐ retinopathy ☐ lupus
☐ colitis ☐ stroke/cva ☐ neuropathy
☐ diabetes (fill out diabetes section) ☐ mononucleosis
☐ Other (specify)_____

24. Please list your current medications?

_____
_____
_____
_____
_____

25. Is there any other history related to health and hearing that we should know about?

_____
_____

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Diabetes History

1. What type of diabetes do you have?
☐ Type 1 (IDDM)   ☐ Type 1A   ☐ Type 1B   ☐Type 2
☐ MODY   ☐ Secondary   ☐ Other (specify)_____

2. Age and year you were diagnosed? _____

3. Who made the diagnosis? _____

4. Were any genetic tests performed?
☐ Yes   ☐ No   ☐ Not sure
If yes what test and result

_____

5. What type of insulin do you currently use and the dose? Type
_____   Dose _____

6. How do you currently treat your diabetes?
☐ shots/pen   ☐ pump   ☐ diet   ☐ exercise
☐ other (specify) _____

7. How often do you take insulin each day on average?
☐ 1x a day   ☐ 2 x a day   ☐ 3 x a day   ☐ 4 or more
☐ insulin pump

8. Do you often miss your meds or insulin?
☐ Never   ☐ 1-3 x a month   ☐ 1-3 x a week   ☐ daily

9. Have you ever had episodes of ketoacidosis?
☐ Yes   ☐ No   ☐ Not sure;   if yes how often, when last

_____

10. Have you ever had severe hypoglycemia that required help?
☐ Yes   ☐ No   ☐ Not sure;   if yes how often, when last

_____

11. Have you been hospitalized in the past year for diabetes related complications?

☐ Yes   ☐ No   ☐ Not sure;   if yes how often, when last

_____

12. How would your doctor rate your diabetes control?

☐ excellent   ☐ good   ☐ fair   ☐ needs much work

13. Has your diabetes control ever been poor?

☐ Yes ☐ No, if yes when _____ and how long_____

14. How often do you test your blood sugar?

☐ less than 1 x wk   ☐ less than 1 x day   ☐ 1-2 x a day
☐ 3 x a day   ☐ 4 or more x day   ☐ only when sick
☐ never

15. Have you ever had the following related to your diabetes?

☐ high bp   ☐ high cholesterol or fat   ☐ Addison disease
☐ kidney disease   ☐ celiac disease   ☐ Hyper thyroid
☐ Hypo thyroid   ☐ damaged retina/vision   ☐ neuropathy
☐ Cardiovascular disease ☐ coma ☐ Rheumatoid Arthritis
☐ obesity/overweight ☐ abdominal pain ☐ Other specify _____
☐ Colitis ☐ Chron's Disease

16. Does anyone else in your family have diabetes?

☐ Yes   ☐ No;   if yes, who _____

17. Please list the dates and levels of your most recent blood sugar/glycated hemoglobin tests.

Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____
Test_____ Date_____ Level_____

Lifestyle

1. How often over the past 7 days did you exercise or participate in physical activity for at least 20 minutes that made you sweat or breathe hard? _____

2. How often over the past 7 days did you participate in a physical activity for at least 20 min that did not make you sweat and breathe hard? _____

3. During the past 12 months how many team sports did you play? _____

4. How much time do you watch tv during an average weekday? hrs average weekend day? hrs _____

5. How much time do you spend on the computer or playing video games during an average weekday? hrs _____ weekend day? hrs _____

6. How would you consider your diet?
☐ very healthy   ☐ healthy ☐ somewhat healthy   ☐ unhealthy

7. How often do you eat fast food or junk food?
☐ < 1 x week   ☐ 2-3 x week   ☐ almost every day   ☐ several times a day

8. How often do you eat vegetables and fruit?
☐ < 1 x week   ☐ 2-3 x week   ☐ almost every day   ☐ several times a day