Objective measures of function of the peripheral auditory system in adults with diabetes mellitus type 1 and type 2: A systematic review and meta-analysis

by

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Abstract

Objective: This study aimed to systematically review and analyse the available peer-reviewed literature reporting on the results of distortion product otoacoustic emissions (DPOAEs), transient evoked otoacoustic emissions (TEOAEs) and click auditory brainstem responses (c-ABRs) in adults with type 1 and type 2 diabetes mellitus (T1DM and T2DM).

Method: A comprehensive literature search was conducted across three electronic databases to identify English; peer-reviewed articles that included results of OAEs (DPOAEs and TEOAEs) and c-ABR tests in adult subjects with DM. Articles were selected according to predetermined selection criteria and critically reviewed independently by two researchers.

Results: 15 studies met the inclusion criteria for the systematic review while nine articles qualified for inclusion in the meta-analysis. DPOAE studies reported significantly reduced amplitudes with only one study reporting larger amplitudes. Abnormal TEOAEs were reported in all TEOAE studies, although these abnormalities were not always significant. Significantly delayed c-ABRs were reported in all ABR studies. Analysis of c-ABR mean wave latencies identified longer latencies for DM subjects, particularly for wave III and V, as well as for IPL I-III and I-V.

Conclusions: Subjects with T1DM and T2DM may present with clinical or subclinical impairment of the cochlear outer hair cells and both the peripheral and central auditory pathway.

Keywords

Diabetes mellitus

DM Type 1

DM Type 2

Auditory

Hearing loss

Outer hair cells

Auditory nerve

Distortion product otoacoustic emissions

Transient-evoked otoacoustic emissions

Auditory brainstem responses

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List of Abbreviations

ABR	Auditory Brainstem Responses
ADA	American Diabetes Association
AGE	Advanced Glycation End products
c-ABR	click-evoked Auditory Brainstem Response
dB	decibels
HL	Hearing Level
nHL	normal Hearing Level
SL	Sensation Level
SPL	Sound Pressure Level
DM	Diabetes Mellitus
DPOAE	Distortion Product Otoacoustic Emissions
IDF	International Diabetes Federation
IPL	Inter-peak Latency
kHz	kilohertz
MeSH	Medical Subject Heading
ms	millisecond
OAE	Otoacoustic Emissions
PKC	Protein Kinase C
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
ROS	Reactive Oxygen Species
SD	Standard Deviation
SNR	Signal-to-Noise Ratio
SOAE	Spontaneous Otoacoustic Emission
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

TEOAE Transient-Evoked Otoacoustic Emissions

WHO World Health Organisation

Chapter 1

Introduction

1. Diabetes mellitus

The occurrence of diabetes mellitus (DM) has increased over the last decade. It is estimated to affect more than 415 million adults worldwide, and is expected to increase to 642 million by 2040 (International Diabetes Federation [IDF], 2015). One in eleven adults suffer from this disease, while approximately 542 000 children suffer from type 1 DM worldwide. In 2015, the IDF reported approximately 14.2 million people suffering from DM in Africa with a prevalence of approximately 2.3 million in South Africa.

DM is considered a non-communicable disease along with cardiovascular disease, cancer and chronic respiratory disorders (Reubi, Herrick, & Brown, 2016). These diseases form a part of the quadruple burden of disease which affects South Africa, and consists of HIV/AIDS, tuberculosis, non-communicable diseases, injuries, and maternal and child mortality (Rath et al., 2015; Reubi et al., 2016).

Diabetes mellitus is a metabolic disorder which causes disturbances of carbohydrate, protein and fat metabolism (World Health Organization [WHO], 1999) and various pathologic changes in the body. It is defined as chronic hyperglycaemia that may have various underlying processes as aetiology (Holt & Kumar, 2010). In DM, the body either produces insufficient insulin, is not able to use insulin effectively, or both. Diabetes mellitus may present as part of a separate condition, including certain genetic syndromes, endocrinopathies, infections and even cystic fibrosis (American Diabetes Association [ADA], 2008; Holt & Kumar, 2010). Various types of DM exist although type 1 diabetes, type 2 diabetes and gestational diabetes are the three most prevalent types (IDF, 2015).

Type 1 diabetes mellitus (T1DM) is typically diagnosed in children and adolescents, although it may also be diagnosed in adults. It is characterised by absolute insulin deficiency due to a cellular-mediated autoimmune destruction of beta cells found in

the pancreas (ADA, 2015; Holt & Kumar, 2010). This leads to impaired production and secretion of insulin. Individuals with T1DM typically present with hyperglycaemia and symptoms such as excessive thirst, weight loss, polyuria, blurred vision, and in severe cases ketoacidosis. They require insulin treatment to prevent severe complications and, in severe cases, to ensure survival (Holt & Kumar, 2010; The Diabetes Control and Complications Trial Research Group, 1993).

Type 2 diabetes mellitus (T2DM) is commonly diagnosed in adults and may stay undiagnosed for many years (WHO, 2016). Type 2 diabetes mellitus is a consequence of a relative insulin deficiency associated with insulin resistance (Holt & Kumar, 2010). The underlying aetiology of insulin resistance may vary, possibly stemming from lifestyle, dietary, and genetic factors. Defects in adipocyte (a type of fat cell found in connective tissue) function, and inherited and acquired defects in mitochondrial function play a role in causing insulin resistance (Petersen & Shulman, 2006). Obesity or an increased percentage of body fat, age, and ethnicity are additional risk factors for developing T2DM. Additionally, T2DM may be more prevalent in individuals with hypertension and dyslipidaemia, as well as in those with prior gestational DM (ADA, 2008). Individuals with T2DM can usually control their DM through diet and exercise, oral medication or insulin injections. Severe complications may occur if either type of DM remains undiagnosed and uncontrolled (Holt & Kumar, 2010).

2. Complications of DM

Complications in individuals with DM typically stem from the detrimental effects of hyperglycaemia on various mechanisms and pathways in the body (ADA, 2008; Fowler, 2008). Hyperglycaemia may induce oxidative stress and increase protein kinase C (PKC) activation (Creager, Lüscher, Cosentino, & Beckman, 2003; Paneni, Beckman, Creager, & Cosentino, 2013). Further, it may cause an imbalance between nitric oxide and accumulation of reactive oxygen species (ROS), resulting in endothelial dysfunction. Hyperglycaemia and increased ROS are further implicated in affecting the polyol pathway, advanced glycation end products (AGEs), and also PKC activation (Brownlee, 2001, 2005). These mechanisms subsequently cause

alterations in structure and function of blood vessels and underlie multiple complications.

Diabetic microangiopathy is also considered to be one underlying cause of vascular complications. Microangiopathy is a disease of small blood vessels (Barnett, 1993), characterised by endothelial proliferation, accumulation of intimal glucoprotein and thickening of the basement membrane in capillaries, as a result of hyperglycaemia (Maia & de Campos, 2005).

All of the above-mentioned mechanisms may contribute to the pathogenesis of macrovascular complications and microvascular complications (ADA, 2008; Fowler, 2008). Macrovascular complications may include coronary artery disease, peripheral arterial disease and stroke, while microvascular complications in patients with DM encompass diabetic retinopathy, nephropathy and neuropathy (ADA, 2008; Fowler, 2008).

3. Diabetes mellitus-related hearing loss

Hearing loss in DM patients has been investigated for almost 150 years. Despite this, reports of hearing loss in patients with DM are still largely varied and controversial, not only in terms of pathogenesis, but also in terms of the prevalence, correlations with clinical characteristics, and audiologic findings.

A higher prevalence of hearing loss has been reported in individuals with DM compared to individuals without DM (Bainbridge, Hoffman, & Cowie, 2008; Horikawa et al., 2013; Sunkum & Pingile, 2013). This increased prevalence occurred regardless of age (Horikawa et al., 2013). Correlations have been found between hearing loss and characteristics such as DM complications (Çelik, Yalçin, Çelebi, & Öztürk, 1996; Sunkum & Pingile, 2013), poorly controlled DM (Adebola et al., 2016; Agarwal et al., 2013; Lerman-Garber et al., 2012; Pessin et al., 2008; Sunkum & Pingile, 2013), and duration of DM (Çelik et al., 1996; Hou, Xiao, Ren, Wang, & Zhao, 2015; Pessin et al., 2008; Sunkum & Pingile, 2013). However, other studies contradicted these findings (Agarwal et al., 2013; Dąbrowski, Mielnik-Niedzielska, & Nowakowski, 2013; Díaz de León-Morales, Jáuregui-Renaud, Garay-Sevilla, Hernández-Prado, & Malacara-Hernández, 2005; Weng, Chen, Hsu, & Tseng,

2005), which has made it difficult for researchers to prove any definite link between DM and certain characteristics of these patients. This lack of consensus between studies may be due to differences between study populations, such as differences in varying duration of DM, different age groups, complications or lack thereof and individual susceptibility to complications.

Hearing loss in subjects with DM has been reported as progressive (Díaz de León-Morales et al., 2005; Pemmaiah & Srinivas, 2011) or sudden (Fukui et al., 2004; Weng et al., 2005), bilateral sensorineural hearing loss (Agarwal et al., 2013; Botelho, Carvalho, & Silva, 2014; Hou et al., 2015; Pemmaiah & Srinivas, 2011), occasionally unilateral (Agarwal et al., 2013), and occurring in the high frequencies (Botelho et al., 2014; Pemmaiah & Srinivas, 2011; Ren et al., 2009). However, a low- or mid-frequency hearing loss has also been reported (Bainbridge, Hoffman, & Cowie, 2011; Taylor & Irwin, 1978). The degree of hearing loss also varied greatly, ranging from minimal and mild in some patients (Adebola et al., 2016; Agarwal et al., 2013; Lerman-Garber et al., 2012), to moderate, moderately severe and even severe in a few patients (Adebola et al., 2016; Pemmaiah & Srinivas, 2011). Therefore, it is evident that there is still little consensus regarding the exact profile of hearing loss in patients with DM. However, most authors seem to be in agreement that it presents as a bilateral, sensorineural hearing loss (Adebola et al., 2016; Agarwal et al., 2013; Botelho et al., 2014; Díaz de León-Morales et al., 2005; Fukui et al., 2004; Hou et al., 2015; Lerman-Garber et al., 2012; Weng et al., 2005).

Metabolic disturbances and microvascular impairments caused by hyperglycaemia may be associated with hearing impairment in individuals with DM (Fukushima et al., 2005, 2006; Kariya et al., 2010; Lisowska, Namysłowski, Morawski, & Strojek, 2001a; Wackym & Linthicum, 1986; Weng et al., 2005). Multiple hypotheses regarding the exact mechanisms of hearing loss exist. Cochlear microangiopathy and auditory neuropathy are specifically suggested as origins of the sensory and neural hearing impairment, respectively (Akinpelu, Mujica-Mota, & Daniel, 2014; Fukushima et al., 2005, 2006; Lasagni et al., 2015; Wackym & Linthicum, 1986). A synergistic effect of apoptosis and oxidative stress caused by hyperglycaemia, noise, and hypertension, has also been suggested as a contributing factor (Fukushima et al., 2006). Furthermore, it has been suggested that metabolic complications may contribute to alterations in cochlear micromechanics (Lisowska et al., 2001a).

Genetic mutation in mitochondrial DNA, resulting in mitochondrial dysfunction, has also been attributed to hearing loss in DM subjects. A study by Kadowaki and colleagues (1994) reported an association between this mutation and maternally inherited DM. Furthermore, they found an association with sensory hearing loss in 61 percent of these subjects.

It is evident that the hearing loss in subjects with DM is of sensory or neural origin. While pure tone audiometry provides a description of the nature of the hearing loss, it is merely a behavioural test procedure and does not provide objective information to distinguish between a sensory and a neural hearing loss. Objective assessments of the peripheral auditory system are valuable in quantifying the type of hearing loss (Katz, Medwetsky, Burkard, & Hood, 2009). Otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs) may be used for this purpose to assess at a cochlear level and auditory nerve level respectively.

4. Otoacoustic emissions and diabetes mellitus

Otoacoustic emissions were originally discovered by Kemp in 1978 and provide an objective assessment of cochlear outer hair cell function. Kemp (1978) found evidence of nonlinear emissions of sound energy, produced by the auditory system in response to acoustic impulses. In his study, he established the presence of these emissions in all subjects with normal hearing but absence thereof in subjects with a hearing loss of cochlear origin. These factors led to the hypothesis that the emissions originated in the cochlea.

Otoacoustic emissions are a by-product of the electro-motility of cochlear outer hair cells, produced either spontaneously or in response to electrical stimulation (Kemp, 2002). Emissions may be recorded by inserting an ear canal probe into the ear canal through which either click or tonal stimuli are delivered to the auditory system.

Three types of OAEs have been described, namely: spontaneous otoacoustic emissions (SOAEs), transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs).

Spontaneous otoacoustic emissions are measured without the use of external stimulation and may often present in normal hearing ears (Katz et al., 2009; Kuroda, 2007). However, SOAEs have a low incidence rate in normal hearing ears resulting in a high false-positive rate. This means that they are not useful in distinguishing between normal hearing and hearing loss if the subject has absent SOAEs, which decreases SOAEs clinical and diagnostic value (Katz et al., 2009; Kuroda, 2007). Therefore, the current study only discussed TEOAEs and DPOAEs since they are of greater clinical and diagnostic value than SEOAEs. Additionally, studies reporting on OAEs in DM reported on TEOAEs and DPOAEs more often than SOAEs.

Transient evoked OAEs are evoked using click or tone-burst stimuli with a fixed frequency range (Katz et al., 2009; Kemp, 2002). Responses are typically evoked between 1-4 kHz but may be weak and or absent above 4 kHz. Distortion product otoacoustic emissions require tonal stimuli to be evoked. Two pure tone stimuli, f1 and f2, are presented simultaneously so that the frequency of f2 is greater than that of f1 (Kemp, 2002; Rupa, 2002). Non-linear modulation of f1 and f2 occurs within the cochlea, resulting in additional frequency components being generated. DPOAEs allow testing of individual frequencies over a broad frequency range when compared to the fixed frequency range of TEOAEs (Kemp, 2002; Rupa, 2002). As the degree of hearing losses increases, the DPOAE amplitudes decrease. DPOAEs are also typically absent in hearing losses with thresholds greater than 50 dB HL to 60 dB HL (Gorga et al., 1997).

The value of OAEs lies in their high frequency specificity and sensitivity for detecting damage to the cochlea (Attias, Horovitz, El-Hatib, & Nageris, 2001; Berninger & Westling, 2011; Kemp, 2002; Rupa, 2002). This makes them useful in detecting not only clinical but also subclinical hearing impairments, ensuring that early intervention can occur. Rupa's study (2002) further showed that DPOAEs high test-retest reliability is valuable for monitoring changes to cochlear function over time. Clinically, DPOAEs and TEOAEs may be used as an objective measurement for screening and monitoring purposes. Not only are they useful for distinguishing a sensory hearing loss from a neural hearing loss, but they have also proven to be of value in the screening and testing of difficult-to-test populations, including newborns (Berninger & Westling, 2011). Finally, OAEs are important in the monitoring of cochlear function

(Rupa, 2002), including patients with noise-induced hearing loss (Attias et al., 2001) and patients receiving ototoxic treatment (Reavis et al., 2011).

Significantly reduced DPOAEs and TEOAEs have been reported in subjects with DM compared to healthy control subjects, despite normal hearing (Di Nardo et al., 1998; Lisowska, Namysłowski, Morawski, & Strojek, 2001b). Similar results have been found in subjects with DM and hearing loss (Karabulut et al., 2014; Ren et al., 2009). Significant differences of DPOAEs and TEOAEs between DM and healthy participants were not found in all studies, despite reductions in OAE amplitudes (Eren, Harman, Arslanoğlu, & Onal, 2014). Nonetheless, it is evident from the majority of these studies that there is a risk for cochlear dysfunction in DM.

5. Auditory brainstem responses and diabetes mellitus

Auditory brainstem response (ABR) testing objectively assesses the functioning and synchronicity of the auditory neural pathway from the cochlea to the upper brainstem (Katz et al., 2009). It represents the synchronous discharge of neurons in the peripheral and central auditory system in response to click or tone-burst stimuli which appears as five consecutive waves. Each wave represents discharge of neurons from one or more neural generators from the distal end of the vestibular-cochlear nerve to the lateral lemniscus (Jewett & Williston, 1971; Møller, 1998). Each of these waves occurs within in a certain time period (latency) after onset of the stimulus.

Auditory brainstem responses are most typically evoked using click or tone-burst stimuli (Katz et al., 2009). These stimuli are presented unilaterally into the ear through an insert earphone. Click stimuli are broadband stimuli and are characterised by a rapid onset, stimulating a large number of neurons in broad portion of the cochlear partition simultaneously (Katz et al., 2009). This discharge of neurons results in larger, visible peak amplitudes when recording an ABR. It is typically used for neurological ABR assessments (Katz et al., 2009). Tone-burst stimuli are more frequency specific which allows for threshold estimation, but will elicit poorer neural synchrony than clicks (Katz et al., 2009). Responses are recorded by electrodes that may be placed on the forehead, vertex of the head, and on each mastoid (Katz et al., 2009).

This non-invasive assessment has proven to be a highly sensitive screening test (Godey, Morandi, Beust, Brassier, & Bourdinière, 1998; Hall, Smith, & Popelka, 2004) and important in the differential diagnosis of hearing loss, threshold estimation and intraoperative monitoring (Godey et al., 1998; Katz et al., 2009).

Studies that conducted neurological ABR using click stimuli (c-ABR) on subjects with DM reported delays in absolute wave latencies of waves I, III, V, as well as inter-peak latencies (IPLs) I-V (Hou et al., 2015; Lisowska et al., 2001b; Sasso et al., 1999). This indicated a possible neuropathy. Subclinical hearing loss was evident in these studies in normal hearing DM subjects with delays in c-ABR latencies. Lasagni and colleagues (2015) reported no delays in c-ABR latencies in the majority of their DM subjects. Nevertheless, Lasagni and colleagues (2015) did report that 20% of DM subjects had absent waves in one ear. Moghaddam (2011) reported on the prevalence of c-ABRs between DM and non DM subjects and did not find significant differences. However, a small percentage of subjects in his study displayed absent c-ABRs in the right ear (8%) and in the left ear (6%), and both absent c-ABRs and OAEs in 8% of cases. Despite a few studies contradicting these findings, it was made evident by the majority of studies that the auditory neural pathway may be affected by DM.

6. Rationale

The increasing pandemic of DM gives rise to concerns regarding the effect of DM's multiple complications on various bodily systems, as well as the treatment and monitoring thereof. Due to the nature and possible severity of the leading complications of DM, a non-life threatening complication such as hearing loss may easily be overlooked. Reports on c-ABRs and OAEs in subjects with DM are largely varied and inconsistent, and currently little consensus regarding the audiologic profile of these patients exists. Past studies do not always exclude subjects with presbycusis and other conditions that may affect the hearing of DM subjects. Therefore, strict inclusion criteria should be adhered to when selecting studies to ensure that the hearing loss is in fact caused by DM. While pure tone audiometry is valuable in determining the presence of a hearing loss, the significance of OAEs and c-ABRs lies in their ability to collectively assist in differentiating between a sensory

and neural impairment through objective means. Other objective assessments such as may also be of value. However, OAE and c-ABRs are non-invasive and proven to be of high sensitivity and specificity for cochlear and auditory neural pathway function respectively. Further, it is evident through numerous studies that these assessments may assist in identifying subclinical impairments in seemingly normal hearing individuals

7. Problem statement

It is evident throughout the research that hearing loss is indeed an additional complication that may arise in individuals with DM. However, hearing monitoring may not yet be seen as important in the systematic monitoring of these subjects. It is important to determine whether the hearing impairment is more sensory or neural in origin to ensure that correct interventions are implemented.

While previous reviews have attempted to describe the results of either c-ABRs or OAEs in DM subjects, this review and meta-analysis will attempt to describe results of both tests in one study to highlight the importance of using both assessments for more accurate differential diagnosis and in future monitoring.

Chapter 2

Methodology

1. Aim

The main aim of this study was to systematically review and analyse the available peer-reviewed literature reporting on the results of OAEs and c-ABRs in adults with T1DM and T2DM.

2. Research design

A systematic review and meta-analysis of peer-reviewed literature were utilised for this study.

A systematic review aims to answer a research question by using systematic and explicit methods to identify, select, and critically appraise relevant research. Subsequently, collection and analysis of data from studies included in the review is conducted using these methods (Moher, Liberati, Tetzlaff, & Altman, 2009). A systematic review was conducted to provide insight into OAE and c-ABR response parameters reported in adults with T1DM and T2DM. This provided clarification of auditory sensory and neural complications to expect in these patients. Additionally, it contributed to providing a rationale for systematic monitoring of patients with DM to ensure early detection and intervention of hearing loss. This review also allowed gaps in research on the topic of DM and hearing loss to be determined.

A meta-analysis allows the integration of results of studies included in the systematic review, through the use of statistical techniques (Moher et al., 2009). A meta-analysis was conducted to provide further clarification of the c-ABR response parameters that may typically be seen in patients with DM.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (Moher et al., 2009) was used as a guide to structure this study and improve the reporting of this systematic review and meta-analysis.

3. Ethical considerations

The nature of this study did not warrant for the ethical considerations typically deliberated in a human study. Nonetheless, certain ethical considerations were still of importance.

4. Research clearance

Prior to commencement of the study, ethical approval was obtained from both the Research Committee of the Department of Speech-Language Pathology and Audiology, University of Pretoria, as well as the Research Ethics Committee of the Faculty of Humanities (Appendix A).

4.1. Reliability and validity

Reliability and validity of the current study was ensured in the following ways:

- Reliable and valid electronic databases were used to conduct data collection.
- Only predetermined search terms and strategies were used to conduct the search. They also allowed replication of the search, should a similar study be conducted in future.
- Pre-determined inclusion and exclusion criteria were adhered to in the selection of articles to be included in the review and meta-analysis.
- All selected articles were read by two reviewers prior to inclusion in the study and underwent a critical appraisal process. This prevented bias and ensured that only articles valid to the aim of this study were included.
- Risk of bias was determined for each included study to prevent any bias impacting results for this study.

4.2. Risk of bias

Assessing the risks of bias is an important part of any systematic review as bias may impact results (Moher et al., 2009). In the current study, The Cochrane Collaboration's tool for assessing risk of bias by Higgins and Green (2011) was used for this purpose (Appendix B).

4.3. Plagiarism

Plagiarism was prevented by adhering to strict guidelines of referencing and citing. All sources used in the study were included in the bibliography and in-text referencing was used where a source was cited in the text (see Appendix C for plagiarism declaration).

4.4. Data storage

Data will be stored electronically, on a compact disc (CD), as well as in hard copy (in a file). These will be stored at the Department of Speech-Language Pathology and Audiology for 15 years as per regulations of the University of Pretoria.

5. Selection criteria

Selection criteria ensure the validity, applicability and comprehensiveness of the review, and allows selection of studies to occur in a systematic manner and without bias (Liberati et al., 2009). Therefore, stringent selection criteria were applied to ensure reliable and valid reporting of articles pertaining only to the aim of this study (Table 1). These criteria were determined before articles were collected.

Table 1: Selection criteria

Criteria	Rationale
Inclusion criteria	
Studies including subjects with T1DM or T2DM.	The aim of this study was to review and analyse data of both types of DM.
Studies including subjects with ages above 18 and below 60 years of age.	The aim of this study was to review and analyse data of adult subjects, not child subjects. T2DM commonly manifests in adulthood (World Health Organization, 2016). Therefore, data on this type of DM would be more readily available in adult studies than in studies on children. The upper age limit prevented effects of presbycusis (Bonfils, Bertrand, & Uziel, 1988).
Studies including age- and gender-matched healthy control group who underwent the same assessments as the DM group.	This ensured that accurate comparisons could be made and relevant conclusions drawn.
Studies including descriptions of DPOAE, TEOAE or c-ABR response parameters.	The aim of this study required this data to be reviewed.
Peer-reviewed cross-sectional, case-controlled or prospective cohort studies.	Highest level of evidence required.
Exclusion criteria	
Studies not specifying the type of DM, or self-reported DM.	This ensured that only studies reporting on T1DM or T2DM subjects that received the diagnosis from a clinician were included.
Studies including subjects with additional conditions, syndromes or risk factors for hearing loss. This resulted in the exclusion of articles in which it was not clarified whether subjects with a history of noise exposure, ototoxicity, or history of middle ear pathology were excluded.	These conditions may have caused hearing loss or increased subjects' risk for it. This would make it difficult to draw accurate correlations between response parameters measured in the studies and DM.
Studies describing subjects older than 60 years of age.	This avoided effects of presbycusis on hearing and specifically OAE results (Bonfils et al., 1988).
Systematic reviews, chapters in a book, conference proceedings, letters to the editor, and abstracts.	This ensured that original research was reported on or reviewed.
Studies reporting on animal subjects.	The aim of this study was to review research conducted on human subjects.

6. Data collection procedure

6.1. Systematic review

Prior to the commencement of a comprehensive literature search, relevant search terms were determined. This ensured that articles obtained in the search were valid to the aim of this research study. Terms utilised in the aim of the research study were extrapolated and relevant synonyms were assigned. Additional terms relevant to the topic of DM and hearing loss were also determined. Finally, limiters were identified for each database to increase the specificity of the search and limit the number of irrelevant articles found.

The primary search terms determined to search databases were “diabetes mellitus”; “type 1 diabetes”; “type 2 diabetes”; insulin dependent diabetes”; “non-insulin dependent diabetes”. Secondary search terms included: “hearing”; “hearing loss”;

"otoacoustic emissions"; "auditory brainstem responses"; "brainstem auditory evoked potentials"; and "brainstem auditory evoked responses".

Limiters were set to include only peer-reviewed journal articles and English articles. A limiter for the date of publications was originally set to include only articles published after 1978 at which time OAEs were first described by Kemp. However, it was determined that without this limiter the search still produced identical results. Therefore, this limiter was deemed unnecessary and was omitted.

A comprehensive literature search was conducted across electronic databases to identify peer-reviewed articles that included results of OAEs (DPOAEs and TEOAEs) and c-ABR tests in subjects with DM. The following electronic databases were searched: PubMed, Medline (Ovid), and Scopus. Various search strategies were applied for each database, including title, abstract, keywords and medical subject heading (MeSH) terms (see Table 2), and utilising the pre-determined search terms.

Table 2: Search strategies

	Search strategy	Identifiers	Limiters	Results
Scopus	Title, abstract and keywords	"diabetes mellitus" OR "type 1 diabetes" OR "insulin dependent diabetes" OR "type 2 diabetes" OR "non-insulin dependent diabetes" AND "hearing" OR "hearing loss" AND "otoacoustic emissions" OR "auditory brainstem responses" OR "brainstem auditory evoked potentials" OR "brainstem auditory evoked responses"	English; Articles only	188
PubMed	All fields utilising MeSH terms	"diabetes mellitus" OR "type 1 diabetes" OR "insulin dependent diabetes" OR "type 2 diabetes" OR "non-insulin dependent diabetes" AND "hearing" AND "hearing loss" * *AND "otoacoustic emissions" *AND "auditory brainstem responses" *AND "brainstem auditory evoked potentials"	English; Journal articles	96
Medline	Keywords	"diabetes mellitus" OR "type 1 diabetes" OR "insulin dependent diabetes" OR "type 2 diabetes" OR "non-insulin dependent diabetes" AND "hearing" AND "hearing loss" * *AND "otoacoustic emissions" *AND "auditory brainstem responses" *AND "brainstem auditory evoked potentials"	English; Journal articles	43

The titles and abstracts of search results were considered by the researcher, using pre-determined inclusion criteria as a guide. Articles not qualifying for inclusion in this research study were excluded and duplicates were removed. Full-text articles

were obtained and assessed. Once again, pre-determined inclusion criteria were utilised and all studies not pertaining to this criteria were excluded. Finally, a hand search of reference lists of articles qualifying for inclusion was conducted to identify relevant articles missed in the database search.

Studies that complied with the inclusion criteria underwent a critical appraisal process. To avoid bias, two reviewers, independently from each other, appraised the selected studies using a critical review form for quantitative studies by Potvin (2007), modified from a critical review form for quantitative studies from Law et al. (1998) (see Appendix D for Critical review form). This process allowed researchers to critically evaluate the content of each subject, which further ensured that valid and reliable studies were selected. Studies that passed the critical appraisal were included in the systematic review and data extraction commenced.

Data extraction sheets were formulated by the researcher prior to data collection, using the PRISMA statement as a guide (Moher et al., 2009). To avoid bias, supervisors were consulted to review the data extraction sheet independently of each other. After final selection of articles for the systematic review, data was extracted and recorded using these sheets (Appendix E). Information extracted from each selected article included:

1) Title of article,
2) Year published,
3) Characteristics of subjects (number of subjects in DM and healthy control subjects; mean age, gender, mean duration of disease; HbA1c; complications; hearing status),
4) Test parameters for DPOAEs, TEOAEs and c-ABRs respectively,
5) Outcome measures for DPOAEs, TEOAEs and c-ABRs respectively, as well as significant differences found between subjects with DM and healthy control subjects for which p-values were $p<.05$, $p<.01$ and/or $p<.001$,
6) Correlations found between clinical characteristics and tests
7) Conclusion of study,
8) Level of evidence.

6.2. Meta-analysis

All studies included in the systematic review that assessed c-ABRs were considered for inclusion in the meta-analysis. Studies were only included in the meta-analysis if c-ABR outcomes were reported as means and standard deviations (SDs) and if all other inclusion criteria were met. This was required to ensure that the results obtained through the meta-analysis were relevant and of high value.

The following outcome measures were extracted for DM groups and control groups:

1) Mean absolute wave latencies (I, III and V),
2) Mean inter-peak latencies (I-III, III-V and I-V) of c-ABR waves.

An analysis of studies including OAEs was not conducted, as the data of these studies was generated and presented using different frequencies and units. This caused difficulties in the integration and analysis of this data.

The data collection procedure for both the systematic review and subsequent meta-analysis is depicted in Figure 1.

7. Data analysis

A meta-analysis was conducted to analyse and summarise results of the studies included in the systematic review (Moher et al., 2009). Data analysis was performed using Microsoft Excel 2010. Mean differences and the standard deviations of each study selected for inclusion in the meta-analysis were documented, and averages were computed.

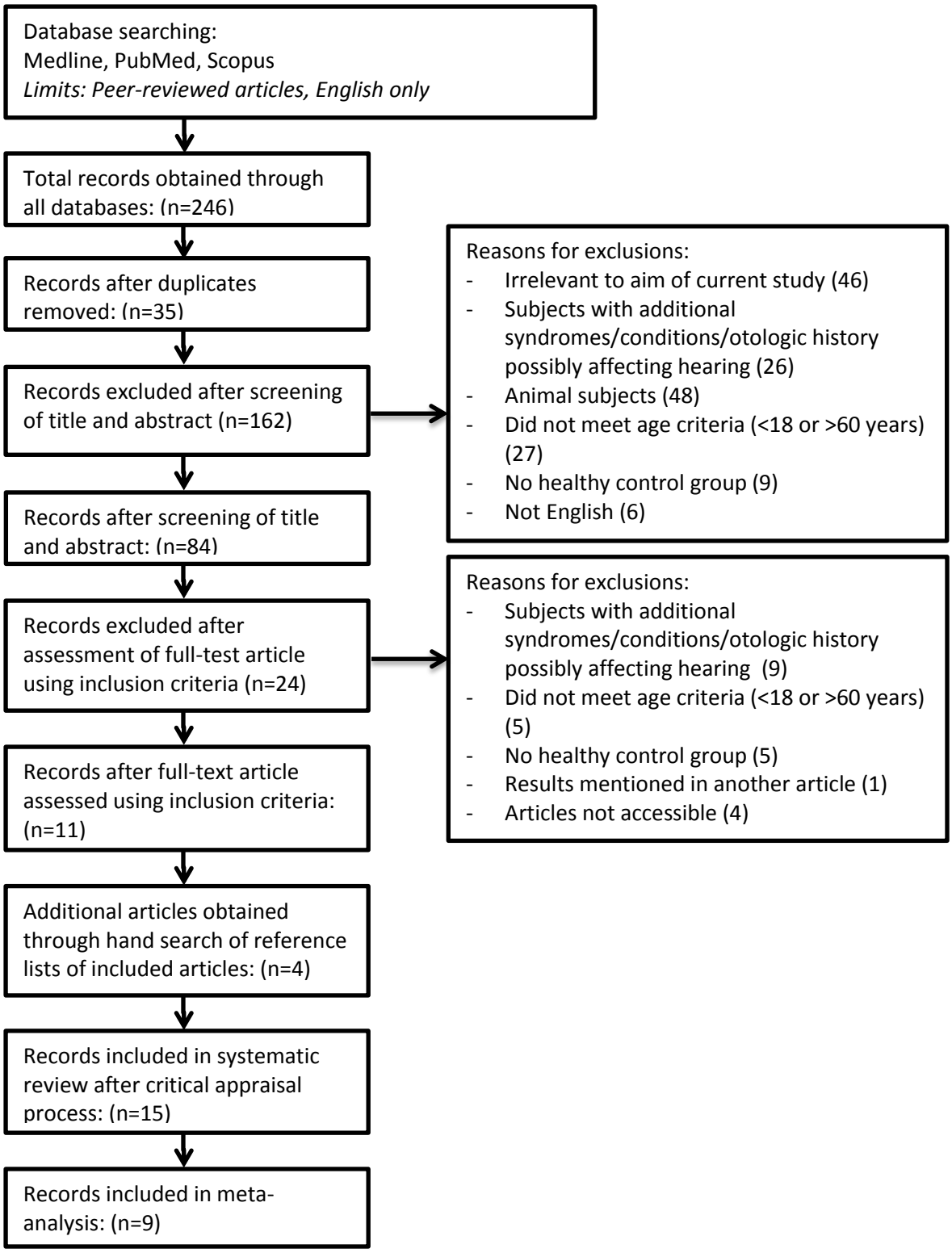

Figure 1: Data collection procedure

Chapter 3

Results

1. Introduction

Records obtained through searches of electronic databases were screened by title and abstract. The records that did not comply with the inclusion criteria of this study were excluded. After the removal of any duplicates, 35 full-text articles were assessed using pre-determined inclusion criteria. A hand search of reference lists of articles considered eligible resulted in an additional four articles that were included in the review. Finally, 15 articles underwent a critical appraisal process and were included in the systematic review, of which nine articles were included in the meta-analysis

Table 3 summarises the characteristics of the 15 studies that met all inclusion criteria for the review. Publication dates for articles ranged from 1998 - 2015. Five articles reported on T1DM, nine articles reported on T2DM and one article reported on both T1DM and T2DM. There were 12 reports on c-ABR, eight on DPOAE and seven on TEOAE. All studies included were level three evidence. Control subjects were age- and gender matched, and did not present with DM or any other medical conditions.

Table 3: Characteristics of included studies (n=15)

Author (Year)	Type of DM	Subjects (DM/Control)	Mean Age (years) (DM/Control)	Mean Duration of DM (years)
DPOAE studies				
Di Nardo et al. (1998)	Type 1 (with neuropathy)	32/44	33.8/31.6	15.2 ± 8.4
	Type 1 (without neuropathy)	15	33.9	15.4 ± 5.2
Ottaviani, Dozio, Neglia, Riccio, & Scavini (2002)	Type 1	60/58	31.0/29.1	17.5± 8.9
Hou et al. (2015)	Type 1	50/50	25.7/24.7	5.8 ± 4.5
Lasagni et al. (2015)	Type 1	31/10	33.2/32	25.7 ± 4.2
Lisowska et al. (2001b)	Type 2 (with microangiopathy)	17/33	28.2/ 31.7	9.6
	Type 2 (without microangiopathy)	25	36.2	18.5
Erdem, Ozturan, Miman, Ozturk, & Karatas (2003)	Type 2	21/22	48.6/46.7	
Ren et al. (2009)	Type 2	50/50	40.8/41.0	7
Karabulut et al. (2014)	Type 2	50/51	49.8/47.9	8.1 ± 5.8
TEOAE studies				
Di Nardo et al. (1998)	Type 1 (with neuropathy)	32/44	33.8/31.6	15.2 ± 8.4
	Type 1 (without neuropathy)	15	33.9	15.4 ± 5.2
Ottaviani et al. (2002)	Type 1	60/58	31.0/29.1	17.5± 8.9
Dąbrowski, Mielnik-Niedzielska, & Nowakowski (2011)	Type 1	31/26	29.1/30.3	< 10
Hou et al. (2015)	Type 1	50/50	25.7/24.7	5.8 ± 4.5
Sasso et al. (1999)	Type 2	110/106	48.4/47.9	8.1 ± 4.1
Erdem et al. (2003)	Type 2	21/22	48.6/46.7	
Ren et al. (2009)	Type 2	50/50	40.8/41.0	7
c-ABR studies				
Ottaviani et al. (2002)	Type 1	60/58	31.0/29.1	17.5± 8.9
Durmus, Yetiser, & Durmus (2004)	Type 1	17/17	24.3/22.6	6.44
	Type 2	26/20	57.5/51.2	
Dąbrowski et al. (2011)	Type 1	31/26	29.1/30.3	< 10
Hou et al. (2015)	Type 1	50/50	25.7/24.7	5.8 ± 4.5
Lasagni et al. (2015)	Type 1	31/10	33.2/32	25.7 ± 4.2
Sasso et al. (1999)	Type 2	110/106	48.4/47.9	8.1 ± 4.1
Lisowska et al. (2001b)	Type 2 (with neuropathy)	17/33	28.2/ 31.7	9.6
	Type 2 (without neuropathy)	25	36.2	18.5
Durmus et al. (2004)	Type 2	26/20	57.5/51.2	6.44
Díaz de León-Morales et al. (2005)	Type 2	94/94	50/50	7.2 ± 5.4
Ren et al. (2009)	Type 2	50/50	40.8/41.0	7
(R. Gupta, Aslam, Hasan, & Siddiqi, 2010)	Type 2	25/25	46.8/45.7	>5
Baweja et al. (2013)	Type 2	116/100	44.6/47.8	5.38
(S. Gupta et al., 2013)	Type 2	126/106	45.7/46.8	5.38 ± 6.14

(Key: c-ABR = click-evoked auditory brainstem response; DM = diabetes mellitus; DPOAE = distortion product otoacoustic emissions; TEOAE = transient-evoked otoacoustic emissions)

Table 4 provides a summary of hearing status, as well as OAE and c-ABR response parameters of DM subjects reported in studies included in the review. Eight articles reported on subjects with normal hearing. In these studies, normal hearing was either part of the inclusion criteria of the studies and confirmed by pure tone audiometry or formed part of the method. Additionally, it should be noted that these eight studies required both DM subjects and healthy control subjects to present with normal hearing. Three studies did not report on the hearing status of the subjects. The majority of DPOAE studies reported reduced amplitudes of some significance with only one study reporting larger amplitudes. Abnormal TEOAEs were reported in all TEOAE studies, although these abnormalities were not always significant. Finally, significantly delayed c-ABR absolute latencies and IPLs were reported in all c-ABR studies.

Table 4: Hearing status and significant OAE and c-ABR response parameters for DM subjects reported in DM studies

Author (Year)	Hearing status	DPOAEs	TEOAEs	c-ABRs
Di Nardo et al. (1998)	Normal hearing	DM subjects with neuropathy: Significantly reduced amplitudes at 1.306-5.2 kHz (p<.05) DM subjects without neuropathy: significantly reduced amplitudes at 3.284-5.2 kHz (p<.01). Reduced below 2 SD of control mean values in 32% of all DM subjects, for all frequencies.	DM with neuropathy: significantly reduced (p=.03) No significant difference between DM groups, but TEOAE more reduced in DM subjects with neuropathy. Reduced below 2 SDs of control mean values in 15% of DM subjects.	not reported
Sasso et al. (1999)	Normal hearing or slight hypoacusis (< 30 dB HL)		Absent in 51.8% of DM subjects compared to control subjects (p<.001).	Significantly delayed latency for waves I, III, V & IPL I-V (p<.05).
Lisowska et al. (2001b)	Normal hearing	Significantly reduced amplitude in middle and high frequencies (f2=1 kHz to f2= 6 kHz) (p<.05).	not reported	Waves I, III, and V (p<.0001), IPL I-V (p<.001) significantly prolonged.
Ottaviani et al. (2002)	Normal hearing	Significantly reduced (p<.05; p<.01; p<.001) at all frequencies except 4.306 kHz and 5.121 kHz. Most significance (p<.001) in middle frequencies (between .949 and 1.662 kHz).	Mean reproducibility and response intensity significantly reduced (p<.001). Significant difference at 1-4 kHz (p<.001). Present in both ears in 43 DM subjects (72%). Absent in 5 DM subjects (8%). 12 DM subjects (20%) with significantly reduced TEOAEs in contralateral ear compared to the remaining 43 DM subjects with present TEOAEs in both ears (p<.001).	Significantly delayed wave I (p<.01), III (p<.001) and V (p<.01).
Erdem et al. (2003)	Normal hearing (< 30 dB HL)	Significantly reduced amplitudes at 4 kHz (p<.05).	No significant difference found in the presence/absence compared to healthy controls.	not reported
Durmus et al. (2004)	Normal hearing (< 20 dB HL)	not reported	not reported	Waves I, III, V (p<.05) and IPL I-V and III-V (p<.005) prolonged significantly. Prolonged more significantly in T2 DM group (p< .05).
Díaz de León-Morales et al. (2005)	Normal, sloping to mild loss at 8 kHz.	not reported	not reported	Wave V, IPL I-V & III-V significantly prolonged (p<.01).
Ren et al. (2009)	HL (> 25 dB HL) in high frequencies (4 kHz & 8 kHz).	Significantly reduced amplitudes at 2.0 kHz, 3.0 kHz, 4.0 kHz (p<.01).	Significantly reduced amplitudes (p<.05). No significant difference between ears in DM subjects at all frequencies except 4 kHz. RE: smaller amplitudes at 4 kHz than LE (p<.05)	Significant delays of wave V & IPL I-V (p<.01).
(R. Gupta et al., 2010)	not reported	not reported	not reported	The following waves were significantly delayed: 70 dB HL: Wave III (p=.01), V (p=.045) & IPL I-III and III-V (p<.001); 80 dB HL: Wave III, V, IPL I-III & III-V (p<.001),and I-V (p<.028); 90 dB HL: wave III (p<.001), V (p=.002 & IPL I-III (p<.001), I-V(p<.001), III-V (p=.036)

Dąbrowski et al. (2011)	Normal hearing (n= 25); mild HL (>20 dB HL) (n= 5); moderate HL (>40 dB HL) (n= 1). Thresholds significantly higher at 3 - 6 kHz (p<.005) and 8-12 kHz (*p*<.05) compared to control subjects.	not reported	Significantly reduced amplitudes at 1.2-3.5 kHz band (*p*<.001), 1.5 kHz (*p*=.002), 2 kHz (*p*<.001) and 4 kHz (*p*=.017).	Significantly prolonged wave V (*p*=.025).and I-V (*p*=.017) with IPL I-III close to significance (*p*=.059).
Baweja et al. (2013)	not reported	not reported	not reported	Wave V & IPL I-V significantly prolonged in both ears (R: p=.021 & p=.0381; L: p=.028 & p=.016); and IPL I-III in right ear only (*p*=.028).
(S. Gupta et al., 2013)	not reported	not reported	not reported	Waves III & V, IPL III-V & I-V significantly prolonged in both ears, and wave IV in right ear (p=.02).
Karabulut et al. (2014)	Sensorineural HL (>15 dB HL) at all frequencies.	Significant difference of SNR at all frequencies except 1 kHz (*p*<.05).	not reported	
Hou et al. (2015)	Deficit with elevated thresholds at .25, 1, 2, 4, & 8 kHz in RE, and at .25, .5, 1, 4, and 8 kHz in LE ; 48% with HL (> 25 dB) in some frequencies	Normal range of DPOAE amplitudes, but significantly larger amplitudes (>20 dB SPL) in high frequencies, at 4.0, 6.0 kHz (with both ears) and 8.0 kHz (with left ear) (*p*<.01). 70% of DM subjects showed HL defined by DPOAE.	No significance. Average amplitudes within normal or near normal range. 20 DM subjects (40%) with HL defined by TEOAE: 9 (18%) in which TEOAE not detected & 11 (22%) with abnormal amplitudes. Mild impairment at low and medium frequencies.	Significantly delayed wave III & V and IPL I-V (both ears) as well as IPL I-III (left ear only) (*p*<.01)
Lasagni et al. (2015)	Normal hearing (<25 dB HL), but significantly higher mean thresholds than control subjects. (R: 14.3 ± 4.6 vs. 9.9 ± 2.5 dB, L: 13.0 ± 3vs. 9.9 ± 2.6 dB)	Reduced at all frequencies. Statistically significant between 2.8 and 4 kHz (<.05).	not reported	No significant difference in absolute latencies of individual waves or I-III and I-V intervals. Absent waves in 20% of DM subjects. Wave IV pattern detected in 61.3% of DM subjects, associated with prolonged IPL I-V (*p*<.05)

(Key: c-ABR = click-evoked auditory brainstem responses; HL = hearing loss; DPOAE = distortion product otoacoustic emissions; TPOAE = transient-evoked otoacoustic emissions; RE = right ear; LE = left ear; kHz = kilohertz; dB HL = decibels hearing level)

2. Otoacoustic Emissions

2.1. Distortion-product otoacoustic emissions

All articles included in the study described abnormal DPOAE amplitudes in which abnormal was defined as either absent, or reduced amplitudes or, in one study (Hou et al., 2015), as significantly larger amplitudes (>20 dB SPL).

Reduced DPOAE amplitudes of DM subjects compared to healthy control subjects were reported in seven articles (Di Nardo et al., 1998; Erdem et al., 2003; Karabulut et al., 2014; Lasagni et al., 2015; Lisowska et al., 2001b; Ottaviani et al., 2002; Ren et al., 2009). Five of these articles documented significant reductions of DPOAE amplitudes in the DM subjects in middle to high frequencies, ranging from 0.949 kHz to 6 kHz (Di Nardo et al., 1998; Lasagni et al., 2015; Lisowska et al., 2001b; Ottaviani et al., 2002; Ren et al., 2009), while one article reported only significant reduced amplitudes at 4 kHz (p<.05) (Erdem et al., 2003). Upon considering individual absolute values, Di Nardo et al. (1998) reported DPOAEs reduced below 2 SDs of control mean values in 32% of all DM subjects, for all frequencies. Lasagni et al. (2015) reported absent DPOAEs in the right and left ears in approximately 35% and 39% of DM subjects, respectively. Significant differences were reported between the levels of signal-to-noise ratio (SNR) of DM subjects and healthy control subjects at all frequencies, except 1 kHz in a study (p<.05) by Karabulut et al. (2014). Finally, Hou et al. (2015) reported larger DPOAE amplitudes in DM subjects compared to healthy control subjects in high frequencies (p<.01). In their study, 35 DM subjects (70%) presented with hearing impairment defined by DPOAEs, of which three DM subjects (6%) had absent DPOAEs and 32 (64%) DM subjects had abnormal DPOAES (<5 dB SPL or >20 dB SPL).

2.2. Transient evoked otoacoustic emissions

These articles reported on TEOAE results using various mediums of reporting. Merely two articles (Dąbrowski et al., 2011; Ottaviani et al., 2002) documented mean amplitudes and standard deviations measured in DM subjects while other articles

used graphs to depict results or only reported on the presence or absence of TEOAEs. Abnormal TEOAEs were defined as absent, or reduced in amplitude.

Significantly reduced TEOAE amplitudes in DM subjects were reported in four articles (Dąbrowski et al., 2011; Di Nardo et al., 1998; Ottaviani et al., 2002; Ren et al., 2009). Dąbrowski et al. (2011) found significantly reduced amplitudes at 1.2 to 3.5 kHz band (p<.001), 1.5 kHz (p=0.002), 2 kHz (p<.001), and 4 kHz (p=.017) in DM subjects when compared to healthy control subjects. Di Nardo et al. (1998) reported that 15% of DM subjects had amplitudes reduced below 2 SDs of control mean values, and found significantly reduced TEOAEs in DM subjects with neuropathy compared to healthy control subjects (p=0.03). No significant differences were obtained between DM subjects without neuropathy and healthy control group, or between the two DM groups. However, TEOAEs were more reduced in the DM group with neuropathy. Ottaviani et al. (2002) reported five DM subjects (8%) in their study with absent emissions in both ears, while 12 DM subjects (20%) had significantly reduced TEOAEs in at least one ear, compared to the 43 DM subjects (72%) with present TEOAEs in both ears (p<.001). However, TEOAEs in subjects with present TEOAEs were significantly reduced compared to healthy control subjects (p<.05). One study reported absent TEOAEs in 51.8% of DM subjects compared to 4.7% in healthy control subjects (Sasso et al., 1999). Erdem et al. (2003) reported no significant differences in the existence of TEOAES in their study groups, while Hou et al. (2015) also reported normal or near normal average mean amplitudes without significant differences between DM and healthy control subjects. However, Hou et al., (2015) reported no detection of TEOAE in nine DM subjects (18%) and abnormal amplitudes (<5 dB SPL or >20 dB SPL) in 11 DM subjects (22%), with mild impairment in the low and medium frequencies.

3. Auditory brainstem responses

All articles reporting on c-ABRs reported significant abnormalities in DM subjects, in which abnormal may be defined as absent, delayed absolute wave latencies or prolonged IPLs at supra-threshold stimulus levels.

Three articles reported delays in waves I, III, V that were of significance (p<.05) (Durmus et al., 2004; Sasso et al., 1999) and high significance (p<.001) (Lisowska et al., 2001b). They also reported significant delays of IPL I-V where p<.05 (Sasso et al., 1999), p<.005 (Durmus et al., 2004) and p<.001 (Lisowska et al., 2001b), as well as a delay of IPL IIII-V in one article (p<.005) (Durmus et al., 2004). Waves III, V, and IPL I-V were reported delayed, both significantly (p<.05) (S. Gupta et al., 2013) and highly significantly (p<.01) (Hou et al., 2015). Additionally, S. Gupta et al. (2013) also reported significant delays of IPL III-V (p<.05). R. Gupta et al (2010) also reported significant delays of waves III, V and IPL I-III, III-V and I-V at 70 dB nHL, 80 dB nHL and 90 dB nHL. Four studies reported only significant delays in wave V and IPL I-V with the following p-values: p<.05 (Baweja et al., 2013) and p<.01 (Díaz de León-Morales et al., 2005; Ren et al., 2009) for both wave V and IPL I-V latencies, and p=.025 and p=.017 for wave V and IPL I-V respectively (Dąbrowski et al., 2011). Of these studies, Baweja et al. (2013) also reported delays of IPL I-III in one ear (p=.028), and Díaz de León-Morales et al. (2005) also reported IPL III-V as delayed (p<.01). Finally, Lasagni et al. (2015) reported no significant differences between absolute latencies and IPL I-III and IPL I-V between DM subjects and healthy controls, but waves were absent in 20% of DM subjects. They did report a higher prevalence of wave IV compared to healthy controls (Right: 55%, Left: 61.3% in DM subjects vs. Right: 10%, Left: 10% in healthy controls, p<.05). DM subjects with wave IV presented with prolonged IPL I-V compared to DM subjects without wave IV (p<.05).

Six articles presented assessment results of both OAEs and c-ABRs, and reported reduced OAE amplitudes, and delayed c-ABR latencies in DM subjects compared to healthy control subjects (Dąbrowski et al., 2011; Hou et al., 2015; Lisowska et al., 2001b; Ottaviani et al., 2002; Ren et al., 2009; Sasso et al., 1999).

Nine articles of those selected for review reported means and SDs of absolute latencies and IPLs of c-ABRs. One article reported results in terms of median and interquartile range, while two articles depicted results on graphs for which mean values and SDs could not be obtained.

Data was grouped for 645 DM subjects and 585 healthy control subjects according to stimulus intensities presented in these articles (Table 5). Means and SDs for

absolute wave latencies and IPLs were pooled to obtain averages for the following: 242 DM subjects and 206 healthy control subjects for clicks of 60 dB SL (Baweja et al., 2013; S. Gupta et al., 2013), and 94 DM subjects and 94 healthy controls at 80 dB SL (Díaz de León-Morales et al., 2005). Data for 56 DM subjects and 51 control subjects was grouped at 70 dB nHL (Dąbrowski et al., 2011; R. Gupta et al., 2010), for 108 DM subjects and 95 healthy controls at 80 dB nHL (Durmus et al., 2004; R. Gupta et al., 2010; Lisowska et al., 2001b), and for 25 DM subjects and 25 healthy controls at 90 dB nHL (R. Gupta et al., 2010). Analysis for 110 dB nHL included 110 DM subjects and 106 control subjects (Sasso et al., 1999) and for 100 dB SPL 60 DM subjects and 58 control subjects (Ottaviani et al., 2002). Two articles documented values for right and left ears separately (Baweja et al., 2013; S. Gupta et al., 2013). Therefore, average values were calculated in each of these articles representing both ears.

Meta-analysis of nine articles showed the following for DM subjects: the means of wave III were reported above 3.84 ms at all intensities except 60 dB SL, and below 3.92 ms, in DM subjects, whereas wave III latencies ranged between 3.50 ms and 3.79 ms in control subjects. Mean wave V latencies were reported at and above 5.8 ms and below 5.95 ms at all intensities, except 100 dB SPL where the latency was 5.67 ms, in DM subjects. In control subjects, mean wave V latencies occurred below 5.6 ms at 60 dB SL, 80 dB nHL, 90 dB nHL, 110 dB nHL and 100 dB SPL. Mean IPL I-III values ranged between 2.22 ms to 2.27 ms at 80 dB SL, 70 dB nHL, 80 dB SL, 110 dB nHL and 100 dB SPL for DM subjects. Mean IPL I-III at 60 dB SPL was well below this range (2.09 ms) and at 90 dB nHL considerably above this range (2.47 ms). Mean IPL III-V ranged between 1.79 ms and 2.11 ms in DM subjects, and between 1.86 ms and 2.02 ms in control subjects. Finally, mean IPL I-V was reported above 4.04 ms and below 4.57 ms in DM subjects, and between 3.84 ms and 4.04 ms in control subjects.

Table 5: c-ABR data from selected studies

				Wave I (ms)				Wave III (ms)				Wave V (ms)			
		Number of subjects (n=)		DM		Control		DM		Control		DM		Control	
Studies	**Intensity**	**DM**	**Control**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
(Baweja et al., 2013; S. Gupta et al., 2013)	60 dB SL	242	206	1.65	0.33	1.61	0.17	3.72	0.36	3.58	0.18	5.80	0.44	5.40	0.25
(Diaz de Leon-Morales et al., 2005)	80 dB SL	94	94	1.62	0.23	1.62	0.20	3.85	0.25	3.78	0.22	5.95	0.32	5.76	0.30
(Dąbrowski et al., 2011; R. Gupta et al., 2010)	70 dB nHL	56	51	1.66	0.13	1.66	0.13	3.92	0.24	3.70	0.27	5.92	0.26	5.63	0.26
(Durmus et al., 2004; Gupta et al., 2010; Lisowska et al., 2001)	80 dB nHL	108	95	1.64	0.10	1.58	0.09	3.88	0.12	3.64	0.12	5.86	0.13	5.57	0.12
(R. Gupta et al., 2010)	90 dB nHL	25	25	1.44	0.06	1.44	0.07	3.92	0.28	3.50	0.41	6.02	0.30	5.52	0.39
(Sasso et al., 1999)	110 dB nHL	110	106	1.67	0.13	1.60	0.13	3.89	0.12	3.79	0.15	5.82	0.21	5.57	0.21
(Ottaviani et al., 2002)	100 dB SPL	60	58	1.61	0.13	1.54	0.10	3.87	0.18	3.74	0.14	5.67	0.21	5.55	0.18
				IPL I-III (ms)				IPL III-V (ms)				IPL I-V (ms)			
		Number of subjects (n=)		DM		Control		DM		Control		DM		Control	
Studies	**Intensity**	**DM**	**Control**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
(Baweja et al., 2013; S. Gupta et al., 2013)	60 dB SL	242	206	2.09	0.30	2.04	0.20	1.99	0.41	1.86	0.23	4.04	0.41	3.84	0.26
(Diaz de Leon-Morales et al., 2005)	80 dB SL	94	94	2.23	0.30	2.17	0.31	2.11	0.36	1.98	0.34	4.34	0.37	4.14	0.39
(Dąbrowski et al., 2011; R. Gupta et al., 2010)	70 dB nHL	56	51	2.25	0.19	2.04	0.23	1.99	0.17	1.93	0.16	4.24	0.25	3.97	0.22
(Durmus et al., 2004; R. Gupta et al., 2010; Lisowska et al., 2001)	80 dB nHL	108	95	2.26	0.10	2.05	0.10	1.99	0.03	1.95	0.03	4.22	0.15	3.93	0.11
(R. Gupta et al., 2010)	90 dB nHL	25	25	2.47	0.25	2.05	0.36	2.09	0.14	2.02	0.06	4.57	0.31	4.08	0.34
(Sasso et al., 1999)	110 dB nHL	110	106	2.22	0.10	2.11	0.10	1.86	0.17	1.81	0.15	4.12	0.22	3.90	0.20
(Ottaviani et al., 2002)	100 dB SPL	60	58	2.27	0.18	2.20	0.14	1.79	0.15	1.81	0.17	4.06	0.19	4.01	0.18

(Key: DM = Diabetes mellitus; IPL = Inter-peak latency; dB SL = decibel Sensation Level; dB nHL = decibel normal Hearing Level; dB SPL = decibel Sound Pressure Level; ms = millisecond)

Chapter 4

Discussion and Conclusion

This study aimed at systematically reviewing and analysing the OAE and ABR response parameters commonly reported in adults with T1DM and T2DM. Results of this review indicated that subjects with DM present with impaired cochlear and auditory neural functioning.

1. Otoacoustic emissions

This review identified that DM subjects appeared to present with reduced DPOAE amplitudes compared to control subjects across included studies, with the mid and high frequencies affected more often than the low frequencies (Di Nardo et al., 1998; Hou et al., 2015; Lasagni et al., 2015; Lisowska et al., 2001b; Ottaviani et al., 2002; Ren et al., 2009). This indicates damage to the outer hair cells of the basal and middle turns of the cochlea, where high and mid frequencies are detected (Raphael & Altschuler, 2003). One study reported damage to the high frequencies in DM subjects without neuropathy, while DM subjects with neuropathy presented with damage to both the mid and high frequencies in DPOAEs (Di Nardo et al., 1998). Neuropathy in DM subjects may only manifest at a later stage of the disease. Therefore, it can be inferred that these differences between the two groups reported by Di Nardo et al. (1998) may indicate a progression of OHC damage as DM progresses, affecting the basal and then the middle region of the cochlea before the apical region. However, this progression was not as evident in other studies.

Metabolic disturbances may be a cause of this impaired function of outer hair cells, as suggested by Lisowska et al. (2001a). Lisowska and colleagues (2001a) found no significant correlation between the presence of microangiopathy and reduced OAE amplitudes, indicating that reduced OAEs were not necessarily caused by microvascular complications. Díaz de León-Morales et al. (2005) reported on pure tone audiometry and c-ABRs in DM subjects and found no relation between auditory

dysfunction and microvascular complications such as diabetic peripheral neuropathy and retinopathy. Díaz de León-Morales et al. (2005) also suggested metabolic disturbances as a cause for auditory impairment in DM subjects. Metabolic disturbances may be related to effects of hyperglycaemia which typically include: oxidative stress, activation of the polyol pathway, generation of ROS, non-enzymatic glycation related to hyperactivity of ROS, and activation of PKC (Creager et al., 2003; Ren et al., 2009). It has also been argued that the lack of correlation between microangiopathy and DPOAE amplitude reduction is consistent with knowledge of cochlea vascularisation (Lisowska et al., 2001a). The cochlea has a rich supply of blood vessels, numerous connections between blood vessels, and alternative capillary pathways, ensuring adequate circulation. Therefore, damage to blood vessels in this system in the cochlea may not necessarily result in changes to cochlear functioning (Lisowska et al., 2001b).

The base to apex pattern of outer hair cell damage observed in many studies in this review has also been observed in subjects with presbycusis or ototoxicity (Bhardwaj, Verma, Chopra, & Sobti, 2016; Yang, Schrepfer, & Schacht, 2015). A study attempting to explain basal outer hair cell susceptibility to damage by ototoxic agents found that basal outer hair cells were more susceptible to damage by ROS than apical outer hair cells (Sha, Taylor, Forge, & Schacht, 2001). This provided an explanation for the base-to-apex pattern of outer hair cell damage in ototoxicity. These effects of ROS on outer hair cells tie in with the hypothesis provided by Lisowska et al. (2001a), who suggested a link between reduced DPOAE amplitudes and the toxic influence of increased ROS on outer hair cells. Increased production of ROS caused by effects of hyperglycaemia may indeed occur in DM (Creager et al., 2003; Paneni et al., 2013), and may cause oxidative stress and consequent cell death (Yang et al., 2015). Therefore, this hypothesis provides a reasonable explanation for damage to basal outer hair cells in DM before apical outer hair cells.

Multiple studies in this review reported reduced DPOAE and TEOAE amplitudes in DM subjects with normal hearing (Di Nardo et al., 1998; Erdem et al., 2003; Lasagni et al., 2015; Lisowska et al., 2001b; Ottaviani et al., 2002; Sasso et al., 1999). This indicated subclinical outer hair cell damage. Subjects had no reported risk factors for hearing loss or damage to outer hair cells, such as ototoxicity and noise exposure. They were also below the age of 60 years, which excluded any possible effect of

presbycusis. A cause of early outer hair cell damage may be early effects of the metabolic disturbances caused by hyperglycaemia, since microvascular complications may only occur at a later stage of DM (Lisowska et al., 2001a).

Notably, one study reported significantly larger rather than reduced amplitudes in DM subjects compared to control subjects (Hou et al., 2015). They defined abnormal DPOAES as occurring at <5 dB SPL or >20 dB SPL. Larger rather than reduced amplitudes were also reported in tinnitus subjects with no hearing loss but hyperacusis (Sztuka, Pospiech, Gawron, & Dudek, 2010). Sztuka et al (2010) suggested that higher DPOAE amplitudes may be caused by increased motility of the cochlear outer hair cells induced by decreased efferent fibre activity.

Hou et al. (2015) reported no significant differences between DM and control groups and average amplitudes were within normal or near normal ranges. However, they did report some abnormal amplitudes in 22% of patients, with hearing impairment defined by TEOAE in mid and low frequencies, and 18% of patients in their study presented with no TEOAE. Hou et al. (2015) reported 48% of DM subjects with a hearing impairment. It was not specified which of these subjects also presented with abnormal TEOAEs. However, abnormal TEOAEs are to be expected in subjects with hearing loss. Click stimuli used in measuring TEOAEs activate the whole cochlea. However, TEOAEs are typically only evoked between 1-4 kHz (Kemp, 2002). Therefore, early damage in high or ultra-high frequency regions of the cochlea alone may not immediately result in abnormal TEOAEs (Di Nardo et al., 1998). Conversely, DPOAEs are able to determine single frequencies over a broad frequency range and identify hearing loss in the mid and high frequencies more accurately than in the low frequencies (Gorga et al., 1997; Kemp, 2002). This may result in more accurate detection of earlier cochlear dysfunction. The mean duration of DM in the study by Hou et al. (2015) was 5.8 years. Therefore, the subjects were in the early stages of DM and any damage that may already have occurred to the cochlear outer hair cells may not have progressed further than the high frequencies.

Reasons other than metabolic disturbances have been provided for impaired function of outer hair cells in patients with DM. These reasons also stem from the detrimental effects of hyperglycaemia in these patients causing microvascular complications. Microangiopathy of the vessels in the basilar membrane and stria

vascularis, atrophy of vessels of stria vascularis, and damage to the outer hair cells of the basal turn of the cochlea in T1DM and T2DM subjects has previously been reported (Fukushima et al., 2005, 2006). They also identified complete loss of the stria vascularis in the middle and apical turn in some subjects. Additionally, Fukushima and colleagues (2005) reported a correlation between thickening of the vessels in the basilar membrane and loss of outer hair cells in T1DM subjects. However, they did not find this correlation in T2DM subjects (Fukushima et al., 2006). The basilar membrane and stria vascularis both play a role in vibration and contraction of outer hair cells. Due to its large supply of blood vessels, the stria vascularis may be particularly susceptible to microangiopathy and subsequent ischemia (Mom, Chazal, Gabrillargues, Gilain, & Avan, 2005). This may result in damage and impairment of function. In turn, this may be detrimental to the transduction of sound waves and contraction of outer hair cells causing reduced amplitudes of OAEs (Mom et al., 2005). As previously mentioned, outer hair cells located on the basal turn may be affected first (Bhardwaj et al., 2016; Yang et al., 2015), resulting in impairment of high frequencies and subsequent low amplitudes of OAEs as seen in articles included in this review. Despite evidence of microvascular complications causing damage to the cochlea, other studies have found no correlation between OAEs and microvascular complications (Díaz de León-Morales et al., 2005; Lisowska et al., 2001a). Microvascular complications tend to occur in the later stages of DM. Therefore, it may be concluded that initial damage to the cochlea may occur due to metabolic disturbances caused by hyperglycaemia. As the disease progresses, microvascular complications may develop and cause additional damage to the cochlea.

2. Auditory brainstem responses

Some reviewed studies reported significant delays in waves I, III and V simultaneously (Durmus et al., 2004; Lisowska et al., 2001b; Sasso et al., 1999), along with IPL I-V (Lisowska et al., 2001b; Sasso et al., 1999) and both IPL III-V and IPL I-V by Durmus et al. (2004). A delay in wave I may indicate a conductive component. However, all three studies used stringent selection criteria to exclude subjects with abnormal tympanometry, conductive loss, ear pathology identified after

an examination by an ear, nose and throat specialist, and anyone with a history of middle ear pathology. Subjects in all three studies presented with normal hearing. Durmus et al. (2004), Lisowska et al. (2001b), and Sasso et al. (2004) concluded that their results indicated a peripheral and central impairment. Meanwhile, other studies reported no delays of wave I but delays of wave III, V and IPL I-V (Hou et al., 2015). In addition to delayed wave III, V, and IPL I-V, R. Gupta et al. (2010) reported further delays of IPL III-V while S. Gupta et al. (2013) also reported delays of IPL I-III and IPL III-V at certain intensities. Hou et al. reported a hearing loss in 48% of DM subjects. However, R. Gupta et al (2010) and S. Gupta et al. (2013) did not report on the hearing status of their subjects. They did exclude subjects with a history or family history of hearing loss. Results of these three studies indicate a delay in conduction time of the auditory pathway at the level of brainstem and midbrain which may be caused by neurodegeneration (R. Gupta et al., 2010; S. Gupta et al., 2013; Hou et al., 2015). Finally, delays of wave V, IPL III-V and IPL I-V were reported in some studies (Baweja et al., 2013; Díaz de León-Morales et al., 2005) while only delays of wave V and IPL I-V were reported by Dabrowski et al. (2011) and Ren et al. (2009). This indicated primarily central auditory pathway impairment. Baweja et al. (2013) did not report on the hearing status of their subjects and Dabrowski et al. (2011) reported normal hearing in 84% of subjects with only a mild hearing loss in the other 16%. Finally, normal sloping to mild hearing loss, and hearing loss in the high frequencies was reported by Díaz de León-Morales et al. (2005) and Ren et al. (2009) respectively. Therefore, it appears that both peripheral and central auditory pathways may be affected by DM.

Only one study reported normal neural transmission, which was evident by the significant delay of all absolute wave latencies and only small but not significant delays in IPLs (Ottaviani et al., 2002). It may be argued that these results indicate a conductive component. However, in the study by Ottaviani et al. (2002), subjects with any ear pathology were excluded. Subjects presented with normal hearing and reduced OAEs in the study by Ottaviani et al. (2002). Nonetheless, they found a significant correlation between the presence of a general diabetic peripheral neuropathy in DM subjects and delays of wave V and IPL III-V. A possible diffuse peripheral neuropathy affecting the auditory pathway at a subclinical level was provided as an explanation for these findings (Ottaviani et al., 2002).

Delays in c-ABR waves even occurred in subjects with normal hearing (Baweja et al., 2013; Dąbrowski et al., 2011; Durmus et al., 2004; S. Gupta et al., 2013; Lisowska et al., 2001b; Ottaviani et al., 2002). Additionally, reduced OAE amplitudes were also reported in some of these studies (Dąbrowski et al., 2011; Lisowska et al., 2001b; Ottaviani et al., 2002). These findings indicated that DM subjects may present with subclinical impairments of the peripheral and central auditory pathway which may have been overlooked if only pure tone audiometry was assessed.

Interestingly, delays of wave V were reported in subjects with a short duration of DM (less than 10 years) across various studies (Baweja et al., 2013; Dąbrowski et al., 2011; Díaz de León-Morales et al., 2005; Ren et al., 2009). In fact, Dąbrowski et al. (2011) reported longer latencies of wave V, IPL I-III and IPL I-V in subjects with shorter duration of T1DM compared to T1DM subjects with longer duration of DM. Akinpelu et al. (2014) found significant delays of ABR latencies across studies in their review, and highlighted delays of wave V particularly. Similar to the current study, Akinpelu et al. (2014) also reported duration of DM less than 10 years in the majority of T2DM subjects with wave V delays. Akinpelu et al. (2014) suggested that delayed latencies in subjects with shorter duration of DM may indicate early onset of DM-related complications in the central auditory pathway. While a short duration of DM was evident in many of the studies reporting delays of waves I, III and V, three studies in the current review found these delays in subjects with a longer duration of DM. R. Gupta et al. (2010) reported a delay in c-ABR waves in 11 of 12 T2DM subjects that had a duration of DM longer than 10 years. Delays in subjects with longer duration of DM were also reported by Lisowska et al. (2001b) and Ottaviani et al. (2002).

Through analysis of the mean c-ABR latencies across studies (Table 5), it was observed that prolongation of mean latencies of DM subjects compared to control subjects seemed largest for waves V and IPL I-V, followed by waves III and IPL I-III. IPLs III-V only displayed minor delays when comparing latencies of DM subjects and control subjects, while the results of mean latencies of wave I were similar between groups. Findings of this analysis indicate delayed auditory neural transmission and a dysfunction of both the peripheral and central auditory pathway. Similar findings have been reported in a recent review and analysis of data available on hearing

function in T1DM subjects, specifically data of pure tone audiometry and ABR (Teng et al., 2016).

Peripheral and central neuropathy in the auditory pathway may stem from the detrimental effects of insulin and hyperglycaemia on the nervous system, which includes damage caused by microvascular complications. Microangiopathy has been implicated in causing auditory nerve damage (Lasagni et al., 2015). R. Gupta et al. (2010) and Ottaviani et al. (2002) found a correlation between impairment in the auditory nerve pathway and diabetic peripheral neuropathy. However, not all studies have found this correlation. Lisowska et al. (2001b) as well as Díaz de León-Morales et al. (2005) found no significant correlations between microvascular complications, such as diabetic peripheral neuropathy and retinopathy, and prolongation of c-ABR latencies. Additionally, a negative correlation between diabetic peripheral neuropathy and cognitive dysfunction and brain abnormalities was found by Manschot et al. (2008). These findings were based on a standardized neurological examination, neuropsychological examination and brain MRI. Manschot et al. (2008) suggested that central and peripheral neurological complications in DM may occur due to different aetiologies. In the current study, the small number of studies with T1DM and T2DM did not allow for concrete and reliable comparisons to be made between the two. However, no significant differences were noted between results of T1DM and T2DM studies that were included.

An alternative theory to explain delayed latencies and the lack of correlation with microvascular complications involves neurodegenerative changes occurring in the central nervous system (Baweja et al., 2013; S. Gupta et al., 2013; Lisowska et al., 2001b). In the past, histopathological studies have also identified demyelination of cranial nerves in DM subjects (Reske-Nielsen, Lundbæk, & Rafaelsen, 1965). This may explain the reduced neural transmission (Rance et al., 2014), evident by the delays in IPLs reported in multiple studies included in this review and identified in the analysis. Finally, DM may also cause metabolic disturbances in brain glucose metabolism, as well as oxidative stress in the central nervous system (Duarte, Moreira, & Oliveira, 2012). This may cause a delay in central conduction time (Baweja et al., 2013).

3. Strengths and limitations

Strengths of this study included the adherence to an age criteria for subjects in included studies and only the inclusion of studies in which subjects did not have prior risk factors for hearing loss. This eliminated alternative causes of hearing loss including presbycusis, noise-induced hearing loss, ototoxicity and middle ear pathology, and ensured reliable and valid reporting. Additionally, the inclusion of both OAE and c-ABR provided a more comprehensive overview of the function of the auditory pathway. There are some limitations to this study that may be seen as contributors to bias. Only studies published in English were included which may have resulted in a number of additional studies with valuable results being excluded due to a difference in language. Additionally, it was not possible to conduct a meta-analysis of cochlear function as OAE parameters were reported using different frequencies and units across those studies. This resulted in difficulties in obtaining mean averages of amplitudes and analysing the OAE data. Finally, heterogeneity among results may exist due to differences between studies including differences in clinical characteristics of the study populations and number of subjects in control and DM groups.

4. Clinical implications

This study may provide audiologists and health care providers with more clarity regarding the outer hair cell and auditory nerve pathway function of these patients. Outer hair cells as well as the auditory nerve pathway may be impaired despite displaying normal hearing, or only a mild hearing loss. Therefore, the hearing of these patients should be assessed and monitored using both pure tone audiometry and objective measurements such as OAEs and c-ABRs. Additionally, this study may contribute to providing a rationale for the systematic monitoring of patients with DM. This may result in earlier detection and intervention of hearing loss in these patients.

5. Recommendations for further research

Further research on OAEs and peripheral, and especially central auditory pathway impairment in DM subjects is recommended. Damage to outer hair cells reported in included studies occurred in a similar pattern as in subjects with ototoxicity. Therefore, it may be of interest to determine the value of extended high frequency audiometry and OAEs for monitoring purposes in DM, since these measures are also used in ototoxicity monitoring (American Academy of Audiology, 2009). Furthermore, it may be of value to include middle and late latency auditory evoked potentials in further research studies to obtain more information about the functioning of the central auditory pathway. Studies including larger sample sizes are recommended, as well as longitudinal studies. These may allow for more clinically relevant findings and more investigation into relationships between hearing loss and various characteristics of DM subjects. The relationship between the duration of DM and delayed ABR latencies should also be investigated further. Finally, it may be of interest to further investigate possible detrimental effects of insulin on the auditory system by comparing results of a T1DM subjects with results of T2DM using large sample sizes to allow accurate and reliable comparisons to be made.

6. Conclusions

It can be concluded that T1DM and T2DM subjects may present with clinical or subclinical impairment of the cochlear outer hair cells and both the peripheral and central auditory pathway. This is evidenced by reduced OAE amplitudes and delayed c-ABR responses in DM subjects with hearing loss or, more notably, in subjects with normal hearing. Damage to outer hair cells may occur more often in the high frequencies, progressing to mid and low frequencies. Evidence of damage to peripheral or central auditory pathways occurs not only in DM subjects with a longer duration of DM, but also in those with shorter duration of DM. This provides a rationale for monitoring of cochlear and auditory neural pathway function of DM subjects from time of diagnosis.

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Appendices

Appendix A: Ethical clearance

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

26 August 2016

Dear Prof Vinck

Project:	**Function of the peripheral auditory system in adults with diabetes mellitus type 1 and type 2: A systematic review and meta-analysis**
Researcher:	**N Köstlin**
Supervisor:	**Dr B Heinze**
Department:	**Speech-Language Pathology and Audiology**
Reference number:	**12104800(GW20160818HS)**

Thank you for the application that was submitted for ethical consideration.

I am pleased to inform you that the above application was **approved** by the **Research Ethics Committee** on 25 August 2016. Data collection may therefore commence.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. Should the actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

The Committee requests you to convey this approval to the researcher.

We wish you success with the project.

Sincerely

pp.

Prof Maxi Schoeman
Deputy Dean: Postgraduate Studies and Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail:tracey.andrew@up.ac.za
Kindly note that your original signed approval certificate will be sent to your supervisor via the Head of Department. Please liaise with your supervisor.

Research Ethics Committee Members: **Prof MME Schoeman (Deputy Dean)**; Prof KL Harris; Dr L Blokland; Dr R Fasselt; Ms KT Govinder; Dr E Johnson; Dr C Panebianco; Dr C Puttergil; Dr D Reyburn; Prof GM Spies; Prof E Taljard; Ms B Tsebe; Dr E van der Klashorst; Mr V Sithole

Appendix B: The Cochrane Collaboration's tool for assessing risk of bias

(Higgins & Green, 2011)

The Cochrane Collaboration's tool for assessing risk of bias

Reviewer's Initials: _____ Study ID: _____ Date (dd/mm/yy): _____

Domain	Description	Risk of Bias	Consensus (circle)
Random sequence generation		Was the allocation sequence adequately generated? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Allocation concealment		Was allocation adequately concealed? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Blinding of participants and personnel	*Subjective outcomes*	Was knowledge of the allocated intervention adequately prevented during the study? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes		
Blinding of outcome assessment	*Subjective outcomes*	Was knowledge of the allocated intervention adequately prevented during the study? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes		
Incomplete outcome data	*Subjective outcomes*	Were incomplete outcome data adequately addressed? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes		
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Other sources of bias		Was the study apparently free of other problems that could put it at a high risk of bias? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Overall risk of bias	*Subjective outcomes*	LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes	LOW / HIGH / UNCLEAR	

Appendix C: Plagiarism declaration

UNIVERSITY OF PRETORIA

FACULTY OF HUMANITIES

RESEARCH PROPOSAL & ETHICS COMMITTEE

DECLARATION

Full name : Nicole Köstlin_____

Student Number : 12104800_____

Degree/Qualification: MA (Audiology)_____

Title of thesis/dissertation/mini-dissertation: Function of the peripheral auditory system in adults with diabetes mellitus type 1 and type 2: A systematic review and meta-analysis_____

I declare that this thesis / dissertation / mini-dissertation is my own original work. Where secondary material is used, this has been carefully acknowledged and referenced in accordance with university requirements.

I understand what plagiarism is and am aware of university policy and implications in this regard.

_____ _____

SIGNATURE **DATE**

Appendix D: Critical review form for quantitative studies

(Law et al., 1998)

Critical Review Form

Quantitative Studies

REFERENCE:

STUDY PURPOSE:	Outline the purpose of the study (i.e., study objective or aim):
Was the purpose stated clearly? ___Yes ___No	
LITERATURE:	Describe the justification of the need for this study (3-4 key points)
Was relevant background literature reviewed? ___Yes ___ No	⇒
DESIGN:	Describe the study design:
____randomized ____cohort (population - based) ____ before and after ____ case-control ____cross-sectional (1+ group at 1 point in time) ____single case design ____case study	Can the author answer the study question with the study design? Were the design and/or method used introducing biases. If so describe:

SAMPLE SIZE: Sample Description (e.g., age, gender, diagnosis, other characteristics)

N =

Was sample size justified?

____Yes How was sample identified? Was it a representative sample?

____No

____N/A

If there were more than one group, was there similarity and differences between the groups? Describe:

Was Power Discussed?

____Yes

____No

____N/A Was informed consent and assent obtained?

OUTCOMES:

Specify the frequency of outcome measurement (i.e., pre, post, follow-up):

Outcome areas	List measures used	Reliable and Valid?
(e.g., self care, productivity)	(e.g., Sensory Profile, VMI)	
⇒	⇒	⇒

INTERVENTION: Provide a short description of the intervention including type of intervention, who delivered it, how often and in what setting.

Intervention was described in detail?

____Yes

____No

____Not addressed

Contamination was

avoided?

___Yes

___No

___Not addressed

RESULTS: What were the results?

Results were reported in terms of statistical significance?

___Yes

___No

___NA

___Not addressed

Outcomes	Results	Statistical Significance
⇒	⇒	⇒

Was the analysis, that is the type of statistically tests used, appropriate for the type of outcome measures and the methodology?

___Yes

___No

___Not addressed

Explain:

If not statistically significant (i.e., $p < 0.05$ or 0.01), was study big enough to show an important difference if it should occur (power and sample size)?

Clinical importance was reported?

____Yes

___No

___Not addressed

What is the clinical importance of the results (that is even if the results were statistically significant were the differences large enough to be clinically meaningful?

Drop-outs were reported?

If yes, why did they drop out? How were drop-out participants included in the statistical analysis?

___Yes

___No

CONCLUSIONS AND CLINICAL IMPLICATIONS:	What did the author concluded?
The conclusions made by the authors were appropriate given study methods and results.	What were the main limitations of the study as stated by the author(s) and from your point of view?
___Yes	What are the implications of these results for your practice?
___No	

Potvin 2007 modified from Law, Stewart, Pollock, Letts, Bosch, & Westmorland, 1998

Appendix E: Tables of data for systematic review

Table of clinical characteristics of subjects in included studies

Table of clinical characteristics of subjects in included studies

				Clinical Characteristics							
Year	**Author**	**Title**	**Participant group**	**Group size (n=)**	**Male (n=)**	**Female (n=)**	**Mean age ±SD (years)**	**Mean duration of DM (years)**	**HbA1c**	**Complications**	**Hearing status**
1998	Di Nardo, Ghirland, Paludetti, Cercone, Saponara, Del Ninno, Di Girolamo, Magnani, & Di Leo	Distortion-Product otoacoustic emissions and selective sensorineural loss in IDDM	T1DM (with diabetic peripheral neuropathy)	32	15	17	33.8 ± 5.4	15.2 ± 8.4	8 ± 2.2	neuropathy	normal hearing at all frequencies
			T1DM (without diabetic peripheral neuropathy)	15	8	7	33.9 ± 5.9	15.4 ± 5.2	7.3 ± 1.1		
			Healthy control	44	22	22	31.6 ± 4.6	n/a			
1999	Sasso, Salvatore, Tranchino, Cozzolino, Caruso, Persico, Gentile, Torella, & Torella	Cochlear dysfunction in type 2 diabetes: A complication independent of neuropathy and acute hyperglycaemia	T2DM	110	56	54	48.4 ± 5.7	8.1 ± 4.1	6.7 ± 0.3%		normal hearing or some with slight hypoacusis (<30 dB)
			Healthy control	106	53	53	47.9 ± 6.9	n/a	4.4 ± 0.3%		
2001	Lisowska, Namyslowski, Morawski, & Strojek	Early identification of hearing impairment in patients with type 1 diabetes mellitus	Group A: T1DM without microangiopathy	17			28.2 ± 6.7	9.6	8.6%		normal hearing
			Group B: T1DM with microangiopathy	25			36.2 ± 7.9	18.5	9.2%	microangiopathy	
			Healthy control	33			31.7	n/a			

									Clinical Characteristics		
Year	**Author**	**Title**	**Participant group**	**Group size (n=)**	**Male (n=)**	**Female (n=)**	**Mean age ±SD (years)**	**Mean duration of DM (years)**	**HbA1c**	**Complications**	**Hearing status**
2002	Ottaviani, Dozio, Neglia, Riccio, & Scavini	Absence of otoacoustic emissions in insulin-dependent diabetic patients: Is there evidence for diabetic cochleopathy?	T1DM	60	35	25	31.0 ± 6.23	17.5 ± 8.9	8.1 ± 1.8% 21 subjects with HbA1c ≤ 7.2%	retinopathy (n=26), microalbuminuria (n=9), clinical peripheral neuropathy (n=17)	normal hearing at all frequencies
			Healthy control	58	29	29	29.1 ± 5.75	n/a			
2003	Erdem, Ozturan, Miman, Ozturk, & Karatas	Exploration of the early auditory effects of hyperlipoproteinemia and diabetes mellitus using otoacoustic emissions	T2DM	21	10	11	48.6		(reported fasting blood glucose)		normal hearing (< 30 dB HL)
			Healthy control	22	11	11	46.7	n/a			
2004	Durmus, Yetiser, & Durmus	Auditory brainstem evoked responses in insulin-dependent (ID) and non-insulin-dependent (NID) diabetic subjects with normal hearing	T1DM	17	13	4	24.3	6.44	(only reported blood glucose)	neuropathy (n=3)	normal hearing (< 20 dB HL)
			T2DM	26	13	13	57.5			neuropathy (n= 13)	
			Healthy control A	17	11	6	22.6	n/a			
			Healthy control B	20	14	6	51.2	n/a			
2005	Diaz de León-Morales, Jáuregui-Renaud, Garay-Sevilla, Hernández-Prado & Malacara-Hernández	Auditory impairment in patients with type 2 diabetes mellitus	T2DM	94	17	77	50 ± 6	7.2 ± 5.4	10.76 ± 2.64% 62% of subjects had HbA1c > 8 %	diabetic retinopathy (n= 14) ; diabetic peripheral neuropathy (n= 67); microalbuminuria (n= 12)	Normal, sloping to mild loss at 8000 Hz.
			Healthy control	94	17	77	50 ± 6	n/a			

									Clinical Characteristics		
Year	**Author**	**Title**	**Participant group**	**Group size (n=)**	**Male (n=)**	**Female (n=)**	**Mean age ±SD (years)**	**Mean duration of DM (years)**	**HbA1c**	**Complications**	**Hearing status**
2009	Ren, Zhao, Chen, Xu, Brown, & Xiao	Hearing loss in middle-aged subjects with type 2 diabetes mellitus	T2DM	50	32	18	40.8 ± 6.3	7	8.9 ± 2.1% 61% of subjects had GHbA1c > 8%		Deficit (>25 dB) in high frequencies (4000 Hz and 8000 Hz)
			Healthy control	50	30	20	41.0 ± 5.7	n/a			
2010	Gupta, Aslam, Hasan, & Siddiqi	Type -2 diabetes mellitus and auditory brainstem responses- a hospital based study	T2DM	25	13	12	46.8	>5		Diabetic peripheral neuropathy (n=13), retinopathy (n=2), nephropathy (n=1)	N/a
			Healthy control	25	17	8	45.7	n/a			
2011	Dąbrowski, Mielnik-Niedzielska, & Nowakowski	Involvement of the auditory organ in type 1 diabetes mellitus	T1DM	31	23	8	29.1 ± 7.1	<10	29% of subjects with HbA1c < 7%	retinopathy (n=3)	Normal hearing at all frequencies (n= 25); mild HL (>20 dB HL); (n= 5) moderate HL (>40 dB HL) (n= 1). Thresholds significantly higher at 3 -6 kHz (p<.005) and 8-12 kHz (p<.05) compared to controls.
			Healthy control	26	7	19	30.3 ± 7.8	n/a			

									Clinical Characteristics		
Year	**Author**	**Title**	**Participant group**	**Group size (n=)**	**Male (n=)**	**Female (n=)**	**Mean age ±SD (years)**	**Mean duration of DM (years)**	**HbA1c**	**Complications**	**Hearing status**
2013	Baweja, Gupta, Mittal, Kumar, Singh & Sharma	Changes in brainstem auditory evoked potentials among north indian females with type 2 diabetes mellitus	T2DM	116		116	44.6 ± 5.83	5.38 ± 6.14	Reported significant difference between fasting blood glucose levels of both groups.		n/a
			Healthy control	100		100	47.8 ± 6.11	n/a			
2013	Gupta, Baweja, Mittal, Kumar, Singh, & Sharma	Brainstem auditory evoked potentials abnormalities in type 2 diabetes mellitus	T2DM	126	126		45.7 ± 6.63	5.68 ± 3.16	Reported significant difference between fasting blood glucose levels of both groups.		n/a
			Healthy control	106	106		46.8 ± 6.11	n/a			
2014	Karabulut, Karabulut, Dağli, Bayazit, Bilen, Aydin, Güler, & Bayramoğlu	Evaluation of outer hair cell function and medial olivocochlear efferent system in patients with type II diabetes mellitus	T2DM	50	16	34	49.8 ± 5.1	8.1 ± 5.8	8.1 ± 2.27 Within normal range in only 6% of DM subjects.		Sensorineural HL (>15 dB HL) at all frequencies.
			Healthy control	51	18	33	47.9 ± 4.8	n/a			

									Clinical Characteristics		
Year	**Author**	**Title**	**Participant group**	**Group size (n=)**	**Male (n=)**	**Female (n=)**	**Mean age ±SD (years)**	**Mean duration of DM (years)**	**HbA1c**	**Complications**	**Hearing status**
2015	Hou, Xiao, Ren, Wang & Zhao	Auditory impairment in young type 1 diabetics	T1DM	50	26	24	25.7 ± 9.9	5.8 ± 4.5	9.78 ± 2.8 66% of subject had GHbA1c > 7.5% considered uncontrolled.	neuropathy (6%); retinopathy (6%); nephropathy (18%)	Deficit with elevated thresholds at .25, 1, 2, 4, & 8 kHz in RE, and at .25, .5, 1, 4, and 8 kHz in LE ; 48% with hearing impairment (> 25 dB) in some frequencies
			Healthy control	50	26	24	24.7 ± 6.1	n/a	5.00 ± 0.3		
2015	Lasagni, Giorano, Lacilla, Raviolo, Trento, Camussi, Grassi, Charrier, Cavallo, Albera, Porta & Zanone	Cochlear, auditory brainstem responses in type 1 diabetes: relationship with metabolic variables and diabetic complications	T1DM	31	17	14	33.2 ± 2.3	25.7 ± 4.2		Hypertension (n=7); Retinopathy (n=26); Microalbuminuria (n=4)	Normal hearing (<25 dB HL) at all frequencies (but significantly higher thresholds than control) (R: 14.3 ± 4.6 vs. 9.9 ± 2.5 dB, L: 13.0 ± 3vs. 9.9 ± 2.6 dB)
			Healthy control	10			32 ± 1	n/a			

Table of recording parameters of included studies

Table of recording parameters of included studies				
		Recording parameters		
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**
1998	Di Nardo, Ghirland, Paludetti, Cercone, Saponara, Del Ninno, Di Girolamo, Magnani, & Di Leo	ILO92 Otoacoustic Distortion Product Analyser (Otodynamics); Equilevel primaries used, presented at 70 dB SPL; f2/f1 ratio: 1.21-1.23; S/N ratio > 6 dB for 95% of ears; 1/4-octave intervals	Otodynamic Analyzer (ILO88); Nonlinear difference method used; stimulus level: 80 dB SPL (± 5 dB); click rate: 50/sec; time analysis: 20 ms; 260 clicks, twice for each ear; Band-pass filter: 976-4882 Hz	
1999	Sasso, Salvatore, Tranchino, Cozzolino, Caruso, Persico, Gentile, Torella, & Torella		Otodynamic Analyzer (ILO 88; Amplaid, Milan, Italy); stimulus unfiltered 80-µ click; 80 dB SPL; 260 clicks	Amplaid MK 15 evoked-response system; clicks; alternating polarity; intensity: 110 dB nHL; rate: 21/s; 2000 clicks; earlobe electrode and vertex surface electrode.
2001	Lisowska, Namyslowski, Morawski, & Strojek	ILO 92 analyser (Otodynamics); L1=L2, f2/f1= 1.22; increase in 5 dB steps from 35 to 70 dB SPL; criterion level: I/O response two SD above mean value of noise floor.		EP-Test system; 2000 clicks; intensity: 80 dB nHL; rate: 31/s; alternating polarity; duration: 0.1 ms; filters: 200 to 2000 Hz.
2002	Ottaviani, Dozio, Neglia, Riccio, & Scavini	ILO 92 system (v 4.2 V, Otodynamics); intensity: 70 dB; automatically determined ratio between f1 and f2 (1.22)	ILO 92 system (v 4.2 V, Otodynamics); Intensity: between 75 and 90 dB SPL; two sets of 256 responses to clicks averaged; Analysis time: 20.5 ms; band-pass filters: between 600 and 6000 Hz	MK 15 Amplaid Amplifon System; clicks; intensity: 100 dB SPL; alternating polarity; duration: 0.1-ms; averaging: 2000 stimuli; filters: 50-3000 Hz; scalp electrodes used.

		Recording parameters		
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**
2003	Erdem, Ozturan, Miman, Ozturk, & Karatas	ILO-96 cochlear emission analyzer (Otodynamics, London); f2/f1= 1.22; f1= 65 dB; f2= 55 dB;	Clicks; 80 µs duration; stimulus level: 80±3 dB per SPL; click rate: 50/sec; post-stimulus analysis: 2 to 20 ms; 260 sweeps; noise rejection level: 47 dB; Response if amplitude ≥3 dB above noise floor; Reproducibility ≥ 60 percent	
2004	Durmus, Yetiser, & Durmus			Biomedical, Neurodiagnostic systems; Nicolet ET-200 amplifier; 100-µs-duration alternating clicks presented monaurally; intensity: 80 dB nHL; rate: 20/s; masking noise: 40 dB nHL; impedances: ≤ 5kΩ; band-pass filters: 15-3000 Hz; analysis time: 12 ms; averaging: 1500; electrode montage: active electrode- mastoid
2005	Diaz de León-Morales, Jáuregui-Renaud, Garay-Sevilla, Hernández-Prado & Malacara-Hernández			Audix version 2, Neuronic; Clicks; Intensity: 80 dB; rate: 11.7 and 67.4 click/sec.; 1mV sensitivity; 1 mV gain; filters: 1-3 kHz; averaging: 2000 stimuli; electrode montage: mastoids & high forehead
2009	Ren, Zhao, Chen, Xu, Brown, & Xiao	L1= 65 dB SPL; L2= 55 dB SPL; f2/f1= 1.22	click; 80 dB SPL	EP25 system (Audiometrics); clicks; intensity:130 dB SL; rate: 11.0 and 80.1 clicks/sec; 1 mV sensitivity; 10 mV gain; 0.5-4 kHz filters; 2000 stimuli; disk electrodes on mastoid & high forehead

		Recording parameters		
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**
2010	Gupta, Aslam, Hasan, & Siddiqi			IHS-BERA; Intensities: 70 dB, 80 dB, 90 dB
2011	Dąbrowski, Mielnik-Niedzielska, & Nowakowski		Sout Sport 580-OAE SP6 Analyser (Bio-logic Systems Corp.); 'non-linear' click stimulus; 80 µs duration; repetition rate: 50 Hz; intensity: 80 dB. Lack of OAE: < 6 dB at 1.2-3.5 kHz	Centor-C analyser; click; intensity: 70 dB nHL; contralateral ear masking: 30 nHL duration: 100 µs; repetition rate: 19.1 Hz; electrode montage: forehead (positive); ipsilateral mastoid (negative), chin (ground).
2013	Baweja, Gupta, Mittal, Kumar, Singh & Sharma			RMS EMG EP Marc-11 Channel machine; broad-band clicks; intensity: 60 dB SL; rate: 11.1 Hz, masking in contralateral ear; averaging: 2000 stimuli; filters: 100 and 3000 Hz; impedance: below 5 kΩ; electrode montage: M1 and M2, Fz, Cz
2013	Gupta, Baweja, Mittal, Kumar, Singh, & Sharma			RMS EMG EP-11 Channel; broad-band clicks; intensity: 60 dB SL; rate: 11.1 Hz, masking in contralateral ear; averaging: 2000 stimuli; filters: 100 and 3000 Hz; impedance: below 5 kΩ; electrode montage: M1 and M2, Cz, Fz
2014	Karabulut, Karabulut, Dağli, Bayazit, Bilen, Aydin, Güler, & Bayramoğlu	ILO 292 USB OAE analyser, version 6; f1= 65 dB, f2= 55 dB, 2f2/f1= 1.22; 500 sweeps or 100 s; noise rejection level: 49.5 dB SPL; point/octave, 2	(contralateral suppression of TEOAEs)	

Recording parameters

Year	Author	DPOAE	TEOAE	ABR
2015	Hou, Xiao, Ren, Wang & Zhao	Masen Capellia system (GN Otometrics); L1= 65 dB SPL, L2= 55 dB SPL; f2/f1= 1.22; Abnormal OAE if: > 20 dB SPL or ≤ 5 dB SPL	Masen Capellia system (GN Otometrics); 80 dB SPL; 'non-linear' click	Ep25 system (Audiometrics); intensity: 130 dB SPL; rate: 11.0, 80.1 clicks/sec; repetitions 2000; filters: 0.5-4 kHz; electrode montage: mastoids, high forehead Abnormal ABR defined as difference of latencies > 0.4 ms at same wave between the left and right side or the latencies more than mean +standard deviation of healthy group.
2015	Lasagni, Giorano, Lacilla, Raviolo, Trento, Camussi, Grassi, Charrier, Cavallo, Albera, Porta & Zanone	92 ILO Otodynamic Analyser; f1= 70 dB, f2= 60 dB; f2/f1= 1.22; present if: >3 dB greater than background noise		MK 22 PLUS OTO 2011; clicks; alternating polarity; frequency: 11 stimulations/s; duration: 100 µs; analysis time: 12 ms; Fz, love or preauricular mastoid space

Response parameters and conclusions of included studies

Response parameters and conclusions of included studies							
		Response parameters (Results of studies)					
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
1998	Di Nardo, Ghirland, Paludetti, Cercone, Saponara, Del Ninno, Di Girolamo, Magnani, & Di Leo	DM with neuropathy compared to control subjects: Significantly reduced amplitudes at 1.306-5.2 kHz (p<.05). DM subjects without neuropathy compared to control subjects: Amplitude for higher frequencies (3.284-5.2 kHz) was significantly lower (p< .01). Considering individual absolute values, DPOAEs were reduced below 2 SDs of control mean values in 32% of all DM patients, for all frequencies.	Mean TEOAE amplitudes significantly reduced in diabetic group (ANOVA: F - 3.5; P = 0.03) with neuropathy (7.6 ± 3.2 dB; Scheffe's test: P = 0.03), but not in DM without neuropathy (9.5 ± 4.3 dB) with respect to mean TEOAE amplitude of control subjects (11 ± 3.1). No significant difference between DM groups. Mean TEOAE of DM patients with neuropathy was more reduced than mean TEOAE of DM patients without neuropathy. Considering individual absolute values, TEOAEs were reduced below 2 SDs of control mean values in 15% of all DM patients, for all frequencies.		No significant correlations between EOAEs and duration of disease or HbA1c	T1DM patients show early abnormalities of micromechanical properties of OHCs. In T1FM patients without subclinical diabetic peripheral neuropathy: damage is limited to higher frequencies, detected only by DPOAEs. In T1DM patients with diabetic neuropathy: damage also involves middle frequencies, detected by TEOAEs & DPOAEs. DPOAEs seem of greater clinical interest than TEOAEs. DPOAEs seem to be more frequency specific and can be recorded at any chosen frequency, incl. high frequencies.	III

Response parameters (Results of studies)

Year	Author	DPOAE	TEOAE	ABR	Correlations with clinical characteristics	Conclusions	Level of Evidence
1999	Sasso, Salvatore, Tranchino, Cozzolino, Caruso, Persico, Gentile, Torella, & Torella		e-OAEs impaired in 51.8% of DM subjects, compared with 4.7% of control subjects (p<.001).	Significantly longer latency for waves I, III, V & IPL I-V in DM groups (present & absent e-OAEs) vs control group (p<.05). No significant difference in ABRs between DM subjects with present OAEs or DM subjects with absent OAEs.	DM subjects with impaired e-OAEs (absent e-OAEs) were older, longer duration of DM, poorer metabolic control & greater peripheral diabetic neuropathy. Higher mean plasma glucose values in subjects with absent OAEs vs present OAEs, but not statistically significant.	T2DM show higher prevalence of impaired e-OAE than healthy subjects. Cochlear dysfunction was not associated with auditory nervous pathway injury or with diabetic microvasculopathy. The apparent interference of peripheral neuropathy in e-OAEs loses significance when corrected for the duration of DM.	III
2001	Lisowska, Namyslowski, Morawski, & Strojek	Mean DPOAE amplitudes significantly reduced in DM group compared with control subjects. Reduced mean amplitudes in region of middle & high frequencies (f2= 1 kHz to f2= 6 kHz) (p <.05)). Mean DPOAE in DM group with microangiopathy more reduced than mean DPOAE in DM group without microangiopathy, but no significant differences.		Normal ABR morphology in all groups. Latencies for waves I, III, & V (p<.0001) & IPL I-V (p<.001) were significantly longer in DM subjects than control group. No significant differences between two DM groups.	No correlations between microangiopathy & DPOAE amplitude. No correlations between microvascular complications, peripheral transmission time (wave I), & brainstem conduction parameters in DM subjects.	Alterations in cochlear micromechanics & retrocochlear auditory pathway. Hearing impairment in DM subjects is usually mild and subclinical, and can be detected early by accurate and objective audiometric methods.	III

Response parameters (Results of studies)

Year	Author	DPOAE	TEOAE	ABR	Correlations with clinical characteristics	Conclusions	Level of Evidence
2002	Ottaviani, Dozio, Neglia, Riccio, & Scavini	Significantly reduced (p<.05, p<.01 and p<.001) in DM subjects at all studied geometric mean frequencies, except at 4.306 and 5.121 kHz. Most significant differences (p<.001) observed in middle frequencies (geometric mean frequency between .949 and 1.662 kHz).	Mean reproducibility (60.87 ± 22.62% vs. 82.53 ± 11.54%, p< .001) & response intensity (7.1 ± 4.4 vs. 10.9 ± 4.29 dB SPL, p< .001, Mann–Whitney) significantly reduced in DM subjects. TEOAEs absent in DM 28.3% in at least one ear. 5 of these DM subjects had absent TEOAEs in both ears. In 12 of these DM subjects, intensity recorded in contralateral ear was significantly lower than mean TEOAE intensity in the remaining 43 DM subjects (5.53 ± 2.73 vs. 9.18 ± 3.31 dB SPL, p<.001). Present TEOAEs in both ears of 43 DM subjects. Mean response intensity in both ears significantly lower compared to controls (9.18 ± 3.31 vs. 10.95 ± 4.29 dB SPL, p<.05). Statistically significant difference between the two groups observed at mean frequencies of 1-4 kHz (p<.001).	Significantly longer waves I (p<.01), III (p<.001) & V (p<.01) in DM subjects compared to controls. IPL I-V, I-III & III-V did not differ significantly between the two groups.	Correlations found between latencies of wave V & IPL III-V and the presence of diabetic peripheral neuropathy (p<.05)	Cochleopathy detected in a relevant portion of subjects with T1DM in despite normal audiometric hearing threshold.	III

Response parameters (Results of studies)							
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
2003	Erdem, Ozturan, Miman, Ozturk, & Karatas	No statistically significant differences in frequencies found between any groups except at 4 kHz (p>.05). This statistically significant difference (p<.05) caused by the hypertriglyceridemia group (p=.014) & T2DM group (p=.012) compared with control. Mean DPOAE amplitudes of both groups at 4 kHz were lower than those of control group.	No differences in existence of TEOAEs at all frequencies in the groups (p>.05). At 4 kHz, the p value was very close to limit for statistical significance (p=.055).			Decreased DPOAE amplitudes at 4 kHz in hypertriglyceridemia (HLP) & T2DM subjects without clinical findings indicate prospective effects of HLP & DM. These results are compatible with sensorineural hearing loss observed in cases of hyperviscosity and increased noise susceptibility, as shown before in these patients.	III
2004	Durmus, Yetiser, & Durmus			Significantly prolonged absolute latencies of waves I, III & V in DM group compared to control group (p<.05). Difference between latencies of waves III & V in two DM groups was statistically significant. Latency prolongation was more pronounced in T2DM (p<.05). Comparison of both DM groups separately with control groups indicated IPL I-V and III-V prolonged significantly in DM groups (p<.005). IPL I-III, I-V & III-V were longer in patients older than 30 years than in those younger than 30 years, although not significantly (p>.05).	Duration of DM, blood glucose level, & age not associated with prolonged latencies.	Results indicate a more central than peripheral effect of DM on conduction velocity of auditory nerve. Delayed wave V, IPL I-V and IPL III-V intervals indicate diabetic neuropathy at the level of upper brainstem. ABR may detect slowing of nerve conduction before hearing impairment appears. There appears to be no correlation between duration of DM, presence of neuropathy and metabolic control with the presence of neurophysiologic damage. Close follow-up is needed in DM patients with early identified abnormal ABR.	III

		Response parameters (Results of studies)					
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
2005	Diaz de León-Morales, Jáuregui-Renaud, Garay-Sevilla, Hernández-Prado & Malacara-Hernández			Prolongation of wave V latency & IPL I-V & III-V (p<.01) in DM subjects compared to control subjects. Right/left asymmetry of the latency of wave V more frequent in DM subjects than in control subjects (p<.001).	No significant correlations between clinical characteristics of DM (fasting blood glucose levels, HbA1c, diabetic peripheral neuropathy, retinopathy or albuminuria).	Patients with T2DM can have subclinical hearing loss and impaired ABR independent of diabetic peripheral neuropathy, retinopathy or nephropathy.	III
2009	Ren, Zhao, Chen, Xu, Brown, & Xiao	DM subjects showed smaller amplitude responses than controls. Statistically significant reductions at 2.0, 3.0, 4.0 kHz (p<.01). No significant difference between ears.	DM subjects showed smaller TEOAE amplitudes in right ear compared to control subjects (p<.05). No significant difference between right & left ears except at 4.0 kHz (p<.05)	DM subjects showed prolongation of wave V & IPL I-V latencies (p<.01) compared to control subjects. No significant differences in latencies of waves I, III l & IPL I-III, IPL III-V l.		Middle-aged subjects with T2DM have subclinical hearing loss, impaired ABR and impaired OAEs. The peripheral right ear advantage is being lost in middle-aged subjects with T2DM. DM may aid in accelerating this loss.	III

		Response parameters (Results of studies)					
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
2010	Gupta, Aslam, Hasan, & Siddiqi			At 70 dB: Significant differences in latencies of wave III (p=.01) & IPL III-V (p=.045); highly significant difference in latencies of wave V & IPL I-III, I-V between control and study group (p<.001). At 80 dB: Significant differences in IPL III-V (p=.028) between control and study group; highly significant difference in latencies of wave III, V & IPL I-III & I-V (p<.001). At 90 dB: Significant differences in latencies of wave V (p= .002) & IPL III-V (p= .036), highly significant differences in wave III & IPL I-III & IPL I-V between control and study group (p<.001).	52% of DM subjects had duration of DM 5-10 years, of which 53.84% had delayed ABR. 48% DM subjects had DM duration >10 years, of which 91.66% had delayed ABR. 92.3% of subjects with diabetic peripheral neuropathy had delayed ABR.	This study suggests that if BERA is carried out in patients with DM, involvement of central neuronal axis can be detected earlier.	III

Response parameters (Results of studies)

Year	Author	DPOAE	TEOAE	ABR	Correlations with clinical characteristics	Conclusions	Level of Evidence
2011	Dąbrowski, Mielnik-Niedzielska, & Nowakowski		Absent bilaterally in 6 DM subjects, absent unilaterally in 2 DM subjects. Absent bilaterally in 2 control subjects and absent unilaterally in 1 control subject. Mean amplitude at band range 1.2-3.5 kHz significantly lower in DM group compared to control group (*p*<.001), also at 1.5 kHz (*p*=.002), 2 kHz (*p*<.001) and 4 kHz (*p*=.017).	Significantly prolonged wave V (*p*=.025).and I-V (*p*=.017). IPL I-III was also prolonged in DM group but not statistically significant (*p*= .059).	TEOAE: Negative linear correlation with age (in univariate analysis) (correlation coefficient R = –0.353, *p*=.005). Impact of age on TEOAE amplitude appeared independent of DM duration, metabolic control or UAE (in multivariate analysis). Of the 9 (29.0%) of DM subjects with HbA1C < 7%, mean TEOA amplitude was higher when compared with the remaining 22 subjects with lesser metabolic control. However, no linear correlation between HbA1C level & TEOAE amplitude was found. ABR: Univariate analysis: negative linear correlation between DM duration & latency of wave V (R= -0.256, *p*=.045) &IPL I-V (R= -0.382, *p*=.004). Multivariate analysis: impact of DM duration on wave V and IPL I-V latency was independent of age, HbA1c & UAE. Subjects with shorter duration of DM demonstrated longer latency of wave V (*p*=.023) & IPL I-III (p= 0.026) & I-V (*p*=.030) compared to subjects with longer duration of DM (>5 years).	A relationship between T1DM and auditory organ dysfunction exists with cochlear and retrocochlear involvement up to brainstem level. Subtle yet statistically significant abnormalities detected prior to development of other microvascular complications. The use of audiological tests to monitor DM patients may be considered as a routine procedure.	III

Response parameters (Results of studies)							
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
2013	Baweja, Gupta, Mittal, Kumar, Singh & Sharma			Significantly longer mean latencies of wave V & mean IPL I-V in right ear (*p*=.021 and *p*=.0381 respectively) & left ear (*p*=.028 and *p*=.016, respectively) in DM subjects. Significantly longer mean IPL I-III in right ear of DM subjects (*p*=.028).	ABR wave latencies showed non-significant, positive correlations with duration of DM & FBS levels. Stronger correlation of BAEP latencies with FBS levels than duration of DM.	Significant differences in ABR latencies between T2DM & healthy control which were attributed to central auditory dysfunction associated with T2DM. Routine ABR in DM patients can detect central acoustic neuropathy in the absence of any clinical hearing loss.	III
2013	Gupta, Baweja, Mittal, Kumar, Singh, & Sharma			No significant association between latencies of wave I & II in DM & control subjects in either ear. Significantly longer latencies of waves III & V in DM subjects in both the right ear (*p*=.03 and *p*=.01) & left ear (*p*=.03 and *p*=.009), as well as wave IV in the right ear (*p*=.02). Latency of wave IV in the left ear was comparable between groups. IPL I-III was comparable between both groups in either ear. Significantly longer IPL III-V & I-V in DM subjects in right ear (*p*=.03 and *p*=.02) & left ear (*p*=.02 & *p*=.02).	All latencies showed a non-significant, positive correlation with duration of DM & FBG levels. However, stronger correlation of ABR latencies with FBG levels, as suggested by higher 'r' values.	DM patients may present with early involvement of central auditory pathway which can be detected with fair accuracy with ABR.	III

		Response parameters (Results of studies)					
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
2014	Karabulut, Karabulut, Dağli, Bayazit, Bilen, Aydin, Güler, & Bayramoğlu	Statistically significant differences between levels of SNR of DM subjects & control subjects at all frequencies (p< .05), except 1000 Hz.				Increase of audiometric thresholds at all test frequencies & lower amplitudes of DPOAEs at all frequencies (except at 1000 Hz); impairment of OHC evident in cochlea. T2DM seems to impact OHCs	III
2015	Hou, Xiao, Ren, Wang & Zhao	Both groups had normal range of DPOAE amplitude responses. DM group showed larger amplitude responses at high frequencies than control group; statistically significant with right ear at 4.0, 6.0 kHz & left ear at 4.0, 6.0, 8.0 kHz (p<.01). 35 DM subjects (70%) showed hearing impairment defined by DPOAE. 3 DM subjects obtained no amplitude. 32 DM subjects presented with amplitude >20 dB SPL or ≤5 dB SPL.	DM group showed no significance compared with healthy control group. No statistical significance between right & left ears. 20 subjects with hearing loss defined by TEOAE, 9 subjects who were not detected in TEOAE test, 11 subjects with abnormal amplitudes.	Longer latencies in the right ear (wave III, V, and IPL I-V) & left ear (wave III, V, IPL I-III, and IPL I-V) in DM subjects compared to control subjects (p < 0.01). No difference between right & left ear threshold in DM subjects. Thirty DM subjects (60%) had abnormal ABR.	Triglyceride was positively associated with the hearing impairment defined by DPOAE (p<.01). Age & GHbA1c associated with TEOAE impairment. ABR of DM subjects was significantly related to GHbA1 & microalbuminuria (p<.01). Higher GHbA1 or/and microalbuminuria level may worsen hearing loss in DM.	Higher auditory thresholds, slower auditory conduction time and cochlear impairment in T1DM. HDL-cholesterol, DM duration, systemic blood pressure, microalbuminuria, GHbA1, triglyceride & age may affect the auditory function T1DM subjects	III

Response parameters (Results of studies)							
Year	**Author**	**DPOAE**	**TEOAE**	**ABR**	**Correlations with clinical characteristics**	**Conclusions**	**Level of Evidence**
2015	Lasagni, Giorano, Lacilla, Raviolo, Trento, Camussi, Grassi, Charrier, Cavallo, Albera, Porta & Zanone	DPOAE not detected in at least one frequency in about one third of DM group. DPOAE intensities reduced at all frequencies compared with controls, statistically significant at frequencies between 2.8 & 4 kHz (p<.05).		No difference in absolute latencies of individual waves or IPL I-III & IPL I-V between DM subjects & controls. Absent waves in one ear of six DM subjects. No evidence of neurinoma or demyelinating disease via MRI. Wave IV detected on more than half of DM subjects, with higher prevalence than in controls. DM subjects with wave IV had a longer I-V IPL than those without IV.	DPOAE: DM subjects with retinopathy showed lower DPOAE intensity than those without retinopathy. Association between diastolic blood pressure & DPOAE (p<.05). ABR: Wave IV associated with systolic blood pressure. Wave V & IPL I-V correlated with systolic blood pressure.	Subclinical auditory alterations can be detected in young adult patients with T1DM. A role for both neurological and vascular pathogenic mechanisms is suggested. These findings indicate that the ear is a potential additional window to assess neurologic and vascular function in DM.	III