Critical Review:
Are Otoacoustic Emissions Effective for Characterizing Subclinical Auditory Impairment in Normal Hearing Individuals with Type I Diabetes Mellitus?

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This critical review evaluated eight studies examining otoacoustic emissions (OAEs) in normal hearing individuals with Type I diabetes mellitus (DM) to determine if they are effective for characterizing subclinical auditory impairment as a result of the disease. All were prospective, non-randomized clinical cohort studies. Results indicate that despite normal hearing thresholds, otoacoustic emission amplitude levels are lower in individuals with Type I DM. It is suggested that otoacoustic emissions testing can be effective for identifying impairment attributable to Type I DM in a discrete area along the auditory pathway. However, OAEs cannot solely be used to characterize the nature of the auditory impairment given the complexity of the auditory system. Additional studies involving larger sample sizes, varied selection procedures and criteria and in depth afferent and efferent auditory pathway evaluation to the level of the auditory cortex are recommended before one can characterize the nature of the auditory impairment as a result of Type I diabetes mellitus.

Introduction

Type I Diabetes Mellitus (DM) occurs when the body does not produce insulin. Without insulin, cells in the body are unable to access glucose, and the resulting high levels of glucose in the blood stream can cause neuropathy and/or microangiopathy, microvascular complications causing a decrease in the flow of blood usually present as retinopathy or nephropathy in individuals with diabetes (Canadian Diabetes Association, 2005-2010). Hearing loss has also been an associated effect of Type I DM. With Type I representing approximately 10% of the diabetes population, many audiologists have seen an increase in the number of patients with this disease (Canadian Diabetes Association, 2005-2010).

A major point of controversy in research examining diabetes and hearing loss surrounds the effects of diabetes on the physical structures of the auditory pathway. Auditory impairment resulting from Type I may be a result of localized microangiopathy, neuronal degeneration or diabetic encephalopathy. It may also be due to the derangement in glucose metabolism and hyperactivity of free oxygen radicals (Hilali, Das & Boulton, 2003). Pathological changes and metabolic disturbances as a result of Type I diabetes may result in cochlear, retrocochlear or combined cochlear-retrocochlear pathology. Conventional audimetric tests are not sensitive to the initial phases of auditory impairment as a result of diabetes, nor are they capable of determining the site of lesion and/or pattern of the impairment (Lisowska, Namyslowski, Morawski & Strojek, 2001).

Otoacoustic emissions (OAEs) are sounds generated in the cochlea by the motility of the outer hair cells. Since their discovery by Kemp in 1997, OAEs have become an important tool in the assessment of auditory function, specifically cochlear function as OAEs are very sensitive to outer hair cell damage. The sensitivity of OAEs to cochlear damage may allow audiologists to discover auditory impairment before the onset of hearing loss as measured by conventional audimetry or before the impairment progresses further to other auditory structures (Lonsbury-Martin & Martin, 2007).

There are three types of OAEs that have been examined extensively: Spontaneous OAEs (SOAEs) are produced by the cochlea in the absence of acoustic stimuli. SOAEs are not widely used clinically as they require special measurement techniques and not all individuals with normal hearing thresholds produce them (Lonsbury-Martin & Martin, 2007). Transient evoked OAEs (TEOAEs) are elicited by a click train or tone burst. TEOAEs are widely used clinically however there is limited to testing the 1-4kHz range where the measurement amplitudes are highest (Lonsbury-Martin & Martin, 2007). Distortion-product OAEs (DPOAEs) are elicited at a particular place on the basilar membrane by two pure tones presented simultaneously. The largest DPOAE is elicited at 2f1-f2, where f2 is the higher frequency and the f2/f1 ratio is 1.22. The clinical utility of DPOAEs is high as they possess the largest measurable frequency range (Lonsbury-Martin & Martin, 2007).

Due to the current controversy surrounding the effects of Type I DM on the auditory pathway, specifically site
of lesion, a critical review of the literature examining the results of OAE testing in normal hearing individuals with Type I DM is necessary to establish if a subclinical impairment exists as a result of Type I DM, and to determine if OAEs are an appropriate clinical tool for characterizing this impairment.

Objectives

The primary objective of this paper is to analyze and critically evaluate selected studies that have examined the results of otoacoustic emission testing in normal hearing individuals with Type I DM. The secondary objective is to generate implications on the findings with regards to the effectiveness of otoacoustic emissions to characterize the potential auditory impairment as a result of Type I DM, as well as provide future directions for research.

Methods

Search Strategy

Computerized search databases, including PubMed, SCOPUS and MedLine were searched using the following key words: ((Otoacoustic Emissions) OR (OAE)) AND ((Diabetes) OR (Diabetic) OR (Diabetes Mellitus)) AND ((Type I) OR (Insulin-Dependent)).

The search was limited to original journal articles with human participants written in the English language.

Selection Criteria

The studies selected for inclusion in this critical review were required to administer and evaluate otoacoustic emissions testing in individuals with Type I DM. Participants were required to have normal hearing as measured using conventional pure-tone audiometry. Diagnosis of Type I DM by a medical professional was necessary.

Data Collection

Results of the literature search yielded eight original journal articles consistent with the previously stated criteria. Each of the eight articles was a prospective non-randomized clinical cohort study with a level 2b of evidence using the experimental design decision tree.

Results

Transient-Evoked Otoacoustic Emissions

Hilali, Das & Boulton (2003) and Di Leo et al. (1997) examined TEOAE amplitude levels in normal hearing adults with Type I DM and healthy age and sex matched controls it identify possible sub-clinical cochlear pathology. Adults with Type I DM were sub-divided based on the presence of microangiopathy or neuropathy. History of ear disease, noise exposure, ototoxic drug exposure, and family history of hearing loss were criteria for exclusion. Participants underwent pure tone audiometry, admittance testing and stapedial reflex testing prior to OAE testing. Presence of abnormal hearing thresholds in the 250-8000Hz range and abnormal middle ear function were also criteria for exclusion. TEAOEs were elicited with a non-linear filtered 80us click stimulus presented at 80+4 dB SPL (Hilalis et al., 2003) or 80+6 dB SPL (DiLeo et al., 1997) at a rate of 50 clicks per second. The click stimulus was presented through a soft foam tip used to seal the probe in the ear canal. The analysis time was 20ms and an average of 260 clicks was obtained from each ear and then averaged. A band-pass filter of 976-4882Hz was set (DiLeo et al., 1997).

The Hilial et al (2003) study included 21 normal hearing adults with Type I DM. There were 8 uncomplicated diabetics, 5 with microangiopathy and 5 with neuropathy. Results were compared with 30 healthy controls. The groups were compared using Student’s unpaired t-tests. Statistical analysis revealed significantly reduces mean TEOAE response amplitudes in all participants with Type I DM in comparison to the control group, (p<0.001). In analysis of the sub-divided groups, uncomplicated diabetics showed lower TEAOE amplitudes than the control group (p=0.005) and diabetics with microangiopathy have lower TEOAE amplitudes than uncomplicated diabetics (p=0.001). No differences were found between the uncomplicated diabetics and those with neuropathy.

The study by Di Leo et al. (1997) included 48 normal hearing adults with Type I DM. 12 participants showed signs of neuropathy and 19 participants displayed signs of microangiopathy. Results were compared with 30 healthy controls. Degree of metabolic control, measured as HbAc1 levels, and duration of disease was also determined. Student’s unpaired t-test revealed lower mean EOAЕ amplitudes in all diabetics when compared to controls (t=2.6, p=0.01). Analysis of the sub-divided diabetes group using a one-way ANOVA revealed that the diabetic adults with signs of peripheral neuropathy have lower mean EOAЕ amplitudes than those without neuropathy (F=4.1, p=0.02; Scheffe’s test p=0.03). Similarly, diabetics with retinopathy have lower mean TEOAE amplitudes than those without (t=2.2, p=0.02).

No correlations were found between EOAЕ amplitude levels and duration of disease or degree of metabolic control.

Overall, results from Hilali et al. (2003) and Di Leo et al. (1997) demonstrate that adults with Type I DM have lower TEAOE amplitudes than healthy controls despite similar hearing thresholds. These TEOAE amplitudes are further reduced when diabetic microangiopathy or neuropathy is present.

Distortion-Product Otoacoustic Emissions
Lisowski, Namyslowski, Morawski & Strojek (2001) evaluated DPOAEs in 42 normal hearing adults with Type I DM and 33 age and sex matched controls in two separate studies to evaluate cochlear mechanics in adults with Type I DM and to identify a possible site of lesion. Participants with Type I DM were sub-divided based on the presence of microangiopathy. 17 participants had microangiopathy and 25 did not. Degree of metabolic control and duration of disease was also determined (Lisowski et al. 2001b). History of ear disease, noise exposure, ototoxic drug exposure, head or ear trauma and a family history of hearing loss were criteria for exclusion. All participants underwent pure tone audiometry, admittance testing and stapedial reflex testing prior to OAE testing. An abnormal result in any of the above testing was also criteria for exclusion. DPOAEs were elicited bilaterally with 2 independent probe tones mixed in the ear canal at an f2/f1 ratio of 1.22. DPOAE amplitude levels were recorded at 2f2-f1 for f2 values at 1000Hz intervals from 1-6kHz. DPOAE responses were evaluated as an input/output function as the f1 and f2 ratio remained constant while the levels (L1=L2) increased in 5dB steps from 35-70dB SPL. The criterion was set as an I/O response 2 SD above the noise floor. In both studies, Lisowski et al. (2001) and Lisowski et al. (2001b), analysis with the nonparametric Mann-Whitney test and Student’s unpaired t-test revealed lower mean DPOAE amplitudes in all diabetics when compared to the control group (p<0.05). Significant differences were seen at 5kHz and 6kHz for the lowest stimulus levels and spanned the entire 1-6kHz frequency range at stimulus levels of 55dB and greater. DPOAE amplitudes were not significantly different between the diabetics with and without microangiopathy. No correlations were found between DPOAE amplitude levels and degree of microangiopathy, duration of disease or metabolic control using Spearman and Pearson tests of correlation and regression.

Overall the results of Lisowski (2001a and b) suggest that despite similar thresholds, adults with Type I DM have lower DPOAE amplitudes than healthy controls. Contrary to the results reported by Hilalı et al. (2003) and Di Leo et al. (1997), the presence of diabetic microangiopathy does not result in further reduction of OAE amplitudes.

**Transient-Evoked & Distortion-Product Otoacoustic Emissions**

Ottaviani, Dozio, Neglia, Ricco & Scavini (2002) and Di Nardo et al. (1998) compared TEOAEs and DPOAEs in normal hearing adults with Type I DM to age and sex matched healthy controls to identify possible subclinical cochlear dysfunction, specifically within the outer hair cells. Participants with Type I DM were sub-divided based on the presence of microangiopathy (Ottaviani et al., 2002) or neuropathy (Ottaviani et al., 2002; Di Nardo et al., 1998). Degree of metabolic control and duration of disease was also determined. Participants underwent pure tone audiometry, admittance testing and stapedial reflex testing prior to OAE testing. Positive otologic history, presence of abnormal hearing thresholds in the 250-8000Hz range and abnormal middle ear function were criteria for exclusion. TEAOEs were elicited with a non-linear click stimulus kept between 75 – 90 dB SPL (Ottaviani et al., 2002) or 80±5 dB SPL (Di Nardo et al., 1998) presented at a rate of 50 clicks per second (Di Nardo et al., 1998). The analysis time was 20ms and an average of 256 clicks was obtained twice from each ear and then averaged. Ottaviani et al. (2002) set the bandpass at 600-6000Hz where as Di Nardo et al., 1998 set it at 976-4882Hz. DPOAEs were elicited with 2 independent probe tones mixed in the ear canal at an f2/f1 ratio of 1.22. DPOAE amplitude levels were recorded at 2f1-f2 for f2 values spanning 818Hz–5164Hz (Ottaviani et al., 2002) or 700Hz-6000Hz (Di Nardo et al., 1998). The level of the stimulus remained constant at 70 dB SPL. The stimulus for both types of OAE testing was presented through a soft foam tip used to seal the probe in the ear canal. Reproducibility and intensity of the response was analyzed for both types of OAEs. The Ottaviani et al. (2002) study included 60 normal hearing adults with Type 1 DM. There were 35 diabetics with microangiopathy and 17 with signs of peripheral neuropathy. Results were compared with 58 healthy controls. The nonparametric Mann-Whitney test and Student’s unpaired t-tests were used to determine statistical significance. TEAOEs were absent in at least one ear in 28.3% of the diabetes group. Analysis including all 60 diabetic adults, and including only those with bilateral TEOAEs revealed significantly lower reproducibility and mean response intensity levels in adults with Type I DM when compared to the control group (p<0.001, p<0.001 respectively). In DPOAE analysis, the diabetic group was found to have lower mean DPOAE amplitude values at all tested f2 frequencies except 4306Hz and 5121Hz (the two highest tested), (p<0.05). The largest differences between the diabetes and control group were found in the 949-1662Hz range (p<0.001). A positive correlation was found between TEAOE and DPOAE responses in both the adults with DM and controls (p<0.05). No correlations were found between TEOAE and DPOAE response amplitudes and neuropathy, retinopathy, metabolic control, duration of disease or age. The Di Nardo et al. (1998) study included 47 normal hearing adults with Type 1 DM. 15 diabetics presented with signs of peripheral neuropathy. Results were compared with 44 healthy controls. One-way ANOVA revealed lower mean TEOAE amplitudes in diabetics.
with neuropathy when compared to controls ($F=3.5$, $p<0.05$). A significant difference in TEAOE amplitude levels was not found between diabetics without neuropathy and the control group. Analysis revealed lower DPOAE amplitudes in diabetics with signs of neuropathy at $f_2$ values spanning 1306–5200Hz ($p<0.05$). Lower DPOAE amplitudes were also found in diabetics without neuropathy at $f_2$ values spanning 3284–5200Hz ($p<0.01$). No correlations were found between TEAOE and/or DPOAE response amplitudes and metabolic control or duration of disease.

Overall, results from Ottaviani et al. (2002) and DiNardo et al. (1998) illustrate that DPOAE amplitude levels are reduced in adults with Type I DM when compared to healthy controls despite similar hearing thresholds. In comparing adults with and without diabetic neuropathy, Di Nardo et al. (1998) found that TEAOE and DPOAE amplitudes are lower in adults with signs of neuropathy than in controls. Where as DPOAE amplitude levels are also lower in diabetics without signs of neuropathy (across a smaller frequency range), TEAOE amplitude levels are not. These results also suggest that there may be reduced sensitivity between the two methodologies to the effects of diabetic neuropathy on an identified sub-clinical auditory impairment in the outer hair cells. Alternatively, the larger band-pass employed by Ottaviani et al. (2002) may have contributed to the TEAOE amplitude reduction found in their study. However, the presence of further reduced outer hair cell function implies diabetic neuropathy may exacerbate auditory system damage as a result of Type I DM.

**Transient-Evoked Otoacoustic Emission Suppression**

Namyslowski et al. (2001) and Ugar et al. (2009) investigated the effects of contralateral suppression of TEAOEs in normal hearing children with Type I DM and age and sex matched healthy controls to determine presence of dysfunction in the efferent auditory system of children presenting no evidence of symptomatic neuropathy. History of ear disease, ototoxic drug exposure, head or ear trauma another metabolic disease and a family history of hearing loss were criteria for exclusion, as were noise exposure and craniofacial anomalies (Ugar et al., 2009) All of the children underwent pure tone audiometry, admittance testing and stapedial reflex testing prior to OAE testing. An abnormal result in any of the above testing was also criteria for exclusion. Degree of metabolic control and duration of disease was also determined. Initial TEAOEs were elicited with a non-linear filtered 80us click stimulus presented between 75–80 dB SPL (Ugar et al., 2009) or at 80, 70, and 60 dB SPL in the ear canal (Namyslowski et al. 2001). The stimulus was presented at a rate of 50 clicks per second. An average of 260 clicks was obtained from each ear.

Namyslowski et al. (2001) included 32 children with Type I DM in their study and compared the results with 30 healthy controls. Following initial measurement of TEAOE amplitudes for the 3 click stimuli levels, a 1kHz or 2kHz pure tone was presented contralaterally (CS) to the ear with the lower initial TEAOE amplitude at 70 dB SPL and 60 dB SPL. The CS was presented at 30dB SL and 50dB SL (re: 70 and 60 dB SPL) resulting in 5 TEAOE measurement conditions for each stimulus levels: without CS, with CS of 1kHz at 30 SL, with CS of 1kHz at 50 SL, with CS of 2kHz at 30 SL, with CS of 2kHz at 50 SL. Student’s unpaired t-test revealed no significant differences in initial mean TEAOE amplitude levels between the children with Type I DM and healthy controls. In the presence of a 1 or 2 kHz pure-tone presented contralaterally, one-way ANOVA revealed greater reduction of initial TEAOE amplitude level in the control group than in children with Type I DM for both the 30 and 50 dB SL conditions ($p<0.05$). The study by Ugar et al. (2009) included 30 normal hearing children with Type I DM and 31 healthy controls. The researchers were blind about whether the child being tested was in the control group or the DM group. Prior to initial TEAOE amplitude evaluation, presence of SOAEs was evaluated bilaterally in the 50-6000Hz region. Following initial TEAOE evaluation, a continuous broadband white noise was delivered to the contralateral ear at 40dB SL (re: 70dB SPL). Initial TEAOE amplitude reduction and reproducibility were measured in the 1-4 kHz region. DPOAEs were also elicited with 2 independent probe tones mixed in the ear canal at an $f_2/f_1$ ratio of 1.22. DPOAE amplitude levels were recorded at 2f1-f2 for $f_2$ values spanning 1000–6000Hz The level of the stimulus remained constant at 70 dB SPL. The stimulus was presented through a soft foam tip used to seal the probe in the ear canal. Analysis using Student’s unpaired t-tests, the nonparametric Mann-Whitney test and the Kolmogorov-Smirnov test revealed SOAEs in 45% of children with DM and 32% of children in the control group ($p<0.05$). No significant differences in initial mean TEAOE amplitude was found between the children with Type I DM and healthy controls. In the presence of contralateral broadband noise, TEAOE amplitude reduction was significantly greater in the control group than in the DM group at 2000Hz and 4000Hz ($p<0.05$). No significant differences in mean DPAOE amplitude levels were found between children with and without Type I DM. A negative correlation was found between metabolic control and TEAOE amplitudes at 3000Hz and 4000Hz in the diabetes group before ($r$=-0.25, $p=0.04$; $r$=-0.37, $p<0.004$) and after contralateral suppression ($r$=-0.30, $p<0.02$; $r$=-0.33, $p<0.002$).
Taken together, these results demonstrate reduced TEOAE suppression in children with Type I DM when a pure tone or broadband noise is presented contralaterally in comparison to controls despite similar thresholds and no differences in initial TEOAE amplitude levels (Namysłowski et al. 2001, Ugar et al., 2009).

**Conclusion and Recommendations**

In a review of the literature three predominant themes emerge:

1. Adults with Type I DM have lower TEOAE and DPOAE amplitudes than healthy controls despite similar hearing thresholds. This suggests possible presence of a subclinical auditory impairment affecting outer hair cell function (Hilali et al., 2003; Di Leo et al., 1997; Lisowski et al., 2001(a and b); Ottaviani et al., 2002 and DiNardo et al., 1998).

2. These TEOAE and DPOAE amplitudes are further reduced when diabetic microangiopathy or neuropathy is present. Further reduction in outer hair cell function may imply that diabetic microangiopathy or neuropathy exacerbate auditory system damage as a result of Type I DM. However, not all authors reported increased reduction of OAE amplitudes in adults with diabetic complications.

This suggests that there may be differences in sensitivity between the two OAE test methodologies to the effects of diabetic microangiopathy or neuropathy on an identified sub-clinical auditory impairment in the outer hair cells. An alternative explanation is that despite different test procedures, individual and group differences in degree of diabetic complications across studies may be responsible for the unrelated results (Hilali et al., 2003; Di Leo et al., 1997; Lisowski et al., 2001(a and b); Ottaviani et al., 2002 and DiNardo et al., 1998).

3. TEOAE suppression in children with Type I DM is not as evident when a pure tone or broadband noise is presented contralaterally in comparison to healthy controls despite similar thresholds and no differences in initial TEOAE amplitude levels. This study points towards a different type/site of auditory impairment than the previous studies. TEOAE amplitudes in children with Type I DM remain large in the presence of contralateral stimulation suggesting the impairment is not in the outer hair cells but rather in the efferent system monitoring outer hair cell motility (Namysłowski et al. 2001, Ugar et al., 2009). The lack of significant difference in initial TEAOE amplitude levels may be in part due to the fact that children may have more robust OAEs than adults. Children also have a shorter duration of diabetes and no microangiopathy or neuropathy to add to possible auditory impairment.

The auditory system is a very complex combination of afferent and efferent pathways spanning to the primary and associated auditory cortices in the brain. OAEs do not assess the entire auditory pathway and given individual variability in diabetic complications, degree of metabolic control, and disease duration, one cannot assume damage caused by this disease is localized to a specific site. As discussed earlier presence of diabetic microangiopathy or neuropathy does not always correlate with greater degree of auditory impairment. In fact, three of the studies in this review also examined Auditory Brainstem Response latencies and found a delay in wave I, II and V absolute latencies but not in interpeak latencies (Di Leo et al., 1997; Lisowski et al., 2001b; Ottaviani et al., 2002). Di Leo et al. (1997) did not find differences between adults with Type I DM and controls when examining middle and long latency responses as well. These findings were consistent across groups regardless of neuropathy.

In conclusion, a review of the literature suggests that OAEs are useful for identifying sub-clinical auditory impairment as a result of Type I DM, however, characterization of this impairment requires an in depth assessment of afferent and efferent auditory pathways to the level of the brainstem and cannot be determined based on OAE testing alone.

Future research in this area should include TEOAE, DPOAE, OAE suppression, ABR, middle and long latency response assessment. Inclusion criteria should specify what constitutes normal hearing thresholds and participants should be recruited from a variety of sources. Participants should be grouped based on age, duration of disease, metabolic control, microangiopathy and neuropathy and researchers should be blind to the groupings.

**Clinical Implications**

Until a test battery designed to assess the entire auditory pathway is feasible in a clinical setting, and a more thorough understanding of the widespread effects of Type I DM is achieved, a significant change to clinical practice is not recommended. However, alongside a thorough case history including: duration of disease, age of onset and frequency of HbA1C monitoring, OAE screening is a quick non-invasive clinically feasible procedure for potentially identifying or detecting auditory impairment.

**References**


