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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Auditory-vestibular function in adults with Type 1 Diabetes Mellitus

by

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A dissertation submitted in fulfilment of the requirements for the degree MA (Audiology) at the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria

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Declaration of Originality

I, Andriëtte Heystek (student number: 14017726), understand what plagiarism is and am aware of the Universities' policy in this regard. I declare that this research dissertation is my own original work and has not previously been submitted. Where other people's work has been used, it has been properly acknowledged and referenced according to the University of Pretoria's requirements.

_____ _____

Andriëtte Heystek Date

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
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53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

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Abstract

Diabetes mellitus (DM) is a universal health problem. According to the International Diabetes Federation (IDF), 425 million people world-wide are affected by DM. With such high incidence of DM, health professionals aim to avoid possible secondary disorders which impact health related quality of life (HRQoL) (Kamali, Hajiabolhassan, Fatahi, Esfahani, et al., 2013)(a). These secondary disorders include disorders of the inner ear.

The aim of the current study was to describe auditory-vestibular function in adults with type 1 DM and to determine the impact of the disease on their risk of falls and HRQoL. Data from this group was compared to data obtained from a control group of non-diabetic age and gender matched adults. A total of 30 type 1 DM participants and 30 non-diabetic participants were included in the study. Participants underwent a series of tests. Auditory tests: otoscopy, acoustic immittance measurements and air conduction (AC) pure tone audiometry were done. Vestibular tests included cervical- and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs) and video head impulse test (vHIT). Fall risk assessments included dynamic gait index (DGI), berg balance scale (BBS) and timed up and go test (TUG). Participants also completed the EQ-5D-5L Health Questionnaire.

A significant difference was observed between the diabetic and non-diabetic groups' 4-tone pure tone average (PTA) and thresholds for frequencies 250Hz-4000Hz in the left ear and at 250Hz-8000Hz in the right ear. No significant differences were present in cVEMPs between the two groups. The diabetic group was more likely to have absent oVEMPs on the right. For the right ear a significant difference was present between the diabetic and non-diabetic participants median oVEMP N1 latency but was still within normal limits for both groups. For both ears a significant difference was present in oVEMP amplitude. A significant difference was present between the diabetic and non-diabetic groups' vHIT anterior gain and posterior gain for the left and right ear respectively. The fall risk assessment scores in the current study indicated a low fall risk and good mobility in both groups. Diabetic participants rated their HRQoL to be significantly poorer than the non-diabetic participants.

Type 1 DM individuals had a significantly higher occurrence of auditory dysfunction, a higher occurrence of vestibular dysfunction but not for risk of falling compared to the non-diabetic participants. Furthermore, diabetic participants were found to have a significantly poorer HRQoL. Hearing and vestibular function tests as well as psychosocial support need to be considered as an integral part of type 1 DM patient's management strategy. The auditory- and vestibular function of individuals with type 1 DM should be closely monitored to better prevent further damage that places them at a higher risk of falls and serious life threatening injuries which will decrease patients HRQoL.

Keywords

Type 1 diabetes mellitus

Hearing loss

Vestibular function

Quality of life

Risk of falling

List of Abbreviations and Acronyms

AC	Air Conduction
BBS	Berg Balance Scale
BC	Bone Conduction
BMI	Body Mass Index
cVEMP	Cervical Vestibular Evoked Myogenic Potential
DGI	Dynamic Gait Index
DM	Diabetes Mellitus
ENG	Electronystagmography
GHbA1c	Glycated haemoglobin (Serum haemoglobin)
HDL	High Density Lipoprotein
HL	Hearing Loss
HRQoL	Health Related Quality of Life
IDF	International Diabetes Federation
LDL	Low Density Lipoprotein
oVEMP	Ocular Vestibular Evoked Myogenic Potential
SBAH	Steve Biko Academic Hospital
SCC	Semi-circular Canal
SCM	Sternocleidomastoid
TBI	Traumatic Brain Injury
TSH	Thyroid Stimulating Hormone
TUG	Timed Up and Go
VAS	Visual Analogue Scale
VEMP	Vestibular Evoked Myogenic Potential
vHIT	Video Head Impulse Test
WHO	World Health Organization

Chapter 1: Introduction

1.1 Diabetes mellitus

Diabetes mellitus is a universal health problem. This metabolic disorder is characterized by partial or absolute insulin deficiency due to inadequate insulin production or deficient sensitivity of target tissues to the action of insulin (Rigon, Garcia Rossi, & Cóser, 2007). Diabetes mellitus is a world-wide pandemic that can lead to public health and socio-economic problems. People that live in developing countries, minority groups and disadvantaged communities are at a greater risk for these problems (Mbanya, Motala, Sobngwi, Assah, & Enoru, 2010).

Diabetes mellitus is classified according to the aetiology of the disorder (American Diabetes Association, 2017). The two major types of DM can be distinguished as follows: type 1 DM is characterized by the loss of beta cells with total or relative insulin deficiency causing hyperglycemia and hypoinsulinemia (Jauregui-Renaud, 2016; Rigon et al., 2007). The pancreas produces little or no insulin. Type 2 DM is characterised by insulin resistance, whereby the target tissue has a lowered level of response to the insulin produced by the pancreas (Kamali et al., 2013)(a). The body therefore does not use insulin properly. Another type of DM is gestational diabetes. This type of diabetes is usually diagnosed during the second or third trimester of pregnancy. Pregnancy can predispose women to DM. Gestational DM develop when the pancreatic function cannot overcome the diabetogenic environment caused by pregnancy. Gestational DM can cause health problems for both the mother and the baby. Long term effects for the baby include DM during childhood, obesity, impaired motor function and hyperactivity. There is also a higher risk for birth complications such as preterm birth. The mother has an increased risk of developing type 2 DM after the pregnancy (Hoffert Gilmartin, Ural, & Repke, 2008). In addition, DM can be attributed to other causes including monogenic diabetes syndromes, diseases of the exocrine pancreas and drug- or chemical induced diabetes (American Diabetes Association, 2017). Type 2 DM is the most common type of diabetes, accounting for more than 90% of all cases (Amod et al., 2012), while type 1 DM accounts for 10-15% of all cases (Rance et al., 2014).

According to the International Diabetes Federation (IDF), 425 million people world-wide are affected by DM. An estimated 16 million DM cases in Africa were reported in 2017 and by 2045 this estimate is expected to increase to 41 million. Additionally, it is estimated that two-thirds of people with DM in Africa are undiagnosed (IDF, 2017). Nearly half of the deaths due to high blood glucose occur before the age of 70 and the World Health Organization (WHO) predicts that DM will be the seventh leading cause of death by 2030 (WHO, 2017). Because of the high number of individuals with DM health professionals aim to avoid possible secondary disorders caused by DM, which may impact the individuals' quality of life (QOL) (Kamali et al., 2013)(a). To prevent secondary disorders optimal glycaemic control as well as avoiding and treating coexisting risk factors are necessary (Dornhorst & Merrin, 1994). These secondary disorders include disorders of the inner ear.

1.2 Diabetes mellitus complications

Deficits in insulin secretion or insulin action caused by DM lead to abnormalities in carbohydrate, protein and fat metabolism (Klagenberg, Zeigelboim, Jurkiewicz, & Martins-Bassetto, 2007). Diabetes mellitus also interferes with the metabolism of glucose and causes chronic hyperglycaemia commonly known as high blood sugar. Hyperglycaemia is a typical complication associated with type 1 -and type 2 DM. It is said to be the main causal factor for the incidence and development of angiopathy (Jauregui-Renaud, 2016). Angiopathy refers to a disease of the blood vessels, characterized by the abnormal development of new blood vessels (Xu, Kanasaki, Kitada, & Koya, 2012). Diabetic angiopathy causes microvascular and macrovascular complications.

Microvascular complications can be described as complications that permanently affect the small blood vessels in the body (Fowler, 2008). The narrowing of small blood vessels leads to damage and failure of various organs and tissues of the body causing diabetic nephropathy, neuropathy and retinopathy (Fowler, 2008; Kamali et al., 2013)(a). Macrovascular complications affect the larger blood vessels in the peripheral or coronary vascular system. Macrovascular complications include the process of atherosclerosis which causes narrowing of the arterial walls in the body (Fowler, 2008). This leads to coronary artery disease, peripheral arterial disease and stroke.

The primary cause of morbidity and mortality in DM is the direct and indirect effects of hyperglycemia on the human vascular tree (Fowler, 2008). In addition to the above mentioned complications, abnormal glucose metabolism, which causes hyperglycaemia, can effect proper functioning of the inner ear structures (Rigon et al., 2007).

1.3 Diabetes mellitus effects on the inner ear

The inner ear consists of the sensory organs for hearing and balance which include the cochlea and vestibular end-organs. These organs are innervated by the eighth cranial nerve and share the same blood supply (Stach, 2010). Due to the shared nerve and blood supply, DM can cause damage not only to the auditory system, but also to the vestibular end-organs (Ward et al., 2015).

Glucose and insulin levels need to be balanced for appropriate inner ear functioning (Malucelli et al., 2012). Even minor changes in blood glucose can affect the inner ear (Kamali et al., 2013)(a) and lead to alterations in auditory- and/or vestibular function (David, Finamor, & Buss, 2015). Symptoms of auditory dysfunction can include hearing loss, tinnitus and aural fullness, while symptoms of vestibular dysfunction can include vertigo, dizziness or imbalance (Klagenberg et al., 2007).

The metabolic changes that occur in DM such as hyperglycaemia, hyperinsulinemia and hypoglycaemia could possibly cause angiopathy and neuropathy, which can lead to any type of hearing loss and vestibular dysfunction (David et al., 2015). The effective functioning of the inner ear depends on the stability of the internal environment as created by microcirculation (Xipeng et al., 2013). Oxygen and nutrient rich blood are delivered to body tissues including the inner ear through small blood vessels. Sensory hair cells in the inner ear are vulnerable to ischemia therefore microcirculation is necessary to maintain the ion and fluid balance in the inner ear (Shi, 2011). Abnormalities in microcirculation can cause end-organ damage (Struijker-boudier, 2007). Angiopathy negatively effects this microcirculation, by it reducing the transport and flow of blood to the inner ear (David et al., 2015). Complications in cochlear blood supply can lead to cochlear dysfunction (Xipeng et al., 2013). The vestibular end-organ also depends on a constant supply of oxygen and glucose which is impeded by angiopathy (David et al., 2015).

Another cause to consider related to vestibulocochlear manifestations in DM is neuropathy. Neuropathy can be described as the progressive degeneration of nerve fibres' axons (David et al., 2015). Diabetic neuropathy is characterised by a decrease in motor and sensory activity of the peripheral nerves, as well as demyelination of nerves which in turn cause a decrease in the conduction velocity. This in turn can lead to labyrinth dysfunction (David et al., 2015).

1.4 Diabetes mellitus and hearing loss

Diabetes mellitus is the metabolic disorder most commonly associated with auditory dysfunction (David et al., 2015). The relationship between DM and hearing loss has been studied by various researchers (Dąbrowski, Mielnik-niedzielska, & Nowakowski, 2011; Gawron, Pospiech, Orendorz-Fraczkowska, & Noczynska, 2002; Hou, Xiao, Ren, Wang, & Zhao, 2015; Jauregui-Renaud, 2016; Teng et al., 2017). However, the relationship between DM and hearing loss still remains controversial (Ciorba, Aimoni, & Bovo, 2012).

Previous research (Kalkan, Bayram, Gökay, Cura, & Mutlu, 2018; Özel, ÖzkiriŞ, Gencer, & Saydam, 2013; Pandey, Pandit, & Kumar Pandey, 2016; Prakash & Sumathi, 2013; Herrera-Rangel et al., 2015; Razzak, Bagust, Docherty, Hussein, & Al-Otaibi, 2015; Sahu & Sinha, 2015; Ward et al., 2015) focused primarily on the auditory and vestibular function of people with type 2 DM due to its higher incidence, but it is still unclear if the same alterations occur in those with type 1 DM. The limited studies that reported on type 1 DM found a close link between hearing loss and diabetes (Austin et al., 2009; Dąbrowski et al., 2011; David et al., 2015; Hou et al., 2015; Malucelli et al., 2012; Rance et al., 2014; Teng et al., 2017; Xipeng et al., 2013). Individuals with any type of DM can experience symptoms such as tinnitus and aural fullness (David et al., 2015). In a systematic review and meta-analysis of the association of type 1 DM with auditory dysfunction, researchers found that individuals with type 1 DM have a significantly higher prevalence of hearing loss compared to healthy controls with a pooled odds ratio of 49.08 (Teng et al., 2017). The hearing loss proved to be mild or subclinical, bilateral, progressive, sensorineural and predominantly in the high frequencies (Dąbrowski et al., 2011; Hou, Xiao, Ren, Wang, & Zhao, 2015; Jauregui-Renaud, 2016; Teng et al., 2017). However sudden unilateral hearing loss can also occur (Malucelli et al., 2012). Due

to the high frequency nature of the hearing loss associated with DM, individuals usually do not notice a decline in hearing (Xipeng et al., 2013).

Dabrowski et al. (2011) reported that the mean hearing threshold for type 1 DM participants was worse in the higher frequencies (3000Hz-12000Hz) when compared to that of healthy participants. A total of 6/31 (19.35%) type 1 DM participants had hearing loss compared to only 3/26 (11.54%) healthy participants. The mean transient evoked otoacoustic emissions (TEOAE) amplitude for the type 1 DM participants were smaller. Auditory brainstem responses (ABR) were also affected. The wave V latency and wave I-V interamplitude latency were longer compared to that of the healthy participants. A study by Malucelli and colleagues (2012) found type 1 DM individuals to have a higher mean hearing threshold at any frequency. A total of 23/30 (76,7%) diabetic individuals had hearing loss compared to only 12/30 (40%) non-diabetic participants. Hou and colleagues (2015) found significantly elevated audiometric thresholds at 250Hz, 1000Hz, 2000Hz, 4000Hz, and 8000Hz in the right ear and in the left ear at 250Hz, 500Hz, 1000Hz, 4000Hz and 8000Hz in the type 1 diabetic participants, compared to non-diabetic participants. The mean of the pure tone thresholds for these frequencies were still within normal limits for both groups (<25dBHL). Nevertheless, in total 24/50 (48%) individuals with DM presented with hearing loss.

Auditory dysfunction proves to be related to disease duration, high density lipoprotein (HDL) cholesterol level, systemic blood pressure, microalbuminuria, glycosylated haemoglobin (GHbA1c), triglyceride and age of the patient (Hou et al., 2015). The study by Hou and colleagues (2015) indicated that a longer disease duration, a lower HDL cholesterol level and a higher systolic blood pressure level may increase type 1 diabetics' risk of hearing loss. Another study concluded that poorly controlled and complicated diabetic individuals are at an even higher risk of developing hearing loss (Sunkum & Pingile, 2013).

In contrast, other studies found that hearing loss is not that frequent in type 1 DM individuals compared to healthy controls (De Espana, Biurrun, Lorente, & Traserra, 1995; Pessin et al., 2008; Tavakoli, Talebi, Shushtari, Tehrani, & Faghihzadeh, 2014). Pessin et al. (2008) only found 4/40 (10%) diabetic individuals with a mild

sensorineural hearing loss, predominantly in the high frequencies. De Espana et al. (1995) reported that hearing loss in DM individuals is not a usual feature. In the study type 1 DM individuals were divided into two groups, group A consisted of type 1 early diabetics and group B consisted of type 1 chronic diabetics. In group A 0/17 (0%) had hearing loss and only 9/30 (30%) in group two. In another study, pure tone audiometric thresholds in 15 type 1 DM participants and 10 healthy controls showed normal hearing in all the participants (Tavakoli et al., 2014). The incidence of hearing loss in diabetic individuals varies from 0% to 93% (Chamyal, 1997). These contradictory findings may be due to different study populations and test methods used.

1.5 Diabetes mellitus, vestibular dysfunction and risk of falling

Vestibular dysfunction is still a newly recognized secondary manifestation of DM (Schubert et al., 2010). Literature is generally sparse on this topic (Gawron et al., 2002). The central and peripheral vestibular system are affected by microangiopathy (Prakash & Sumathi, 2013). Microangiopathy causes ischemia of the vestibular apparatus and alters the inner ear fluid metabolism leading to labyrinthine dysfunction (Kalkan et al., 2018). The range of vestibular end-organ impairment, specifically in individuals with type 1 DM, seems to depend mainly on the presence and character of hypoglycaemic incidents (Gawron et al., 2002). Furthermore the duration of the disease and to some degree, the control of blood glucose levels, may also affect vestibular end-organ impairment in type 1 DM (Gawron et al., 2002).

To date only a few studies reported vestibular dysfunction in individuals with type 1 DM (Gawron et al., 2002; Kamali et al., 2013; Kamali, Hajiabolhassan, Fatahi, & Nasliesfahani, 2013; Klagenberg et al., 2007; Prakash & Sumathi, 2013; Rigon et al., 2007; Scherer & Lobo, 2002; Tavakoli et al., 2014). Klagenberg and colleagues (2007) performed video electronystagmography tests (VENG) including spontaneous nystagmus test, positional nystagmus test, pendular tracking test, optokinetic nystagmus test, pre-and post-rotary nystagmus with the pendular swing rotary test, and investigation of pre- and post-caloric nystagmus. All the test results were within normal limits except caloric results which were not. A total of 18/30 (60%) of the individuals with type 1 DM included in their study had vestibular dysfunction. Of these individuals 13/30 (43%) did not report feelings of dizziness. Another study

performed VENG tests, including semi-spontaneous nystagmus test, directional/fixating nystagmus test, optokinetic nystagmus test, pendular tracking test, decreasing pendular caloric test and caloric test. Similarly only the caloric test results were abnormal in 7/19 (36.84%) type 1 DM individuals (Rigon et al., 2007).

Scherer and Lobo (2002) performed an electronystagmographic (ENG) evaluation including spontaneous nystagmus test, semi-spontaneous nystagmus test, pendular tracking, optokinetic nystagmus test and pre- and post-caloric nystagmus. Peripheral vestibular dysfunction was found in 8/12 (66.7%) individuals with type 1 DM as indicated by altered caloric test results. In the group with abnormal results, 62.5% of the individuals did not report any dizziness symptoms. Therefore the vestibular end-organ can be affected in individuals with type 1 DM, even when such individuals do not have any symptoms or complaints (Rigon et al., 2007; Scherer & Lobo, 2002). Interestingly, Gawron et al. (2002) reported that the metabolic disturbances found in type 1 DM cause disturbances in the peripheral vestibular structures, but mostly in the central structures as shown by impaired optokinetic responses observed in 36/95 (37.89%) diabetic participants, spontaneous nystagmus in 10/95 (10.53%) individuals and the presence of positional nystagmus in 21/95 (22.11%) individuals.

When comparing cervical vestibular evoked myogenic potential (cVEMP) results of participants with type 1 DM with healthy controls, the cVEMP responses of individuals with type 1 DM were more affected than healthy participants (Kamali et al., 2013)(b). The latencies of P1 and N1 were significantly longer in individuals with type 1 DM. No correlation was found between VEMP responses and GHbA1c levels and the average blood glucose concentration over three months. Additionally, there were no differences in the absolute and relative amplitudes of the VEMP responses between the experimental and control group (Kamali et al., 2013)(b). Another study compared the cVEMP responses of 15 individuals with type 1 DM, 15 individuals with type 2 DM and 10 healthy participants. The researchers concluded that only the cVEMP amplitudes were statistically different between type 1 DM participants and non-diabetic participants (Tavakoli et al., 2014). Further detailed information for the two above mentioned research studies could not be retrieved because the original article could not be translated. Individuals with type 1 DM and complications such as neuropathy are at an even higher risk for vestibular dysfunction compared to

individuals without neuropathy (Kamali et al., 2013)(a). Kamali and colleagues studied the cVEMP responses of participants with DM and neuropathy, participants with DM without neuropathy and healthy participants. Mean peak latencies of P1 and N1 for individuals with DM and neuropathy were longer for individuals with DM without neuropathy and healthy participants, however the exact number of participants with abnormal test results were not reported (Kamali et al., 2013)(a).

Only one study to date on type 1 DM participants included the video head impulse test (vHIT) in their research design to investigate horizontal SSC function (Rance et al., 2014). However, the researchers only performed the horizontal vHIT in ten type 1 DM participants and ten non-diabetic participants. The average bi-directional gain for all the type 1 DM participants were normal (>0.68) except for one that had an asymmetrical gain.

Diabetes mellitus is not only associated with vestibular dysfunction but also an increased risk of falls. The vestibular system provides spatial orientation information to maintain balance in static and dynamic conditions. Due to this function, vestibular dysfunction as seen in DM is associated with an increased risk of falls and balance problems (Silva, Lin, Staecker, Whitney, & Kluding, 2016; Yang, Hu, Zhang, & Zou, 2016). Falls can lead to a decline in functional and emotional status (Schubert et al., 2010), which in turn decreases QOL (Yang et al., 2016). A recent literature review concluded that especially older adults with DM are at risk of falling with a risk ratio of 1.64. The risk of falls seems to be even higher for those individuals using insulin treatment with a risk ratio of 1.94 compared to a risk ratio of 1.27 for those not using insulin treatment. (Yang et al., 2016). Even after adjusting for retinopathy and peripheral neuropathy, vestibular dysfunction independently increases the odds of falling more than 2-fold (odds ratio 2.3) in individuals with DM (Schubert et al., 2010).

Current knowledge of vestibular function in type 1 DM individuals is limited. To our knowledge, the nature of utricle function in type 1 DM individuals has not been investigated yet. Due to this limited knowledge, the true nature and extent of vestibular dysfunction in type 1 DM is still unclear.

1.6 Rationale

Vestibular- and hearing dysfunction can be overlooked if only certain parts of the inner ear are tested as previous research studies have done. Since type 2 DM is the most common, previous research primarily focused on the vestibular function of people with type 2 DM but it was unclear if the same alterations occured in those with type 1 DM. In its current format the rationale for specifically studying the effects of type 1 DM remains unclear. The aim of the present study was to describe auditory-vestibular function in a group of adults with type 1 DM, and to determine the impact of the disease on their risk of falling and health related quality of life (HRQoL).

Chapter 2: Methodology

2.1 Research aim

This study aimed to describe auditory-vestibular function in adults with type 1 DM, their risk of falls and HRQoL, in comparison with healthy non-diabetic adults.

2.2 Research design and setting

This prospective research was quantitative, quasi-experimental- and cross-sectional in nature. Two groups were observed to determine the incidence of a specific outcome (De Rango, 2016). Quantitative/numerical data (Zulfiqar & Bhaskar, 2016) was collected in the form of decibels, seconds, VEMP latencies and vHIT gains. To be able to establish a potential association (Thompson & Panacek, 2006) between type 1 DM and inner ear dysfunction a quasi-experimental design was used. Furthermore a control group was included in the study to be able to closely compare and identify differences in test results between participants with type 1 DM and those without DM. To as far as possible study the independent effect of type 1 DM on the inner ear not all volunteers were included in the study, only volunteers who met the inclusion and exclusion criteria (Setia, 2016).

The testing of the participants in the diabetic (experimental) group took place at the Diabetic Clinic of Steve Biko Academic Hospital (SBAH) under the guidance of Prof Paul Rheeder (Head of clinic), the Diabetes Centre of Mediclinic Heart Hospital under the guidance of Dr Mary Seeber, Diabetes Centre Hatfield under the guidance of Dr Betsie Kloppers and at Dr Frans Erasmus Diabetic Clinic under the guidance of Dr Frans Erasmus. The healthy, non-diabetic participants (control group) included friends and family of the researcher that were tested at the Department of Speech-Language Pathology and Audiology, University of Pretoria.

2.3 Ethical considerations and informed consent

To ensure that this research study complied with ethical standards, the World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects (page 4) were followed.

2.3.1 Permission

Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (Appendix A).

Ethical clearance was also obtained from the Research Ethics Committee of the Faculty of Humanities, University of Pretoria (Appendix B).

Permission to invite the patients with type 1 DM to participate in this study were obtained from the Head of the Diabetic Clinic at SBAH, Prof Paul Rheeder (Appendix C), the Head of the Diabetes Centre at Mediclinic Heart Hospital, Dr Mary Seeber (Appendix D), Dr Betsie Kloppers at the Diabetes Centre Hatfield (Appendix E) and from Dr Frans Erasmus, at Dr Frans Erasmus Diabetic Clinic (Appendix F).

Permission to invite the patients from the Diabetic clinic at SBAH with type 1 DM to participate in this study and to access patients' files were obtained from Dr Ernest Kenoshi, chief executive officer (CEO) of SBAH (Appendix G).

Permission to access patients' files was requested from the Head of the Diabetes Centre at Mediclinic Heart Hospital (Appendix H).

Permission to access patients' files was requested from Dr Frans Erasmus at Dr Frans Erasmus Diabetic Clinic (Appendix I).

2.3.2 Informed consent

An informed consent letter (Appendices J and K) was given to each participant in the diabetic group and the non-diabetic group before testing started. Participants were informed in the letter and verbally about which procedures will be performed and what to expect in detailed sections:

(i) introduction and general orientation to the research study,

(ii) Explanation of the purpose of the study,

(iii) Explanation of the procedures and assessments included in the study,

(iv) Explanation of the possible risks and benefits involved in the study,

(v) Explanation of the rights of the participants,

(vi) Assurance that the research study has received ethical approval from the Faculties' research ethics committees,

(vii) Contact information of the researcher,

(viii) Clarification that there will be no compensation for participating in the study,

(ix) Assurance that participants personal information and assessment results will be kept confidential, and

(x) Assurance that participation in the study was voluntary and that participants were free to withdraw from the study if they wanted to.
Participants had to provide written consent to participate in the study before data collection commenced.

2.3.3 Confidentiality

Personal information and results were kept strictly confidential in the data collection, analysis and reporting process (Vanclay et al., 2013). An alpha numeric code (for example A1, B1) was allocated to each participant during data collection. The participants' data were saved and reported using this code.

2.3.4 Protection from harm

The participants in this research study participated voluntarily. The participants were informed of tests to be performed and what was expected of them both verbally and in the informed consent letters (Appendices J and K). They knew that the study did not entail procedures that could potentially harm them. The participants performed physical activities for the fall risk tests (Appendices L,M,N). During the activities support was provided to prevent them from falling and appropriate rest time was given. The participants could withdraw from the study at any time. They were informed that data already collected would be excluded from the study and that their withdrawal would not affect their treatment at the Diabetic Clinic.

2.3.5 Honesty

Participants were given access to their own test results as well as to the results of the study. The participants were informed that the study will be submitted to a scientific journal for publication.

2.3.6 Plagiarism

The study complies with the University of Pretoria policy on plagiarism. A declaration of originality is included (page 2).

2.3.7 Reliability and validity

Reliability and validity were ensured by testing all participants in similar environments and conditions using the same calibrated equipment. All participants

were given the same instructions and the same assessments were performed on each participant. Furthermore test sequences for necessary assessments such as the video head impulse test (vHIT) were randomized to avoid participants pre-empting the movements which can influence test results. To compensate for tester bias another professional person assisted in identifying and marking waveforms for assessments including cervical vestibular evoked myogenic potentials (cVEMPs) and ocular vestibular evoked myogenic potentials (oVEMPs).

2.3.8 Referrals

The participants did not benefit directly from the study, but the results did help to identify any possible auditory and/or vestibular problems. Participants with hearing thresholds of >15dBHL (Clark 1981) and any other auditory related symptoms were referred to an audiologist for further testing and treatment. Participants with any vestibular problems as shown by the presence of any vestibular related symptoms, abnormal cVEMP, oVEMP, vHIT test results and functional balance problems were also referred to an audiologist for further diagnostic testing and management. If any other ear-related diseases were identified such as occluding earwax and outer/middle ear pathologies, participants were referred to an Ear-Nose-Throat Specialist or general practitioner. If participants indicated feelings of anxiety and/or depression on the EQ-5D-5L Health Questionnaire (Appendix O) they were referred to a psychologist/psychiatrist. (Appendices P and Q).

2.3.9 Data storage

The data from this research study will be stored in digital and hard copy format for a period of 15 years at the Department of Speech-Language Pathology and Audiology, University of Pretoria. Stored data will be used for future research by other researchers (Appendix R)

2.4 Participants

2.4.1 Participant selection criteria

A purposive sampling method was employed to recruit the participants with type 1 DM. Participants were deliberately chosen to be included in the study due to their certain qualities (Etikan, Musa, & Alkassim, 2016). Participants in the diabetic and

the non-diabetic group had to meet certain criteria to be able to participate in the study.

Table 1 summarizes the inclusion criteria for the type 1 diabetic group, table 2 for the non-diabetic group and table 3 the exclusion criteria for all participants.

Table 1: Inclusion criteria for the diabetic group

Inclusion criteria for the diabetic group	
Inclusion criteria	**Rationale**
Male and female participants between the ages of 18-59	In order for participants to provide legal consent they needed to be 18 years or older (Strode, Slack, & Essack, 2010). The incidence of presbycusis increases for people older than 55 (Kovalova et al., 2016). Acoustic VEMP responses are also affected by age. The VEMP response rates as well as inter-peak amplitudes decrease for people 60 years or older (Su, Huang, Young, & Cheng, 2004). Therefore only participants younger than 60 years old were included in the study.
Participants who have used insulin within the first year after being diagnosed with DM	Individuals with type 1 DM need to administer insulin daily in order to survive because of deficient insulin production by the pancreas, therefore they need to monitor their blood glucose level regularly (World Health Organization, 2017). If the patient was not yet diagnosed with a specific type of DM the above mentioned contributed to determining whether the patient has type 1 DM or type 2 DM.

Table 2: Inclusion criteria for the non-diabetic group

Inclusion criteria for the non-diabetic group	
Inclusion criteria	**Rationale**
Age and gender matched participants	Participants in the non-diabetic group were matched with the participants in the diabetic group according to age and gender. This ensured accurate comparison between healthy participants and those with DM.
Healthy participants without DM	Participants without a diagnosis of DM were included in the non-diabetic group in order to study and compare the impact that DM has on individuals' auditory-vestibular functioning. Participants were required to undergo a finger prick test to determine their blood glucose levels. Participants with a result between 4-8mmol/L were included in the non-diabetic group (Abbott Diabetes Care, 2018).

Table 3: Exclusion criteria for the diabetic and non-diabetic group

Exclusion criteria for the diabetic and non-diabetic group	
Exclusion criteria	**Rationale**
Participants with a history of noise exposure (occupational and recreational)	Prolonged exposure to high levels of noise is associated with damage to the hair cells in the cochlea, causing permanent hearing loss (Sliwinska-Kowalska & Davis, 2012). Chronic noise exposure increases the risk of damage to the vestibular end-organ (Gabr & Emara, 2014).
Participants with a history of ototoxic medication use (medicines to treat HIV, TB, cancer, heart disease etc.)	Medications such as aminoglycosides and platinum compounds with known ototoxic side effects can cause permanent hearing loss and vestibular dysfunction (Purushothaman et al., 2018; Schellack & Naude, 2013).
Participants with middle ear pathology	Individuals with a conductive pathology were excluded from the study, as identified by: -type B and type C tympanogram results (Mohamed & Brookler, 2007),

	-the presence of an air-bone gap on the audiogram (Nickbakht & Borzoo, 2014). Middle ear pathology attenuates the stimulating sound and the AC VEMP are poorly elicited (Mahdi, Amali, Pourbakht, Yazdi, & Bassam, 2013).
Participants who have severe symptomatic neuropathy	Diabetic peripheral neuropathy and diabetic autonomic neuropathy are common types of diabetic neuropathy. Diabetic peripheral neuropathy, diabetic autonomic neuropathy and vestibular dysfunction are associated with foot ulcers, postural instability while walking, abnormal distribution of foot pressure and falls. These participants will also not be able to complete the risk of falls assessments due to their greater risk of falling (Kim et al., 2012).
Participants with peripheral arterial obstructive disease in their legs	According to Kim et al. (2012) participants with peripheral arterial obstructive disease should be excluded. The most common symptom of peripheral arterial obstructive disease is intermittent claudication, that is pain, cramping, or aching in the calves and thighs that appears when walking or exercising but is relieved by rest (American Diabetes Association , 2003). These participants will not be able to complete the risk of falls assessments of the current study.
Participants with a history of chronic alcohol abuse	Disorders influencing autonomic function such as participants with a history of chronic alcohol abuse should be excluded (Kim et al., 2012). Alcohol abuse affects auditory thresholds, with some frequencies affected more than others (Upile et al., 2007). Not only does alcohol abuse affect hearing, it also interferes with vestibular function causing balance problems (Bellé, do Amaral Sartori, & Rossi, 2007).
Participants with co-morbid diseases such as hypothyroidism (not on Eltroxin), liver cirrhosis, or chronic hepatitis	An abnormal level of Thyroid hormones is related to labyrinth dysfunctions (Santos & Bittar, 2012). Hypothyroidism can cause elevated levels of lipids circulating in the blood. Studies have shown that the peripheral and central vestibular system can be affected by thyroid disorders (Santos & Bittar, 2012). According to Kim et al. (2012) participants with any diseases and disorders such as hypothyroidism, liver cirrhosis and chronic hepatitis that can possibly cause peripheral neuropathy and negatively affect autonomic function should be excluded from the study (Kim et al., 2012).
Participants who had a stroke or a traumatic brain injury (TBI)	Participants with a TBI and those who had a stroke were excluded from the study. Studies indicate that post-traumatic dizziness or vertigo is a regular complaint following brain injuries. Vestibular testing of patients with head trauma indicate that it may damage the peripheral and central vestibular structures (Kolev & Sergeeva, 2016). In another study, the incidence of vestibular dysfunction in participants with a TBI was 80%, of which specific vestibular pathology ranges between 30%-65% (Scherer & Schubert, 2009). Furthermore, many people experience problems with balance and gait activities after they had a stroke (Jonsdottir & Cattaneo, 2007).
Participants who smoke	According to Kumar, Gulati, Singhal, Hasan, & Khan. (2013) smoking is significantly associated with hearing loss. This may be due to the well-known vascular changes and the consequent cochlear hypoxia connected to smoking (Pouryaghoub, Mehrdad, & Mohammadi, 2007).
Participants with a severe to profound hearing loss (hearing thresholds worse than 60dBHL)	Severe to profound hearing loss potentially influences both cVEMP and oVEMP responses (Bansal, Sahni, & Sinha, 2013). Bansal et al., (2013) reported reduced inter-peak amplitudes in participants with severe to profound hearing loss. Therefore participants with hearing thresholds worse than 60dBHL at any frequency between 250-8000Hz were excluded from the study.

2.4.2 Participant selection procedure

Figure 1 illustrates the procedures followed to recruit and select participants in the diabetic and non-diabetic group.

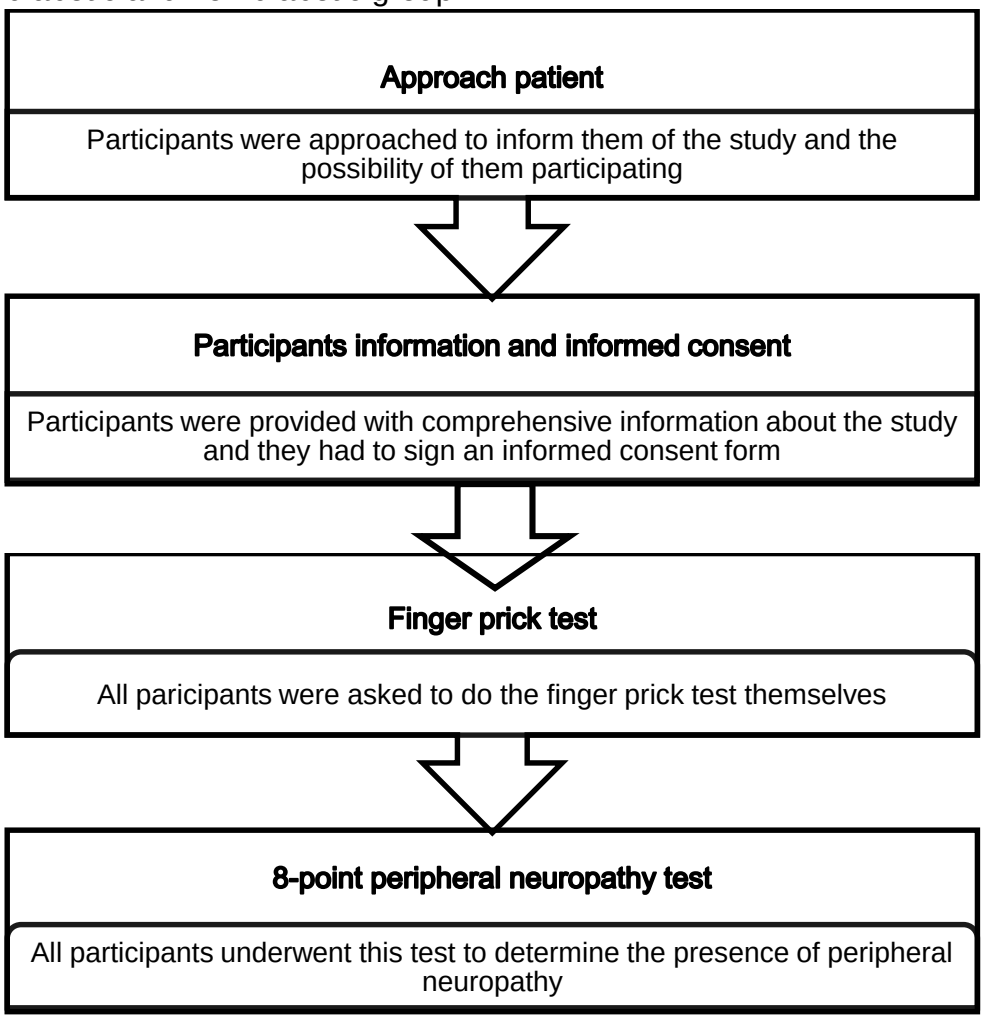

Figure 1: Participant selection procedure

Diabetic group: once patients had been invited and informed about the study, and agreed to participate, written consent was provided. Participants were then asked to perform a finger prick test themselves in the assessment room to determine their blood glucose levels (participants used their own blood glucose monitoring system). Non-diabetic group: Once patients had been invited and informed about the study, and agreed to participate, written consent was provided. The participants also underwent a finger prick test to determine their blood glucose levels to ensure that it is within normal limits. The participants were asked to do a finger prick test themselves in the assessment room with the Contour Plus One blood glucose monitoring system. This system is a home-based kit used to screen and monitor blood glucose levels. Only participants with a blood glucose level between 4mmol/L

and 8mmol/L were included in the study. This is the recommended range of the National Institute for Health and Clinical Excellence (NICE) and the International Diabetes Federation (Abbott Diabetes Care, 2018).

Lastly the 8-point peripheral neuropathy test was conducted by the researcher for both the diabetic and non-diabetic group as part of the exclusion of participants with severe peripheral neuropathy. Once the volunteers met all the criteria (Tables 1, 2 and 3), data collection proceeded (see Figure 2).

2.5 Data Collection

2.5.1 Data collection procedure

After the participant had been identified as a suitable candidate for the study by the participant selection procedure as described in figure 1, data collection commenced. The participant underwent a single assessment lasting a minimum of two hours at the Diabetic Clinic of SBAH/Diabetes Centre of Mediclinic Heart Hospital/Diabetes Centre Hatfield/Dr Frans Erasmus Diabetic Clinic. Participants in the non-diabetic group were tested at the Department of Speech-Language Pathology and Audiology-University of Pretoria.

Figure 2 illustrates the data collection procedures used for both the diabetic and non-diabetic groups.

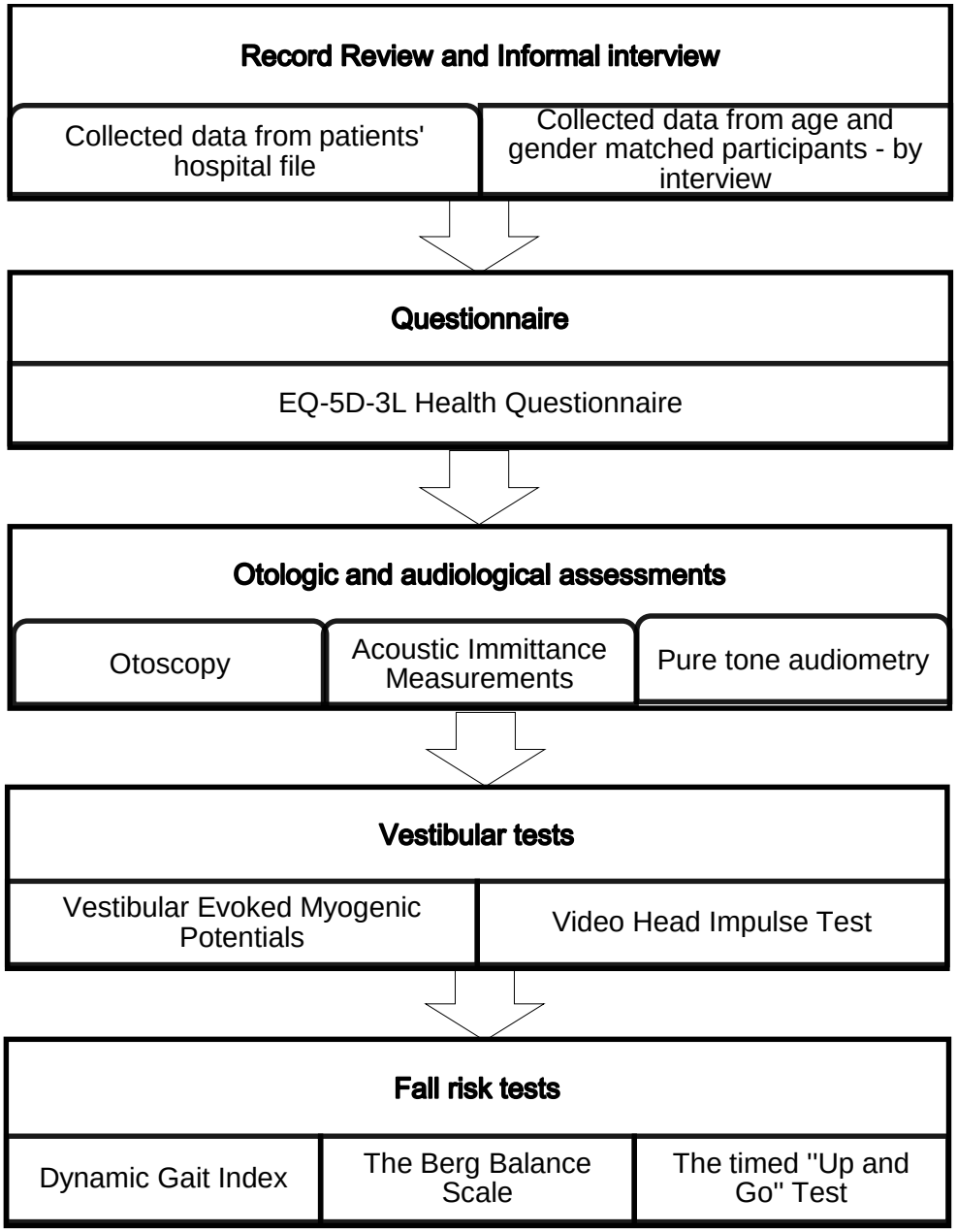

Figure 2: Data collection procedure

2.5.2 Medical information and demographic data collected for participants

Information was collected from the type 1 DM patients' hospital file (Appendix S). For the non-diabetic group an informal interview using the data capture sheet was conducted (Appendix T). The following information was collected for both groups during data collection:

Age (in years with the last birthday taken into account)

Gender

Height
Weight
BMI (BMI will be classified as underweight (BMI < 18.50 kgm), normal weight (18.50 kgm), overweight (25kgm < BMI < 30.0 kgm) and obese (BMI > 30.0 kgm))

Additional information collected during data collection for the participants with type 1 DM:
Tests for blood glucose, GHbA1c and Lipid profile (total cholesterol, LDL and HDL)
Thyroid function tests (T4 and TSH)
Results of micro-vascular complications:
-Retinopathy (examination of the eyes)
-Nephropathy (kidney function: s-creatinine and s-urea)
-Peripheral neuropathy (examination of the feet)
Any evidence of:
-Angina
-Ischemic heart disease
-Stroke

2.5.3 Health Related Quality of Life questionnaire (EQ-5D-5L)
In order to obtain a simple descriptive profile as well as a single index value for the participants' health status they were asked to complete the EQ-5D-5L questionnaire. The EQ-5D-5L is a standardized HRQoL questionnaire that was designed by the EuroQol Group (1987) in 2005. The questionnaire is used to measure participant's perception of their health status and comprises 5 dimensions: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort and (5) anxiety/depression together with five levels of severity: level 1 indicating no problem, level 2 indicating slight problems, level 3 indicating moderate problems, level 4 indicating severe problems and level 5 indicating extreme problems (Herdman et al., 2011). The participant had to choose the level of severity at each dimension that applies to them and tick the box next to it. This decision results in a 1-digit number expressing the level selected for that dimension. The participants then had to use the EQ Visual Analogue Scale (VAS) to rate their health and plot it on the vertical, visual analogue scale where 100 is considered the ''best imaginable health state'' and 0 is considered the ''worst imaginable health state''.

2.5.4 Otologic and audiological assessments

Otoscopy was performed with a WelchAllyn Pocket Otoscope, to ensure that the participants have a healthy external ear canal and tympanic membrane. Participants' middle ear functioning was measured by performing tympanometry. A GSI Tympstar, Grason-Stadler. Eden Prairie, MN, USA machine with a diagnostic Y-226Hz probe tone was used. Jerger (1970) tympanometry norms were followed: middle ear pressure (-100 to +50daPa), ear canal volume (0.8 to 2.0ml) and static compliance (0.3 to 1.8ml). Screening acoustic reflexes were also measured at 500, 1000, 2000 and 4000Hz. Reflexes were regarded as present and normal if elicited at 70-90dBSPL (Ünsal et al., 2016). Participants with any external ear and/or middle ear pathologies were excluded from the study.

Automated diagnostic AC pure tone audiometry was performed to determine the presence, type and degree of hearing loss. A portable computer operated audiometer - KUDUwave Type 2 Clinical Audiometer (IEC 60645-1/2) manufactured by eMOYOdotNET, Johannesburg, South Africa was used (Swanepoel, Matthysen, Eikelboom, Clark, & Iii, 2015). The KUDUwave was connected to and operated with a notebook computer (Acer Aspire E1-532, running Microsoft Windows 8). The KUDUwave was transported to the different clinics. Insert earphones (ER3A-Insert earphones, Etymotic Research, Elk Grove Village, IL, USA) were used as transducers covered by circumaural earcups (Swanepoel et al., 2015). Participants responded by pressing a button that was connected via a USB cable to the KUDUwave device to allow recording of responses. The KUDUwave also monitored the ambient noise levels during testing by means of a microphone located on the circumaural earcups. Air conduction (AC) was conducted at 250Hz-8000Hz. If the AC threshold was $\geq$20dBHL bone conduction was tested through the bone oscillator attached to the circumaural headband. Masking was automatically applied where necessary.

The degree of hearing loss was determined by the participant's 4-tone pure tone average (500Hz, 1000Hz, 2000Hz and 4000Hz). Clarks' (1981) classification of degree of hearing loss were used: normal $\leq$15dBHL, slight hearing loss 16dBHL to 25dBHL, mild hearing loss 26dBHL to 40dBHL, moderate hearing loss 41dBHL to 55dBHL, moderately severe 56dBHL to 70dBHL, severe 71dBHL to 90dBHL and

profound ≥91dBHL. Participants with an AC threshold worse than 60dBHL at any frequency between 250Hz-8000Hz were excluded from the study as severe to profound hearing loss negatively influences both cVEMP and oVEMP responses (Bansal et al., 2013)

2.5.5 Vestibular evoked myogenic potentials (VEMPs)

Vestibular evoked myogenic potentials are clinically used to assess the functioning of the otolith organs and the vestibular nerve. Two different types of VEMPs can be distinguished: cVEMPs and oVEMPs.

Air conduction cVEMPs specifically assess the functioning of the saccule and the inferior vestibular nerve, whereas AC oVEMPs assess the functioning of the utricle and the superior vestibular nerve (Bansal et al., 2013). Both the cVEMP and oVEMP are evoked by acoustic stimulation and a response is measured in the presence of a myogenic response (Felipe & Kingma, 2013).

Both cVEMPs and oVEMPs were performed on all participants. They were seated on a standard upright chair for the duration of the procedure (Kim et al., 2014). The VEMPs were carried out using the Biologic Navigator Pro auditory evoked response system version 7.2.1 connected to an Acer laptop. The Biologic Navigator Pro was manufactured by Natus Medical, USA. Insert earphones were used as transducers (ER3A-Insert earphone, Etymotic Research, Elk Grove Village, IL, USA). A 500Hz AC toneburst stimulus was presented at 95dBnHL with alternating polarity.

Participants' skin was cleaned with Nuprep scrub and reusable gold cup electrodes with Ten20 conductive paste were positioned and kept in place with micropore tape. Impedances were ideally kept under 5kΩ.

For the cVEMPs: the active electrode was placed on the mid-portion of the sternocleidomastoid muscle (SCM) on the side of the test ear. The ground electrode was placed on the high forehead and the reference electrode was placed on the upper sternum. Participants were asked to turn and lower their head toward the opposite side of the test ear, which is considered the best VEMP test position due to the consistent level of SCM muscle tension (Kim et al., 2014). The first positive peak was marked as P1 and the negative peak as N1. Normal latencies for P1 were considered as $\leq$ 19msec and for N1 $\leq$ 28msec (Isaradisaikul, Navacharoen, Hanprasertpong, & Kangsanarak, 2012). The inter-peak amplitude was the sum of the amplitudes of these repeated responses.

For the oVEMPs: the active electrode was placed under the eye on the inferior oblique muscle of the eye contralateral to the test ear. The ground electrode was placed on the high forehead and the reference electrode was placed on the side of the nose bridge. This nose referenced electrode placement results in increased reliability and a large amplitude (Leyssens et al., 2017). Participants were asked to look upward as far as they could without moving their head. The first negative trough was marked as N1 and the positive peak as P1. Normal latencies for N1 were considered as $\leq$ 11.1msec and for P1 $\leq$ 17.6msec (Leyssens et al., 2017). The inter-peak amplitude was the sum of the amplitudes of these repeated responses.

Figure 3 illustrates the electrode montages used for cVEMP and oVEMP testing.

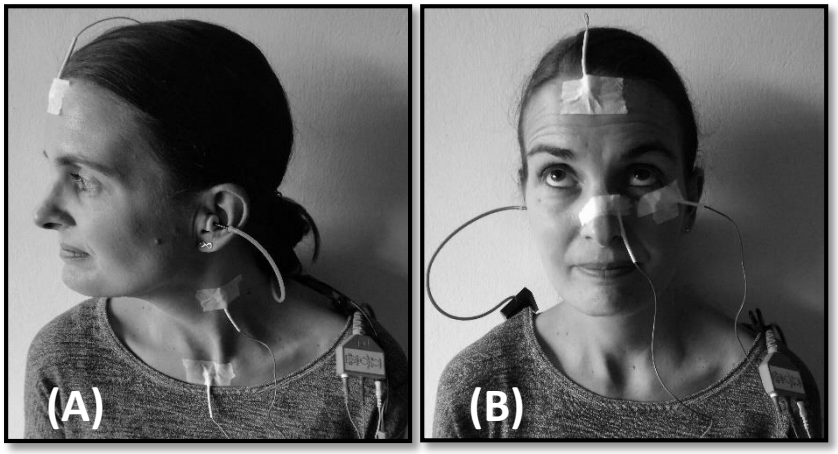

Figure 3: Electrode montages

Key: (A) cVEMP electrode montage, (B) oVEMP electrode montage; permission was obtained from this participant to use images of her in this research study.

Waveforms were repeated to test for wave reproducibility and to reduce artefacts. The cVEMPs and oVEMPs were classified as normal when: (i) there were identifiable P1 and N1 waveforms; (ii) latencies fell within the normal limits.

The cVEMPs and oVEMPs were considered as abnormal when: (i) there were no identifiable P1 and N1 waveforms; (ii) latencies fell above the upper limits of the waveform latencies.

2.5.6 Video head impulse test (vHIT)

The vHIT has become the gold standard for vestibular testing in the high frequency region (Guinand et al., 2017). The vHIT makes it possible to synchronously record and objectively assess head and eye movements (Guinand et al., 2017). The vHIT is used to identify overt and covert saccades and to examine the gain of the vestibulo-ocular reflex (VOR) for all six semicircular canals (Salman & Issam, 2017). For this study the vHIT was carried out with the Otometrics ICS Impulse system version 4.10 with video frenzel goggles manufactured by Natus Medical, Denmark. Participants were tested in a well-lit room, seated in a standard upright chair, with an eye level target 1 meter in front of them. The goggles were tightened to prevent any artefacts caused by slippage (Suh et al., 2017).

Before testing proceeded the vHIT system was calibrated. Participants were asked to follow the red laser projected on the wall in front of them. Calibration values represent the difference between the focus of the left and right eye on the red laser. Values >27 Delta were re-calibrated as suggested by the manufacturing company Otometrics. For the lateral vHIT, participants were instructed to keep their head facing straight forward and look at the target on the wall. Both the researchers' hands were placed at the base of the participants head ensuring no contact was made with the cheeks and the goggle strap to prevent slippage. The researcher then performed quick but small horizontal head impulses in a unexpected manner (Guinand et al., 2017; Halmagyi et al., 2017). Results were considered normal if: the VOR gain value was >0.8 with no present covert and overt catch-up saccades (McGarvie et al., 2015).

For the vertical vHIT participants were instructed to turn their head 45 degrees to the right or left. The researcher placed one hand on top of the participants head and the other hand under the chin. The researcher then performed quick but small head impulses in the direction of the left anterior and right posterior (LARP) plane as well as the right anterior and left posterior (RALP) plane (Halmagyi et al., 2017). For healthy participants it was evident that after approximately 10 seconds there was a smooth compensatory eye movement with equal velocity to that of the head velocity but in the opposite direction (Halmagyi et al., 1990). Results were considered abnormal if: (i) the VOR gain value was <0.8 for the lateral canals and <0.7 for the vertical canals, and/or (ii) covert or overt catch-up saccades were present (McGarvie et al., 2015).

Figure 4 illustrates the head movement procedure for the lateral vHIT test and the vertical vHIT tests (RALP and LARP).

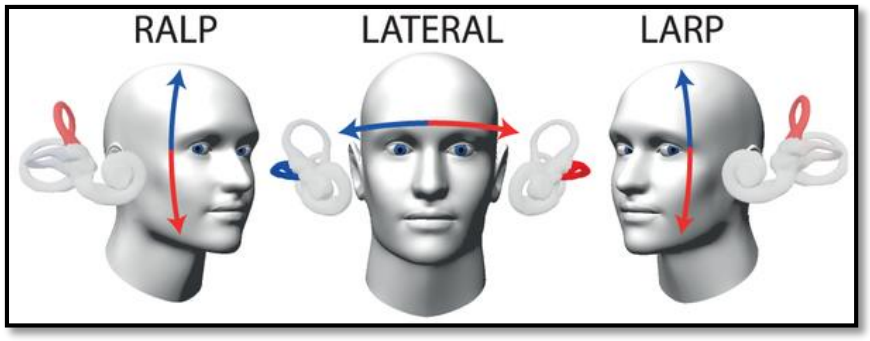

Figure 4: Head movements for the lateral and vertical vHIT tests (image from MacDougall, McGarvie, Halmagyi, Curthoys, & Weber, 2013).

2.5.7 Dynamic Gait Index (DGI)

The DGI was developed by Shunway-Cook and Woollacott, to evaluate functional stability in older people and to assess their risk of falling while performing several gait activities (Jonsdottir & Cattaneo, 2007). As the DGI measures gait instability it is considered as a good indicator for fall risks in people with vestibular disorders (Herman, Inbar-borovsky, Brozgol, Giladi, & Jeffrey, 2009).

The DGI consists of eight different activities that vary in complexity. Participants were asked to complete the following tasks: (i) gait on a level surface, (ii) change in gait speed, (iii) gait with horizontal head turns, (iv) gait with vertical head turns, (v)

gait and pivot turn, (vi) step over obstacle, (vii) step around obstacles, and (viii) going up stairs. Participants were given a score of 0 to 3, where 0 equals severe impairment and 3 equals normal performance. A total score out of 24 was then calculated, scores <19 have been associated with a higher risk of falls (Herman et al., 2009).

2.5.8 Berg Balance Scale (BBS)

The BBS was created to assess patients' static and dynamic balance by observing them while sitting, standing and changing posture. Therefore the BBS is often used to evaluate risk of falls based on the assessment of a patient's balance. Multiple studies have indicated that the BBS has a high validity and reliability on diverse target populations. It is often used for the assessment of balance in patients with chronic diseases (Park & Lee, 2017).

Participants were asked to complete 14 different functional activities: (i) sitting to standing, (ii) standing unsupported for 2min, (iii) sitting with back unsupported, (iv) standing to sitting, (v) transfer from one chair to another, (vi) standing with eyes closed, (vii) standing with feet together, (viii) reaching forward with an outstretched arm, (ix) retrieving an object form the floor, (x) turning to look behind each shoulder, (xi) turning 360 degrees, (xii) placing alternate feet on a step, (xiii) standing with one foot in front of the other, and (xiv) standing on one leg. These activities took 15 to 20 minutes to complete (Park & Lee, 2017).

Each participant was given a score of 0 to 4 for each activity, where 0 was equal to an inability to perform the task and 4 was equal to an ability to complete the task independently. Thereafter a total score out of 56 was calculated. A score of 41 to 56 indicated a low risk of falls, 21 to 40 indicated a medium risk of falls and less than 20 indicated a high risk of falls (Berg, Wood-Dauphine, & Gayton, 1989).

2.5.9 The Timed Up and Go Test (TUG)

The TUG test is a reliable tool used to assess a participant's functional mobility. The test was developed in 1991 as a modified version of the Get up and Go test. With the modified version the participant is timed while performing the task. It has been proved that the time score is reliable and that it can assess a participants' ability to safely go about their daily living (Podsiadlo & Richardson, 1991). The TUG test is

recommended as a screening for falls risk by the American Geriatric Society, the British Geriatric Society and the Society of Nordic Geriatricians (Barry, Galvin, Keogh, Horgan, & Fahey, 2014).

The test procedure is quite simple and quick to administer. Participants were seated on a standard length chair, with their backs against the chair. They were instructed to stand up, walk at a comfortable pace to the cone placed 3m from the chair, turn around, walk back to the chair and sit down again. If participants use a walking aid they were requested to also use it during the procedure. The researcher also observed whether participants were unstable while turning around to walk back to the chair. Participants were timed during the task and the time was documented in seconds. The stopwatch was started on the command go and stopped when the participant was seated on the chair. A time of 10 seconds or less was classified as normal and a time of more than 10 seconds was classified as abnormal with a high risk of falls (Herman, Giladi, & Hausdorff, 2011; Podsiadlo & Richardson, 1991).

2.6 Data analysis

The data were analysed with the statistical software Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and Rstudio version 3.5.1 (R Core Team (2018). R: A language and environment for statistical computing. R: Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). The samples were described as means and standard deviations with medians and interquartile ranges as well as numbers and percentages. A p value of <0.05 was regarded as statistically significant. Descriptive statistics were provided based on the distribution of the data. Most data were regarded as non-parametric except age and vHIT gains. As the data were paired, paired *t*-tests were used for age and vHIT gains and Wilcoxon exact tests for the non-parametric comparisons (exact as there were ties present). To compare paired proportions exact symmetry tests (exact because of the small numbers) were used. Due to the relatively small numbers in the study the comparison of proportions should be regarded as exploratory. As there was no single specific hypothesis being tested, 30 participants per group were used to provide sufficient power (80%) to detect a difference between 0.5 and 1 standard deviation between groups. Odds

ratios (OR) were calculated where needed, (Affected diabetics/Unaffected diabetics) / (Affected non-diabetics/Unaffected non-diabetics).

Chapter 3: Results

The results of the audio-vestibular tests, fall risk assessments and the health related quality of life questionnaire obtained from 30 type 1 diabetic participants were compared with 30 age and gender matched non-diabetic participants without a history of inner ear disease. (Eight participant's data in the non-diabetic group were used more than once, as their age and gender matched with several diabetic participants).

3.1 Study participants

Table 4 summarizes the demographic features of the study participants.

Table 4: Demographic features of the study participants

Characteristic	Diabetic group (n=30)	Non-diabetic group (n=30)	N	*p* value
Age (Years)	35.4 (±12.4)	35.2 (±12.4)	60	0.93
Gender:			60	1.00
Female	20 (67%)	20 (67%)	-	-
Male	10 (33%)	10 (33%)	-	-
BMI	24.8 (±3.7)	27.2 (±5.9)	59	0.04*
SBP	132.3 (±19.5)	123.3 (±12.3)	58	0.043*
DBP	80.5 (±12.5)	82.5 (±9.6)	58	0.49
Monofilament test:			60	0.39
3/8	1 (3%)	0 (0%)	-	-
6/8	0 (0%)	1 (3%)	-	-
7/8	0 (0%)	1 (3%)	-	-
8/8	29 (97%)	28 (93%)	-	-
Disease duration (Years)	16.2 (±12.8)	-	30	-
Current blood glucose (mmol/L)	8.1 [5.8;10.7]	5.2 [5.0;6.0]	60	<0.001***
Retinopathy	9 (30%)	-	-	-
Kidney failure	2 (7%)	-	-	-
Peripheral neuropathy	3 (10%)	-	-	-
GHbA1c	14.0 (±17.4)	-	12	-
Blood glucose (mmol/L)	10.9 (±3.7)	-	12	-
Total cholesterol (mmol/L)	5.0 (±1.5)	-	12	-
LDL (mmol/L)	2.9 (±1.1)	-	12	-
HDL (mmol/L)	1.5 (±0.5)	-	12	-
Urea (mmol/L)	5.3 (±1.6)	-	9	-
Creatinine (mmol/L)	74.0 [61.2;78.8]	-	12	-

Statistical test used for age, gender, BMI, SBP, DBP and monofilament test: paired t-test. Statistical test used for current blood glucose: Wilcoxon paired exact test. Gender: Chi Square test. BMI (body mass index), DBP (diastolic blood pressure), GHbA1c (glycated hemoglobin), HDL (high density lipoprotein), LDL (low density lipoprotein), mmol/L (millimole per litre), SBP (systolic blood pressure). ***Very significant, *Significant.

For both the diabetic and non-diabetic group some data could not be obtained or were not available, as indicated by the N values in the above table. The mean age for both the diabetic and non-diabetic group were very similar, 35.4 (±12.4) years for the diabetic group and 35.2 (±12.4) years for the non-diabetic group. Both groups consisted of 67% females and 33% males. If available, participants' weight and height were collected in order to calculate BMI. For the diabetic group the mean BMI was 24.8 kg/m^2 (±3.7) and for the non-diabetic group a higher mean BMI of 27.2 kg/m^2 (±5.9) was obtained. The *p* value of 0.04; paired *t*-test indicates a significant difference in BMI between the two groups. A significant difference in systolic blood pressure between the two groups was also present as indicated by the *p* value of 0.043; paired *t*-test with a mean systolic blood pressure of 132.3 (±19.5) for the diabetic group and 123.3 (±12.3) for the non-diabetic group. However for the diastolic blood pressure no significant difference was present between the two groups. The mean disease duration of type 1 DM was 16.2 (±12.8) years with a median blood glucose level of 8.1 mmol/L compared to 5.2 mmol/L for the non-diabetic group.

3.2 Otologic and audiological assessment results

Table 5 shows the AC pure tone audiometry results for test frequencies ranging from 250 to 8000Hz for each ear separately. A 4-tone PTA at 500, 1000, 2000 and 4000Hz was calculated for each ear. Furthermore the participants' hearing was classified according to the degree of hearing loss using Clarks's classification system as: normal $\leq$15dBHL, slight hearing loss 16dBHL to 25dBHL, mild hearing loss 26dBHL to 40dBHL or moderate hearing loss 41dBHL to 55dBHL (Clark, 1981). Middle ear data collected (tympanometry and reflex measurements) were only collected to identify participants to be excluded from the study and therefore it was not included in the analysis of the audiometric data.

Table 5: Audiological assessment results of the study participants (Median and .25; .75)

Left ear			
	Diabetic group (n=30)	**Non-diabetic group (n=30)**	***p* value**
250Hz	20.0 [15.0;28.8]	12.5 [5.0;20.0]	<0.001***
500Hz	20.0 [15.0;28.8]	15.0 [10.0;20.0]	<0.001***
1000Hz	15.0 [10.0;20.0]	10.0 [5.0;18.8]	0.002**
2000Hz	15.0 [10.0;23.8]	12.5 [5.0;15.0]	0.029*
4000Hz	10.0 [0.0;23.8]	5.0 [0.0;10.0]	0.005**
8000Hz	12.5 [5.0;25.0]	10.0 [0.0;22.5]	0.194
4-tone PTA	14 [10; 22]	10 [5;16]	0.005**
Right ear			
	Diabetic group (n=30)	**Non-diabetic group (n=30)**	***p* value**
250Hz	20.0 [11.2;25.0]	10.0 [5.0;10.0]	<0.001***
500Hz	20.0 [11.2;25.0]	10.0 [5.0;20.0]	0.001**
1000Hz	15.0 [10.0;20.0]	10.0 [5.0;15.0]	0.014*
2000Hz	15.0 [10.0;20.0]	10.0 [5.0;15.0]	<0.001***
4000Hz	10.0 [0.0;20.0]	0.0 [0.0;5.0]	0.004**
8000Hz	10.0 [5.0;28.8]	0.0 [0.0;10.0]	0.001**
4-tone PTA	15.0 [8.5;22.0]	7.5 [3.0;12.0]	<0.001***

Statistical test used for the thresholds at frequencies 250Hz-8000Hz and the 4-tone PTA: Wilcoxon paired exact test. The statistical test used for the degree of hearing loss: exact symmetry test. Hz (Hertz: frequency), HL (hearing loss), 4-tone PTA (4 pure tone average). ***Very significant, **Very significant, *Significant.

Left ear: A statistically significant difference was observed between the diabetic and non-diabetic groups' median AC thresholds for frequencies 250Hz-4000Hz as well as the 4-tone PTA of the left ear. Although the average 4-tone PTA for both groups still indicates normal hearing, poorer thresholds were obtained for the diabetic group at all the frequencies. Diabetic participants were more likely to have hearing loss at the lower frequencies (250Hz-500Hz). The only frequency with no statistical difference in the left ear was 8000Hz as indicated by a *p* value of 0.194; Wilcoxon paired exact test. With concern to the degree of hearing loss only 18/30 (60%) diabetic participants had normal hearing compared to 20/30 (67%) non-diabetic participants ($p < 0.0001$; exact symmetry test).

Right ear: There was a statistically significant difference observed between the diabetic and non-diabetic groups' median AC thresholds at all the frequencies (250Hz-8000Hz) as well as the 4-tone PTA of the right ear. The average 4-tone PTA

for both groups still indicates normal hearing, however poorer thresholds were obtained for the diabetic group at all the frequencies. Similarly to the left ear, diabetic participants were more likely to have hearing loss at the lower frequencies (250Hz-500Hz). With concern to the degree of hearing loss only 15/30 (50%) diabetic participants had normal hearing compared to 19/30 (63%) non-diabetic participants (p=0.008; exact symmetry test).

Figure 5 illustrates the degree of hearing loss in the right- and left ear of the participants in both groups.

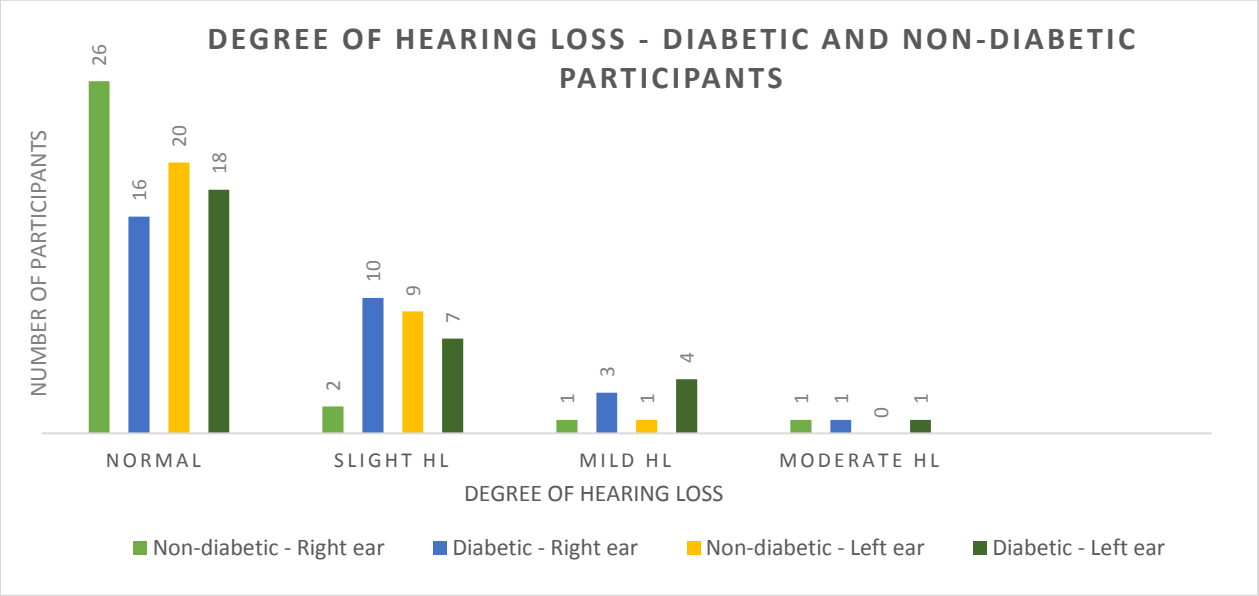

Figure 5: Degree of hearing loss in the right and left ears for the diabetic and non-diabetic group.

3.3 Vestibular evoked myogenic potentials (VEMPs) results

Table 6 describes the results obtained from the cVEMP and oVEMP assessment for the participants who had present responses (n=ears with present responses). The P1 and N1 latencies, inter-peak amplitudes and ARs for each ear are described.

Table 6: cVEMP and oVEMP latencies and inter-peak amplitudes (Median and .25; .75)

Left				Right			
	Diabetic group	**Non-diabetic group**	***p* value**		**Diabetic group**	**Non-diabetic group**	***p* value**
cVEMP (n=60)				**cVEMP (n=60)**			
P1 (ms)	15.6 [14.6;17.0]	16.3 [14.8;17.9]	0.51	P1 (ms)	16.6 [14.7;17.8]	15.8 [14.8;17.2]	0.24
N1 (ms)	24.6 [23.4;26.5]	23.8 [22.8;24.9]	0.108	N1 (ms)	25.2 [23.5;27.2]	23.8 [22.8;25.4]	0.051
IP amplitude (μV)	17.8 [9.98;35.6]	20.9 [13.4;33.6]	1.00	IP amplitude (μV)	15.5 [7.65;34.4]	23.1 [14.0;40.2]	0.119
oVEMP (n=54)			0.22	**oVEMP (n=54)**			0.031*
N1 (ms)	10.0 [9.40;10.4]	9.61 [9.61;10.0]	0.20	N1 (ms)	10.0 [9.82;10.9]	9.61 [9.19;10.2]	0.036*
P1 (ms)	15.0 [14.4;15.4]	14.8 [13.8;15.2]	0.173	P1 (ms)	14.8 [14.2;15.7]	14.6 [14.2;15.0]	0.165
IP amplitude (μV)	6.08 [3.70;14.2]	11.6 [6.73;22.4]	0.046*	IP amplitude (μV)	7.98 [3.15;14.1]	16.0 [5.99;25.4]	0.005**

Statistical test used for cVEMP P1, cVEMP N1, cVEMP amplitude, oVEMP N1, oVEMP P1 and oVEMP amplitude: Wilcoxon paired exact test. The statistical test used for oVEMP present: exact symmetry test. *IP* (interpeak), μV (microvolt), ms (milliseconds). **Very significant, *Significant.

Left: The cVEMPs were bilaterally present in both groups. The median P1 and N1 latencies were within clinical norms. There were no significant differences in these latencies between groups. Despite no significant differences, 4/30 (13%) diabetic participants had delayed cVEMP P1 latencies and 6/30 (20%) had delayed cVEMP N1 latencies on the left. All of the non-diabetic participants had normal cVEMP P1 and N1 latencies on both sides. The median interpeak amplitudes did not show significant differences between the two groups.

Figure 6 illustrates the left oVEMP amplitude results for the diabetic and non-diabetic participants.

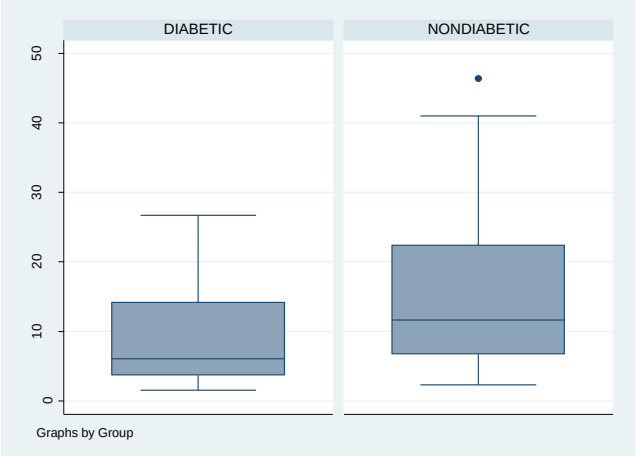

Figure 6: Boxplot of the left ears oVEMP amplitude for the diabetic and non-diabetic group.

The oVEMPs were absent in 5/30 (17%) diabetic participants on the left side compared to 1/30 (3%) non-diabetic participants. No significant differences were present in the left oVEMP P1 and N1 latency. Despite no significant differences, 4/30 (13%) diabetic participants had a delayed oVEMP N1 latency compared to only 1/30 (3%) non-diabetic participants. None of the participants had delayed oVEMP P1 latencies. The median interpeak amplitudes showed significant differences between the two groups. A median oVEMP amplitude for the diabetic group of 6.08 and 11.6 for the non-diabetic group were obtained. Overall the oVEMP amplitude for the diabetic participants were smaller than the amplitude for the non-diabetic participants.

Right: The cVEMPs were bilaterally present in both groups. The median P1 and N1 latencies were within clinical norms. There were no significant differences in these latencies between groups. Despite no significant differences, 4/30 (13%) diabetic participants had delayed cVEMP P1 latencies and 7/30 (23%) had delayed cVEMP N1 latencies. All of the non-diabetic participants had normal cVEMP P1 and N1 latencies on both sides. The median interpeak amplitudes did not show significant differences between the two groups.

Figure 7 illustrates the right oVEMP amplitude results for the diabetic and non-diabetic participants.

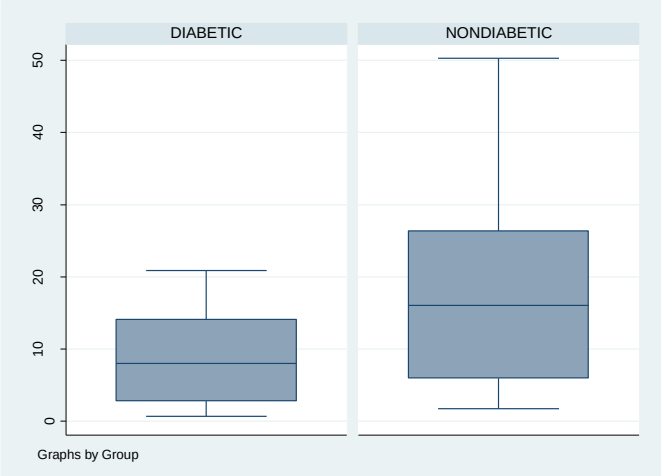

Figure 7: Boxplot of the right ears oVEMP amplitude for the diabetic and non-diabetic group.

The oVEMPs were absent in 6/30 (20%) diabetic participants on the right side compared to none in the non-diabetic group. A significant difference was present in the right oVEMP N1 latency, however the N1 median latency were still within clinical norms. For the right N1 latencies, 5/30 (17%) diabetic participants had a delayed latency compared to only 1/30(3%) non-diabetic participants. None of the participants had delayed oVEMP P1 lantencies. The median interpeak amplitudes showed significant differences between the two groups. Overall the oVEMP amplitude for the diabetic participants was smaller than the amplitude for the non-diabetic participants.

3.4 Video head impulse test (vHIT) results

Table 7 describes the lateral, RALP and LARP vHIT results for the diabetic and non-diabetic group in terms of gain and the presence/absence of overt and covert saccades.

Table 7: Video head impulse test results, gain and saccades

vHIT gain: left ear (n=30)				**vHIT saccades: left ear (n=30)**			
Canal	**Diabetic group Mean (STD)**	**Non-diabetic group Mean (STD)**	***p* value**	**Canal**	**Diabetic group n(%)**	**Non-diabetic group n(%)**	***p* value**
Lateral	0.9 (±0.1)	0.9 (±0.1)	0.168	**Lateral**	1 (3%)	0 (0%)	1.00
Anterior	0.8 (±0.2)	0.9 (±0.1)	<0.001***	**Anterior**	2 (7%)	0 (0%)	0.50
Posterior	0.9 (±0.2)	0.9 (±0.1)	0.56	**Posterior**	4 (13%)	2 (7%)	0.69
vHIT gain: right ear (n=30)				**vHIT saccades: right ear (n=30)**			
Lateral	1.0 (±0.1)	1.0 (±0.1)	0.62	**Lateral**	2 (7%)	0 (0%)	0.50
Anterior	0.8 (±0.2)	0.8 (±0.2)	0.33	**Anterior**	3 (10%)	0 (0%)	0.25
Posterior	0.9 (±0.2)	0.9 (±0.1)	0.026*	**Posterior**	5 (17%)	1 (3%)	0.22

Statistical test used for lateral gain, anterior gain and posterior gain: Wilcoxon paired exact test. Statistical test used for lateral saccades, anterior saccades and posterior saccades: exact symmetry test. ***Very Significant, *Significant.

Left: There was a significant difference between the diabetic and non-diabetic groups' anterior gain as indicated by the *p* value 0.0009; Wilcoxon paired exact test. A mean gain of 0.8 (±0.2) for the diabetic group was obtained and a mean gain of 0.9 (±0.1) for the non-diabetic group. A total of 7/30 (23%) diabetic participants had an abnormal low gain compared to none of the non-diabetic participants. However no significant differences were present for lateral gain, lateral saccades, anterior saccades, posterior gain and posterior saccades. As indicated by the *p* values:

0.168, 1.00, 0.50, 0.56 and 0.69. Despite no significant differences 4/30 (13%) diabetic participants had abnormal low gains for the lateral canal and the posterior canal compared to none of the non-diabetic participants. With regard to the presence of overt and covert saccades, 1/30 (3%) of diabetic participants had present lateral saccades compared to none of the non-diabetic participants. As for anterior saccades 2/30 (7%) of the diabetic group had present saccades, and none in the non-diabetic group. Furthermore posterior saccades were present in 4/30 (13%) of the diabetic participants and only 2/30 (7%) of the non-diabetic participants.

Right: There was a significant difference between the diabetic and non-diabetic groups posterior gain as indicated by the *p* value 0.02; Wilcoxon paired exact test. With a mean gain of 0.9 (±0.2) for the diabetic group and a mean gain of 0.9 (±0.1) for the non-diabetic group. A total of 4/30 (13%) diabetic participants had an abnormal low gain compared to none of the non-diabetic participants. No significant differences were present for any other vHIT parameters on the right as indicated by the *p* values in the above table. Despite no significant differences present, 1/30 (3%) diabetic participants had an abnormal low gain in the lateral canal compared to none of the non-diabetic participants. Furthermore, a total of 7/30 (23%) diabetic participants had an abnormal gain in the anterior canal compared to only 3/30 (10%) non-diabetic participants. With regards to the presence of overt and covert saccades, 2/30 (7%) diabetic participants had present lateral saccades compared to none of the non-diabetic participants. As for anterior saccades 3/30 (10%) of the diabetic group had present saccades, and none in the non-diabetic group. Furthermore posterior saccades were present in 5/30 (17%) of the diabetic participants and only 1/30 (3%) of the non-diabetic participants.

3.5 Fall risk assessment results

Table 8 summarizes the risk of falling for the diabetic and non-diabetic participants. The DGI, BBS and TUG were administered.

Table 8: Fall risk assessment results (Median and .25; .75)

	Diabetic group (n=30)	Non-diabetic group (n=30)	*p* value
DGI (/24)	24.0 [23.0;24.0]	24.0 [24.0;24.0]	0.035*
BBS (/56)	56.0 [55.0;56.0]	56.0 [55.0;56.0]	0.27
TUG (sec)	7.35 [6.64;8.05]	7.41 [6.94;7.86]	1.00
Unstable: n(%)	1 (3%)	0 (0%)	1.00
Walking aid: n(%)	0 (0%)	0 (0%)	-

Statistical test used for DGI, BBS, TUG: Wilcoxon paired exact test. Statistical test used for unstable: exact symmetry test. BBS (berg balance scale), DGI (dynamic gait index), and TUG (timed up and go). *Significant.

A significant difference in the DGI score was found between the diabetic and non-diabetic group as indicated by the *p* value 0.035; Wilcoxon paired exact test. Diabetic participants were more likely to obtain a lower score for the DGI than non-diabetic participants (OR: 3.9). Despite the significant difference only 1/30 (3%) diabetic participants obtained an abnormal score (<19). No significant differences were present for the other two fall risk assessments: the BBS and TUG. None of the participants had an abnormal score for the BBS. Furthermore, only one participant in each group obtained an abnormal score for the TUG (>10s).

3.6 Health Related Quality of Life Questionnaire (EQ-5D-5L) results

Table 9 summarizes the results of the HRQoL for all the participants obtained from the EQ-5D-5L health questionnaire. Each of the five dimensions in the questionnaire mobility, selfcare, usual activities, pain and discomfort as well as anxiety and depression, were scored using five levels of severity.

Table 9: EQ-5D-5L Health Questionnaire results (n and %)

Health dimension	Diabetic group (n=30)	Non-diabetic group (n=30)	*p* value
Mobility:			0.50
1	29 (97%)	28 (93%)	-
2	1 (3%)	0 (0%)	-
3	0 (0%)	2 (7%)	-
4	0 (0%)	0 (0%)	-
5	0 (0%)	0 (0%)	
Selfcare:			0.50
1	30 (100%)	28 (93%)	-
2	0 (0%)	0 (0%)	
3	0 (0%)	2 (7%)	-
4	0 (0%)	0 (0%)	-
5	0 (0%)	0 (0%)	-
Usual activities:			0.070
1	22 (73%)	29 (97%)	-
2	7 (23%)	1 (3%)	-
3	0 (0%)	0 (0%)	-
4	0 (0%)	0 (0%)	-
5	1 (3%)	0 (0%)	-
Pain and discomfort:			0.074
1	19 (63%)	24 (80%)	-
2	8 (27%)	3 (10%)	-
3	2 (7%)	3 (10%)	-
4	1 (3%)	0 (0%)	-
5	0 (0%)	0 (0%)	-
Anxiety and depression:			0.27
1	19 (63%)	24 (80%)	-
2	6 (20%)	6 (20%)	-
3	4 (13%)	0 (0%)	-
4	1 (3%)	0 (0%)	-
5	0 (0%)	0 (0%)	-
VAS Median (.25; .75)	80.0 [70.0;90.0]	95.0 [90.0;100]	<0.0001***

Statistical test used for mobility, selfcare, usual activities, pain and discomfort, anxiety and depression: exact symmetry test. Statistical test used for VAS: Wilcoxon paired exact test. Five levels of severity: 1(no problem), 2(slight problems), 3(moderate problems), 4(severe problems), 5(extreme problems). VAS (visual analogue scale). ***Very Significant.

No significant differences were found in the five health dimensions where participants had to rate their health status. Although no significant differences were present it can be seen from the diabetic participants' responses that they are more likely to experience problems in three health domains: usual activities (OR: 10.9), pain and discomfort (OR: 2.3) and anxiety and depression (OR: 2.3). When participants had to to rate their overall health and plot it on a vertical axis, diabetic participants rated their HRQoL to be poorer than the non-diabetic participants (p<0.0001; Wilcoxon paired exact test). The score for the diabetic participants HRQoL was 80/100 compared to the non-diabetic participants' of 95/100.

3.7 Summary

Figure 8 illustrates the number of diabetic participants with inner ear dysfunction.

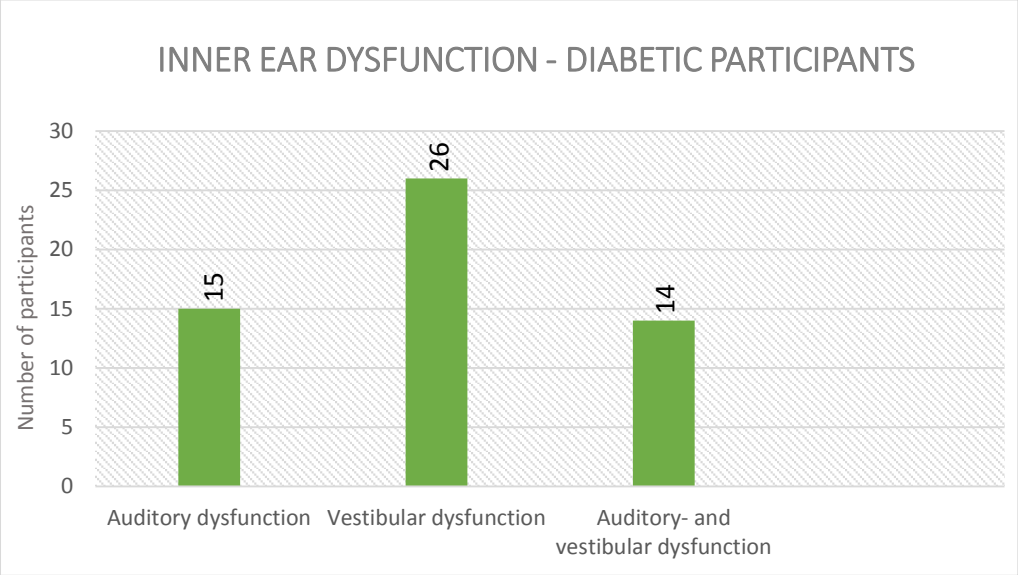

Figure 8: Inner ear dysfunction in the diabetic participants.

The presence of hearing loss in both ears were higher in the type 1 DM participants compared to the non-diabetic participants. In total 15/30 (50%) diabetic participants had either a bilateral or unilateral hearing loss compared to 11/30 (37%) non-diabetic participants (OR: 1.7). Vestibular dysfunction was described as abnormal vHIT results and/or abnormal VEMP results. Therefore, a total of 26/30 (87%) diabetic participants had vestibular dysfunction compared to only 7/30 (23%) non-diabetic participants (OR: 24.2). Overall, 14/30 (47%) diabetic participants had hearing loss together with vestibular dysfunction compared to only 4/30 (13%) non-diabetic participants.

Chapter 4: Discussion and conclusion

4.1 Discussion of results

The current research study aimed to describe auditory-vestibular function in adults with type 1 DM, and to determine the impact of the disease on their risk of falls and HRQoL. Data from this group was compared to data obtained from a control group of non-diabetic age and gender matched adults. This main aim was achieved by performing AC pure tone audiometry, vestibular tests (cVEMPs, oVEMPs and vHIT), three fall risk assessments (BBS, DGI and TUG) as well as a quality of life questionnaire (EQ-5D-5L questionnaire). The results of this research study showed a significantly higher occurrence of auditory dysfunction in the type 1 DM participants compared to the non-diabetic participants. Type 1 DM participants also showed a higher occurrence of vestibular dysfunction but not for risk of falling. Diabetic participants were found to have a significantly poorer HRQoL.

4.1.1 Hearing loss and type 1 diabetes mellitus

The association between hearing loss and DM has been researched since it was first mentioned by Jordan in 1857 (David et al., 2015). However the exact cause and effect correlation between hearing loss and DM are still not clear (Malucelli et al., 2012). Diabetes mellitus is a global health burden that is predicted to be the seventh leading cause of death in 2030. According to the International Diabetes Federation (IDF, 2017) 425 million people world-wide are affected by DM. Diabetes mellitus can lead to blindness, kidney failure, heart attacks, stroke and lower limb amputation (WHO, 2018). As mentioned DM can also lead to hearing loss (Akinpelu, Mujica-Mota, & Daniel, 2013; Teng et al., 2017). Among the leading causes of the Global Burden of Disease hearing loss is ranked 15th, furthermore hearing loss is the 2nd leading cause of years lived with a disability (WHO, 2002). Due to these detrimental effects of DM and hearing loss, the structural and functional changes in individuals with DM should be well defined to allow creation of new ways of preventing and managing damage to the inner ear (Xipeng et al., 2013).

The inner ear is dependent on a continuous supply of oxygen and glucose rich blood as created by microcirculation (Rybak, 1995). Diabetes mellitus impairs this constant

supply of blood and can lead to inner ear dysfunction. Numerous studies conclude that type 1 DM is closely linked to hearing loss (Austin et al., 2009; Celik, Yalcin, Celeni, & Ozturk, 1996; Dąbrowski et al., 2011; David et al., 2015; Hou et al., 2015; Malucelli et al., 2012; Okhovat et al., 2011; Rance et al., 2014; Teng et al., 2017; Xipeng et al., 2013). In a recent literature review that included 252 DM participants and 253 non-diabetic participants, the pooled odds ratio for the prevalence of hearing loss in type 1 DM individuals versus non-diabetics was 49.08 (Teng et al., 2017). The hearing loss associated with type 1- and 2 DM proves to be mild or subclinical, bilateral, progressive, sensorineural, and predominantly in the high frequencies (Akinpelu et al., 2013; Botelho, Da Silva Carvalho, & Silva, 2014; Dąbrowski et al., 2011; Teng et al., 2017). According to the theory of tonotopicity, DM first causes damage to the hair cells at the basal end of the cochlea which then present as a high frequency hearing loss (Vesperini et al., 2011). In contrast, other studies proves that all the frequencies are effected in type 1 DM individuals and not only the high frequencies (Hou et al., 2015; Lasagni et al., 2016; Malucelli et al., 2012; Okhovat et al., 2011).

The audiometric findings from the current study are in agreement with existing literature that found significantly elevated mean audiometric thresholds at all the frequencies in type 1 diabetic participants compared to non-diabetic participants. However with the mean pure tone thresholds still within normal limits (Hou et al., 2015; Lasagni et al., 2016; Okhovat et al., 2011). The results of the current study showed higher 4 tone-PTAs and audiometric thresholds at all the frequencies in the diabetic participants compared to the non-diabetic group, but were still within the normal limits at 1000Hz-8000Hz ($\leq$15dBHL). Diabetic participants' lower frequencies were more likely to have hearing loss (250Hz-500Hz). The occurrence of hearing loss in the current study closely correlates with the study by Hou et al. (2015) that found 24/50 (48%) type 1 DM participants to have a hearing loss. In the current study a total of 15/30 (50%) diabetic participants had either a bilateral or unilateral hearing loss ($\geq$16dBHL) compared to 11/30 (37%) non-diabetic participants. Of these participants 11/30 (37%) type 1 DM participants had a bilateral hearing loss, compared to only 3/30 (10%) non-diabetic participants. Unilateral hearing loss was present in more non-diabetic participants, 8/30 (27%) compared to 4/30 (13%) diabetic participants. Overall, the odds ratio from the current study indicated that the

risk of hearing loss was 1.7 times higher in individuals with type 1 DM than in healthy individuals. It has to be considered that early damage in the cochlea could have been missed, as conventional pure tone audiometry cannot detect the earliest damage in the cochlea (David et al., 2015; Ottaviani, Dozio, Neglia, Riccio, & Scavini, 2002).

In contrast to the above mentioned studies some research studies reported that type 1 DM participants only have higher audiometric thresholds at high frequencies (Botelho et al., 2014; Dąbrowski et al., 2011). Some authors even reported that there is no link between hearing loss and DM (De Espana et al., 1995; Pessin et al., 2008; Tavakoli et al., 2014). These disparities in results could be due to a number of variations in the research design. Firstly sample size; some studies only have limited study participants compared to others. Smaller sample sizes are not necessarily representative of the specific study population. Secondly, it is very difficult to study the independent effect of DM on the inner ear as various other variations and complications can have an influence on auditory function. For example: the age of the participants and the exclusion of any other factors that could influence auditory function such as ototoxic medication, noise exposure, middle ear pathology etc. Thirdly, the test methods used. Some studies only used one test procedure to assess auditory function while other studies include several test procedures namely pure tone audiometry, ABR and OAE.

Auditory dysfunction proves to be related to disease duration, HDL level, systemic blood pressure, microalbuminuria, GHbA1c, triglyceride and age of the patient. A longer disease duration can increase type 1 diabetics' risk for hearing loss (Hou et al., 2015; Okhovat et al., 2011; Pudar, Vlaski, Filipovic, & Tanackov, 2010; Seidl et al., 1996). In the current study the mean disease duration of the type 1 diabetic individuals was 16.2 years, with a maximum of up to 42 years. Pudar and colleagues (2010) correlated a higher risk for hearing loss in individuals with a longer disease duration, hearing loss was especially prominent in individuals with a disease duration of more than 10 years.

Fluctuations in blood glucose can affect the endolymph in the inner ear and cause hydroelectrolytic imbalance (Hou et al., 2015). The median blood glucose level of

type 1 DM individuals on the day of the assessment was 8.1 mmol/L with 11/30 (37%) individuals above the normal 8mmol/L, as recommended by the National Institute for Health and Clinical Excellence (NICE) and the International Diabetes Federation (Abbott Diabetes Care, 2018). Sustained high blood glucose levels cause an increase in GHbA1c production. These higher GHbA1c and/or microalbuminuria levels can aggravate hearing loss in individuals with DM (Hou et al., 2015). In the current study the mean GHbA1c level for the type 1 DM individuals was 14%, higher than the normal 7% (Schubert et al., 2010). Hou and colleagues (2015) correlated high GHbA1c levels with damage to the OHC's in the cochlea.

4.1.2 Vestibular dysfunction and type 1 diabetes mellitus

The auditory and vestibular systems are both innervated by the eighth cranial nerve and share the same blood supply (Stach, 2010). Therefore, due to this shared nerve and blood supply, DM can cause damage not only to the auditory system but also to the vestibular end-organs (Ward et al., 2015). Vestibular dysfunction is still a newly recognized secondary manifestation of DM (Schubert et al., 2010). In general literature is sparse concerning this topic (Gawron et al., 2002). To date only a few studies reported vestibular dysfunction in individuals with type 1 DM (Gawron et al., 2002; Kamali et al., 2013; Kamali et al., 2013; Klagenberg et al., 2007; Prakash & Sumathi, 2013; Rigon et al., 2007; Scherer & Lobo, 2002; Tavakoli et al., 2014).

Previous research primarily focused on caloric testing (Gawron et al., 2002; Klagenberg et al., 2007; Rigon et al., 2007; Scherer & Lobo, 2002) and cVEMPs (Kamali et al., 2013; Kamali et al., 2013; Tavakoli et al., 2014) to determine the vestibular function of type 1 DM participants. The cVEMPs showed a higher occurrence of abnormal response parameters in type 1 DM participants than in non-diabetic participants (Kamali et al., 2013; Kamali et al., 2013; Tavakoli et al., 2014). However studies differ in concluding what parameters of the cVEMP response were affected. Two studies (Kamali et al., 2013; Kamali et al., 2013) found that the mean P1- and N1 latencies were significantly delayed in individuals with type 1 DM. However no difference in the absolute and relative amplitudes of the VEMP responses between the experimental and control group were evident. Interestingly another study (Tavakoli et al., 2014) compared the cVEMP responses of 15 individuals with type 1 DM, 15 individuals with type 2 DM and 10 healthy participants.

The researchers concluded that only the cVEMP amplitudes were statistically smaller in the type 1 and type 2 DM participants compared to the non-diabetic participants.

In contrast to the above mentioned research, the current study showed no significant differences in the cVEMP results between the diabetic and non-diabetic participants. Similar to Kamali et al. (2013), all the participants in the DM group (n=30) had present cVEMPs. No significant differences were present in cVEMP P1- and N1 latencies and the cVEMP amplitude between the two groups. Despite no significant differences, 17/30 (57%) diabetic participants had either a delayed P1- and/or N1 latency. Delayed VEMP latencies in individuals with DM can be indicative of neuropathy (Ward et al., 2015), as neuropathy is one of the most common complications associated with DM (Fowler, 2008). However according to Murofushi et al., 2001 damage to the vestibular nerve only may be insufficient to cause abnormal VEMP latencies. Brainstem lesions, especially those in the vestibulospinal tract, are suspected to be responsible for delayed P1 latencies. Brainstem and midbrain lesions have been connected to DM (Siddiqi, Gupta, Aslam, Hasan, & Khan, 2013). Possible reasons for the inconsistency in VEMP results could be due to a number of reasons. Firstly sample size as some studies only have limited study participants compared to others. Larger sample sizes increases the sensitivity of the hypothesis while smaller sample sizes are not necessarily representative of the specific study population. Secondly, different exclusion and inclusion criteria. For example: the age of the participants, the duration of disease, the exclusion of any other factors that could influence vestibular function such as ototoxic medication, head trauma, middle or inner ear infections etc.

To our knowledge, the nature of utricular function as determined by means of oVEMPs in type 1 DM individuals has not yet been described. However Kalkan and colleagues (2018) reported oVEMP findings in type 2 DM participants with polyneuropathy, DM participants without polyneuropathy and healthy controls. A significant difference was found in the oVEMP amplitudes between the three groups for both ears. The DM participants with polyneuropathy had the smallest oVEMP amplitude of the three groups followed by the DM participants without polyneuropathy. No significant differences were found in the P1- and N1 latencies. In

contrast to Kalkan et al. (2018) that found present oVEMP responses in all the participants, in the current study participants in the diabetic group were more likely to have absent oVEMPs on the right than participants in the non-diabetic group. For the right ear a significant difference was present between the diabetic and non-diabetic participants median oVEMP N1 latency but were still within the normal range for both groups. Similarly to the study by Kalkan and colleagues (2018), a significant difference was only present in the oVEMP amplitude for both ears between the two groups. Overall the oVEMP amplitude for the diabetic participants was smaller than the amplitude for the non-diabetic participants. Abnormalities in oVEMP amplitude can be interpreted as utricular dysfunction (Kalkan et al., 2018).

In addition to the limited utricle function studies in type 1 DM individuals, only one previous study investigated horizontal semicircular canal (SSC) function in type 1 DM participants using vHIT. Rance et al. (2014) performed the horizontal vHIT in type 1 DM individuals, to evaluate the participants' vHIT gain. The average bi-directional gain for all the participants was normal (>0.68) except for one. This one asymmetrical gain indicated a unilateral peripheral vestibulopathy. In the current study horizontal and vertical vHITs were performed. The gain together with the presence of overt and covert saccades was investigated in a manner similar to Kalkan and colleagues (2018), who reported vHIT findings in type 2 DM participants and healthy controls. The researchers reported no significant differences in gain for all the SSC's between the two groups. In the current study there was a significant difference between the diabetic and non-diabetic groups' left anterior gain (p=0.001) and right posterior gain (p=0.02), suggesting a decrease in anterior- and posterior canal functioning for diabetic participants. However no significant differences were present in the lateral gain for either ear, right anterior gain and left posterior gain.
In contrast to the study by Kalkan and colleagues (2018) that found no overt- or covert saccades in any of the participants, in the current study, despite no significant differences, diabetic participants had more overt and covert saccades for all three SSC's than the non-diabetic participants on both sides.
Other tests of vestibular system function for type 1 DM participants previously reported included the velocity step test, caloric tests, positional and spontaneous nystagmus tests as well as ocular motor tests (pursuit tracking and optokinetic nystagmus test) (Gawron et al., 2002; Klagenberg et al., 2007; Rigon et al., 2007;

Scherer & Lobo, 2002). An increased occurrence of vestibular dysfunction in type 1 DM participants were supported by abnormal caloric test results (Klagenberg et al., 2007; Rigon et al., 2007; Scherer & Lobo, 2002). Furthermore, vestibular dysfunction may be sub-clinical considering the absence of vestibular symptoms such as dizziness (Rigon et al., 2007; Scherer & Lobo, 2002). In contrast to the three above mentioned studies, Gawron et al. (2002) reported that the metabolic disturbances found in type 1 DM cause disturbances in the peripheral vestibular structures as evidenced by abnormal caloric and positional nystagmus test results, but mostly in the central structures as shown by impaired optokinetic responses in 36/95 (37.89%) type 1 DM participants, followed by spontaneous nystagmus in 10/95 (10.53%) participants.

The current study is in agreement with existing literature that shows a higher occurrence of vestibular alterations and an increased risk of vestibular dysfunction in type 1 DM individuals. Vestibular dysfunction was described as abnormal vHIT results and/or abnormal VEMP results. Therefore, a total of 26/30 (87%) diabetic participants had vestibular dysfunction compared to only 7/30 (23%) non-diabetic participants (OR: 24.2). However, the pathophysiology in the vestibular end-organs due to DM are not yet clear (Gioacchini et al., 2018) and it has to be considered that vestibular dysfunction can be overlooked if only certain parts of the vestibular system are tested such as in previous research studies.

4.1.3 Risk of falling and type 1 diabetes mellitus

Balance is maintained through the input provided by three systems: vestibular, visual and somatosensory. The inputs from these three systems are processed centrally to maintain balance. Individuals with impaired somatosensory and visual input will rely on their vestibular system to maintain balance (Silva et al., 2016). Common complications associated with DM are retinopathy and peripheral neuropathy which will therefore impair the input from the visual an somatosensory systems and increase diabetics' risk of falls (Gioacchini et al., 2018). In addition, DM is also associated with vestibular dysfunction. Vestibular dysfunction is a known risk factor of falls (Silva et al., 2016). Even when peripheral neuropathy and retinopathy have been excluded as contributing risk factors, vestibular dysfunction independently increases the risk of falls in diabetic individuals (Schubert et al., 2010). Falls can lead

to a decline in functional and emotional status (Schubert et al., 2010), which in turn decreases HRQoL (Yang et al., 2016).

Research about the gait and risk of falls in individuals with DM is still limited (Petrofsky, Lee, Macnider, & Navarro, 2005). Agrawal et al. (2009) evaluated the risk of falls in adults 40 years and older with DM using the Romberg test. The risk of falls was 12 times higher for the DM participants with vestibular dysfunction and complaints of dizziness. The DM participants with vestibular dysfunction but no dizziness complaints still had a significantly higher risk of falls. Furthermore, a recent literature review concluded that especially older adults with DM are at risk for falls with a risk ratio of 1.64. The risk of falls seems to be even higher for those individuals using insulin treatment with a risk ratio of 1.94 compared to a risk ratio of 1.27 for those not using insulin treatment. (Yang et al., 2016).

In contrast to the above research studies, the current study did not show any increased risk of falls in DM. A significant difference was present in one of the risk of falls assessments between the diabetic and non-diabetic group. Diabetic participants were more likely to obtain a lower score for the DGI than non-diabetic participants (OR: 3.9). Despite the significant difference only 1/30 (3%) diabetic participant obtained an abnormal score (<19) for the DGI. No significant differences were present for the other two fall risk assessments: the BBS and TUG. None of the participants had an abnormal score for the BBS. Furthermore, only one participant in each group obtained an abnormal score for the TUG (>10s). It was noted that one type 1 DM participant did poorly in all three fall risk assessments, indicating a high risk of falls. The participant obtained an abnormal score for the DGI (13/24) and completed the TUG in 14.03 seconds. This participant also had a near abnormal score for the BBS (41/56).

The overall maximal/near maximal scores for the DGI, BBS and TUG for both the diabetic and non-diabetic group indicate a low fall risk and good mobility. The DGI has been proved to be an appropriate tool to assess balance function (Herman et al., 2009). Multiple studies have indicated that the BBS has a high validity and reliability on diverse target populations, and is often used for the assessment of balance of individuals with chronic diseases. For the TUG test, it has been proven that the time

score is reliable and that it can assess a participant's ability to safely go about their daily living (Podsiadlo & Richardson, 1991). A possible explanation for the majority of normal scores are the age of the participants in the study. Older adults (60 years and older) with DM have an excessive risk of falls (Yang et al., 2016). Only participants younger than 60 years old were included in the study.

4.1.4 Health related quality of life and type 1 diabetes mellitus

Because DM is such a growing health concern, health professionals aim to expand research in order to be able to avoid possible secondary disorders that can impact the individual's HRQoL (Rigon et al., 2007). Furthermore, the measurement of HRQoL in individuals with DM are considered important for disease management (Bhardwaj, Choudhary, & Sharma, 2018). However the differences in research questions, measurement tools and study samples in the available research makes it difficult to reach consensus regarding management policies (Kiadaliri, Najafi, & Mirmalek-Sani, 2013). In the current study, no significant differences were found in the five health dimensions where participants had to rate their health status using the EQ-5D-5L Health Questionnaire. Although no significant differences were present it can be seen from the diabetic participants' responses that they are more likely to experience problems in three health domains: usual activities, pain and discomfort as well as anxiety and depression. Overall diabetic participants also rated their HRQoL to be significantly poorer than the non-diabetic participants. The score for the diabetic participants HRQoL was 80/100 compared to the non-diabetic participants 95/100.

Previous studies have also shown that DM has an impact on HRQoL (Bhardwaj et al., 2018; Kiadaliri et al., 2013; Nielsen, Ovesen, Mortensen, Lau, & Joensen, 2016). People with DM tend to rate their HRQoL to be poorer than people without DM (Bhardwaj et al., 2018). Bhardwaj et al. (2018) evaluated 60 type 1 DM participants' HRQoL using the standardized quality of life instrument for Indian diabetes individuals. The researchers found that 73%, 23% and 3% of the type 1 DM participants had fair, good and poor HRQoL. Furthermore, the HRQoL of these participants were correlated with disease duration, duration of using treatment and duration of prescribed medication. In addition, the HRQoL seems to be dependent on the presence of complications (Nielsen et al., 2016). Another study found that

participants with type 1 DM HRQoL decreased over time (Hart, Redekop, Bilo, Berg, & Jong, 2005). Due to these findings it is evident that psychosocial support need to be part of type 1 DM individuals' treatment plan.

4.2 Clinical relevance

Results of the current study in conjunction with previous research indicate that individuals with type 1 DM have a higher occurrence and risk of auditory and vestibular dysfunction than those without DM. It is evident that unidentified inner ear damage together with other DM related complications can have a negative effect on individuals HRQoL including their independence, emotional status and social interaction (Rance et al., 2014). Due to these findings hearing and vestibular function tests as well as psychosocial support need to be considered as an integral part of type 1 DM patient's management strategy. The auditory- and vestibular function of individuals with type 1 DM should be closely monitored to better prevent further damage that places them at a higher risk of falls and serious life threatening injuries which will decrease patients HRQoL. If necessary, auditory management should be provided to individuals with DM including hearing aids and aural rehabilitation as well as vestibular management including: vestibular and balance rehabilitation therapy. Furthermore, individuals should be assessed for risk of falls and should be provided with psychosocial support. Health professionals managing individuals with DM have the important role of informing individuals of the effect that DM can have on their inner ear and to make the appropriate referrals. Individuals should be aware of the early signs of hearing loss: tinnitus, difficulty with speech discrimination in noise and signs of vestibular dysfunction: vertigo, dizziness, postural and gait instability as well as problems with gaze stability during head movements. In addition individuals should be taught that they need to closely monitor their hearing and vestibular functioning, even if they do not have any auditory- and/or vestibular symptoms (Rigon et al., 2007; Teng et al., 2017). Previous research have shown that the vestibular end-organ can be affected even when patients do not have any symptoms or complaints (Rigon et al., 2007; Scherer & Lobo, 2002). Furthermore, Agrawal et al. (2009) found that DM patients with vestibular dysfunction but no dizziness complaints still had a significantly higher risk of falls. It is evident that even if a patient does not have any symptoms, vestibular dysfunction can still increase their risk of falls and negatively affect their HRQoL. Patients should therefore have an

auditory- and vestibular assessment as early as possible after DM has been diagnosed and should be monitored regularly to be able to better prevent and treat inner ear dysfunction.

Audiologists should be aware of a DM diagnosis in their patients and should use test methods that are able to identify the earliest of hearing damage (Lisowska, Namysowski, Morawski, & Strojek, 2001). Based on the current studies' results and previous research the following test methods are recommended for the monitoring of hearing in individuals with DM: OAE's, if the equipment is available, to be able to identify the earliest damage to hair cells in the cochlea (Rakesh, Deepali, Dinesh, Singh, & Verma, 2013). If not possible, mobile and automated hearing health technology (HearScreen/HearTest) or pure tone audiometry can also be considered. For vestibular function monitoring in individuals with DM, VEMPs and vHIT are recommended, if the equipment is not available the subjective visual vertical test can be used to assess utricle function as the oVEMPs were affected the most in the current study. Furthermore, the head impulse test and the dynamic visual acuity test can be used to assess SSC function and gaze stability during head movement respectively.

4.3 Critical evaluation

Discussed below are the strengths and limitations of the current study:

4.3.1 Strengths of the study

- The current study expanded on the limited research available about the auditory-vestibular function in type 1 DM individuals.
- The current study combined the assessment of auditory-vestibular function in type 1 DM individuals, their risk of falls and HRQoL. All five of the vestibular end-organs were assessed. Previous studies only incorporated isolated assessments.
- Reliable and standardized test procedures were used in this study to assess auditory and vestibular functioning.
- The order of cVEMP, oVEMP and vHIT testing were randomized for each participant, to avoid order bias.

- Type 1 DM participants were educated about the impact of the disease on their hearing and balance and received information regarding the condition of their auditory and vestibular function.
- Necessary referrals could be made to a general practitioner or ENT when either an outer or middle ear component were identified. When hearing/vestibular dysfunction were identified individuals could be referred to an audiologist. Furthermore, if participants had any psychological symptoms they could be referred to a psychologist.
- Participants in both the diabetic and non-diabetic group were educated on the importance of monitoring their hearing and balance functioning.

4.3.2 Limitations of the study

- Although participants were age and gender matched, the differences in auditory-vestibular function between male and female DM individuals were not determined in the current study.
- Participants were not tested at the same time during the day which could determine if they have recently eaten and could therefore have an influence on their blood glucose level.
- All participants with type 1 DM that fit the inclusion and exclusion criteria were tested regardless of the type of insulin and the combinations of diabetes medication they use.
- All participants were tested regardless of their duration of DM and blood glucose level.
- In previous studies hearing loss in individuals with type 1 DM proves to be predominantly in the high frequencies even beyond 8000Hz (Dąbrowski et al., 2011). In the current study audiometric thresholds were only obtained up until 8000Hz.

4.4 Recommendations for future research

The recommendations listed below can be used for future research studies:

- Although participants were age and gender matched, differences in the auditory-vestibular function between male and female type 1 DM individuals should be investigated.
- Differences in the auditory-vestibular function and disease duration should be further investigated.
- Future studies can investigate the possibility of differences in the auditory-vestibular function of type 1 DM individuals in stages with abnormally high and low blood glucose levels.
- Hearing loss in individuals with type 1 DM proves to be predominantly in the high frequencies (Dąbrowski et al., 2011). More research with hearing testing at frequencies above 8000Hz should be done.
- Only participants older than 18 years old were included in the study. The auditory-vestibular function of children younger than 18 years old with type 1 DM should be further investigated, using a test battery to assess all five vestibular end-organs.
- Further in depth studies should be conducted on individuals with DM focusing on the role and clinical relevance of VEMP testing in identifying early signs of neuropathy.

4.5 Conclusion

In the current study a statistically significant higher occurrence of auditory dysfunction was present in the type 1 DM participants compared to the non-diabetic participants. Type 1 DM participants showed a higher occurrence of vestibular dysfunction but not for risk of falling. Diabetic participants were found to have a statistically significant poorer HRQoL. The findings of the study highlights the importance of monitoring the hearing and vestibular function in individuals with type 1 DM to be able to prevent damage, if any inner ear dysfunction is involved patients should be provided with early intervention to avoid a decrease in their HRQoL.

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Appendix A: Faculty of Health Sciences ethical approval letter

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

1/02/2018

Approval Certificate
New Application

Ethics Reference No: 42/2018

Title: Auditory-vestibular function in adults with Type 1 Diabetes Mellitus

Dear Andriette Heystek

The **New Application** as supported by documents specified in your cover letter dated 24/01/2018 for your research received on the 24/01/2018, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 31/01/2018.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**42/2018**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers; MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

☎ 012 356 3084 deepeka.behari@up.ac.za / fhsethics@up.ac.za http://www.up.ac.za/healthethics
✉ Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60 / 61, 31 Bophelo Road, Gezina, Pretoria

Appendix B: Faculty of Humanities ethical approval letter

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

5 March 2018

Dear Ms Heystek

Project:	**Auditory-vestibular function in adults with type 1 diabetes mellitus**
Researcher:	**A Heystek**
Supervisors:	**Prof B Vinck, Prof P Rheeder and Dr B Heinze**
Department:	**Speech-Language Pathology and Audiology**
Reference number:	**14017726 (GW20180202)**

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** at the meeting held on 1 March 2018. 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.

We wish you success with the project.

Sincerely

Prof Maxi Schoeman
Deputy Dean: Postgraduate Studies and Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail:tracey.andrew@up.ac.za

cc: Prof J van der Linder (Acting-HoD)
Dr B Heinze (Supervisor)
Prof B Vinck (Co-supervisor)
Prof P Rheeder (Co-supervisor)

Appendix C: Permission letter to the head of the Diabetic Clinic Prof Paul Rheeder at Steve Biko Academic Hospital (SBAH)

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

Steve Biko Academic Hospital – Diabetic Clinic

January 2018

Prof Paul Rheeder
Diabetic Clinic
Steve Biko Academic Hospital
Pretoria

Dear Prof Paul Rheeder,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Andriëtte Heystek (Student number: 14017726) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Diabetic Clinic of Steve Biko Academic Hospital. If permission is granted, I plan to start with data collection from January 2018.

The title of my study is: **AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS**

This study will aim to describe auditory-vestibular function in adults who has type 1 diabetes mellitus for 5 years or longer, and will determine the impact of the disease on their health related quality of life. The 30 participants in my experimental group will undergo a single assessment lasting for a minimum of two hours that will take place at the Diabetic Clinic of Steve Biko Academic Hospital. If participants do not have recent blood glucose test results stated in their file, they will be required to undergo a finger prick test performed by the doctor or nurse at the clinic to measure their blood glucose levels. As well as a blood pressure test

with an upper arm blood pressure monitor. The participants will be required to complete a self-administered questionnaire (EQ-5D-3L Questionnaire). Participants will undergo auditory tests (otoscopy, acoustic immittance measurements and pure tone audiometry), vestibular tests (vestibular evoked myogenic potentials and video head impulse test) as well as functional balance assessments (dynamic gait index test, berg balance and the timed "Up and Go" test).

Thank you for considering this request.

If you require any further information, contact:
Andriëtte Heystek (student researcher)
at andriettaheystek@gmail.com or 072 8414 383.

Sincerely,

Andriëtte Heystek
Student Researcher

Dr Barbara Heinze
Research Supervisor
Email: barbara.heinze@up.ac.za

Prof Bart Vinck
Research Co-supervisor
Email: bart.vinck@up.ac.za

I, Prof Paul Rheeder, hereby give written permission for the researchers to conduct this research study at the Diabetic Clinic of Steve Biko Academic Hospital.

Prof Paul Rheeder
Head: Diabetic Clinic of Steve Biko Academic Hospital
Email: paul.rheeder@up.ac.za

Faculty of [illegible]
Department of Speech-Language Pathology and Audiology
[illegible]
Department Sport Science, Physiology and Gerontology
[illegible]
Room [illegible] Private Bag [illegible]

Appendix D: Permission letter to Dr Mary Seeber at Mediclinic Heart Hospital

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

Mediclinic Heart Hospital – Centre for Diabetes

January 2018

Dr Mary Seeber
Centre for Diabetes
Mediclinic Heart Hospital
Pretoria

Dear Dr Mary Seeber,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Andriëtte Heystek (Student number: 14017726) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Diabetes Centre of Mediclinic Heart Hospital. If permission is granted, I plan to start with data collection from January 2018.

The title of my study is: **AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS**

This study will aim to describe auditory-vestibular function in adults who has type 1 diabetes mellitus for 5 years or longer, and will determine the impact of the disease on their health related quality of life. The 30 participants in my experimental group will undergo a single assessment lasting for a minimum of two hours that will take place at the Centre for Diabetes of Mediclinic Heart Hospital. If participants do not have recent blood glucose test results stated in their file, they will be required to undergo a finger prick test performed by the doctor or nurse at the clinic to measure their blood glucose levels. As well as a blood pressure test

with an upper arm blood pressure monitor. The participants will be required to complete a self-administered questionnaire (EQ-5D-3L Questionnaire). Participants will undergo auditory tests (otoscopy, acoustic immittance measurements and pure tone audiometry), vestibular tests (vestibular evoked myogenic potentials and video head impulse test) as well as functional balance assessments (dynamic gait index test, berg balance and the timed "Up and Go" test).

Thank you for considering this request.

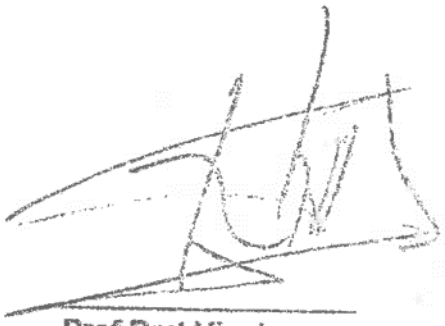
If you require any further information, contact
Andriëtte Heystek (student researcher)
at andrietteheystek@gmail.com or 072 8414 383.

Sincerely,

A Heystek

Andriëtte Heystek
Student Researcher

Dr Barbara Heinze
Research Supervisor
Email: barbara.heinze@up.ac.za



Prof Bart Vinck
Research Co-supervisor
Email: bart.vinck@up.ac.za

Prof Paul Rheeder
Research Co-supervisor
Email: paul.rheeder@up.ac.za

I, Dr Mary Seeber, hereby give written permission for the researchers to conduct this research study at the Centre for Diabetes of Mediclinic Heart Hospital.

M. Seeber

Dr Mary Seeber
Owner: Centre for Diabetes of Mediclinic Heart Hospital
Tel: 012 440 0200

Appendix E: Permission letter to Dr Betsie Kloppers at Diabetes Centre Hatfield

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE PRACTISE

Dr Betsie Kloppers – Diabetes Centre Hatfield

May 2018

Dr Betsie Kloppers
Diabetes Centre
Hatfield
Pretoria

Dear Dr Betsie Kloppers,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Andriëtte Heystek (Student number: 14017726) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Diabetes Centre.

The title of my study is: **AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS**

This study will aim to describe auditory-vestibular function in adults who has type 1 diabetes mellitus, and will determine the impact of the disease on their health related quality of life. The 30 participants in my experimental group will undergo a single assessment lasting for a minimum of two hours that will take place at the Diabetes Centre. If participants do not have recent blood glucose test results stated in their file, they will be required to undergo a finger prick test performed by the doctor or nurse at the centre to measure their blood glucose levels. As well as a blood pressure test with an upper arm blood pressure monitor. The participants will be required to complete a self-administered questionnaire (EQ-5D-3L Questionnaire). Participants will undergo auditory tests (otoscopy, acoustic immittance measurements and pure tone audiometry), vestibular tests (vestibular evoked myogenic

potentials and video head impulse test) as well as functional balance assessments (dynamic gait index test, berg balance and the timed "Up and Go" test).

Thank you for considering this request.

If you require any further information, contact:
Andriëtte Heystek (student researcher)
at andrietteheystek@gmail.com or 072 8414 383.

Sincerely,

A Heystek

Andriëtte Heystek
Student Researcher

B Heinze

Dr Barbara Heinze
Research Supervisor
Email: barbara.heinze@up.ac.za

I, Dr Betsie Kloppers, hereby give written permission for the researchers to conduct this research study at the Diabetes Centre Hatfield.

Dr Betsie Kloppers
Diabetologist: Diabetes Centre Hatfield
Tel: 012 362 8828

Appendix F: Permission letter to Dr Frans Erasmus at Dr Frans Erasmus Diabetic Clinic

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE CLINIC
Dr Frans Erasmus – Diabetic Clinic

February 2018

Dr Frans Erasmus
Diabetic Clinic
29 Jan Booysen Street
Annlin
Pretoria
0182

Dear Dr Frans Erasmus,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Andriëtte Heystek (Student number: 14017726) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Dr Frans Erasmus Diabetic Clinic. If permission is granted, I plan to start with data collection from February 2018.

The title of my study is: **AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS**

This study will aim to describe auditory-vestibular function in adults who has type 1 diabetes mellitus, and will determine the impact of the disease on their risk for falls and health related quality of life. The 30 participants in my experimental group will undergo a single assessment lasting for a minimum of an hour and a half that will take place at the Dr Frans Erasmus Diabetic Clinic. If participants do not have recent blood glucose test results stated in their file, they will be required to undergo a finger prick test performed by the doctor or nurse at the

clinic to measure their blood glucose levels. As well as a blood pressure test with an upper arm blood pressure monitor. The participants will be required to complete a self-administered questionnaire (EQ-5D-3L Questionnaire). Participants will undergo auditory tests (otoscopy, acoustic immittance measurements and pure tone audiometry), vestibular tests (vestibular evoked myogenic potentials and video head impulse test) as well as functional balance assessments (dynamic gait index test, berg balance and the timed "Up and Go" test).

Thank you for considering this request.

If you require any further information, contact
Andriëtte Heystek (student researcher)
at andrietteheystek@gmail.com or 072 8414 383.

Sincerely,

A Heystek

Andriëtte Heystek
Student Researcher

Heinze

Dr Barbara Heinze
Research Supervisor
Email: barbara.heinze@up.ac.za

DR. F.F. ERASMUS
PR. No. 149 2373
29 JAN BOOYSEN ST.
ANNLIN
0129

I, Dr Frans Erasmus, hereby give written permission for the researchers to conduct this research study at the Dr Frans Erasmus Diabetic Clinic.

Dr Frans Erasmus
Owner: Dr Frans Erasmus Diabetic Clinic
Tel: 012 567 7791

DR. ERASMUS FRANS F.
012 567 7791
012 567 7466
MBChB

Appendix G: Permission letter to the CEO of SBAH

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

Steve Biko Academic Hospital

January 2018

Dr Ernest Kenoshi
Chief Executive Officer
Steve Biko Academic Hospital
Pretoria

Dear Dr Ernest Kenoshi,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Andriëtte Heystek (Student number: 14017726) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Diabetic Clinic of Steve Biko Academic Hospital with Prof Paul Rheeder. If permission is granted, I plan to start with data collection from January 2018.

The title of my study is: **AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS**

This study will aim to describe auditory-vestibular function in adults who has type 1 diabetes mellitus for 5 years or longer, and will determine the impact of the disease on their health related quality of life. The results of this study can assist researchers in determining the auditory and balance problems in individuals with type 1 diabetes mellitus compared to healthy participants. If any hearing or vestibular problems are identified in the participants, I will refer them to the Department of Speech-Language Pathology and Audiology – University of Pretoria for further investigation.

Please find attached the Access to Information form as I will be obtaining information from the patient's files.

Thank you for considering this request.

If you require any further information, contact Andriëtte Heystek (student researcher) at andriettehеystek@gmail.com or 072 8414 383.

Sincerely,

Andriëtte Heystek
Student Researcher

Dr Barbara Heinze
Research Supervisor
Email: barbara.heinze@up.ac.za

Prof Bart Vinck
Research Co-supervisor
Email: bart.vinck@up.ac.za

Prof Paul Rheeder
Research Co-supervisor
Email: paul.rheeder@up.ac.za

Permission to access Records / Files / Data base at the Steve Biko Academic Hospital

To: Dr Ernest Kenoshi
Chief Executive Officer
Steve Biko Academic Hospital
Pretoria

From: Andriëtte Heystek
Department of Speech-Language Pathology and Audiology

Re: Permission to do research at the Diabetic Clinic of Steve Biko Academic Hospital

The title of the study is: **Auditory-vestibular function in patients with Type 1 Diabetes Mellitus.**

The study is approved by the relevant Head of Department (HOD),

Dr Jeannie van der Linde: _____

Dr Barbara Heinze, Prof Bart Vick, Prof Paul Rheeder and I are researchers; I am requesting permission on behalf of all of us to conduct a research study using the patients of the Diabetic Clinic of Steve Biko Academic Hospital. We will also require access to the patient files, their permission are requested in the participant consent form to use their clinical information documented in their file.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No.2 of 2000.

The researcher request access to the following information:

-Patients who have Type 1 Diabetes Mellitus for 5 or more years

-The patient's clinical files

We intend to publish the results of the research study in a professional journal and/or at meetings like symposia, congresses, or other meetings of such nature.

Permission to access Records / Files / Data base at .....SBA.....Hospital

TO:
The [CEO] Chief Executive Officer of SBA Hospital

Re: Permission to do research at SBA Hospital

TITLE OF STUDY: Auditory vestibular function in adults with T2 DM

This study is approved by the relevant Head of Department [HOD] Prof G Tintinger Signature GA Tintinger

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a researcher / ~~student~~ at the Department of Audiology at the University of Pretoria / ~~Hospital.~~
I am working with Prof Rheeder. I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records. This study involves clinical research.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Print Name F Rheeder Signature Rheeder
Principal Investigator

On behalf of Andrietta Heystek.

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved, on condition that there will be no cost to the hospital.

Title and name of Chief Executive Officer: Dr ES Mangwana

Name of hospital / clinic: Steve Biko Academic Hospital

Signature: Date: 2018/01/10

GAUTENG PROVINSIALE REGERING
DEPT VAN GESONDHEID
STEVE BIKO AKADEMIESE HOSPITAAL
STEVE BIKO ACADEMIC HOSPITAL
2018 -01- 10
PRIVAATSAK/PRIVATE BAG X160
PRETORIA 0001
GAUTENG PROVINCIAL GOVERNMENT
DEPT OF HEALTH

Appendix H: Permission letter to Dr Mary Seeber at Mediclinic Heart Hospital for access to patient files and records

Permission to access Records / Files / Data base at the
Mediclinic Heart Hospital

To: Dr Mary Seeber
Chief Executive Officer/Information Officer
Mediclinic Heart Hospital
Pretoria

From: Andriette Heystek
Department of Speech-Language Pathology and Audiology

Re: Permission to do research at the Centre for Diabetes of Mediclinic Heart Hospital

The title of the study is: **Auditory-vestibular function in patients with Type 1 Diabetes Mellitus.**

The study is approved by the relevant Head of Department (HOD),

Dr Jeannie van der Linde: _____

Dr Barbara Heinze, Prof Bart Vinck, Prof Paul Rheeder and I are researchers; I am requesting permission on behalf of all of us to conduct a research study on your patients with Type 1 Diabetes Mellitus. We will also require access to the patient files, their permission are requested in the participant consent form to use their clinical information documented in their file.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No.2 of 2000.

The researcher request access to the following information:

-Patients who have Type 1 Diabetes Mellitus for 5 or more years

-The patient's clinical files

We intend to publish the results of the research study in a professional journal and/or at meetings like symposia, congresses, or other meetings of such nature.

We intend to protect the personal identity of the patients by assigning each patient a random code number.

We will not proceed with the research study until we have received approval from the Faculty of Health Science Research Ethics Committee – University of Pretoria.

Yours Sincerely,

Andriëtte Heystek
Principal Investigator
Email: andrietteheystek@gmail.com

PERMISSION TO CONDUCT THE ABOVE RESEARCH STUDY AT THIS HOSPITAL AND TO ACCESS THE INFORMATION AS REQUESTED, IS HEREBY APPROVED, ON CONDITION THAT THERE WILL BE NO COST TO THE HOSPTITAL

Dr Mary Seeber
Chief Executive Officer/Information Officer
Mediclinic Heart Hospital

Date

Appendix I: Permission letter to Dr Frans Erasmus at Dr Frans Erasmus Diabetic Clinic for access to patient files and records

Permission to access Records / Files / Data base at the Dr Frans Erasmus Diabetic Clinic

To: Dr Frans Erasmus
Diabetic Clinic
29 Jan Booysen Street
Annlin
Pretoria
0182

From: Andriëtte Heystek
Department of Speech-Language Pathology and Audiology

Re: Permission to do research at the Dr Frans Erasmus Diabetic Clinic

The title of the study is: **Auditory-vestibular function in patients with Type 1 Diabetes Mellitus.**

The study is approved by the relevant Head of Department (HOD),

Dr Jeannie van der Linde: _____

Dr Barbara Heinze, Prof Bart Vinck, Prof Paul Rheeder and I are researchers; I am requesting permission on behalf of all of us to conduct a research study on your patients with Type 1 Diabetes Mellitus. We will also require access to the patient files, their permission are requested in the participant consent form to use their clinical information documented in their file.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No.2 of 2000.

The researcher request access to the following information:

-Patients who have Type 1 Diabetes Mellitus

-The patient's clinical files

We intend to publish the results of the research study in a professional journal and/or at meetings like symposia, congresses, or other meetings of such nature.

We intend to protect the personal identity of the patients by assigning each patient a random code number.

We will not proceed with the research study until we have received approval from the Faculty of Health Science Research Ethics Committee – University of Pretoria.

Yours Sincerely,

A Heystek

Andriëtte Heystek
Principal Investigator
Email: andrietteheystek@gmail.com

PERMISSION TO CONDUCT THE ABOVE RESEARCH STUDY AT THIS CLINIC AND TO ACCESS THE INFORMATION AS REQUESTED, IS HEREBY APPROVED, ON CONDITION THAT THERE WILL BE NO COST TO THE CLINIC

Dr Frans Erasmus
Owner
Dr Frans Erasmus Diabetic Clinic

6/3/2018.
Date

DR. ERASMUS FRANS F.
012 567 7791
012 567 7466
MBChB

DR. F.F. ERASMUS
PR. No. 149 2373
29 JAN BOOYSEN ST.
ANNLIN
0129

Appendix J: Type 1 Diabetes Mellitus participant information letter and consent form

INFORMATION LEAFLET AND INFORMED CONSENT FOR TYPE 1 DIABETES MELLITUS PARTICIPANTS

AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS

January 2018

Dear Participant,

1) INTRODUCTION

You are invited to volunteer for a research study that I am conducting for a Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask me Andriëtte Heystek at 072 8414 383. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THE STUDY

The main aim of my study is to describe auditory-vestibular function in adults with type 1 diabetes mellitus, and will determine the impact of the disease on their risk for falls and health related quality of life. An age and gender matched control group will also be included in the study and will consist of participants without diabetes mellitus.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You will undergo a single assessment that will last for one hour at the Diabetic Clinic. If you do not have recent blood glucose test results, you will be required to undergo a finger prick test to determine your blood glucose levels, performed by the doctor or nurse at the centre. As well as a blood pressure test with an upper arm blood pressure monitor. I will collect clinical information from your hospital file and the following procedures will be included in the assessment: hearing tests, several vestibular assessments as well as functional balance assessments. You will also be required to complete a questionnaire (see summary).

Summary of the tests that will be used in this research study:

Assessment category	Test	Expected from participant
Questionnaire	EQ-5D-3L Health Questionnaire	You will need to answer five questions regarding your mobility, self-care, usual activities, pain/discomfort and anxiety/depression. You will also need to indicate your own perceived health state according to the best health state to the worst health state.
Auditory Tests	Otoscopy	Inspection of the ear canal and eardrum with a otoscope, while you are seated upright.
	Acoustic Immitance Measurements	You will not have to respond in any way, a soft probe will be inserted into the ear canal while you are seated upright.
	Pure tone Audiometry	You will be required to press a button when a beep sound is heard trough earphones.
Vestibular Tests	cVEMP	You will lie down on the bed. Soft probes will be inserted into your ear canal while a sound stimulus is presented to you. Electrodes will be placed on your forehead, behind the ear and on the muscle of the neck; you need to lift your head to each side for the duration of the sound.
	oVEMP	You will lie down on the bed. Soft probes will be inserted into your ear canal while a sound stimulus is presented to you. Electrodes will be placed below the eye, on the side of the nose and on the forehead; you will need to look upwards for the duration of the sound.
	vHIT	You will have to put up specialized glasses, while the researcher move your head from side to side and up and down using quick movements.
Fall risk tests	Dynamic gait index testing	You will be scored on a 24-point scale that will assess the following: walking on a flat surface level, change of walk speed, walk ability with your head turned horizontally, walk ability with your head turned vertically, your ability to turn around while walking, your ability to step over obstacles, your ability to step around obstacles and walking up the stairs turning at the top of the staircase and then walking downstairs.
	The Berg balance Scale	You will perform 14 different tasks while being timed. The tasks are: sitting to standing movement, standing unsupported, sitting unsupported, standing to sitting movement, transfer of positioning, standing with eyes closed, standing with feet together, reaching forward with an outstretched arm, retrieving an object from the floor, turning to look backwards, turning 360 degrees, placing alternate feet on a chair, standing with one foot in front of the other and standing on one foot at a time.
	Timed “Up and Go” Test	You will need to stand up from a chair, walk a distance of 3 meters at a comfortable pace, turn around, walk back to the chair and sit down. This will be done twice.

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study, during the activities support will be provided to prevent you from falling and appropriate rest time will be given.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If a hearing- or vestibular problem is identified, you will be referred to the Department of Speech-Language Pathology and Audiology for further investigation.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this research study is voluntary. You can withdraw from the study at any time; data already collected will be excluded from the study. This will not affect your treatment at the Diabetic Clinic.

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Humanities and the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria.

8) INFORMATION AND CONTACT PERSON

The contact person for this study is Ms Andriëtte Heystek. If you have any questions about the study feel free to contact me at 072 8414 383 or at andrietteheystek@gmail.com. Alternatively you can contact my supervisor, Dr Barbara Heinze at barbara.heinze@up.ac.za or my co-supervisors Prof Bart Vinck at bart.vinck@up.ac.za or Prof Paul Rheeder at paul.rheeder@med.up.ac.za.

9) COMPENSATION

You will not be paid for participating in the study; no extra costs are expected to be concurred by you.

10) CONFIDENTIALITY AND ANONYMITY

Personal information and the results of the tests from participants will be kept strictly confidential. A numeric code will be allocated to each participant; this code will only be known to the researchers and supervisors. Results will be anonymously used in an article. All the results will be stored safely for a period of 15 years, as per university policy, this data may be used for future research.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I hereby agree to participate in the above mentioned research project. I have read the above information and understand what is required of me in this research study. I acknowledge that my results may be used anonymously for research purposes. I am aware that I participate voluntarily and that I may withdraw from the research study at any time.
I have received a signed copy of this informed consent agreement.

.....	.....
Participant name	Date
.....	.....
Participant signature	Date
.....	.....
Investigator's name	Date

....
Investigator's signature Date

....
Witness name and signature Date

VERBAL INFORMED CONSENT

I, the undersigned, have read and explained fully to the participant the information leaflet, which explains the nature, process, risks, discomforts and benefits of the study, in which I have asked the participant to participate in.

The participant acknowledges that the results may be used anonymously for research purposes. The participant indicates that she/he understand what is expected of them. She/he understands that there is no penalty should she/he wish to withdraw from the study. This withdrawal will have no effect on his/her medical treatment in any way. I hereby certify that the participant has agreed to participate in this study.

Participant's Name _____
(Please print)

Person seeking consent _____
(Please print)

Signature_____Date_____

Witness's name_____
(Please print)

Signature _____Date_____

Appendix K: Non-diabetic group participant information letter and consent form

HEALTHY PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS

January 2018

Dear Participant,

1) INTRODUCTION

You are invited to volunteer for a research study that I am conducting for a Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask me Andriëtte Heystek at 072 8414 383. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THE STUDY

The main aim of my study is to describe auditory-vestibular function in adults with type 1 diabetes mellitus, and will determine the impact of the disease on their risk for falls and health related quality of life. An age and gender matched control group will also be included in the study and will consist of participants without diabetes mellitus. You will form part of this group.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You will undergo a single assessment that will last for one hour at the Department of Speech-Language Pathology and Audiology, University of Pretoria. You will be required to undergo a finger prick test (with the Accu-Check Active Blood Glucose Monitoring System) to determine your blood glucose levels. As well as a blood pressure test with an upper arm blood pressure monitor. The following procedures will be included in the assessment: hearing tests, several vestibular assessments as well as functional balance assessments. You will also be required to complete a questionnaire (see summary).

Summary of the tests that will be used in this research study:

Assessment category	Test	Expected from participant
Questionnaire	EQ-5D-3L Health Questionnaire	You will need to answer five questions regarding your mobility, self-care, usual activities, pain/discomfort and anxiety/depression. You will also need to indicate your own perceived health state according to the best health state to the worst health state
Auditory Tests	Otoscopy	Inspection of the ear canal and eardrum with a otoscope, while you are seated upright
	Acoustic Immitance Measurements	You will not have to respond in any way, a soft probe will be inserted into the ear canal while you are seated upright
	Pure tone Audiometry	You will be required to press a button when a beep sound is heard trough earphones
Vestibular Tests	cVEMP	You will lie down on the bed. Soft probes will be inserted into your ear canal while a sound stimulus is presented to you. Electrodes will be placed on your forehead, behind the ear and on the muscle of the neck; you need to lift your head to each side for the duration of the sound
	oVEMP	You will lie down on the bed. Soft probes will be inserted into your ear canal while a sound stimulus is presented to you. Electrodes will be placed below the eye, on the side of the nose and on the forehead; you will need to look upwards for the duration of the sound
	vHIT	You will have to put up specialized glasses, while the researcher move your head from side to side and up and down using quick movements
Fall risk tests	Dynamic gait index testing	You will be scored on a 24-point scale that will assess the following: walking on a flat surface level, change of walk speed, walk ability with your head turned horizontally, walk ability with your head turned vertically, your ability to turn around while walking, your ability to step over obstacles, your ability to step around obstacles and walking up the stairs turning at the top of the staircase and then walking downstairs
	The Berg balance Scale	You will perform 14 different tasks while being timed. The tasks are: sitting to standing movement, standing unsupported, sitting unsupported, standing to sitting movement, transfer of positioning, standing with eyes closed, standing with feet together, reaching forward with an outstretched arm, retrieving an object from the floor, turning to look backwards, turning 360 degrees, placing alternate feet on a chair, standing with one foot in front of the other and standing on one foot at a time
	Timed “Up and Go” Test	You will need to stand up from a chair, walk a distance of 3 meters at a comfortable pace, turn around, walk back to the chair and sit down. This will be done twice

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study, during the activities support will be provided to prevent you from falling and appropriate rest time will be given.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If a hearing- or vestibular problem is identified, you will be referred to the Department of Speech-Language Pathology and Audiology for further investigation.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this research study is voluntary. You can withdraw from the study at any time; data already collected will be excluded from the study.

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Humanities and the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria.

8) INFORMATION AND CONTACT PERSON

The contact person for this study is Ms Andriëtte Heystek. If you have any questions about the study feel free to contact me at 072 8414 383 or at andrietteheystek@gmail.com. Alternatively you can contact my supervisor Prof Bart Vinck at bart.vinck@up.ac.za or my co-supervisor Dr Barbara Heinze at barbara.heinze@up.ac.za or Prof Paul Rheeder at paul.rheeder@med.up.ac.za.

9) COMPENSATION

You will not be paid for participating in the study; no extra costs are expected to be concurred by you.

10) CONFIDENTIALITY AND ANONYMITY:

Personal information and the results of the tests from participants will be kept strictly confidential. A numeric code will be allocated to each participant; this code will only be known to the researchers and supervisors. Results will be anonymously used in an article. All the results will be stored safely for a period of 15 years, as per university policy, this data may be used for future research.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I hereby agree to participate in the above mentioned research project. I have read the above information and understand what is required of me in this research study. I acknowledge that my results may be used anonymously for research purposes. I am aware that I participate voluntarily and that I may withdraw from the research study at any time.
I have received a signed copy of this informed consent agreement.

.....	.....
Participant name	Date
.....	.....
Participant signature	Date
.....	.....
Investigator's name	Date
.....	.....
Investigator's signature	Date

....
Witness name and signature Date

VERBAL INFORMED CONSENT

I, the undersigned, have read and explained fully to the participant the information leaflet, which explains the nature, process, risks, discomforts and benefits of the study, in which I have asked the participant to participate in.

The participant acknowledges that the results may be used anonymously for research purposes. The participant indicates that she/he understand what is expected of them. She/he understands that there is no penalty should she/he wish to withdraw from the study. This withdrawal will have no effect on his/her medical treatment in any way. I hereby certify that the participant has agreed to participate in this study.

Participant's Name _____
(Please print)

Person seeking consent _____
(Please print)

Signature_____Date_____

Witness's name_____
(Please print)

Signature _____Date_____

Appendix L: Dynamic Gait Index Test

DYNAMIC GAIT INDEX SCORE SHEET

Randomized participant number: _____
Date of visit: _____

1. Gait level surface _____

Instructions: Walk at your normal speed from here to the next mark (6m)
Grading: Mark the lowest category that applies.

(3) Normal: Walks 6m, no assistive devices, good sped, no evidence for imbalance, normal gait pattern
(2) Mild Impairment: Walks 6m, uses assistive devices, slower speed, mild gait deviations.
(1) Moderate Impairment: Walks 6m, slow speed, abnormal gait pattern, evidence for imbalance.
(0) Severe Impairment: Cannot walk 6m without assistance, severe gait deviations or imbalance.

2. Change in gait speed _____

Instructions: Begin walking at your normal pace (for 2m), when I tell you "go," walk as fast as you can (for 2m). When I tell you "slow," walk as slowly as you can (for 2m).
Grading: Mark the lowest category that applies.

(3) Normal: Able to smoothly change walking speed without loss of balance or gait deviation. Shows a significant difference in walking speeds between normal, fast and slow speeds.
(2) Mild Impairment: Is able to change speed but demonstrates mild gait deviations, or not gait deviations but unable to achieve a significant change in velocity, or uses an assistive device.
(1) Moderate Impairment: Makes only minor adjustments to walking speed, or accomplishes a change in speed with significant gait deviations, or changes speed but has significant gait deviations, or changes speed but loses balance but is able to recover and continue walking.
(0) Severe Impairment: Cannot change speeds, or loses balance and has to reach for wall or be caught.

3. Gait with horizontal head turns _____

Instructions: Begin walking at your normal pace. When I tell you to "look right," keep walking straight, but turn your head to the right. Keep looking to the right until I tell you, "look left," then keep walking straight and turn your head to the left. Keep your head to the left until I tell you "look straight," then keep walking straight, but return your head to the center.
Grading: Mark the lowest category that applies.

(3) Normal: Performs head turns smoothly with no change in gait.
(2) Mild Impairment: Performs head turns smoothly with slight change in gait velocity, i.e., minor disruption to smooth gait path or uses walking aid.
(1) Moderate Impairment: Performs head turns with moderate change in gait velocity, slows down, staggers but recovers, can continue to walk.
(0) Severe Impairment: Performs task with severe disruption of gait, i.e., staggers outside 0.4m path, loses balance, stops, reaches for wall.

4. Gait with vertical head turns _____
Instructions: Begin walking at your normal pace. When I tell you to “look up,” keep walking straight, but tip your head up. Keep looking up until I tell you, “look down,” then keep walking straight and tip your head down. Keep your head down until I tell you “look straight,“ then keep walking straight, but return your head to the centre.
Grading: Mark the lowest category that applies.

(3) Normal: Performs head turns smoothly with no change in gait.
(2) Mild Impairment: Performs head turns smoothly with slight change in gait velocity, i.e., minor disruption to smooth gait path or uses walking aid.
1) Moderate Impairment: Performs head turns with moderate change in gait velocity, slows down, staggers but recovers, can continue to walk.
(0) Severe Impairment: Performs task with severe disruption of gait, i.e., staggers outside 0.4m path, loses balance, stops, reaches for wall.

5. Gait and pivot turn _____
Instructions: Begin walking at your normal pace. When I tell you, “turn and stop,” turn as quickly as you can to face the opposite direction and stop.
Grading: Mark the lowest category that applies.

(3) Normal: Pivot turns safely within 3 seconds and stops quickly with no loss of balance.
(2) Mild Impairment: Pivot turns safely in > 3 seconds and stops with no loss of balance.
(1) Moderate Impairment: Turns slowly, requires verbal cueing, requires several small steps to catch balance following turn and stop.
(0) Severe Impairment: Cannot turn safely, requires assistance to turn and stop.

6. Step over obstacle ____

Instructions: Begin walking at your normal speed. When you come to the shoebox, step over it, not around it, and keep walking.

Grading: Mark the lowest category that applies.

(3) Normal: Is able to step over the box without changing gait speed, no evidence of imbalance.

(2) Mild Impairment: Is able to step over box, but must slow down and adjust steps to clear box safely.

(1) Moderate Impairment: Is able to step over box but must stop, then step over. May require verbal cueing.

(0) Severe Impairment: Cannot perform without assistance.

7. Step around obstacles _____

Instructions: Begin walking at normal speed. When you come to the first cone (about 2m away), walk around the right side of it. When you come to the second cone (2m past first cone), walk around it to the left.

Grading: Mark the lowest category that applies.

(3) Normal: Is able to walk around cones safely without changing gait speed; no evidence of imbalance.

(2) Mild Impairment: Is able to step around both cones, but must slow down and adjust steps to clear cones.

(1) Moderate Impairment: Is able to clear cones but must significantly slow, speed to accomplish task, or requires verbal cueing.

(0) Severe Impairment: Unable to clear cones, walks into one or both cones, or requires physical assistance.

8. Steps _____

Instructions: Walk up these stairs as you would at home, i.e., using the railing if necessary. At the top, turn around and walk down.

Grading: Mark the lowest category that applies.

(3) Normal: Alternating feet, no rail.

(2) Mild Impairment: Alternating feet, must use rail.

(1) Moderate Impairment: Two feet to a stair, must use rail.

(0) Severe Impairment: Cannot do safely.

TOTAL SCORE: _____ / 24

Interpretation: ≤ 19/24 = predictive of falls in the elderly, ≥ 20/24 = safe ambulators

References

1. Herdman SJ. Vestibular Rehabilitation. 2nd ed. Philadelphia, PA: F.A.Davis Co; 2000.

2. Shumway-Cook A, Woollacott M. Motor Control Theory and Applications, Williams and Wilkins Baltimore, 1995: 323-324

Appendix M: Berg Balance Scale

Berg Balance Scale

The Berg Balance Scale (BBS) was developed to measure balance among older people with impairment in balance function by assessing the performance of functional tasks. It is a valid instrument used for evaluation of the effectiveness of interventions and for quantitative descriptions of function in clinical practice and research. The BBS has been evaluated in several reliability studies. *A recent study of the BBS, which was completed in Finland, indicates that a change of eight (8) BBS points is required to reveal a genuine change in function between two assessments among older people who are dependent in ADL and living in residential care facilities.*

Description:
14-item scale designed to measure balance of the older adult in a clinical setting.

Equipment needed: Ruler, two standard chairs (one with arm rests, one without), footstool or step, stopwatch or wristwatch, 15 ft walkway

Completion:

Time: 15-20 minutes

Scoring: A five-point scale, ranging from 0-4. "0" indicates the lowest level of function and "4" the highest level of function. Total Score = 56

Interpretation:
41-56 = low fall risk
21-40 = medium fall risk
0 –20 = high fall risk

A change of 8 points is required to reveal a genuine change in function between 2 assessments.

Berg Balance Scale

Name: _____ Date: _____

Location: _____ Rater: _____

ITEM DESCRIPTION	SCORE (0-4)
Sitting to standing	_____
Standing unsupported	_____
Sitting unsupported	_____
Standing to sitting	_____
Transfers	_____
Standing with eyes closed	_____
Standing with feet together	_____
Reaching forward with outstretched arm	_____
Retrieving object from floor	_____
Turning to look behind	_____
Turning 360 degrees	_____
Placing alternate foot on stool	_____
Standing with one foot in front	_____
Standing on one foot	_____

Total _____

GENERAL INSTRUCTIONS

Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:

- the time or distance requirements are not met
- the subject's performance warrants supervision
- the subject touches an external support or receives assistance from the examiner

Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing is a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5, and 10 inches. Chairs used during testing should be a reasonable height. Either a step or a stool of average step height may be used for item # 12.

Berg Balance Scale

SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hand for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or stabilize
( ) 0 needs moderate or maximal assist to stand

STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding on.
( ) 4 able to stand safely for 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unsupported

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely for 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assist to sit

TRANSFERS
INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cuing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays safely
( ) 0 needs help to keep from falling

STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding on.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds

Berg Balance Scale continued…

REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)

( ) 4 can reach forward confidently 25 cm (10 inches)
( ) 3 can reach forward 12 cm (5 inches)
( ) 2 can reach forward 5 cm (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.

( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)

( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.

( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cuing
( ) 0 needs assistance while turning

PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.

( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in > 20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete > 2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)

( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding on.

( ) 4 able to lift leg independently and hold > 10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold ≥ 3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.
( ) 0 unable to try of needs assist to prevent fall

( ) TOTAL SCORE (Maximum = 56)

Appendix N: The Timed “Up & Go” Test

Directions

The timed "Up and Go" test measures, in seconds, the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm [18in], arm height 65 cm [25.6 in]), walk a distance of 3 meters (118 inches, approximately 10 feet), turn, walk back to the chair, and sit down. The subject wears their regular footwear and uses their customary walking aid (none, cane, walker). No physical assistance is given. They start with their back against the chair, their arms resting on the armrests, and their walking aid at hand. They are instructed that, on the word "go" they are to get up and walk at a comfortable and safe pace to a line on the floor 3 meters away, turn, return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a stopwatch or a wristwatch with a second hand can be used to time the trial.

Instructions to the patient

"When I say 'go' I want you to stand up and walk to the line, turn and then walk back to the chair and sit down again. Walk at your normal pace."

Variations

You may have the patient walk at a fast pace to see how quickly they can ambulate. Also you could have them turn to the left and to the right to test any differences.

*Podsiadlo D, Richardson S. The timed "up and go": a test of basic functional mobility for frail elderly persons. *JAGS* 1991; 39: 142-148.

Scoring

Time for 'Up and Go' test _____sec.
Unstable on turning?
Walking aid used? Type of aid: _____

Appendix O: EQ-5D-5L Health Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

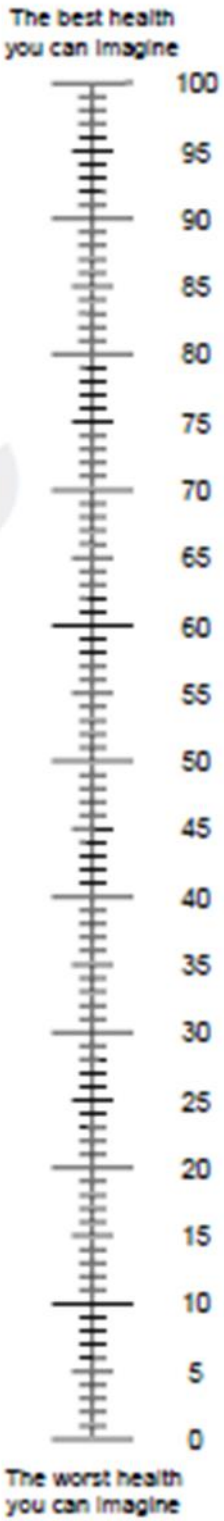
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix P: Feedback letter for participants with abnormal test results

PARTICIPANT FEEDBACK LETTER

AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS

Participant: _____

Date of assessment: _____

Hospital: _____

Dear Participant,

Thank you for participating in the above mentioned research study.

The following tests were performed:

Auditory evaluation

Otoscopic Examination
Tympanometry
Acoustic Reflex Measurements
Pure tone audiometry

Vestibular evaluation

Cervical Vestibular Evoked Myogenic Potentials (cVEMPs)
Ocular Vestibular Evoked Myogenic Potentials (oVEMPs)
Video Head Impulse Test

Fall risk tests

Dynamic Gait Index
The Berg Balance Scale
The timed up and go test

Considering the test results obtained, it is recommended that you visit an:

- ☐ Audiologist for a diagnostic hearing evaluation
- ☐ Audiologist for further vestibular testing
- ☐ Ear Nose and Throat Specialist/General Practitioner
- ☐ Other

Reasons for referral

_____
_____
_____

Kind Regards,

_____
Andriëtte Heystek
(Student Researcher)

Appendix Q: Feedback letter for participants with normal test results

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

PARTICIPANT FEEDBACK LETTER

AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS

Participant: _____

Date of assessment: _____

Hospital: _____

Dear Participant,

Thank you for participating in the above mentioned research study.

The following tests were performed:

Auditory evaluation

Otoscopic Examination
Tympanometry
Acoustic Reflex Measurements
Pure tone audiometry

Vestibular evaluation

Cervical Vestibular Evoked Myogenic Potentials (cVEMPs)
Ocular Vestibular Evoked Myogenic Potentials (oVEMPs)
Video Head Impulse Test

Fall risk tests

Dynamic Gait Index
The Berg Balance Scale
The timed up and go test

Considering the normal test results obtained for the auditory- and vestibular evaluation there is no need for further assessment. It is only recommended to visit an audiologist if you notice a change in your hearing and/or balance.

Kind Regards,

_____
Andriëtte Heystek
(Student Researcher)

Appendix R: Declaration for the storage of research data and/or documents

Principal Investigator's Declaration for the storage of research data and/or documents

I, the Principal Investigator(s), Andriëtte Heystek of the following trial/study titled:
AUDITORY-VESTIBULAR FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS
will be storing all the research data and/or documents referring to the above mentioned trial/study at the following non-residential address:
Department of Speech-Language Pathology and Audiology

University of Pretoria

Corner of Lynnwood Road and Roper Street

Hatfield

South Africa

I understand that the storage for the abovementioned data and/or documents must be maintained for a minimum of 15 years from the end of this trial/study.

Start date of the study: January 2018

Anticipated end date of study: September 2018

SPECIFIC PERIOD OF DATA STORAGE AMOUNTING TO NO LESS THAN 15 YEARS:

February 2018 until February 2033

A Heystek

Principal Researcher
Andriëtte Heystek

01/12/2017

Date

Dr Barbara Heinze

01/12/2017

Date

Appendix S: Data capture sheet for participants with type 1 diabetes mellitus

DATA CAPTURE SHEET FOR PARTICIPANTS WITH TYPE 1 DIABETES MELLITUS

Auditory-vestibular function in adults with Type 1 Diabetes Mellitus

Date of assessment: _____

Hospital: _____

Randomized participant number: _____

Contact number: _____

Duration of type 1 diabetes mellitus: _____

Age: _____

Gender: _____

Height: _____

Weight: _____

BMI: _____

- ☐ Overweight: 25-29.9
- ☐ Obese I: 30-34.9
- ☐ Obese II: 35-39.9
- ☐ Obese III: >40

Blood results in file	
Blood Glucose	
GHbA1c	
Blood pressure	
Total Cholesterol	
LDL	
HDL	

Urea	
Creatinine	
T4	
TSH	

Microvascular complications stated in file:

	Yes	No
Retinopathy:	□	□
Nephropathy:	□	□
Peripheral Neuropathy:	□	□
End-organ damage:	□	□

Medications and duration of medication use:

_____

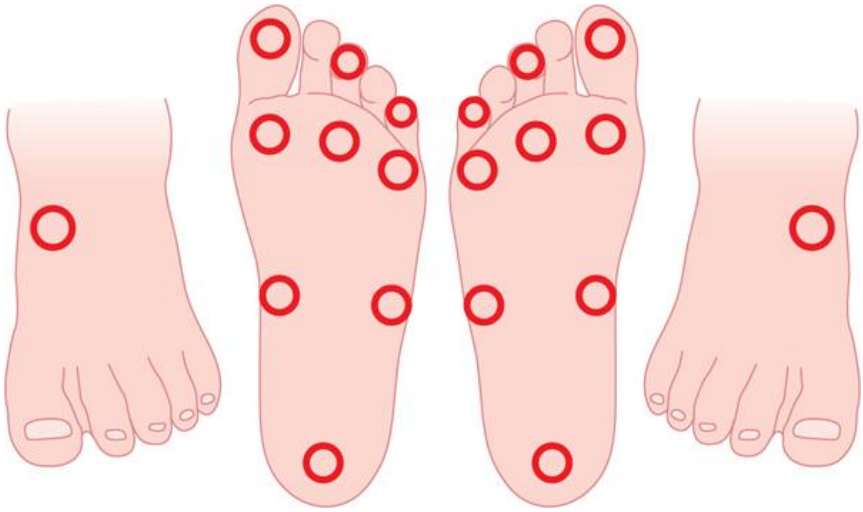
_____

_____

Current Blood Pressure: _____

Current Blood Glucose: _____

8-Point Peripheral Neuropathy Test:



Otoscopy:

Right ear	Left ear

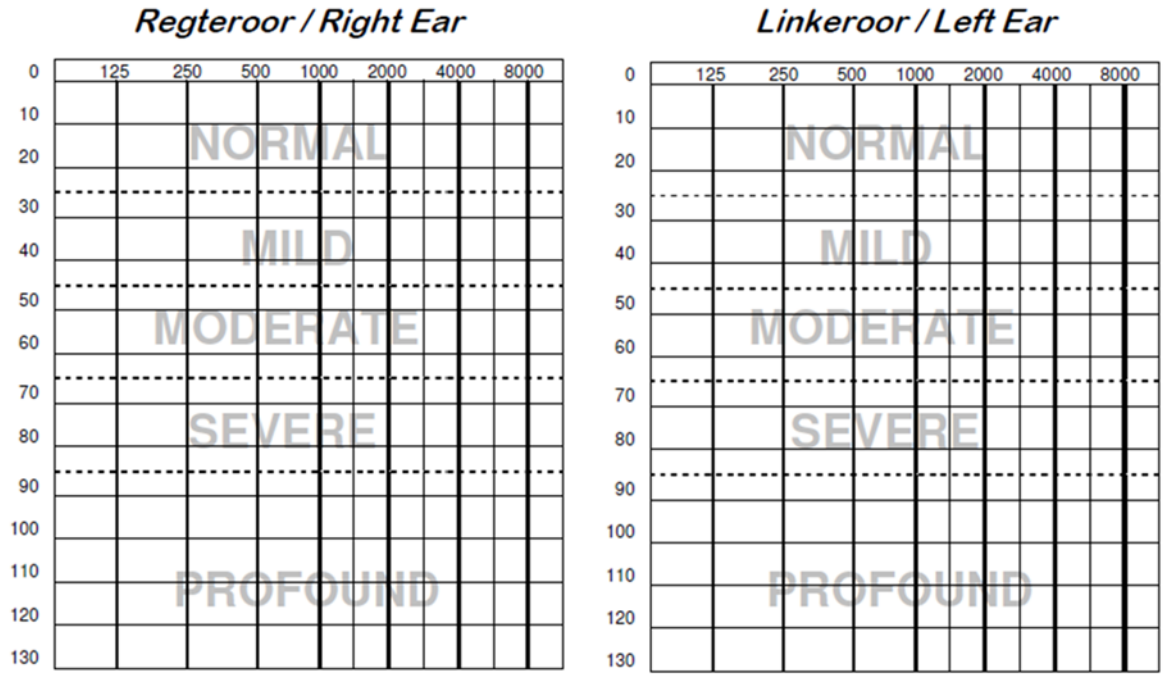
Tympanometry:

	Right ear	Left ear
Tympanogram type		
Ear canal pressure		
Static compliance		
Ear canal volume		

Acoustic reflex measurements:

	Right ear	Left ear
500Hz		
1000Hz		
2000Hz		
4000Hz		

Pure tone audiometry:



Dynamic Gait Index:

Total score: _____/24

The Berg Balance Scale:

Total score: _____/56

The timed "Up and Go" Test:

Time: _____sec

Unstable on turning: Yes □ No □

Walking aid used: Yes □ No □

Type of aid: _____

Vestibular Evoked Myogenic Potentials:

Cervical Vestibular Evoked Myogenic Potentials (cVEMPs):

Ear	P1 latency (ms)	N1 latency (ms)	Inter-peak amplitude (μV)	Asymmetry ratio (%)	Normal (N) Abnormal (A)
Left					
Right					

Ocular Vestibular Evoked Myogenic Potentials (oVEMPs):

Ear	N1 latency (ms)	P1 latency (ms)	Inter-peak amplitude (μV)	Asymmetry ratio (%)	Normal (N) Abnormal (A)
Left					
Right					

Video Head Impulse Test:

Canal	Gain	Covert saccades	Overt saccades	Normal (N) Abnormal (A)
Left lateral				
Right lateral				
Left anterior				
Right posterior				
Right anterior				
Left posterior				

Appendix T: Data capture sheet for healthy participants

DATA CAPTURE SHEET FOR HEALTHY PARTICIPANTS

Auditory-vestibular function in adults with Type 1 Diabetes Mellitus

Date of assessment: _____

Hospital: _____

Randomized participant number: _____

Contact number: _____

Age: _____

Gender: _____

Height: _____

Weight: _____

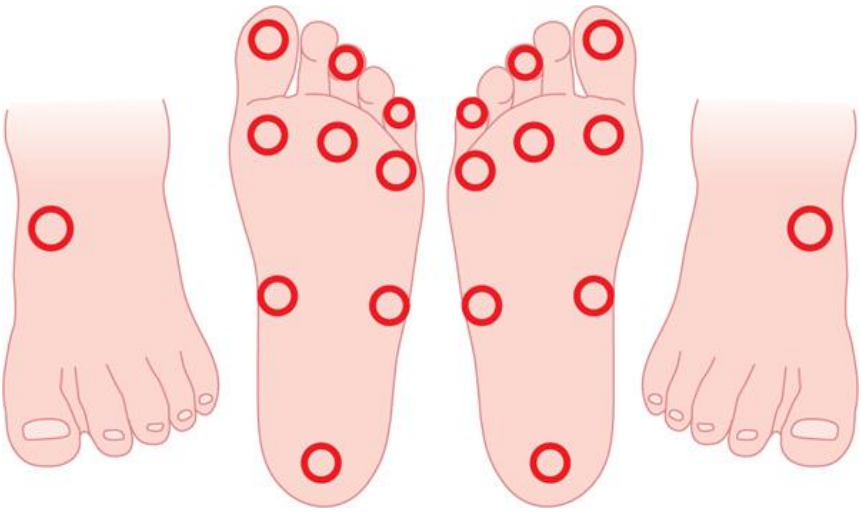
BMI: _____

- ☐ Overweight: 25-29.9
- ☐ Obese I: 30-34.9
- ☐ Obese II: 35-39.9
- ☐ Obese III: >40

Current Blood Pressure: _____

Current Blood Glucose: _____

8-Point Peripheral Neuropathy Test:



Otoscopy:

Right ear	Left ear

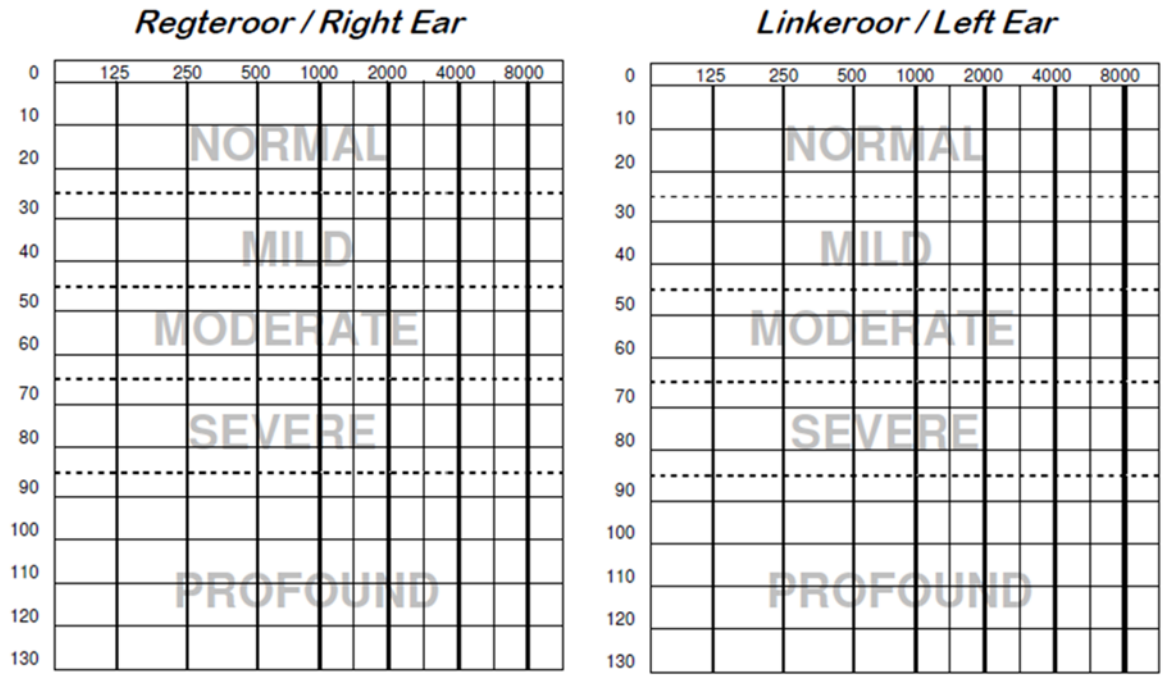
Tympanometry:

	Right ear	Left ear
Tympanogram type		
Ear canal pressure		
Static compliance		
Ear canal volume		

Acoustic reflex measurements:

	Right ear	Left ear
500Hz		
1000Hz		
2000Hz		
4000Hz		

Pure tone audiometry:



Dynamic Gait Index:

Total score: _____/24

The Berg Balance Scale:

Total score: _____/56

The timed "Up and Go" Test:

Time: _____sec

Unstable on turning: Yes □ No □

Walking aid used: Yes □ No □

Type of aid: _____

Vestibular Evoked Myogenic Potentials:

Cervical Vestibular Evoked Myogenic Potentials (cVEMPs):

Ear	P1 latency (ms)	N1 latency (ms)	Inter-peak amplitude (μV)	Asymmetry ratio (%)	Normal (N) Abnormal (A)
Left					
Right					

Ocular Vestibular Evoked Myogenic Potentials (oVEMPs):

Ear	N1 latency (ms)	P1 latency (ms)	Inter-peak amplitude (μV)	Asymmetry ratio (%)	Normal (N) Abnormal (A)
Left					
Right					

Video Head Impulse Test:

Canal	Gain	Covert saccades	Overt saccades	Normal (N) Abnormal (A)
Left lateral				
Right lateral				
Left anterior				
Right posterior				
Right anterior				
Left posterior				

Appendix U: Letter of clearance from the Biostatistician

LETTER OF CLEARANCE FOR STATISTICS

Auditory-vestibular function in adults with type 1 Diabetes Mellitus.

Andriëtte Heystek
For MA Audiology

I hereby confirm that I am aware of the project and will undertake to assist with the statistical analysis of the data generated from the project.

The Data Analyses will consist of

- Descriptive statistics (means, medians, standard deviation and range, numbers and percentages)
- 2 Group comparisons will be made using the appropriate statistics for data (continuous and categorical) taking into account that data was matched at an individual level for example Wilcoxon matched pairs test or the McNemar test.

Sample size

- A sample size of 30 participants in each group allows detection of differences between 1 and ½ standard deviation with 80% power and alpha set at 0.05. It will also detect a difference in proportions of 20% or more.

Name: Prof P Rheeder

Signature _____ _____

Date: 2 February 2019