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Audiovestibular function in Adults with Type 2 Diabetes Mellitus

By

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Abstract

Diabetes is one of the most prominent health emergencies of the 21st century affecting millions worldwide. Approximately 415 million individuals had diabetes in 2015, more than 10% living in the Sub-Saharan Africa region. Diabetes is a chronic illness and is classified according to aetiology. Type 2 diabetes accounts for more than 90% of cases. The disease is initially asymptomatic resulting in 30% to 85% of cases remaining undiagnosed. Due to the delayed diagnosis, approximately 20% of the individuals will have developed secondary complications. Disorders of the auditory and vestibular systems are often associated with diabetes; however, the extent and nature of these vestibular manifestations are still unknown.

A main aim of this research study was to investigate the audiovestibular function, risk of falling and health related quality of life (HRQL) in adults with type 2 diabetes, compared to findings of non-diabetic age and gender matched controls. This was achieved through testing the audiovestibular function (pure tone audiometry, video head impulse testing, and cervical and ocular vestibular evoked myogenic potentials), fall risk utilising three assessments (TUG, BBS and DGI), and HRQL utilising a self-administered (EQ-5D-5L).

A cross-sectional research design was employed. A purposive sampling method was employed to recruit the type 2 diabetics. The mean age was 49.1 years (± 6.2), 57.1% were female and had an average BMI of 31.6 ± 7.6 ($p < 0.001$; t-test). The HbA1c for the type 2 diabetic participants was 9.3% (± 2.2) and had disease durations of 15.36 years (± 9.67). No significant difference between the two groups was observed in the pure tone audiometry results. Although there was a significant difference between the two groups at 500Hz in the left ear ($p = 0.007$; t-test), indicating poorer hearing for the type 2 diabetics. Overall, there were no significant difference between the two groups was observed in video head impulse testing. There was, however, a significant difference between the two groups in the presence of saccades for the right lateral canal ($p = 0.002$; McNemar test of symmetry). The type 2 diabetics had a 1.5 times higher risk of having absent cVEMP results. Furthermore, the type 2 diabetics had a 1.3 times higher risk of having absent oVEMP results. For the cVEMPs, 53.6% of the type 2 diabetics cVEMPs were absent (unilateral/bilateral),

compared to 25% of the non-diabetic controls. For the oVEMPs, 74.1% of the type 2 diabetics oVEMPs were absent (unilateral/bilateral), compared to 53.6% of the non-diabetic controls. A significant difference between the two groups was obtained for the averaged TUG test ($p=0.046$; t-test), indicating a risk of falling amongst the type 2 diabetics. There were no significant differences between the two groups in the BBS and DGI scores. There was no significant difference between the two groups for the EQ-5D-5L questionnaire. There was, however, a significant difference between the two groups for the health dimension mobility ($p=0.032$; t-test).

The type 2 diabetic participants had a higher occurrence of audiovestibular dysfunction, higher risk of falling and poorer HRQL than the non-diabetic adults, and should be examined and monitored through the progression of the disease. If there are any auditory or vestibular involvements, further assessments should be considered to minimize the functional limitations of quality of life.

Keywords

Hearing Loss

Health Related Quality of Life

Risk of Falling

Type 2 Diabetes

Vestibular dysfunction

List of Abbreviations and Acronyms

AC	Air Conduction
ADA	American Diabetes Association
AR	Asymmetry Ratio
β-cell	Beta Cell
BBS	Berg Balance Scale
BC	Bone Conduction
BMI	Body Mass Index
cVEMP	Cervical Vestibular Evoked Myogenic Potential
DCCT	Diabetes Control and Complications trials
DGI	Dynamic Gait Index
HbA1c	Glycated haemoglobin (Serum haemoglobin)
HL	Hearing Loss
HRQL	Health Related Quality of Life
IDF	International Diabetes Federation
oVEMP	Ocular Vestibular Evoked Myogenic Potential
SA	South Africa
SAHS	Southern African Hypertension Society
SCC	Semicircular Canals
SCM	Sternocleidomastoid
TUG	Timed “Up & Go”
VAS	Visual Analogue Scale
VEMP	Vestibular Evoked Myogenic Potential
vHIT	video Head Impulse Test
VOR	Vestibulo-Ocular Reflex
WHO	World Health Organisation
YLD	Years living with disability

Chapter 1

INTRODUCTION

“The diabetes tsunami is here. And we in South Africa are in trouble.” Dr Larry Distiller
(Health24.com, 2014).

1.1 General orientation

According to the International Diabetes Federation (IDF) and the World Health Organisation (WHO), the rising tide in obesity and diabetes mellitus are one of the most prominent health emergencies of the 21st century (IDF, 2015; WHO, 2016). The prevalence of diabetes has escalated globally and is more widespread than previously documented (Chen, Magliano, Zimmet, 2012; IDF, 2015; WHO, 2016). The disease no longer affects the predominantly wealthy nations but also the low and middle income countries (Chen et al., 2012; IDF, 2015; WHO, 2016). The IDF (2015) estimated that 415 million individuals had diabetes in 2015, with more than 10% of those individuals (14.2 million) living in the Sub-Saharan Africa region. By 2040, these figures are expected to increase to 642 million globally and 34.2 million in Sub-Saharan Africa. There were 2.28 million known cases of diabetes and almost 1.39 million undiagnosed diabetic cases in South Africa in 2015 (IDF, 2015). Furthermore, the IDF (2015) reported that of the 321,100 diabetic deaths, 79% of the deaths occurred in cases where the diabetics were younger than 60 years of age.

Diabetes was described as the sixth leading cause of disability in 2015 (Chatterjee, Khunti & Davies, 2017). According to the WHO (2016) and Chatterjee et al. (2017), diabetes places significant socioeconomic pressure not only on the individual with the disease, but also on the global health-care system and the wider global economy. The complications that arise from diabetes have profound psychological and physical consequences that further diminish health related quality of life (HRQL) for diabetic individuals (Rubin & Peyrot, 1999; IDF, 2015; WHO, 2016; Chatterjee et al., 2017). The dramatic increase in the prevalence of diabetes places an enormous burden on the health care system and wider global economy (IDF, 2015; WHO, 2016; Chatterjee et al., 2017). This economic burden has been linked not only to the direct medical costs, but also to the indirect costs that are associated with acute diabetic complications (WHO, 2016). Consequences may include the possible decline in productivity and loss of wages,

premature mortality as diabetic complications are health threatening, poorer general HRQL and the overall negative impact of the disease on the nation's gross domestic product (WHO, 2016). The IDF (2013) further estimated the total global health-care spending on diabetes and its treatment more than tripled from the period of 2003 to 2013.

In addition to diabetes being the sixth leading cause of disability, the WHO (2016) described diabetes as one of the four priority non-communicable diseases. As part of the United Nation's 2013 Agenda of Sustainable Development, member states set a target to reduce the premature mortality resulting from these non-communicable diseases by at least one third (WHO, 2016). It is envisaged that this can be achieved by providing universal health coverage and accessible medications at affordable prices (WHO, 2016). On the other hand, the WHO (2016) cautions that the combination of the increase in prevalence of diabetes globally and increasing lifespans of diabetic individuals due to modern medicine and health care may lead to a changing spectrum of the types of morbidity that are associated with diabetes and the resulting diabetic complications.

According to Rubin and Peyrot (1999) there are several factors that affect the overall HRQL in diabetic individuals including disease specific medical factors such as the type and duration of diabetes, treatment regimen, level of glycemic control and the presence of additional vascular (micro and macro) complications. This study (Rubin & Peyrot, 1999) indicated that as a result of diabetes and the secondary complications that arise from the disease that diabetics are prone to having poorer HRQL compared to non-diabetic individuals especially regarding physical functioning and well-being and those with increasing age. Additionally, numerous authors (Lustman, Anderson, Freedland, deGroot, Carney, Clouse, 2000; Egede, Zheng & Simpson, 2003; Finkelstein et al., 2003; Nichols & Brown, 2003) have shown an association between diabetes and depression (Goldney, Fisher, Phillips & Wilson, 2004). Depressive disorders, an important public health issue, have been associated with outcomes of chronic diseases such as diabetes and also contribute to this increased economic burden of additional medical costs (Finkelstein et al., 2003). According to the aforementioned literature, it is clear that diabetic individuals are prone to having poorer HRQL as a result of the disease and the associated complications and that these various contributing factors should be considered when treating diabetic individuals (Goldney et al., 2004).

1.2 Epidemiology of diabetes

Diabetes is a complex metabolic disorder that is characterized by chronic hyperglycaemia with disturbances in the protein, carbohydrate, and fat metabolism (Amod et al., 2012; WHO, 2016; American Diabetes Association [ADA], 2017). It results from abnormalities with the insulin hormone, which is responsible for the regulation of blood glucose within the body (Amod et al., 2012; WHO, 2016; ADA, 2017). According to the Society for Endocrinology, Metabolism and Diabetes of South Africa, the pathogenic processes involved in the development of this metabolic disorder are: (i) insulin deficiency as the beta cells (β -cells) of the pancreas stop producing insulin, since they are impaired or destroyed, or (ii) insulin resistance as the cells in the body become resistant to insulin, (iii) combination of both processes (Amod et al., 2012).

Diabetes can be classified according to aetiology as type 1 diabetes, type 2 diabetes, gestational diabetes, or specific types of diabetes due to other known causes (ADA, 2017). The WHO (2016) and the ADA (2017) describe the categories of diabetes as follows: (i) type 1 diabetes (previously known as insulin-dependent or juvenile diabetes) is due to autoimmune β -cell destruction in the pancreas leading to an absolute insulin deficiency, with strong genetic predispositions, (ii) type 2 diabetes (previously known as non-insulin-dependent or adult-onset diabetes) is due to a progressive loss of β -cell insulin secretion, frequently against the background of insulin resistance, (iii) gestational diabetes is diagnosed in the second or third trimester of pregnancy and was not evident prior to gestation and (iv) specific types of diabetes due to other causes; such as monogenic diabetes syndromes (e.g., neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (e.g., cystic fibrosis) and drug- or chemical-induced diabetes (e.g., excessive glucocorticoid use and medications used for the treatment of HIV/AIDS).

1.3 Type 2 diabetes

Type 2 diabetes accounts for more than 90% of all diabetic cases and is a major public health problem (Amod et al., 2012; Chatterjee et al., 2017). Type 2 diabetes can be attributed to sedentary lifestyles, excessive fat and sugar diets, urbanisation, and the increase in obesity that is seen worldwide (Amod et al., 2012; Chatterjee et al., 2017). Furthermore, it has recently been observed in younger individuals than previously

documented (Frisina, Mapes, Kim, Frisina, & Frisina, 2006; Alberti, Zimmet, & Shaw, 2007; Amod et al., 2012; Hong, Buss & Thomas, 2013). According to the WHO (2016), type 2 diabetes is initially asymptomatic in nature and very gradual in onset. This can explain why 30% to 85% of diabetic cases remain undiagnosed for long periods of time (Amod et al., 2012). These type 2 diabetic individuals do not experience any symptoms and therefore do not seek timely medical attention (WHO, 2016). It is only when medical complications arise that these individuals are diagnosed with diabetes (Amod et al., 2012; WHO, 2016). Consequently, approximately 20% of type 2 diabetic individuals will already have developed diabetic related complications when diagnosed (Amod et al., 2012). The WHO (2016) has cautioned that the longer individuals live with undiagnosed and untreated diabetes, the more severe their overall health related complications are likely to be.

1.4 Vascular complications of diabetes

Diabetes affects the small blood vessels within the body and the resulting condition is known as diabetic microangiopathy (Vojtková, Čilijaková, & Bánovčín, 2012). Diabetic microangiopathy is hyperglycemic-induced due to the constant high levels of glucose within the blood and has detrimental effects on the vasculature within the body (Akinpelu, Mujica-Mota & Daniel, 2014). This has been identified as the main pathology behind the various diabetic complications (Akinpelu et al., 2014). Diabetic microangiopathy causes both macrovascular and microvascular complications.

Macrovascular complications usually involve atherosclerosis due to the higher blood lipid levels that are present within the body. A stroke is twice as likely to occur in individuals with diabetes, as compared to the normal, healthy population; coronary artery disease and congestive heart failure is three to five times as likely to occur; and amputation of a foot as a result of gangrene is 50 times as likely to occur (ADA, 2017).

Microvascular complications affect the small blood vessels throughout the body, resulting in possible retinopathy, nephropathy, and peripheral neuropathy (Kumar & Clark, 2005; Agrawal, Carey, Della Santina, Schubert, & Minor, 2010; Vojtková et al., 2012; Ward et al., 2015; WHO, 2016; ADA, 2017). Retinopathy, a potential to become blind, results from the increased thickness of the capillary basement membrane and the increased permeability of the retinal capillaries. Nephropathy develops due to renal hypertrophy that is

associated with raised glomerular filtration rates, as increased glomerular filtration pressure damages the glomerulus and can lead to renal failure (WHO, 2016; ADA, 2017). Peripheral neuropathy results in a loss of sensation of the lower extremities, due to damage of the nerves in the peripheral nervous system (WHO, 2016; ADA, 2017). This occurs as a result of occlusion of the vasa nervorum, which disrupts the function and structure of these nerves (WHO, 2016; ADA, 2017). The aforementioned diabetic vascular complications are irreversible and degenerative in nature (Karabulut et al., 2014; Konukseven et al., 2014). Of significance to the current investigation is that these diabetic vascular complications may also involve damage to the auditory and vestibular end organs within the inner ear (Agrawal et al., 2010; Ward et al., 2015).

Both the duration and the degree of hyperglycemia play a major role in the development of diabetic complications (Agrawal et al., 2010; Ward et al., 2015). These diabetic complications are known to be more pronounced in patients with uncontrolled diabetes and are linked to their glycated hemoglobin (HbA1c \geq 6.5 - 7%) control (Agrawal, et al., 2010; Karabulut et al., 2014; Konukseven et al., 2014; WHO, 2016; ADA, 2017). Furthermore, the duration of uncontrolled diabetes is of importance, as diabetic retinopathy, nephropathy, and neuropathy tend to manifest only 10 to 20 years after diagnosis in young diabetic patients (ADA, 2017). According to the ADA (2017), these complications present sooner in older diabetic patients, possibly due to the fact that their diabetes was left undiagnosed and untreated for longer periods of time prior to diagnosis. Interestingly, the Diabetes Control and Complications Trial (DCCT) - a medical study conducted by the United States National Institute of Diabetes and Digestive and Kidney Diseases and published in 1993 - showed that if diabetes is better controlled (HbA1c is \leq 6.5%), there is a 60% reduction in the development and progression of microvascular complications (retinopathy and nephropathy), as observed over a nine year period (ADA, 2017).

1.5 Diabetes, the inner ear and hearing function

The inner ear is located deep within the temporal bone, has a highly vascularised nature, and is surrounded by a bony labyrinth (Agrup, Gleeson, & Rudge, 2007). This complex structure houses the cochlea and the vestibular apparatus, both of which are innervated by the eighth cranial nerve and shares the same blood supply (Agrup et al., 2007; Rybak, 1995). These important vascularised structures are dependent on cochlear

microcirculation which continually supplies oxygen and glucose rich blood to the inner ear, after all metabolic waste products have been removed (Rybak, 1995; Xipeng et al., 2013).

Long-term hyperglycemia causes inflammation and a decreased sensitivity of the highly active metabolic vasculature in the inner ear (Xipeng et al., 2013; Hewston & Deshpande, 2016). Xipeng et al. (2013) stated that due to the constant high levels of glucose in the blood of diabetics, glycated hemoglobin is formed and deposited in the walls of the small blood vessels. This leads to increased vessel permeability, irregular growth of the endothelial cells, and a thickened basement membrane that result in a reduced size of the lumens of the blood vessels (Xipeng et al., 2013). As this happens, the nerves become malnourished and their cellular membranes become necrotic (Xipeng, et al., 2013). This results in tissue ischemia and hypoxia, which not only causes damage to single or multiple neural units, but also to the inner ear (Xipeng et al., 2013; Hewston & Deshpande, 2016). These aforementioned researchers (Xipeng et al., 2013; Hewston & Deshpande, 2016) concluded that when the microcirculation of the inner ear is compromised, hearing and vestibular functioning are affected.

The widespread consequences of diabetes have attracted increased attention among numerous researchers concerned with the diabetic population (Agrawal et al., 2010; Hong et al., 2013; Xipeng et al., 2013; Ward et al., 2015). The controversial relationship between diabetes and hearing function has been studied extensively by multiple researchers, with studies dating as far back as 1857 when the possibility was first proposed by Jordo (Smith, Raynor, Prazma, Bunting & Pillsbury, 1995; Fukushima et al., 2006; Hong et al., 2013; Akinpelu, 2014). These studies have not always shown a congruent association between type 2 diabetes and a definite decline in hearing function. Researchers (Cheng et al., 2009; Hong et al., 2013; Horikawa et al., 2013; Xipeng et al., 2013) reported an association between diabetes and hearing loss, while other researchers (Harner, 1981; Hodgson, Talbott, Helmkamp & Kuller., 1987; Dalton, Cruickshanks, Klein, Klein, & Wiley., 1998) reported no associations. Additionally, Smith et al. (1995) reported that the incidence of hearing loss, especially sensorineural hearing loss, ranges from 0% to 93% among diabetic individuals.

Hong et al. (2013) reported that there is a possibility that diabetes affects hearing separately from age-related hearing loss (presbycusis) or, alternatively, that age-related

hearing loss occurs earlier in diabetic individuals. Akinpelu et al. (2013) conducted a systematic review and concluded that there was an overall increased incidence of hearing loss among type 2 diabetic individuals, ranging from 44% to 69.7%, as compared to the incidence of hearing loss (20% to 48.6%) in non-diabetic individuals. Furthermore, Akinpelu et al. (2013) reported that one of the reviewed articles (Bamanie & Al-Noury, 2011) indicated a higher incidence of hearing loss in diabetic individuals who had been suffering from diabetes for 10 years and longer. This further emphasises the correlation between disease duration and hearing function decline (Agrawal et al., 2010; Bamanie & Al-Noury, 2011; Ward et al., 2015). In a meta-analysis study, Akinpelu et al. (2013) performed an overall analysis of pooled odds ratios and determined that the incidence of hearing loss was 1.91 times higher in individuals with type 2 diabetes than in non-diabetic individuals.

Diabetic individuals are known to have an increase likelihood of having hearing loss, tinnitus, and dizziness which arise from inner ear diseases that have been associated with the impaired glucose metabolism (Maia & de Campos, 2005; Xipeng et al., 2013). Hearing loss in diabetic individuals has been described by multiple authors as a bilateral, progressive, sensorineural hearing loss, which predominantly affects the higher frequencies (Axelsson, Sigroth & Vertes, 1978; Maia & de Campos, 2005; Akinpelu et al., 2013). Due to the high frequency nature of this hearing loss, it often goes undetected or is mistaken for presbycusis and not recognised as a direct result of the diabetes (Xipeng et al, 2013). High frequency hearing loss may have substantial detrimental impacts on the overall quality of life of diabetic individuals as it becomes more challenging to understand speech (Maia & de Campos, 2005; Akinpelu et al., 2014).

1.6 Diabetes, vestibular dysfunction and risk of falling

Due to the shared nerve and blood supply of the cochlea and the vestibular apparatus, it is not surprising that diabetes can not only cause changes of hearing function, but can additionally cause vestibular dysfunction.

Agrawal et al. (2010) described vestibular dysfunction, an additional consequence of compromised inner ear functioning, as a newly recognised diabetes-related complication. These researchers demonstrated that participants who had suffered from diabetes for less than five years presented with a 40% increased prevalence of vestibular dysfunction. In

contrast, participants with a six to 10 year history of diabetes showed 61% increased prevalence of vestibular dysfunction. This indicates that the prevalence of vestibular dysfunction increases significantly with longer disease durations (Agrawal et al., 2010; Ward et al., 2015).

A higher prevalence of vestibular dysfunction was also seen in participants who had poor disease control, as indicated by their HbA1c of >7%. In an age adjusted analysis, Agrawal et al. (2010) further found that vestibular dysfunction was increased to 60% odds with poorer disease control. In addition to poor disease control, the participants who had microvascular complications (retinopathy and peripheral neuropathy) were at an even greater risk of developing vestibular dysfunction (Agrawal et al., 2010). Interestingly, Agrawal et al. (2010) further concluded that vestibular dysfunction significantly increased the odds of falling by 2.3 times in type 2 diabetic individuals as compared to the non-diabetic controls. Furthermore, retinopathy and severe peripheral neuropathy increased the odds of falling to a further 2.9 times and 3.3 times respectively. The risk of falling is thus exacerbated by the addition of microvascular complications such as the consequences of retinopathy and severe peripheral neuropathy, and can have debilitating outcomes as vision and mobility are reduced.

The diabetic participants from the study by Agrawal et al. (2013) who had retinopathy (vision worse than 20/40) and severe peripheral neuropathy (at 4-6 insensate sites) had a 71% and a 76% chance respectively of having vestibular dysfunction as measured by the National Health and Nutrition Examination Survey from 2001 to 2004 (Agrawal et al., 2010). These researchers (Agrawal et al., 2010) also observed that participants with diabetes had a 70% chance of having vestibular system abnormalities as determined by the modified Romberg test. This test was used to test the three sensory inputs, namely vision, proprioception and balance, as these sensory inputs are responsible for overall balance and when compromised, result in a 2.6 times increased risk for falls in type 2 diabetics (Agrawal et al., 2009, 2010).

Ward et al. (2015) stated that the effects of diabetes on the vestibular system are not fully understood, and may especially have more implications for older diabetic individuals regarding disability, balance problems, and falls. Ward et al. (2015) demonstrated that there was a definite higher occurrence of vestibular dysfunction among type 2 diabetics with

longer disease durations. In the study by Ward et al (2015), 84% (21 of 25) of the type 2 diabetics had abnormal test performance, as indicated by abnormalities in cervical and ocular vestibular evoked myogenic potential responses (cVEMPs and oVEMPs) and by dynamic visual acuity (DVA) testing. Ward et al. (2015) further determined that 50% of the type 2 diabetic participants had abnormal VEMP results for at least one of the otolith organs, either the utricle or the saccule. In addition to abnormal VEMP results, absent VEMPs (cVEMPs or oVEMPs) were more common in the type 2 diabetic participants than in the controls. Furthermore, semicircular canal (SCC) abnormalities were more common in the diabetic participants as 70% of these participants had abnormal DVA results as confirmed by the impaired test performance of at least one SCC (Ward et al., 2015).

As indicated previously, Agrawal et al. (2010) and Ward et al. (2015) demonstrated that diabetic retinopathy and peripheral neuropathy increases the risk of falling. According to these researchers, this increased risk of falling is mainly caused by postural instability that results from vestibular dysfunction and reduced proprioception. The increased risk of falling affects the overall quality of life for type 2 diabetic individuals (Agrawal et al., 2010; Ward et al., 2015). Currently, increase in episodes of falling, especially in older diabetics, ranks as one of the most costly and incapacitating complications (Agrawal et al., 2010). In addition, Kim et al. (2012) and Hewston and Deshpande (2016) also proved that as much as 10% of falls result in mobility restriction, diminished capacity of self-care, and ultimately a reduced life expectancy.

1.7 Rationale

Uncontrolled diabetes has numerous effects on the various vascular systems throughout the body including the auditory and vestibular structures situated within the inner ear. These aforementioned studies indicated that vascular complications are worsened in diabetics, especially in diabetics with uncontrolled hyperglycaemia (HbA1c >6.5-7%) and disease durations of at least five years and longer. The current study aims to describe the effect of type 2 diabetes on the audiovestibular function, risk of falling and HRQL in adults who have been suffering from type 2 diabetes for more than five years. Data from this group was compared to data obtained from a control group of non-diabetic adults who were matched for age and gender.

Chapter 2

METHODOLOGY

2.1 Main aim

The main aim of this research study was to describe the audiovestibular function, risk of falling and HRQL in adults with type 2 diabetes, and to compare it with non-diabetic age and gender matched adults (control group).

2.2 Research design and setting

A cross-sectional research design was used in this study and quantitative data was yielded. As this was an explorative and descriptive study, a hypothesis or null hypothesis was not required. The sample size included in this research study was relatively small due to a limited time frame for data collection as the researcher had one year for ethical clearance, data collection, analysis of results, and the write up in dissertation format. Approximately 45 type 2 diabetic individuals who met the study requirements were approached at the two test sites and were asked to participate in the study, 17 type 2 diabetic participants declined due to not having enough time on the day or not being willing to participate. All 28 non-diabetic participants approached for control group were willing to participate in this study. The 28 type 2 diabetic participants were recruited from and tested at a tertiary health care facility, Steve Biko Academic Hospital (SBAH), and a private health care facility, Mediclinic Heart Hospital. The 28 non-diabetic healthy age and gender matched group (control group) consisted of friends, family, acquaintances and colleagues of the researcher. Testing of the non-diabetic controls took place at the Department of Speech-Language Pathology and Audiology, University of Pretoria.

2.3 Ethical considerations and informed consent

Ethical approval for this study was firstly obtained from the Research and Ethics Committee at the Department of Speech-Language Pathology and Audiology, University of Pretoria. Once departmental clearance was obtained, ethical approval was sought from and granted by both the Research Ethics Committee of the Faculty of Health Sciences (Appendix A and Appendix B) and the Research Ethics Committee of the Faculty of Humanities (Appendix C), University of Pretoria.

This study was structured in accordance to the Declaration of Helsinki (last updated in October 2013) which guides researchers in biomedical research involving human objects. This study also fully complied with local research and ethical requirements (Appendix D).

2.3.1 Permission

Prof Paul Rheeder and Dr Tanya Kemp, Heads of the Diabetes Clinic at SBAH, gave written permission for the researcher to invite their patients to participate in this research study (Appendix E). Permission was also obtained from the Chief Executive Officer of SBAH, Dr Ernest Kenoshi, to proceed with the research study and to access the patients files (Appendix F). In addition to this tertiary health care facility, a private health care facility also provided consent for the research. Dr Mary Seeber, Head of the Diabetes Clinic at Mediclinic Heart Hospital, provided permission to the researcher to invite her patients to participate in this research study (Appendix G). Furthermore, permission to access the patients' files was also obtained from Dr Mary Seeber at the Mediclinic Heart Hospital (Appendix H).

2.3.2 Informed consent

Written informed consent was obtained from the research participants from the diabetes group and the non-diabetes group, prior to testing (Appendix I and Appendix J). The informed consent letter that was given to the participants of this study explained the research study in detailed sections: (i) an introduction to the research study, (ii) an explanation of the nature and rationale of the study, (iii) an explanation of the test procedures that were to be followed in the study, (iv) an explanation of any possible risks or discomforts to be incurred by participating in the study, (v) any possible benefits of participating in the study, (vi) information regarding the participants' rights before and during participation in the study, (vii) assurance that ethical approval had been obtained for the study, (viii) contact information of the researcher, (ix) clarification that there would be no compensation for participating in the study, and (x) assurance of confidentiality of the participants' information in order to ensure privacy and to protect the participants' anonymity.

Thereafter, the participants had to provide their written consent to participate in the study. The informed consent furthermore clearly stated that participation in this study was

voluntary and the participants were allowed to withdraw at any point in time during the various tests.

2.3.3 Risks and safety

There were no risks involved for the participants who participated in this study. For the diabetes group, participation in this study did not interfere with their medication or with their visit to either of the diabetes clinics. The researcher tested the voluntary diabetes participants before or after their appointment with the medical doctors, or at times that were more convenient to them, such as on the days of medication collections. The participants were, however, requested to complete a few physical activities that were grouped under the fall risk assessments (Appendix K: Timed Up & Go Test; Appendix L: The Berg Balance Scale and Appendix M: Dynamic Gait Index). Appropriate rest time was provided to the participants as necessary and the researcher was continuously available during the testing for support and safety.

2.3.4 Anticipated benefits

The participants did not benefit directly from taking part in this study but their results helped the researchers to determine the occurrence and nature of hearing, vestibular, and balance problems in individuals with type 2 diabetes, as well as the risk of falling and overall health related quality of life. The participants who were diagnosed with any possible auditory problems and/or vestibular problems during testing were referred to an Audiologist for further diagnostic testing and management.

2.3.5 Confidentiality

The participants were informed that all of the information collected by the researcher would be kept confidential. Confidentiality was achieved by allocating a random subject number to each participant's data collection sheet, after which all personal identifiers were removed. In this way the anonymity and privacy of the research participants was ensured and protected during data analysis. Consequently, the study participants would not be identifiable when the research was reported up in an article format and in the dissertation.

2.3.6 Data storage

According to the policy of the University of Pretoria, the data obtained from the research project will be archived at the Department of Speech-Language Pathology and Audiology, University of Pretoria (Appendix N). The data will be archived in digital form and in hard copy format for a period of 15 years.

2.4 Research participants

2.4.1 Participants selection criteria

The type 2 diabetic participants and the non-diabetic controls were required to meet the criteria applicable to their group in order to qualify for participation in this research study. The various criteria are described in Table 1, Table 2 and Table 3.

Table 1 summarizes the various inclusion criteria and the rationale for the criteria relating to the type 2 diabetic participants.

Table 1: Inclusion criteria for the type 2 diabetic group

INCLUSION CRITERION:	RATIONALE:
Participants diagnosed with type 2 diabetes for at least five years prior to participation in this study.	The longer the duration of diabetes, the greater the risk of having vestibular dysfunction. The prevalence of vestibular dysfunction was shown to increase from 40% over a five year period, to 61% over a period of 10 years and longer (Agrawal et al., 2010). According to the WHO (2016), type 2 diabetes is initially asymptomatic in nature, resulting in 30-85% of diabetic cases remaining undiagnosed for long periods of times (Amod et al., 2012; WHO, 2016). It is evident from literature that the duration of diabetes plays a crucial role in the prevalence of vestibular dysfunction and that individuals with type 2 diabetes have on average had the disease longer before a clinical diagnosis was made.
Male and female participants (ages 18 - 59).	According to Janky and Shepard (2009) participants aged 60 years and older should be excluded from Vestibular Evoked Myogenic Potential (VEMP) testing, as numerous studies have indicated that there is a decrease in the VEMP amplitude and an increase in the VEMP threshold with increased age. Results are therefore deemed unreliable due to the impact of age. Presbycusis (age-related hearing loss) is also known to affect elderly individuals and as the age of the study participants increases, so does the risk of age-related hearing loss (Ferrite & Santana, 2005). According to Ferrite and Santana (2005), age related changes can affect both the inner and outer hair cells found in the cochlea, as well as afferent neural fibres and the stria vascularis. A cut off age of 59 years was set so that the effect of diabetes on hearing loss could be shown independently from age-related hearing loss. Furthermore, according to the IDF (2015), there were 321,100 deaths due to diabetes mellitus, with the majority of individuals (79%) being younger than 60 years of age. In agreement with the above mentioned studies, a cut off age of 59 years has been selected for the participants of this study.
Participants who have not used insulin within the first year after being diagnosed with type 2 diabetes.	At least initially, and often throughout their lifetime, individuals with type 2 diabetes do not need insulin treatment (ADA, 2017). Type 2 diabetes is the result of a combination of resistance to insulin and insufficient compensatory insulin secretion. When there is extensive β -cell destruction and no residual insulin secretion, these individuals need insulin for survival (ADA, 2017). However, although these individuals with type 2 diabetes may eventually need insulin treatment, their

disease aetiology is still classified as type 2 diabetes and not as type 1 diabetes (requiring insulin in order to control blood sugar).

Table 2 summarizes the various inclusion criteria and the rationale for the criteria relating to the non-diabetic controls.

Table 2: Inclusion criteria for the non-diabetic controls

INCLUSION CRITERION:	RATIONALE:
Age and gender matched controls.	In order to successfully compare the results in this study, age and gender matched adult controls had to be included in order to determine to what extent type 2 diabetes affects the audiovestibular functioning, risk of falling, and HRQL in the participants with type 2 diabetes compared to non-diabetic age and gender matched controls.
Healthy controls who have not been diagnosed with type 1 diabetes or type 2 diabetes.	The age and gender matched controls were healthy individuals who had not previously been diagnosed with type 1 or type 2 diabetes. This was deemed necessary in order to make a significant age and gender comparison with the type 2 diabetic participants. An unknown underlying condition of diabetes was ruled out using the GlucoPlus Pro Blood Glucose Test Strip® as previously described by pricking the participant's finger.

Table 3 provides the rationale for the exclusion criteria of the diabetic and the non-diabetic group in the research study. Co-morbid disorders may influence the research study's findings and therefore needed to be excluded (Kim et al., 2012).

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

EXCLUSION CRITERION:	RATIONALE:
Participants who have severe symptomatic neuropathy.	According to Kim et al. (2012) participants with severe neuropathy including paresis, muscle weakness or heat dysfunction should be excluded from testing as these individuals are known to present with foot ulcers and instability when walking, and are at greater risk for falling. Consequently, these participants will not be able to complete the vestibular bedside assessments required for this study, namely: the Berg Balance Scale by Berg, Wood-Dauphinee, Williams and Maki (1992), the Dynamic Gait Index by Herdman (2000) and Shumway-Cook and Woollacott (1995) and the Timed up and Go Test by Podsiadlo and Richardson (1991).
Participants with peripheral arterial obstructive disease in their legs.	According to Olin and Sealove (2010) and Kim et al. (2012), participants with peripheral arterial obstructive disease in their legs should be excluded as they may experience classic claudication (an induced cramping pain in the legs as a result of exercise, typically caused by the obstruction of the arteries) leading to pain, tiredness, heaviness and discomfort in their legs. The participants with peripheral arterial obstructive disease in their legs will be unable to complete the above mentioned vestibular bedside assessments required for this study.
Participants with a history of chronic alcohol abuse.	A significant association between hearing function in older adults and moderate alcohol consumption is evident compared to adults who do not consume alcohol (Gopinath, Flood, McMahon, Burlutsky, Smith, & Mitchell, 2010). In addition, Tianwu et al. (2009) stated that a moderate quantity of alcohol in the blood affects not only the vestibular system but also the oculomotor system. Furthermore, it was suggested that reduced vestibular function contributed to postural instability after alcohol consumption (Tianwu et al., 2009). Therefore, participants with a history of chronic alcohol abuse were excluded from this study.
Participants with co-morbid diseases such as hypothyroidism (not on Eltroxin), liver cirrhosis, or	According to Rybak (1995) hypothyroidism, depending on severity, may affect various parts of the vestibular system. Severe

<p>chronic hepatitis.</p>	<p>hypothyroidism can cause central vestibular disorders affecting the cerebellum while mild hypothyroidism may result in peripheral vestibulopathy (Rybak, 1995). A research study regarding hearing loss and renal disease conducted by Bergstrom, Jenkins, Sando and English (1973) indicated that 41% of the participants with hearing loss had ototoxic drug exposure. Wong, Cheong-Lee, Ford and Yoshida (2005) described a study of 73 individuals, where tinnitus and/or hearing loss was reported in 32 of the participants (43.8%) during Interferon (IFN) therapy, and the audiometry results indicated sensorineural hearing losses in 27 of the participants (36.9%). These investigators further reported that hearing loss frequently develops in the later stages of treatment for chronic hepatitis. Therefore, participants with co-morbid diseases such as hypothyroidism, liver cirrhosis, or chronic hepatitis were excluded as the diseases or their medications could negatively affect the auditory system and can result in hearing loss.</p>
<p>Participants who have had a stroke or a traumatic brain injury (TBI).</p>	<p>In a study conducted by Scherer and Schubert (2009), there was an 80% incidence of vestibular dysfunction in participants who had TBI. This was confirmed by caloric assessment results as seven out of the 10 participants had a unilateral vestibular hypo-function and one out of the 10 participants had a bilateral vestibular hypo-function (Scherer & Schubert, 2009). Therefore, participants who have had a TBI were excluded from this study in order to keep the effect of type 2 diabetes on the audiovestibular functioning, risk of falling, and health related quality of life as independent as possible.</p>
<p>Participants who have a history of occupational and recreational noise exposure.</p>	<p>Occupational noise is one of the most significant causes of adult-onset hearing loss (Nelson, Nelson, Concha-Barrientos & Fingerhut, 2005). Long term occupational or recreational noise exposure causes hearing loss and due to a combination of mechanical and metabolic factors (Ferrite & Santana, 2005). Chronic noise exposure damages the cochlear hair cells and the metabolic changes resulting from hypoxia (a shortage of oxygen reaching the organs and tissues in the body) caused by noise induced capillary vasoconstriction (Ferrite & Santana 2005). Therefore, participants who have had occupational or recreational noise exposure were excluded from this study in order to keep the effect of type 2 diabetes on audiovestibular functioning, risk of falling and health related quality of life as independent as possible.</p>
<p>Participants who smoke.</p>	<p>Participants who smoke were excluded from this study as numerous studies have indicated that smoking affects hearing. According to Cruickshanks et al. (1998), cigarette smoking affects hearing through its effect on the anti-oxidative mechanisms on the vasculature supplying the auditory system. An association between cigarette smoking and hearing loss in adults has been found in clinical studies (Cruickshanks et al., 1998). Furthermore, according to Ferrite and Santana (2005) tobacco affects the blood supply to the cochlea as it causes peripheral vascular change. In the current study, the effect of type 2 diabetes on the audiovestibular function, risk of falling and health related quality of life needs to be tested independently from any other damage that could be caused due to smoking.</p>
<p>Participants with middle ear pathology.</p>	<p>Participants who present with a 10dB air-bone gap or more on behavioural audiometric test results, and have tympanometry results that fall outside of normal Type A tympanogram, will be excluded from this study as middle ear infections negatively influence the reliability of audiometric test results as well as VEMP test results due to the conductive component.</p>
<p>Participants with a history of ototoxic medication use.</p>	<p>Participants with a history of ototoxic medication use, for example gentamycin or cisplatin, were excluded from this study as ototoxic medication can cause ototoxic hearing losses. A study conducted by Kim et al. (2012) excluded participants with a drug history of cisplatin or taxol used for their neuropathy. Therefore, participants with a history of ototoxic medication use were excluded from this study.</p>

2.4.2 Study population

A purposive sampling method was employed to recruit the participants with type 2 diabetes. Adults with type 2 diabetes, who met the above required criteria and who were

willing to participate, were included in this study. A clinical diagnosis of type 2 diabetes had to have been made at least five years prior to participating in this study. A clinical diagnosis of type 2 diabetes can be made according to the criteria set by the Society for Endocrinology, Metabolism and Diabetes of South Africa and ADA (2016): (i) Casual/random plasma glucose (PG) ≥ 11.1 mmol/L (≥ 200 mg/dL), (ii) Fasting Plasma Glucose (FPG) ≥ 7.0 mmol/L (≥ 126 mg/dL), where fasting is defined as no caloric intake for at least eight hours, or (iii) HbA1c $\geq 6.5\%$ (48 mmol/mol) (Amod et al., 2012). This test should be performed in a laboratory using a nationally certified method and standardised according to the DCCT assay (Amod et al., 2012).

The non-diabetic control group consisted of healthy volunteers who were age and gender matched to the type 2 diabetic participants. In order to ensure that the non-diabetic controls did not have undiagnosed diabetes, their blood glucose was tested before participating. The researcher used the GlucoPlus Pro Blood Glucose Test Strip® to quantitatively measure the participant's glucose from capillary blood that was pricked from a fingertip. This is a safe and accurate way to rule out undiagnosed diabetes. Results of random blood glucose ≤ 6.5 mmol/L ruled out a diagnosis of diabetes (ADA, 2017).

2.5 Data collection procedures

A detailed description of the methods and test procedures employed during data collection is summarized in Table 4.

Table 4: Summarised data collection protocol according to test sequence

Category and sequence	Purpose/tests
1. Record review and additional information collection	Demographic data and medical records
2. Otologic and audiological assessments	Otoscopy, tympanometry, acoustic reflexes, and pure tone audiometry
3. Vestibular assessments	Video Head Impulse Test (vHIT), Cervical Vestibular Evoked Myogenic Potentials (cVEMPs), and Ocular Vestibular Evoked Myogenic Potentials (oVEMPs)
4. Risk of falling assessments	Timed Up and Go (TUG, Appendix K), Berg Balance Scale (BBS, Appendix L), and Dynamic Gait Index (DGI, Appendix M)
5. Health related quality of life questionnaire	Health Related Quality of Life (EQ-5D-5L) questionnaire (Appendix N)

2.5.1 Record review for the participants with type 2 diabetes

After the type 2 diabetic participants had given their written consent to participate in the research study and for the researcher to access their files (Appendix I), the following information was extracted and captured on the data sheet (Appendix P):

- a) Age (in years with the last birthday taken into account);
- b) Gender;
- c) Weight, height, and calculated BMI classified as underweight ($\text{BMI} < 18.50 \text{ kgm}^{-2}$), normal weight ($18.50 \text{ kgm}^{-2} < \text{BMI} \leq 25 \text{ kgm}^{-2}$), overweight ($25 \text{ kgm}^{-2} < \text{BMI} \leq 30.0 \text{ kgm}^{-2}$), or obese ($\text{BMI} > 30.0 \text{ kgm}^{-2}$) as defined by Kholsa and Lowe (1967), National Institutes of Health (2000) and WHO (2006);
- d) Tests for blood glucose, HbA1c, and lipid profile (total cholesterol, LDL and HDL);
- e) Thyroid function tests (T4 and TSH);
- f) Measurement of blood pressure on the day of testing with a portable Microlife® machine and categorized according to the Southern African Hypertension Society (SAHS) blood pressure classification stages by Milne and Pinkney-Atkinson (2004) as:
 - Normal (Systolic Blood Pressure [SBP] 120-129 or Diastolic Blood Pressure [DBP] 80-84),
 - High normal (SBP 130-139 or DBP 85-89),
 - Stage I mild (SBP 140-159 or DBP 90-99),
 - Stage II moderate (SBP 180-179 or DBP 100-109), or
 - Stage III severe (SBP ≥ 180 or DBP ≥ 110); and
- g) Evaluation of micro-vascular complications:
 - Retinopathy (examination of the eyes);
 - Nephropathy (kidney function: s-creatinine and s-urea); and
 - Peripheral neuropathy (examination of the feet).

2.5.2 Demographic data for the non-diabetic participants

The non-diabetic controls were age and gender matched to the type 2 diabetic participants. After the non-diabetic controls gave their written consent to partake in this research study (Appendix J), a brief medical history was obtained and a random blood glucose test took place prior to participation in order to rule out type 1 or type 2 diabetes. All the required information was captured on the data sheet (Appendix Q):

- a) Weight, height, and calculated BMI as defined by Kholisa and Lowe (1967), National Institutes of Health (2000) and WHO (2006); and
- b) Measurement of blood pressure on the day of testing with a portable Microlife machine and categorized according to the Southern African Hypertension Society (SAHS) blood pressure classification stages as by Milne and Pinkney-Atkinson (2004) (as defined above).

2.5.3 Otologic and audiological assessments

The participants' outer ear functioning was assessed with an otoscopic examination of the external ear canal and tympanic membrane. Participants with occluded ear canals due to excessive cerumen were referred for ear canal management and cerumen removal. Tympanometry was performed using a diagnostic Y-226 Hz probe tone (GSI Tymptstar, Grason-Stadler, Eden Prairie, MN, USA). The following criteria for normal functioning (Jerger, 1970) were used to determine each participant's middle ear functioning: ear canal volume (0.8 to 2.0ml), static compliance (0.3 to 1.8ml), and middle ear pressure (-100 to +50 daPa). Otoscopic examination and middle ear testing were conducted before further testing continued. These tests were performed in order to rule out conductive pathologies such as possible occluded ear canals or otitis media. None of the participants in this study presented with either conditions or had to be referred for further testing.

Diagnostic pure tone audiometry was performed with a KUDUwave Type 2 Clinical Audiometer (IEC 60645-1/2) that was operated by a notebook computer (Acer Aspire E1-532, running Microsoft Windows 8), as validated by Swanepoel et al. (2013). The audiometer hardware was encased within each circumaural ear cup and was powered by the notebook computer. The transducers used were insert earphones (ER3A-Insert earphones, Etymotic Research, Elk Grove Village, IL, USA) covered by the circumaural cups after insertion into the external auditory canal. A response button was connected to the KUDUwave device to record the participant's response to the acoustic stimuli presented (Mahomed-Asmail, Swanepoel & Eikelboom, 2016).

Pure tone audiometry, a behavioral hearing test, was conducted to determine the presence, degree, and type of hearing loss. Pure tone hearing thresholds were obtained using air conduction (AC) at frequencies ranging from 250 Hz to 8000 Hz. Bone conduction

(BC) was performed automatically if the participant's AC score was ≥ 10 dBHL. A 4-tone pure tone average was calculated across 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. The type and degree of hearing loss was based on the participant's 4-tone pure tone average according to the American Speech-Language-Hearing Association (Clark 1981). Hearing was classified as either normal hearing, PTA of ≤ 15 dBHL, or as presenting a hearing loss, PTA of ≥ 16 dBHL (Clark, 1981). Unilateral hearing losses were classified by normal hearing of the better ear (PTA of ≤ 15 dBHL) and by the hearing of the poorer ear (PTA of ≥ 16 dBHL). Bilateral hearing losses were classified by PTA of ≥ 16 dBHL for both ears. Participants who presented with an air-bone gap of ≥ 10 dBHL or with profound hearing losses, as indicated by pure tone thresholds of > 75 dBHL, were excluded from further procedures.

2.5.4 Video head impulse test (vHIT)

Video head impulse testing is widely used as an objective measure of the individual function of each of the six semicircular canals (McGarvie, et al., 2015; Halmagyi et al., 2017). The vHIT is known to quantify the functioning of the vestibular ocular reflex (VOR) by means of a quick and simple test procedure (Curthoys et al., 2016). This test objectively indicates gain values as well as the presence of covert and overt corrective saccades (Curthoys et al., 2016). The vHIT was carried out with the Visual Eyes infrared video-based equipment (Micromedical Technologies Inc. Chatham, Illinois, USA). In order to ensure small pupil dilation, participants were tested in a well-lit room, with an eye-level target at a distance of 1 meter in front of them. Furthermore, in order to obtain reliable results, the goggles were tightened to prevent slippage.

The lateral vHIT test consisted of small, abrupt, unexpected horizontal head movements performed with both of the researcher's hands at the base of the head, away from the goggles strap and the skin of the forehead. For the vertical vHIT tests, the researcher delivered small, abrupt movements in the direction of the planes left anterior right posterior (LARP) and right anterior left posterior (RALP) as described by McGarvie and colleagues (2015) and Halmagyi and colleagues (2017). Figure 1 illustrates the procedures used during vHIT. The researcher's hands were placed on the top of the participants head and under their chin. In healthy subjects, the exact measures of eye movements in response to the passive head impulses show that after a very short latency

of about 10 seconds, there is a smooth compensatory eye movement opposite in direction and equal in velocity to that of the head velocity (Halmagyi et al., 1990; Halmagyi & Curthoys, 1998). Test results were interpreted as abnormal if: (i) the VOR gain value was <0.8 for the lateral canals and <0.7 for vertical canals, or (ii) either covert or overt catch-up saccades were present (McGarvie et al., 2015; Curthoys et al., 2016).

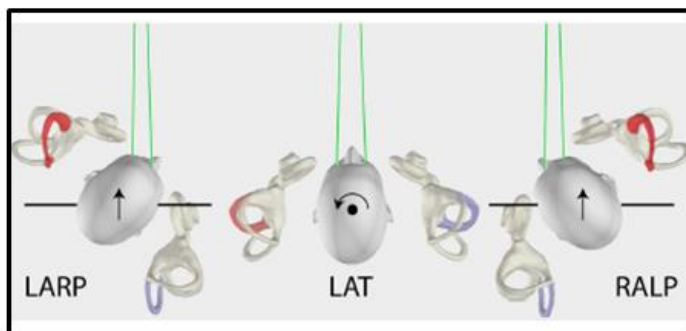


Figure 1 Procedure of performing the vHIT head movements for the lateral vHIT test and for the vertical vHIT test, LARP and RALP (from McGarvie et al., 2015)

2.5.5 Vestibular evoked myogenic potentials (VEMP) testing

Among the recent advancements in objective testing of the vestibular system, VEMPs have been introduced as a method of assessing the saccular and utricular functioning in individuals with various vestibular disorders (Sahu & Sinha, 2015). Air conduction cervical VEMP (cVEMP) testing predominantly reflects the function of the saccule and inferior vestibular nerve (Colebatch, Halmagyi & Skuse, 1994; Welgampola & Colebatch, 2001, 2005) while air conduction ocular VEMP (oVEMP) testing predominantly reflects the function of the utricle and superior vestibular nerve (Iwasaki et al., 2009; Curthoys, 2010; Curthoys, Vulovic & Manzari, 2012).

Participants were seated on a standard chair for both cVEMP and oVEMP testing (Isaradisaikul, Navacharoen, Hanprasertpong & Kanhsanarak, 2012; Konukseven et al., 2015). The testing of the VEMPs was performed with an Interacoustics Eclipse EP 25 auditory evoked (AEP) response system version 1.3 (Interacoustics A/S, Assens, Denmark) which was connected to a Lenovo laptop. An AC tone burst stimulus of 500Hz was presented at an intensity of 97 dBnHL using alternating polarity. Insert earphones (ER3A-Insert earphones, Etymotic Research, Elk Grove Village, IL, USA) with disposable ear tips were used. Prior to positioning the reusable gold cup electrodes with Ten20® conductive

paste, the participant's skin was prepared with alcohol wipes and Nuprep® gel to ensure that the impedances were kept under 5kΩ. In order to ensure that the electrodes were kept securely on the skin, micropore tape was used.

The Jongkees formula was used for the VEMP asymmetry ratio (AR): $[(AL - AS) / (AL + AS)] \times 100$, where 'AL' equals the larger P1-N1 amplitude and 'AS' the smaller P1-N1 amplitude. In order for the VEMP responses to be present and labelled, the responses and their peaks had to be repeated within the correct time intervals to test for wave reproducibility and to eliminate potential artefacts. The VEMP responses were interpreted according to the following guidelines: (i) the presence of identifiable P1 and N1 waveforms; (ii) Latencies above the upper limits of the waveform latencies were considered present yet delayed, and considered abnormal; and (iii) the presence of an amplitude AR of $\geq 40\%$ was considered abnormal as it indicates amplitude differences between the ears (Akin & Murnane, 2008).

With regard to cVEMP testing, ipsilateral electromyography recordings were performed. In order for the cVEMP to be recorded, the participants had to obtain sufficient tonicity of the sternocleidomastoid (SCM) muscle with minimum discomfort (Isaradisaikul et al., 2012). Neck flexion of the SCM muscle was achieved by the participants turning their head contralateral to the side of stimulation in order to generate cVEMP responses without early fatigability and with the most robust amplitudes (Isaacson, Murphy & Cohen, 2006; Isaradisaikul, et al., 2012). The active (inverting) electrode was placed on the ipsilateral mid-portion of the SCM muscle of the test ear, the reference (non-inverting) electrode was placed on the sternum, and the ground electrode was placed on the forehead (Isaradisaikul et al., 2012; Konukseven et al., 2015). For the cVEMP waveform, the first positive peak on the waveform was marked as P1 and the first negative deflection was marked as N1. According to Zapala and Brey (2004) and Isaradisaikul et al. (2012), a latency of ≤ 19 msec was considered normal for P1 and a latency of ≤ 28 msec was considered normal for N1. The peak-to-peak (inter-peak) amplitude was the sum of the amplitudes of these repeated responses.

With regard to oVEMP testing, the participants were instructed to maintain an upward gaze during the stimulation and recording, focusing their gaze on a stationary target on the ceiling. Electromyography recordings from the extra-ocular muscles in the infra-

orbital region were recorded while the stimulus was presented in the contralateral test ear. The active (inverting) electrode was placed under the opposite eye on the inferior oblique muscle from the test ear, the reference (non-inverting) electrode was placed on the nose bridge, and the ground electrode was placed on the forehead (Leyssens, et al., 2016). For the oVEMP waveform, the first negative deflection on the waveform was marked as N1 and the first positive peak was marked P1 (Sandhu et al., 2013; Leyssens, et al., 2016; Vanspauwen et al., 2016). According to Sandhu et al. (2013), Leyssens et al. (2016) and Vanspauwen et al. (2016), a latency of ≤ 11.1 msec was considered normal for N1 and a latency of ≤ 17.6 msec was considered normal for P1. The peak-to-peak amplitude was the sum of the amplitudes of these repeated responses.

Vestibular dysfunction was therefore described as abnormal vHIT results and/or abnormal VEMP results. The vHIT results were classified as abnormal when the gain was abnormally low and/or covert or overt saccades were present. The cVEMP and oVEMP results were classified as abnormal under the following conditions: (i) the presence of an identifiable P1 and N1 waveforms; (ii) Latencies above the upper limits of the waveform latencies were considered present yet delayed, and considered abnormal; and (iii) the presence of an amplitude AR of $\geq 40\%$ was considered abnormal as it indicates amplitude differences between the ears (Akin & Murnane, 2008).

2.5.7 The Timed Up and Go (TUG)

The TUG test was developed and described by Podsiadlo and Richardson in 1991 (Podsiadlo & Richardson, 1991) as a quick measure of performance in mobility and lower peripheral function, and to screen for the risk of falling. Owing in part to its ease of application, quick administrative time, association of risk of falling and sensitivity, the American Geriatrics Society, the British Geriatrics Society, and the Society of Nordic Geriatricians, among others, recommended using the TUG as a screening test for risk of falling (Herman, Giladi & Hausdorff, 2010). The TUG is able to correctly identify older individuals who are at risk of falling, with both sensitivity and specificity ranging from 59 to 89% (Whitney, Marchetti, Schade and Wrisley, 2004; Herman et al., 2010). The TUG test also has high test-retest reliability (Podsiadlo & Richardson, 1991; Steffen, Hacker & Mollinger, 2002). The measured outcome of the TUG is the time in seconds taken to

complete the entire sequence of sitting-to-standing, walking, turning around and returning to the chair (Huang, Hsieh, Wu, Tai, Lin & Lu, 2011).

Despite the TUG test's apparent simplicity, it essentially tests multiple components of balance and mobility (Podsiadlo & Richardson, 1991). A simple sit-to-stand component is a sequence of multiple tasks (Janssen, Bussmann & Stam, 2002). The sequence of sitting-to-standing requires forward movement while still being seated (in preparation for standing), acceleration of the individual both in the anterior-posterior and vertical plane, push-off from a standard chair, and stabilization once in the standing position (Janssen et al., 2002). In addition to the above mentioned tasks, the TUG test also requires suitable initiation of stepping, accelerating, and decelerating, and the preparation to turn around and walk back to the chair. The multiple subtasks of the TUG demand a wide array of responses and appropriate distribution even among healthy individuals. Although the TUG test may consist of general, everyday motor tasks and basic movements, several of these component tasks may be complicated and do require some level of planning, organization, and orientation in space. Turning and even rising from a standard chair require cognitive function. TUG is not only associated with motor performance, it requires intact cognitive function for optimal performance (Pettersson, Engardt, & Wahlund, 2002; Pettersson, Olsson & Wahlund, 2005).

The participants were asked to stand up from a standard chair, walk 3 meters at a comfortable pace, turn around, walk back to the chair and sit down. This task was repeated twice and the averaged time was analysed. A test time of 10 seconds or less was classified as normal and longer test times were classified as abnormal (Podsiadlo & Richardson, 1991; Whitney et al., 2004; Herman et al., 2011). These abnormal test times indicate a high risk of falling (Podsiadlo & Richardson, 1991; Whitney et al., 2004; Herman et al., 2011)

2.5.8 Berg Balance Scale (BBS)

The BBS was developed and described by Berg, Wood-Dauphinee, Williams and Gayton (1989) and is a well-established clinical measure designed to measure balance in elderly individuals. The BBS measures balance by assessing an individual's performance of 14 functional tasks, while being timed in a clinical setting. The time needed to administer the BBS was 15 to 20 minutes. The use of minimal, inexpensive equipment such as a stop

watch, ruler, standard chair and a step or stool of average height is required. The 14 functional tasks varied in complexity and a score of zero to four was given on each task, where zero was equal to an inability to perform the required task and four equalled an ability to complete the given task.

The participants were requested to complete the following 14 functional tasks: (i) sitting to standing, (ii) standing unsupported, (iii) sitting unsupported, (iv) standing to sitting, (v) transfers 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 from the floor, (x) turning to look behind, (xi) turning 360 degrees, (xii) placing alternate feet on a stool, (xiii) standing with one foot in front of the other, and (xiv) standing on one foot. A score of 41 to 56 indicated a low risk of falling, 21 to 40 indicated a medium risk of falling and less than 20 indicated a high risk of falling (Berg et al., 1989).

2.5.9 Dynamic Gait Index (DGI)

The DGI (Shumway-Cook & Woollacott, 1995) is a performance based mobility test that was developed to assess dynamic postural stability in older adults at risk of falling, or with balance and gait dysfunction (Herdman, 2000; Wrisley, Walker, Echternach & Strasnick, 2003; Huang et al., 2011). This fall risk assessment requires the use of minimal, inexpensive equipment such as two boxes for the participants to step over and two cones as obstacles for the participants to walk around. The eight functional walking tasks varied in complexity and a score of zero to three was given on each task, where zero was equal to a severe impairment and three was equal to normal.

The participants were given the following eight functional walking tasks to complete: (i) gait on 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 steps. A maximum score of 24 could be obtained by the participants. Scores of 19 or less have been related to increased risks of falling (Shumway-Cook & Woollacott, 1995).

2.5.10 Health Related Quality of Life (EQ-5D-5L) questionnaire

The EQ-5D-5L was designed in 2005 by the EuroQol Group (1987) as a standard, user-friendly HRQL instrument. This instrument is a self-administered questionnaire that has been used extensively as a patient reported health related outcome measure. It comprises five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and has five levels of severity for each health dimension (Herdman, et al., 2011). The EQ Visual Analogue Scale (VAS) records the participant's self-rated health on a 20 cm vertical, visual analogue scale with the two endpoints labelled: "the best health you can imagine" and "the worst health you can imagine" (Herdman et al., 2011). The VAS can be used as a quantitative measure of health as rated by the participants themselves (Herdman et al., 2011).

The participants were asked to complete the EQ-5D-5L questionnaire in order to quantify their HRQL by evaluating the aforementioned health dimensions (Herdman et al., 2011). Each health dimension was graded according to the five levels of severity for each participant's capabilities: (i) no problems; (ii) slight problems; (iii) moderate problems; (iv) severe problems; or (v) an inability to complete the required task. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The participants then had to quantitatively measure their health state on the EQ Visual Analogue Scale (VAS) out of 100, based on how they felt on the day of testing. Their best health state imaginable was marked as 100 and zero indicated the worst health state imaginable.

2.6 Statistical Analyses

All analyses of data were performed using the statistical software program STATA version 14.0. Descriptive statistics such as means (standard deviation, \pm), median (interquartile range) and percentages (n= %) were used to describe the data. Inferential statistics were used to determine whether there was a significant difference in the audiovestibular, risk of falling, and health-related quality of life between the diabetic and non-diabetic adults. A two group comparison of continuous and categorical data was used taking into account that the patients with diabetes were matched with controls on a case by case basis. For this study, when the data was distributed normally, a parametric statistical

test such as the paired t-test was used. When the data was distributed not normally, a non-parametric statistical test such as the Wilcoxon Sign Rank test was used. For comparison of paired categories (proportions) the McNemar test was used. As this study was exploratory, there was no specific primary hypothesis on which to base the sample size calculation. The sample size of 28 per group allowed detection of differences between 1 and ½ standard deviation with a power of 0.80 and alpha set at 0.05. It detected a difference in proportions of 20% or more with the same power and alpha level as above. The outcomes of this study were common, therefore risk ratios were used instead of odds ratios (xtgee was used with pairs taken into account). Associations were considered statistically significant for 2-sided statistics with a p value <0.05 .

Chapter 3

RESULTS

Results of audiovestibular testing, fall risk assessments, and a health related quality of life questionnaire obtained from 28 type 2 diabetic participants were compared with results of the same measures obtained from 28 age and gender matched control participants without a history of diabetes or inner ear disease.

3.1 Study participants

Table 5 summarizes the demographic features of the study participants. A total of 56 adults participated, comprising of 28 type 2 diabetic participants and 28 non-diabetic controls.

Table 5: Demographic features of the study participants

	ALL (n=56)	Diabetic Group (n=28)	Non-diabetic Group (n=28)	p.value
Age (Years)	49.1 (±6.2)	49.2 (±6.1)	49.0 (±6.4)	0.3262
Gender (%)				0.962
Female	32 (57.1%)	16 (57.1%)	16 (57.1%)	
Male	24 (42.9%)	12 (42.9%)	12 (42.9%)	
Disease Duration (Years)	-	15.36 (9.67)	-	-
Weight (kg)	87.7 (±20.9)	98.4 (±20.1)	77.0 (±15.8)	<0.001
BMI	31.6 (±7.6)	35.4 (±7.7)	27.9 (±5.5)	<0.001
SBP	131.9 (±14.9)	132.9 (±14.4)	131.0 (±15.6)	0.6057
DPB	83.4 (±9.9)	83.7 (±9.5)	83.1 (±10.5)	0.8371
Monofilament Test:				
4/8				
6/8	1 (1.8%)	1 (3.6%)	0 (0.0%)	-
8/8	2 (3.6%)	2 (7.1%)	0 (0.0%)	-
	53 (94.6%)	25 (89.3%)	28 (100.0%)	-
Blood Glucose (mmol/L, SD)	-	10.9 (±4.5)	-	-
HbA1c (% , SD)	-	9.3 (±2.2)	-	-
Total Cholesterol (mmol/L)	-	4.9 (±1.6)	-	-
Triglyceride (mmol/L)	-	1.8 (±1.0)	-	-
LDL (mmol/L, n = 27)	-	2.9 (±1.2)	-	-
HDL (mmol/L, n = 27)	-	1.2 (±0.4)	-	-
Urea (mmol/L, SD)	-	5.6 (±2.2)	-	-
Creatinine (mmol/L)	-	79.1 (±23.8)	-	-
T4 (mmol/L, n = 25)	-	14.1 (±3.7)	-	-
TSH (mmol/L, n = 26)	-	2.0 (±1.3)	-	-

*Statistical Test used for age, gender, weight, BMI and blood pressure: Paired T Test, ± = Standard Deviation, %= percentage, BMI (body mass index), SBP (systolic blood pressure), DBP (diastolic blood pressure), HbA1c (glycated hemoglobin), LDL (low density lipoprotein), HDL (high density lipoprotein), T4 (thyroxine), and TSH (thyroid stimulating hormone).

The mean age of the participants was highly similar for the two groups (diabetic group: 49.1 years, ±6.2, range 34 to 59; control group: 49 years, ±6.4, range 33 to 59). The percentage of female participants for both groups was 57.1% (n=16). The type 2 diabetic participants had mean glycated hemoglobin (HbA1c) of 9.3% (±2.2) and mean disease duration of 15.36 years (±9.67; Inter-Quartile Range [IQR] 7-23.5; range 5-37 years). The participants' height and weight were measured and subsequently their BMIs were calculated. The type 2 diabetic participants had a mean BMI of 35.4 (±7.7) and the non-diabetic adults had a mean BMI of 27.9 (±5.5), indicating a significant difference in BMI between the two groups ($p<0.001$; t-test). The blood pressure stage on average was

classified as high-normal (SBP 130-139 and/or DBP 90-99) for all of the participants (n =56).

3.2 Audiological assessments

Table 6 shows the mean and standard deviation (SD) AC pure tone audiometry thresholds for test frequencies ranging from 250 to 8000 Hz per ear, in the diabetic and non-diabetic groups. All of the participants' hearing was classified according to a calculated 4-tone PTA at 500, 1000, 2000, and 4000 Hz per ear. For this study, slight hearing losses (16-25dBHL) were classified as having a hearing loss present (Clark, 1981).

Table 6: Pure tone audiometry thresholds (dBHL) of the study participants

Mean (SD) thresholds in dBHL for the left ears (n ¹ =28)				Mean (SD) thresholds in dBHL for the right ears (n ¹ =28)			
Frequency	Diabetic Group (Mean, SD)	Non-Diabetic Group (Mean, SD)	p value	Frequency	Diabetic Group (Mean, SD)	Non-Diabetic Group (Mean, SD)	p value
250 Hz	20.5 (±11.3)	20.4 (±10.0)	0.938	250 Hz	24.5 (±19.4)	25.9 (±15.1)	0.725
500 Hz	28.2 (±9.4)	23.0 (±7.0)	0.007*	500 Hz	30.2 (±18.8)	27.9 (±13.4)	0.533
1000 Hz	25.7 (±14.3)	19.6 (±9.3)	0.088	1000 Hz	27.9 (±19.7)	24.8 (±11.4)	0.423
2000 Hz	24.1 (±12.6)	19.6 (±8.3)	0.166	2000 Hz	24.1 (±18.7)	24.8 (±11.6)	0.827
4000 Hz	17.5 (±13.2)	18.2 (±13.1)	0.816	4000 Hz	19.8 (±22.0)	19.6 (±15.6)	0.969
8000 Hz	20.2 (±20.0)	17.5 (±16.7)	0.556	8000 Hz	21.2 (±22.1)	24.5 (±21.1)	0.561
4-Tone PTA	24.1 (±10.4)	20.3 (±7.4)	0.138	4-Tone PTA	26.2 (±18.7)	24.4 (±11.2)	0.597

Statistical Test Used: Paired T Test, ± = Standard Deviation, n¹= number of ears per group, *= significant difference

There were no significant differences observed for the majority of the pure tone audiometry results as indicated by the various *p* values for both the left and right ears in Table 6. There was, however, a significant difference between the two groups at 500 Hz in the left ear (*p*=0.007, t-test), which indicated poorer hearing for the type 2 diabetic participants at this specific frequency. It was also noted that all of the thresholds obtained in the right ears were poorer than the thresholds obtained in the left ears for both groups. Results from Table 6 indicated that, based on their calculated 4-tone PTAs, 89.3% (n=25) of the type 2 diabetics had hearing losses in their left ears, compared to 67.9% (n=19) of the non-diabetic controls. For the right ear, results indicated that 78.6% (n=22) of the type 2 diabetics had hearing losses, compared to 75% (n=21) of the non-diabetic controls. Accordingly, higher 4-tone PTAs were observed amongst the type 2 diabetic participants which indicated poorer hearing in both ears (left PTA: 24.1 ± 10.4; right PTA: 26.2 ± 18.7),

compared to the lower PTAs that were observed amongst the non-diabetic controls (left PTA: 20.3 ± 7.4 ; right PTA: 24.4 ± 1.2). A risk ratio of 1.1 was obtained, showing a 1.1 times higher risk of hearing loss in the type 2 diabetics than in the non-diabetic controls.

The participants hearing was additionally described as bilateral normal hearing (both ears having a PTA ≤ 15 dBHL), or unilateral hearing loss (PTA of the poorer ear ≥ 16 dBHL), or bilateral hearing loss (both ears having a PTA ≥ 16 dBHL), based on their calculated 4-tone PTAs. The occurrence of hearing losses amongst the diabetic and non-diabetic groups is illustrated in Figure 2.

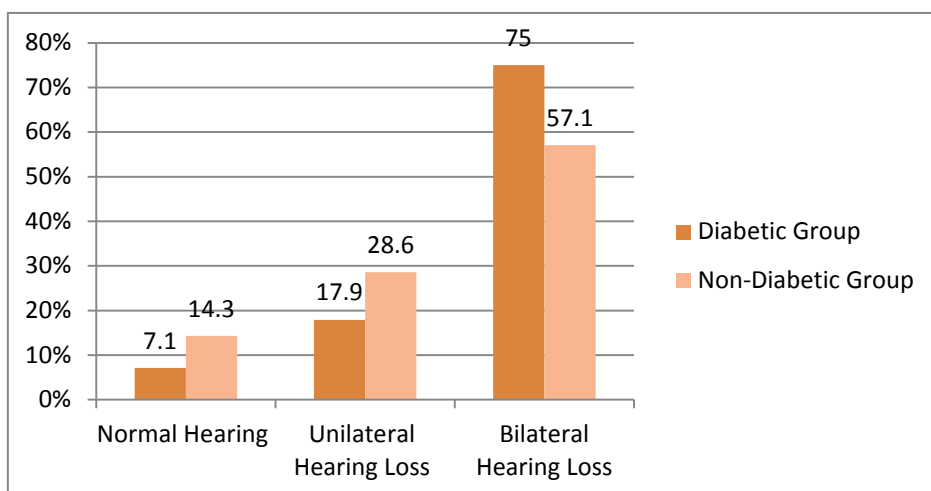


Figure 2 The occurrence of bilateral normal hearing, unilateral hearing losses, and bilateral hearing losses in both groups

There was no significant difference present in the classification of hearing between the two groups ($p=0.421$; McNemar test of symmetry). The majority of hearing losses presented bilaterally as 75% ($n=21$) of the type 2 diabetic participants had bilateral hearing losses, compared to the 57.1% ($n=16$) of the non-diabetic controls. Normal bilateral hearing or unilateral hearing loss was present in only 25% ($n=7$) of type 2 diabetic participants compared to 42.8% ($n=12$) of the non-diabetic controls. Additionally, when the age and gender matched pairs were not taken into account, there was no statistical difference between the classification of hearing in the male and female diabetic and non-diabetic participants of the study ($p=0.548$; Mann-Whitney test).

3.3 Vestibular testing results – vHIT and VEMPs

There was no significant difference in the vestibular functioning of the diabetic participants and non-diabetic controls as indicated by the combined results of the vHIT, cVEMP, and oVEMP testing. Table 7 displays the vHIT gain results of the type 2 diabetic participants and non-diabetic controls. For the vHIT saccades results, the presence of overt or covert saccades was described as saccades being present.

Table 7: Description of vHIT results: gain and saccades

vHIT gain: left ears (n=28) ^a				vHIT saccades: left ears (n=28) ^b			
Canal	Diabetic Group (Med; .25, .75) ^c	Non-Diabetic Group (Med; .25, .75)	p value	Canal	Diabetic Group % (n)	Non-Diabetic Group % (n)	p value
Lateral	0.9 (0.9; 1.0)	0.9 (0.9; 1.0)	0.325	Lateral	89% (25)	54% (15)	0.071
Anterior	1.0 (0.9; 1.1)	1.1 (0.9; 1.1)	0.918	Anterior	93% (26)	86% (24)	0.739
Posterior	0.9 (0.9; 1.1)	1.0 (0.9; 1.1)	0.767	Posterior	86% (24)	71% (20)	0.739
vHIT gain: right ears (n=28)				vHIT saccades: right ears (n=28)			
Lateral	1.00 (0.90; 1.00)	1.00 (0.90; 1.00)	0.356	Lateral	82% (23)	32% (9)	0.002 *
Anterior	1.0 (1.0; 1.1)	1.0 (0.9; 1.1)	0.766	Anterior	89% (25)	79% (22)	0.450
Posterior	1.0 (0.9; 1.1)	1.0 (0.9; 1.1)	0.224	Posterior	86% (24)	71% (20)	0.564

n = number of ears,^a = Wilcoxon Sign Rank test, ^b = McNemar test of symmetry, ^c = Median; Interquartile Range (IQR), * = significant difference

Regarding the mean gain values there were no significant differences observed between the diabetic and non-diabetic groups. The mean gain values were within normal range of the normative data that was used for this study. For the lateral canals, abnormally low gain was present in two of the diabetic participants for the left lateral canal and in one of the diabetic participants for the right lateral canal. None of the non-diabetic controls had abnormally low gain for either of the lateral canal's. For the anterior canals, abnormally low gain was present in one of the diabetic participants and in one of the non-diabetic participants for the left and right anterior canals. For the posterior canals, abnormally low gain was present in one of the diabetic participants for the left posterior canal and in one of the non-diabetic controls for the right posterior canal. Regarding the presence of saccades there were no significant differences between the diabetic and non-diabetic groups, except for a significant difference in the right lateral canal ($p=0.002$; McNemar test of symmetry).

The presence of saccades were observed in the right lateral canals of 82% (n=23) of the type 2 diabetic participants, compared to 32% (n=9) of the non-diabetic controls. This indicated a higher occurrence of overt and covert saccades in the diabetic group than amongst the non-diabetic controls. Furthermore, a risk ratio of 2.3 was obtained, showing a 2.3 times higher risk of right lateral canal dysfunction in type 2 diabetics than in the non-diabetic controls.

Table 8 displays the present cVEMP and oVEMP results in terms of descriptive P1 and N1 latencies, inter-peak amplitudes, and ARs of the study participants. For the cVEMP and oVEMP results, seven ears (five diabetic ears and two non-diabetic ears) were excluded from the analysis due to hearing losses ≥ 75 dBnHL, as previous studies suggest an increased correlation between hearing loss and absent VEMP results (Khan, Balraj & Lepcha, 2013). The seven ears that were excluded were considered abnormal. Absent cVEMP and oVEMP results were also considered abnormal.

Table 8: *cVEMP and oVEMP latencies, inter-peak amplitudes and asymmetry ratios of the study participants*

VEMP response parameters (mean, SD)	Diabetic Group	Non-Diabetic Group	p value
cVEMP	(n=36)	(n=47)	
P1 (ms)	17.2 (\pm 2.1)	18.3 (\pm 4.0)	0.256^a
N1 (ms)	25.4 (\pm 2.5)	25.9 (\pm 2.4)	0.269^a
I-P amplitude (μ V)	29.5 (19.8; 45.9)	37.0 (25.6; 67.0)	0.553^b
AR	19.4 (12.2; 100.0)	19.4 (8.7; 39.0)	0.249^b
oVEMP^b	(n=11)	(n=23)	
N1 (ms)	13.3 (\pm 2.3)	13.3 (\pm 3.9)	-
P1 (ms)	17.5 (\pm 2.9)	17.7 (\pm 4.3)	-
I-P amplitude (μ V)	6.8 (5.4; 6.8)	7.7 (5.1; 14.2)	-
AR	100 (19.0; 100.0)	31.1 (11.2; 100.0)	-

\pm = Standard Deviation, n = number of ears, ms = milliseconds, I-P = interpeak, AR = asymmetry ratio, μ V = microvolt, ^a= paired t-test, ^b= Wilcoxon Sign Rank test (median, IQR)

For the cVEMP and oVEMP results, there were no significant differences observed regarding the mean P1 and N1 latencies, inter-peak amplitudes, and ARs in both of the groups. Table 8 indicates the distribution of the mean P1 and N1 latencies, the median inter-peak amplitude differences, and the ARs of the diabetic and non-diabetic group. With regard to the cVEMPs, the type 2 diabetic participants had a mean P1 latency of 17.2 ms (\pm 2.1), compared to a mean P1 latency of 18.3 ms (\pm 4.0) for the non-diabetic controls. With

regard to the cVEMPs, the type 2 diabetic participants had a mean N1 latency of 25.4 ms (± 2.5), compared to a mean N1 latency of 25.9 ms (± 2.4) for the non-diabetic controls. The cVEMP inter-peak amplitudes of the type 2 diabetic participants were lower than the interpeak amplitudes of the non-diabetic controls. In general, the diabetic participants had larger amplitude ARs than the non-diabetic controls, although the difference was statistically insignificant. Abnormal cVEMP ARs were present in 57.1% ($n=16$) of the type 2 diabetic participants, compared to 35.7% ($n=10$) of the non-diabetic controls, indicative of a difference between the two ears. A risk ratio of 1.5 was obtained, showing a 1.5 times higher risk of the type 2 diabetics having abnormal ARs, either unilaterally absent cVEMP results or ARs $\geq 40\%$ than the non-diabetic controls.

For the oVEMPs, the type 2 diabetic participants had a mean N1 latency of 13.3 ms (± 2.3), compared to a mean N1 latency of 13.3 ms (± 3.9) for the non-diabetic controls. The type 2 diabetic participants had a mean P1 latency of 17.5 ms (± 2.9), compared to a mean P1 latency of 17.7 ms (± 4.3) for the non-diabetic controls. The oVEMP inter-peak amplitudes of the diabetic participants were lower than the inter-peak amplitudes of the non-diabetic controls. Abnormal oVEMP ARs were present in 92.9% ($n=26$) of the type 2 diabetic participants, compared to 71.4% ($n=20$) of the non-diabetic controls. A risk ratio of 1.3 was obtained, showing a 1.3 times higher risk of the type 2 diabetics having abnormal ARs, either unilaterally absent oVEMP results or ARs $\geq 40\%$ than the non-diabetic controls.

Table 9 describes the cVEMP and oVEMP results according to absent waveforms, delayed P1 and N1, and amplitude asymmetry $\geq 40\%$. There were no significant differences found between the two groups in cVEMP ($p=0.760$; McNemar test of symmetry) and oVEMP ($p=0.320$; McNemar test of symmetry) results.

Table 9: Description of the cVEMP and oVEMP parameters

Descriptive VEMP Parameters	Diabetic Group (n=28)	Non-Diabetic Group (n=28)	p value
cVEMPs			
Normal	10 (35.7%)	8 (28.6%)	0.760
Absent unilateral	12 (42.8%)	4 (14.3%)	
Absent bilateral	3 (10.7%)	3 (10.7%)	
Delayed unilateral	3 (10.7%)	6 (21.4%)	
Delayed bilateral	-	4 (14.3%)	
Asymmetry ratio $\geq 40\%$	-	3 (10.7%)	
oVEMPs			
Normal	-	1 (3.6%)	0.320
Absent unilateral	4 (14.3%)	4 (14.3%)	
Absent bilateral	16 (57.1%)	11 (39.3%)	
Delayed unilateral	7 (25.0%)	7 (25.0%)	
Delayed bilateral	1 (3.6%)	5 (17.9%)	
Asymmetry ratio $\geq 40\%$	-	-	

n = number of participants, %

Although there was no significant difference between the two groups as demonstrated by the *p* value, the type 2 diabetic participants had a higher occurrence of absent VEMPs. Abnormal cVEMP results were found in 64.3% (n=18) of the type 2 diabetic participants, compared to 71.4% (n=20) of the non-diabetic controls. Abnormal oVEMP results were found in 100% (n=28) of the type 2 diabetic participants, compared to 96.4% (n=27) of the non-diabetic controls. For the cVEMPs, 53.6% (n=15) of the type 2 diabetics had unilateral or bilateral absent results, compared to 25% (n=7) of the non-diabetic controls. A risk ratio of 2.1 was obtained, showing a 2.1 times higher risk of absent cVEMPs in the type 2 diabetic individuals than the non-diabetic controls. For the oVEMPs, 75% (n=21) of the type 2 diabetics had unilateral or bilateral absent results, compared to 53.6% (n=15) of the non-diabetic controls. This may be of clinical relevance regarding the functioning of the saccule, utricle, inferior- and/or superior vestibular nerve. A risk ratio of 1.3 was obtained, showing a 1.3 times higher risk of absent oVEMPs in type 2 diabetic participants than in the non-diabetic controls.

3.4 Fall risk assessment results

In order to determine the risk of falling for the two groups of participants, the TUG, BBS, and DGI were employed in this research study. Table 10 demonstrates the risk of

falling for the type 2 diabetic participants and the non-diabetic controls. A significant difference between the two groups was obtained in the second trial of the TUG, the averaged TUG test time and the TUG stability. However, there were no significant differences between the two groups in the BBS and DGI scores. The type 2 diabetic participants did in general perform more poorly on the three fall risk assessments. This was demonstrated in either longer performance test times or lower scores. This outcome may be clinically relevant for clinicians when diagnosing and treating diabetic patients. A risk ratio of 2.6 was obtained for all three fall risk assessments, showing a 2.6 times higher risk of falling in individuals with type 2 diabetes than in non-diabetic controls.

Table 10: Fall risk assessments

	All (n =56)	Diabetic Group (n = 28)	Non-Diabetic Group (n = 28)	p value
Timed Up and Go (TUG) test trial 1 (sec)	9.7 (±2.4)	10.3 (±2.8)	9.1 (±1.8)	0.063
Tug test trial 2 (sec)	8.8 (±2.3)	9.4 (±2.7)	8.2 (±1.5)	0.038*
TUG Mean time (sec)	9.3 (±2.3)	9.8 (±2.7)	8.7 (±1.6)	0.047*
TUG Abnormal	19 (33.9%)	13 (46.4%)	6 (21.4%)	0.052
TUG Unstable	5 (8.9%)	5 (17.9%)	-	0.025*
Dynamic Gait Index (DGI, /24)	23.3 (±1.8)	22.9 (±2.3)	23.8 (±0.9)	0.078
DGI Abnormal Score	2 (3.6%)	2 (7.1%)	-	0.157
Berg Balance Scale (BBS, /56)	54.7 (±2.8)	54.0 (±3.7)	55.4 (±1.1)	0.066
BBS Abnormal Score	1 (1.8%)	1 (3.6%)	-	0.317

Statistical Test used for the TUG, DGI and BBS: Paired T Test, Statistical Test used for the abnormal TUG times and well as TUG instability: McNemar Test, Statistical Test used for the abnormal DGI and BBS scores: Wilcoxon Sign Rank Test, ± = Standard Deviation, *= significant difference.

For the TUG test, two test trials were recorded and averaged for the analyses. There was a significant difference between the two groups' for the second recorded trial of the TUG ($p=0.038$, t-test). Overall, when the two TUG test times were averaged, there was a significant difference between the two groups ($p=0.047$, t-test), indicating poorer performance and an increased risk of falling for the type 2 diabetic participants. Abnormal test times were indicated by performance time's >10 seconds (sec). Although the mean test times obtained were within normal range (<10 sec) for both groups, the participants with type 2 diabetes did have longer mean performance times of 9.8 sec (±2.2), compared to the non-diabetic group who had a mean time of 8.7 sec (±1.6). Test times of the type 2 diabetics ranged from 6.23 to 19.34 sec, compared to test times of the non-diabetic controls that ranged from 5.52 to 13.1 sec. Abnormal TUG test times indicating a risk of falling were

obtained by 46.4% (n=13) of the type 2 diabetic participants, compared to 21.4% (n=6) of the non-diabetic group. A risk ratio of 2.6 was obtained for abnormal TUG performances, showing a 2.6 times higher risk of falling in individuals with type 2 diabetes than in the non-diabetic controls. There was a significant difference between the two groups' for the TUG stability ($p=0.025$, t-test) as 17.9% (n=5) of the type 2 diabetic participants were graded unstable while performing the TUG compared to none of the non-diabetic controls being graded unstable.

The DGI was scored out of 24 and a risk of falling was indicated by scores of ≤ 19 . The type 2 diabetic participants had a mean score of 22.9 (± 2.3) out of 24 and the non-diabetic group had a mean of 23.8 (± 0.9) out of 24. Test scores of the type 2 diabetics ranged from 14 to 24, compared to test scores of the non-diabetic controls that ranged from 20 to 24. Only one of the type 2 diabetic participants scored 14 out of 24, indicating a risk of falling.

The BBS was scored out of 56. A score of 41 to 56 indicated a low risk of falling, 21 to 40 indicated a medium risk of falling and less than 20 indicated a high risk of falling (Berg et al., 1989). The type 2 diabetic participants had a mean score of 54 (± 3.7) out of 56 and the non-diabetic group had a mean of 55.4 (± 1.1) out of 56. Test scores of the type 2 diabetics ranged from 37 to 56, compared to test scores of the non-diabetic controls that ranged from 52 to 56. Only one of the type 2 diabetic participants scored 37 out of 56, indicating a medium risk of falling.

3.5 Health Related quality of life results

Table 11 demonstrates the overall HRQL in the diabetic and non-diabetic groups. For the EQ-5D-5L Health Questionnaire, each of the five health dimensions was scored according to five levels of severity. The results are described per age category: 30 years, 40 years, and 50 years. The number of participants (n, %) that scored a particular level for each of the five health dimensions is indicated at each level (L) of severity in each age group and totalled.

Table 11: Health related quality of life (EQ-5D-5L) questionnaire

Health Dimensions	Diabetes Group (ages, years)				Non-Diabetes Group (ages, years)				p value	
	30	40	50	Total (n=28)	30	40	50	Total (n=28)		
Mobility	L 1	2 (100%)	9 (75%)	9 (64.3%)	20 (71.4%)	3 (100%)	9 (90%)	14 (93.3%)	26 (92.9%)	0.032*
	L 2	-	2 (16.7)	4 (28.6%)	6 (21.4%)	-	1 (10%)	1 (6.7%)	2 (7.1%)	
	L 3	-	-	1 (7.1%)	1 (3.6%)	-	-	-	-	
	L 4	-	1 (8.3%)	-	1 (3.6%)	-	-	-	-	
	L 5	-	-	-	-	-	-	-	-	
Self-Care	L 1	2 (100%)	11 (91.7%)	12 (85.7%)	25 (89.3%)	3 (100%)	9 (90%)	14 (93.3%)	27 (96.4%)	0.309
	L 2	-	1 (8.3%)	1 (7.1%)	2 (7.1%)	-	1 (10%)	1 (6.7%)	1 (3.6%)	
	L 3	-	-	1 (7.1%)	1 (3.6%)	-	-	-	-	
	L 4	-	-	-	-	-	-	-	-	
	L 5	-	-	-	-	-	-	-	-	
Usual Activities	L 1	2 (100%)	10 (83.3%)	9 (64.3%)	21 (75.0%)	3 (100%)	9 (90%)	13 (86.7%)	25 (89.3%)	0.222
	L 2	-	1 (8.3%)	3 (21.4%)	4 (14.29%)	-	1 (10%)	1 (6.7%)	2 (7.1%)	
	L 3	-	-	1 (7.1%)	1 (3.57%)	-	-	1 (6.7%)	1 (3.6%)	
	L 4	-	-	1 (7.1%)	1 (3.57%)	-	-	-	-	
	L 5	-	1 (8.3%)	-	1 (3.57%)	-	-	-	-	
Pain/Discomfort	L 1	1 (50%)	5 (41.7%)	5 (35.7%)	11 (39.29%)	1 (33.3%)	6 (60%)	6 (40%)	13 (46.4%)	0.430
	L 2	1 (50%)	5 (41.7%)	7 (50%)	13 (46.43%)	2 (66.7%)	4 (40%)	7 (46.7%)	13 (46.4%)	
	L 3	-	1 (8.3%)	1 (7.1%)	2 (7.14%)	-	-	2 (13.3%)	2 (7.1%)	
	L 4	-	-	1 (7.1%)	1 (3.57%)	-	-	-	-	
	L 5	-	1 (8.3%)	-	1 (3.57%)	-	-	-	-	
Anxiety/Depression	L 1	1 (50%)	5 (41.7%)	8 (57.1%)	14 (50.0%)	1 (33.3%)	6 (60%)	8 (53.3%)	15 (53.6%)	0.748
	L 2	1 (50%)	5 (41.7%)	5 (35.7%)	11 (39.29%)	2 (66.7%)	3 (30%)	7 (46.7%)	12 (42.9%)	
	L 3	-	1 (8.3%)	-	1 (3.57%)	-	1 (10%)	-	1 (3.6%)	
	L 4	-	-	1 (7.1%)	1 (3.57%)	-	-	-	-	
	L 5	-	1 (8.3%)	-	1 (3.57%)	-	-	-	-	
VAS		78.6 (±13.39)				86 (±14.52)				0.070

Statistical Test used: Paired T Test, *= significant difference

There was a significant difference between the two groups for the health dimension mobility ($p=0.032$, t-test), indicative of mobility being more challenging for the type 2 diabetic participants. There were no significant differences between the diabetic and non-diabetic groups in the other four health dimensions (self-care, usual activities, pain/discomfort, and anxiety/depression) as indicated by the various p values in Table 11. However, the type 2 diabetic participants described their overall wellbeing as poorer than that of the non-diabetic group. It was also noted that as the participants' age increased,

their overall HRQL decreased, as reflected by the five levels of severity. The type 2 diabetic participants recorded a VAS score of 78.6, compared to the score of 86 recorded by the non-diabetic controls, indicating poorer overall quality of life ($p=0.070$, t-test). According to the Mann-Whitney test, when the age and gender matched pairs were not taken into account, there was no statistical difference between the male and female diabetic and non-diabetic participants for the scores obtained in the five health dimensions and the VAS (mobility: $p=0.765$; self-care: $p=0.447$; usual activities: $p=0.655$; pain and discomfort: $p=0.207$; anxiety and depression: $p=0.795$; VAS: $p=0.926$).

Chapter 4

DISCUSSION, CLINICAL IMPLICATIONS AND CONCLUSIONS

4.1 Discussion

This research project aimed to describe the audiovestibular function, risk of falling, and overall HRQL in a group of adults with type 2 diabetes and to compare the findings with those obtained from an age and gender matched group of non-diabetic control subjects. This was achieved through one main aim: to describe the audiovestibular function of adults with type 2 diabetes using pure tone audiometry and vestibular testing - vHIT, cVEMPs, and oVEMPs; to determine the risk of falling, utilising three fall risk assessments (TUG, BBS, and DGI), and to determine the overall HRQL, utilising a self-administered questionnaire (EQ-5D-5L questionnaire). The results from this study, despite not being indicative of significant differences between the diabetic and non-diabetic groups, showed a higher occurrence of audiovestibular dysfunction, risk of falling, and poorer HRQL in the type 2 diabetic participants than in the control group.

4.1.1 Hearing loss and type 2 diabetes

In recent years, the auditory system and the occurrence of hearing loss in individuals with diabetes have received increased attention (Frisina et al., 2005; Fukushima et al., 2006; Mitchell et al., 2009; Hong et al., 2013; Ward et al., 2015). Diabetes and hearing loss are both significant health issues and can be described as two of the main burdens of disease that affect millions of individual's worldwide (Hong et al., 2013). The number of individuals with diabetes has more than doubled over the last 30 years and is still steadily rising in prevalence (Danaei et al., 2011; Chen et al., 2012). According to Chatterjee et al. (2017) diabetes was additionally described as the sixth leading cause of disability in 2015. Hearing loss was described as the fourth leading cause of years living with disability (YLDs) in 2013 and in 2015 (Wilson, Tucci, Merson & M O'Donoghue, 2017). Additionally, this worldwide pandemic of hearing loss remains an invisible disability, as other health threatening issues are prioritised over hearing loss (Wilson et al., 2017). Due to the numerous microvascular complications that are known to be associated with diabetes, it has proved worthwhile to examine the relationship between the disease and hearing loss,

although there is limited consensus in this regard (Ma, Gomez-Marin, Lee & Balkany, 1998; Hong et al., 2013; Ward et al., 2015).

The highly vascularised auditory system is dependent on an increased uptake of glucose for the high-energy utilization that is necessary for constant signal processing (Hong et al., 2013). As a result of the impaired metabolic functioning due to diabetes, compromised inner ear functioning may lead to changes in hearing function. Hearing loss related to diabetes has been defined by numerous authors as a bilateral, progressive, sensorineural hearing loss that has a gradual onset, predominantly affecting the higher frequencies (Axelsson et al., 1978; Maia & de Campos, 2005; Bainbridge, Hoffman & Cowie, 2008; Akinpelu et al., 2014). The audiometric findings from the present study are in agreement with the existing literature as 75% (n=21) of the type 2 diabetic participants exhibited a bilateral sensorineural hearing loss as defined by PTAs ≥ 16 dBHL in both ears, compared to 57.1% (n=16) of the non-diabetic controls. Unilateral hearing losses (PTA of the better ear ≤ 15 dBHL; PTA of the poorer ear ≥ 16 dBHL) were more common amongst the non-diabetic controls as 28.6% (n=8) had unilateral hearing losses, compared to 17.9% (n=5) of the type 2 diabetic participants. Only 7.2% (n=2) of the type 2 diabetic participants had normal hearing, compared to 14.3% (n=4) of the non-diabetic controls. Unilateral hearing losses were not as common as bilateral hearing losses amongst the type 2 diabetic participants due to the bilateral nature of the disease (Razzak et al., 2015). According to Razzak et al. (2015) diabetes is consequently known to affect both ears simultaneously and symmetrically as these changes are subtle and cumulate over the years (Razzak et al., 2015).

A well-known concomitant for the numerous microvascular complications that are associated with diabetes is the toxic effect of long-term hyperglycemia. The degree and the duration of hyperglycemia are both major contributors to the development of additional micro- and macrovascular complications in individuals with diabetes (Agrawal et al., 2010; Ward et al., 2015). The mean glycated hemoglobin (HbA1c) of the type 2 diabetic participants of the present research study was 9.3% (SD, 2.2), higher than the normal HbA1c levels of greater or equal to 6.5% to 7% (Agrawal et al., 2010; Karabulut et al., 2014; Konukseven et al., 2014; WHO, 2016; ADA, 2017). In the present research study, 75% (n=21) of the type 2 diabetics had HbA1c levels $\geq 6.5\%$, ranging from 5.4% to 12.7%. Uncontrolled diabetes as indicated by the higher than normal HbA1c levels increase the risk

of diabetes related complications, especially microvascular complications such as retinopathy and peripheral neuropathy (Agrawal et al., 2010). The 28 type 2 diabetic participants of the research study had mean disease durations of 15.36 years, with disease durations ranging from five to 37 years. According to numerous authors (Friedman, Schulman & Weiss, 1975; Miller, Beck, Davis, Jones & Thomas, 1983; Agrawal, et al., 2010; Ward et al., 2015), the effects of longer diabetes disease durations are especially more profound after a period of 10 years, as demonstrated by an increase in these diabetes related microvascular complications. In the present research study, 61% (n=17) of the type 2 diabetics had disease durations of 10 years and longer. Therefore, it is evident that both the degree and duration of diabetes play a crucial role in the diabetes related complications that are found in diabetics (Friedman et al., 1975; Miller, Beck, Davis, Jones & Thomas, 1983; Agrawal et al., 2010; Ward et al., 2015).

The findings from the present research study correspond with existing research that does not indicate an invariable association between diabetes and hearing loss (Harner, 1981; Hodgson, Talbott, Helmkamp & Kuller, 1987; Gates, Cobb, D'Agostino & Wolf, 1996; Dalton, Cruickshanks, Klein, Klein, & Wiley, 1998; Frisina et al., 2006; Mitchell et al., 2009; Akinpelu et al., 2013). Similar to the present study, Gates et al. (1996) found no significant difference in the PTAs (250, 500, and 1000 Hz or 4000, 6000, and 8000 Hz) between diabetic participants and the non-diabetic controls. However, the mean age of the participants from the study was 73 years. The relative contribution of diabetes to the deterioration of the inner ear mechanisms may have been reduced due to the effect that age has on these mechanisms, as age was identified as the most likely contributor to hearing loss in both groups (Gates et al., 1996). Another possible explanation suggested by Gate et al. (1996) is the combined effect of both age and diabetes on the functioning of the inner ear mechanisms (Gates et al., 1996; Frisina et al., 2006). The inclusion of elderly diabetic participants could also be an explanation of why no differences were found, as age-related hearing loss (presbycusis) is known to first affect the higher frequencies (Tay, Ray, Ohri & Frootko, 1995; Uchida et al., 2010). Existing research, however, suggests that pathological similarities do exist in the cochlea with both diabetes and aging, particularly at the basal part of the cochlea and the basement membrane in the capillaries within the stria vascularis, which is responsible for the high frequency sounds (Jorgensen & Buch, 1961). The participants in the present study were younger (49.1 years \pm 6.2) and did not present

with distinct age-related high frequency hearing losses, hence explaining the hearing deficits in the lower frequencies.

In contrast to these research findings, numerous authors reported a definite association between diabetes and hearing loss (Cheng et al., 2009; Akinpelu et al., 2013; Hong et al., 2013; Horikawa et al., 2013; & Xipeng et al., 2013). A study by Bainbridge et al. (2008) found that the prevalence of hearing loss was 21% for the diabetic participants, compared to 9% for the non-diabetic controls (Bainbridge et al., 2008). Data from the National Health and Nutrition Examination Surveys (NHANES) 1999 - 2004 indicated that the prevalence of hearing loss was 34.4% for the diabetic participants, compared to 22.3% for the non-diabetic controls (Cheng et al., 2009). Although the present research study indicated no significant differences in the presence of hearing loss between the two groups, the type 2 diabetics did in general have poorer hearing, compared to the non-diabetic controls who also had hearing losses. According to Akinpelu et al. (2013) the incidence of hearing loss increases especially amongst older diabetics. Moreover, various data suggest that there may be a worsening trend of hearing loss amongst younger individuals with diabetes, which can be linked to the earlier onset of the disease in recent years (Cheng et al., 2009; Hong et al., 2013). Interestingly, the non-diabetic controls showed an increase in hearing loss with increasing age; however, the increase in hearing loss was greater among the type 2 diabetic group (Mitchell et al., 2009; Akinpelu et al., 2013). It is clearly evident that both age and diabetes affect hearing but eventually the distinctive effects of age contribute more to the nature of the hearing loss (high frequency hearing losses) than the disease itself that is experienced in this population of diabetics (Gates et al., 1996; Frisina et al., 2006; Mitchell et al., 2009; Uchida et al., 2010; Akinpelu et al., 2013).

The research results of this present study indicated that in general there were no significant differences in hearing between the diabetic and non-diabetic groups, as determined by ear specific thresholds from frequencies 250 Hz to 8000 Hz and ear specific 4-tone PTAs. In the present study, the greatest deficits in hearing tended to be at the low frequencies (250, 500, and 1000 Hz) and at one of the mid frequencies, 2000 Hz, for the type 2 diabetic participants, where age-related high frequency hearing losses were not yet affecting all of the participants. There was also a significant difference in the audiometric thresholds obtained at 500 Hz ($p=0.007$; t-test) in the left ear, indicating poorer hearing for the type 2 diabetic participants at this frequency. Friedman et al. (1975) and Ma et al.

(1998) also found that the diabetic participants had poorer hearing at 500 Hz. Additionally, there was an overall strong tendency for diabetes to affect the right ear more than the left ear, as reflected by poorer audiometric thresholds. Similarly, Frisina et al. (2009) also reported that the right ear was more affected due to diabetes. A possible explanation for this could be that as the aging process starts and age-related hearing losses begin to develop, the right ear advantage is lost (Frisina et al., 2005; Tadros et al., 2005). The right ear advantage, both peripheral and central, can be described as the right ear being more sensitive to simple sounds and to processing complex sounds such as speech than the left ear in young normal hearing adults (Tadros et al., 2005). Diabetes is known to damage the vascular endothelial walls which lead to asymmetries in the blood supply to the right and left cochlea, with the result that the right vasculature is more affected than the left vasculature (Frisina et al., 2005). This age-related hearing decline along with the right ear advantage is further accelerated by diabetes making the right ear more prone to acquiring a hearing loss (Frisina et al., 2005; Tadros et al., 2005).

It was noted that the participants' high frequencies (4000 and 8000 Hz) were not yet affected to the degree that one would expect due to age-related hearing loss. According to the United States National Centre for Health Statistics (2002) and authors Arvin, Prepageran and Ramam (2013), age-related hearing loss only occurs after the 5th decade of life, with at least 75% of individuals aged 55 years and older having an age-related hearing loss. Taking the research by Arvin et al. (2013) into account, the mean age of the participants of this study (49.1 years) can be a possible explanation of the higher frequencies not yet being as affected as reported by the other researchers, since these participants were slightly younger (Arvin et al., 2013). Alternatively, age-related hearing loss is also believed to occur earlier in type 2 diabetics as their hearing was in general poorer, compared to the non-diabetic controls (Hong et al., 2013).

Attributing hearing loss to diabetes alone is often challenging because of the presence of vascular diseases and other comorbidities such as presbycusis, noise induced hearing loss, hypertension, and atherosclerosis (Kakarlapudi, Sawyer & Staecker, 2003). Such comorbidities may also be present in the non-diabetic controls, contributing to the presence of hearing losses amongst this group (Kakarlapudi et al., 2003). The mechanisms by which diabetes affect the entire body, including the functioning of the inner ear, could explain the earlier presence of hearing loss in these younger individuals with type 2 diabetes (Frisina et

al., 2005; Fukushima et al., 2006; Mitchell et al., 2009; Hong et al., 2013; Ward et al., 2015). Thus, according to Hong et al. (2013) a higher prevalence of hearing loss is reported in diabetic participants, not including elderly diabetic participants. This evidence proves that diabetes affects hearing separately from age-related hearing loss, or that hearing loss occurs earlier in diabetics (Hong et al., 2013). According to Akinpelu et al. (2013), type 2 diabetics have a 2.1 times higher occurrence of hearing loss, compared to non-diabetic controls. Bainbridge et al. (2008) found a 1.1 odds ratio for low- or mid- frequency hearing impairment. Similarly, the type 2 diabetic participants of the present study had a 1.1 times increased risk ratio of hearing loss. Furthermore, it is evident that diabetes does contribute to the presence of hearing loss in individuals with diabetes. Overall, the risk ratio from the present study indicated that the risk of hearing loss was 1.1 times higher in individuals with type 2 diabetes than in individuals without diabetes.

4.1.2 Vestibular dysfunction and type 2 diabetes

Since the inner ear consists of the cochlea and the vestibular apparatus, both of which are innervated by the same nerve and blood supply, it is highly possible that vestibular function in addition to the well-established hearing loss may be compromised in individuals with diabetes (Agrup et al., 2007; Rybak, 1995; Sahu & Sinha, 2015). The prevalence of vestibular dysfunction which can lead to balance disorders has been reported to be around 60% to 75% in diabetic individuals (Jauregui-Renaud et al., 2008). These diabetic individuals are known to be at an increased risk of vestibular dysfunction, but it is not yet clear what part of the vestibular system is most affected by the disease (Razzak, Bagust, Docherty, Hussein & Al-Otaibi, 2015). The pathophysiological mechanisms by which diabetes affects vestibular function may involve parts of or all of the vestibular structures (Makishima & Tanaka, 1965, 1971; Nathan, 1996; Zelenka & Kozac, 1965).

The present research study indicated that there was no significant difference between the two groups in both the VOR gain values and the presence of covert or overt corrective saccades for the vHIT. There was, however, a significant difference in the results of the saccades obtained in the right lateral canal ($p=0.002$; McNemar test of symmetry) between the two groups, indicative of poorer right lateral canal functioning in the type 2 diabetic participants. A risk ratio of 2.3 was obtained, indicating that the risk of right lateral canal dysfunction was 2.3 times more likely in the type 2 diabetics, compared to non-

diabetic controls. This was demonstrated by the presence of saccades as 82% (n=23) of the type 2 diabetic participants had saccades when the right lateral canal was stimulated, as compared to 32% (n=9) of the non-diabetic controls. Thus being indicative of impaired right lateral canal functioning. In the present study, the right side appeared to be more prone to impaired functioning as reflected by both the results of the pure tone testing and the vHIT.

Previous studies have compared vestibular test results between diabetic participants and non-diabetic controls, concluding that type 2 diabetics are prone to having greater dysfunction in the lateral and anterior canal's and the two otolith organs (Kamali et al., 2013; Konukseven et al., 2015; Ward et al., 2015; Kocdor et al., 2016). From the present study, it was evident that the lateral canals were more affected than the anterior and posterior canals. The right lateral canal was prone to be more affected as demonstrated by the presence of saccades and despite a significant difference in the functioning of the left lateral canal ($p=0.071$; McNemar test of symmetry), there was a substantial difference in the presence of saccades between the two groups as 89% (n=25) of the type 2 diabetics had saccades present compared to 54% (n=15) of the non-diabetic controls when the right lateral canals were stimulated. Regarding the individual function of the vestibular end organs, research has also revealed that the functioning of all six SCCs decline with age, starting as early as 40 years (Baloh, Ying & Jacobson, 2003; Brantberg, Granath & Scharf, 2007). Age-related declines in the SCCs have also been indicated as measured by the angular VOR, caloric response, and DVA testing (van der Laan & Oosterveld, 1974; Baloh et al., 2003; Viciano, Ferrer, Palma, Zapata & Lopez-Escamez, 2010). A study by Agrawal et al. (2012) also indicated a significant decline with the aging process in the function of each individual SCC. This was determined by head thrust DVA testing, when adults aged 70 years and older were compared with younger laboratory controls (Agrawal et al., 2012). Halmagyi et al. (2017) suggested that bilateral vestibular loss is often identified with relative sparing of the anterior SCC. With regards to the present study, sparing of the anterior and posterior canals was evident as indicated by normal VOR gain values and the limited presence of saccades. Additionally, the participants of the present study were also not old enough for age to have a definite effect on the functioning of the SCC's.

A study conducted by Agrawal et al. (2012) demonstrated a global decline in vestibular function associated with aging as each of the five vestibular end organs

demonstrated reduced responses compared to the responses of younger individuals. The data suggested that the magnitude of the vestibular decline was asymmetric throughout the vestibular apparatus and that not all of the vestibular end organs were equally affected (Agrawal et al., 2012). Data from the above mentioned study by Agrawal et al. (2012) proved that the majority of adults aged 70 and older had evidence of SCC dysfunction as compared to only half of the same population of adults having saccular dysfunction. Interestingly, only one in five participants of their study had utricular dysfunction. In previous studies conducted by Johnsson and Hawkins (1972) and Igarashi et al. (1993) greater deficits in the functioning of the saccule occurred, compared to deficits of the utricle, when age was taken into account.

In order to determine the functioning of the two otolith organs, the saccule and the utricle, and the inferior and superior vestibular nerve, VEMP testing was employed. The type 2 diabetic participants had a 1.5 times higher risk of having absent cVEMP results, compared to the non-diabetic controls. Furthermore, the type 2 diabetics had a 1.3 times higher risk of having absent oVEMP results, compared to the non-diabetic controls. The findings from the present research study correspond to the above mentioned evidence by Johnsson and Hawkins (1972) and Igarashi et al. (1993) that the functioning of the saccule is more likely to be affected than the functioning of the utricle. There is limited consensus regarding the effects of hearing loss on VEMPs. Colebatch, Halmagyi, and Skuse (1994) and Itoh et al. (2001) stated that the cVEMP waveform is not mediated by the cochlea. The presence of the VEMP response seems to be independent of the degree of hearing loss, as these authors found cVEMPs in participants with profound hearing losses (Ozeki et al., 1999; Wu & Young, 2002). The authors conclude that the absence of cVEMP waveforms suggest the involvement of the saccule or inferior vestibular nerve, rather than the cochlea itself (Papathanasiou et al., 2014).

Wu and Young (2002) also reported that there was no significant difference between the cVEMP amplitudes in the left and right ears of individuals who had a single sided hearing loss (Hong et al., 2008). A study by Bansal, Sahni, and Sinha (2013) reported the presence of cVEMPs (100%) and oVEMPs (66%) in individuals with severe-to-profound hearing loss. However, contradictory research results are common. A study conducted by Hong et al. (2008) found a greater prevalence of abnormal VEMPs in individuals with profound hearing loss than in individuals with less severe hearing losses. Hong et al. (2008)

concluded that profound hearing losses (≥ 90 dBHL) have an undeniably greater effect on the VEMP waveforms than severe hearing losses. A similar study conducted by Khan et al. (2013) suggested an increased correlation between hearing loss and absent VEMP results. Regarding our present study, no significant differences were found between the hearing thresholds of the two groups when hearing losses exceeding 75 dBHL were excluded. One can further assume that the results from the VEMPs reflected the independent effect of diabetes on the otolith organs without severe-to-profound hearing losses as a factor.

In the present study, the absence of both cVEMPs and oVEMPs was found at higher rates in the type 2 diabetic participants, compared to the non-diabetic controls. With regard to the cVEMPs of this study, 53.6% (n=15) of the 2 diabetic participants' cVEMPs were absent (unilateral or bilateral), compared to 25% (n=7) of the non-diabetic controls. Additionally, a research study conducted by Sahu and Sinha (2015) found absent cVEMPs in 53.3% (n=14) of the type 2 diabetics, as opposed to 100% (n=30) present cVEMP responses in the control group. The absences of air conducted cVEMPs are indicative of pathology in the saccule or its innervating neurons. Furthermore, a greater percentage of oVEMPs than cVEMPs were absent in all of the participants. With regard to the oVEMPs, 74.1% (n=20) of the 2 diabetic participants' oVEMPs were absent (unilateral or bilateral), compared to 53.6% (n=15) of the non-diabetic controls. Razzak et al. (2015) characterise the absence of air conducted oVEMPs as suggestive of pathology of the utricles or its innervating neurons, as the utricles provide major input for perceiving static head roll relative to gravity. Additionally, Sahu and Sinha (2015) ruled out pathology of the innervating neurons of the vestibular nerve as the participants' auditory brainstem responses were present and normal, implying normal functioning of the cochlear nerve fibres. Since the cochlear and vestibular nerves are part of the same 8th cranial nerve, the presence of a possible lesion of the vestibular nerve therefore seems less likely (Sahu and Sinha, 2015).

In the present study, 10.7% (n=3) of the type 2 diabetics had delayed cVEMP results (delayed unilaterally), compared to 35.7% (n=10) of the non-diabetic controls (delayed unilaterally and bilaterally). Although the non-diabetic controls had three times more delayed cVEMP results than the type 2 diabetics, the type 2 diabetics had 53.6% cVEMP responses absent, as compared to 25% of the non-diabetic controls. A study by Kamali et al. (2013) on type 1 diabetic participants, observed delayed cVEMP latencies in the diabetic

participants who had peripheral neuropathy. This research suggests that the cVEMP responses may additionally be affected in participants with longer disease durations and poorer disease control (Kamali et al., 2013; Sahu & Sinha, 2015). Konukseven et al. (2015) also observed delayed latency responses in the cVEMPs and oVEMPs in type 2 diabetics, compared to those who were pre-diabetic or the healthy controls. Furthermore, delayed VEMP responses may be indicative of neuropathy similar to the neurovascular damage seen in diabetics with peripheral neuropathy (Konukseven et al., 2015). In VEMP testing, the stimulus is thought to be primarily transduced via the type I vestibular hair cells since previous histopathologic studies of rats with induced diabetes, especially those with longer durations, revealed hair cell atrophy restricted to these hair cells only (Lue, Day, Cheng & Young, 2009). These type I hair cells are also known to be more sensitive to ototoxic medication usage and are likely to show degeneration due to age at a quicker rate (Rauch, Velazquez-Villasenor, Dimitri, Merchant, 2001; Layford-Pike, Vogelheim, Chu, Della Santina & Carey, 2007). These factors suggest an increased vulnerability of these hair cells to oxygen deprivation or metabolic disturbances that can be associated with diabetes (Ward et al., 2015). The morphological changes manifest as hearing loss and vertigo (Sahu & Sinha, 2015).

A study by Li, Layman, Carey and Agrawal (2016) indicated that there are declines in otolith functioning associated with aging, as previous studies support the epidemiologic and pathological findings associated with age in these organs. Dysfunction of the saccule is found to be more common in aging adults, compared to dysfunction of the utricle (Li et al., 2016). Histopathological evidence also reports greater degrees of age-related hair cell loss and degradation of the otoconia in the saccule, compared to the utricle (Johnsson & Hawkins., 1972; Igarashi, Saito, Mizukoshi & Alford, 1993; Rauch et al., 2001; Walther & Westhofen, 2007; Li et al., 2016). Similarly, in the present study it was evident that the saccule was prone to be more affected than the utricle when taking into account absent VEMP results and the risk ratios. Results from a study conducted by Kocdor et al. (2016) indicated that the saccule may not experience the same extent of diabetic angiopathic change as other inner ear sub-sites might. Findings are accordingly consistent with either a differential susceptibility of the vasculature within the saccule to the effects of diabetes, or a chronological order with cochlear and facial nerve vessel damage prior to vestibular end organ damage (Kocdor et al., 2016). As expected, age-related vestibular declines are

observed bilaterally (Takahashi, Fetter, Koenig, & Dichgans, 1990; Agrawal et al., 2012; Davlos-Bichara & Agrawal, 2014).

Interestingly, all of the participants of this study were asymptomatic as they did not report any vestibular symptoms to the researcher while undergoing vestibular testing and the fall risk assessments such as vertigo, imbalance, or oscilopsia. Two possible explanations for the absence of vestibular symptoms are put forward by Sahu and Sinha (2015) and Razzak et al. (2015). Firstly, the absence of vestibular symptoms such as vertigo and imbalance could be justified by the fact that the bilateral distribution of the disease as diabetes is known to affect the entire body including all of the vasculature and therefore does not present asymmetrically as other vestibular disorders are known to do. Furthermore, vestibular symptoms are generally more pronounced when there is a functional asymmetry between the two labyrinths of the ears (Sahu & Sinha, 2015). The second reason could be that central compensation already took place as the disease subtly progressed and that is why the participants remain asymptomatic. Long-term central compensatory mechanisms take effect to recalibrate the vestibular inputs, such as the utricle and saccule, to reduce any asymmetry responses from both sides (Razzak et al., 2015).

Diabetes is slow in onset, progressing over time, and then only later becomes clinically apparent when diabetes related complications have already occurred (Konukseven et al., 2015). Rigon et al. (2007) reported that vestibular involvement might occur despite the absence of vestibular symptoms in diabetic patients causing partial vestibular effects. Although the effects of diabetes may not yet be fully understood, implications for balance and falls have been explored (Ward et al., 2015). In order to determine the risk of falling, three widely employed fall risk assessments were used in the current study. As none of the participants reported any apparent vestibular symptoms, the above explanations by Razzak et al. (2015) and Sahu and Sinha (2015) have to be considered.

4.1.3 Risk of falling and type 2 diabetes

Vestibular function plays a crucial part in postural stability and balance control (Agrawal et al., 2009; Kim et al., 2012). From numerous supporting reports in the literature,

it is evident that vestibular dysfunction is a common comorbidity in diabetic individuals as a result of the progression of the disease (Jauregui-Renaud et al., 2008; Agrawal et al., 2009; Agrawal et al., 2012; Kim et al., 2012; Razzak et al., 2015). It is known that vestibular dysfunction contributes to the risk of falling (Agrawal et al., 2012; Kim et al., 2012).

In this research study, a significant difference was found between the mean TUG test times for the type 2 diabetic participants and non-diabetic controls, and it was evident that the type 2 diabetics had poorer test times indicating an increased risk of falling. The TUG demonstrated that the type 2 diabetics had a 3.2 times higher risk of falling, compared to the non-diabetic controls. Although not statistically significant, this is especially clinically relevant to audiologists treating diabetic patients with vestibular dysfunction resulting in impaired balance and a history of falling. Only 53.6% of the type 2 diabetic participants could complete the TUG in ≤ 10 seconds when a mean was calculated between their two test times, compared to the 78.6% of the non-diabetic controls. It was also noted that the second recorded test time of the TUG was faster for both of the groups as the task was familiar and much easier.

Longer test times for the type 2 diabetic participants could be due to a wide variety of diabetic complications including microvascular complications such as retinopathy and peripheral neuropathy. None of the participants in the research study had severe peripheral neuropathy, as noted in their files by their treating medical doctor and as tested by the researcher (8-point Microfilament test). A possible explanation for a slight decrease in sensitivity of both feet before being clinically diagnosed could explain their longer test times. Another additional explanation could be that the type 2 diabetics had increased weight as indicated by a significant difference in BMIs between the type 2 diabetic participants and non-diabetic controls ($p < 0.001$; t-test) making the diabetics heavier and more liable to experience difficulty in walking around.

One could argue that the additional instruments, the BBS and DGI, are relatively complex fall risk measures (Herman et al., 2011). The BBS is a 14 item scale that is scored from zero to four and is added to make a total score of 56; a higher score indicates better balance (Downs, 2015). The DGI was administered by use of the protocol and instructions described by Shumway-Cook and Woollacott (Shumway-Cook & Woollacott, 1995; Marchetti, Whitney, Blatt, Morris & Vance, 2008). The DGI is an eight item scale that

challenges the participants in many ways such as walking while rotating the head or at various speeds and climbing chairs (Herman et al., 2011). Reliability indexes for the DGI in people with unilateral vestibular disorders have been reported ranging from 64 to 88% (Wrisley, Walker, Echternach & Strasnick, 2003; Hall & Herdman, 2006; Marchetti et al., 2008). Although the DGI was not specifically designed for persons with vestibular disorders, it does include items that are of interest when examining such persons (Wrisley, Marchetti, Kuharsky & Whitney, 2004).

All the scores for the TUG, BBS, and DGI were near maximal score and indicative of good mobility and balance. It was noted, however, that one of the diabetic participants did perform poorly in all three fall risk assessments, indicating a high risk of falling. This specific participant had disease duration of 30 years and reported previous incidences of falling as well as slight numbness of both feet although screened and free of clinically observed peripheral neuropathy (Razzak et al., 2015). Previous studies report a definite correlation between disease duration and further increased diabetic complications (Agrawal et al., 2010; Bamanie & Al-Noury, 2011; Ward et al., 2015). Similarly a study by Agrawal and colleagues (2010) showed a 2.3 times higher risk of falling in diabetic participants. Furthermore, the combination of retinopathy and vestibular dysfunction increased the odds of falling to 2.9 times higher. Interestingly, vestibular dysfunction and severe peripheral neuropathy increased these odds of falling to 3.3 times in the diabetics (Agrawal et al., 2010).

4.1.4 Health Related Quality of Life and type 2 diabetes

In general no significant differences between the diabetic and non-diabetic groups were found on the first component of the self-administered HRQL questionnaire. There was, however, a significant difference in one of the health dimensions, namely mobility ($p=0.032$; t-test). The type 2 diabetic participants recorded a lower score on this health dimension than the non-diabetic controls. It was also noted that as the ages of the participants increased, their overall perception of their HRQL decreased. The type 2 diabetic participants also scored their VAS, the second component of the EQ-5D-5L, lower than the non-diabetic controls.

The results of the present study are in agreement with the psychological and physical consequences that diabetes is known to have on individuals suffering from the disease and, in addition, the overall effect that age has on HRQL (Redkoep et al., 2002; Morgan et al., 2006; Mulhern & Meadows, 2014). The health concerns that are associated with type 2 diabetes are known to have a substantial impact on an individual's HRQL, including mental health and social activities (Mulhern & Meadows, 2014). In the present study, mobility was affected significantly more than the following health dimensions: usual activities, pain and discomfort, anxiety and depression, and self-care, with no significant differences between the two groups in these dimensions. However, the type 2 diabetic participants also scored their usual activities, pain and discomfort, and anxiety and depression as more affected than the non-diabetic controls, as diabetic complications may have greater effects on these health aspects. The type 2 diabetic participants may have experienced more pain and discomfort due to the possible onset of vascular diabetic complications such as retinopathy, nephropathy, and peripheral neuropathy. Although these microvascular complications were not severe enough for a clinical diagnosis or exclusion from this study, these complications may have affected the type 2 diabetic participants. In a study conducted by Morgan and colleagues (2006) it was found that the diabetic individuals who had single or multiple vascular complications had lower HRQL compared to the diabetic individuals without vascular complications.

Typical complaints of type 2 diabetic individuals are symptoms such as numbness and heaviness of the feet, which makes it more difficult to move around. This possibly explains the significant difference between the two groups regarding mobility. Mobility could also be worsened by excessive body weight as there was a significant difference between the BMI's of the two groups ($p < 0.001$; t-test). The prevalence of obesity has dramatically increased in recent years and is known to have negative impacts on the comorbid medical conditions that are associated with diabetes (Williamson et al., 2009). The BMI's for the type 2 diabetic participants was 35.4, compared to the BMI of the non-diabetic controls of 27.9. The disabling effect of diabetes also had a great impact on the emotional wellbeing of the type 2 diabetic participants. Anxiety and depression are common psychological problems that can be found in this population. As the disease worsens, their emotional wellbeing also worsens as the stresses of financial aspects are added on top of ever increasing health concerns already experienced.

Although only one of the five health dimensions showed a statistical difference between the two groups, the type 2 diabetic participants did perform more poorly than the non-diabetic controls. This may have clinical relevance for clinicians (physicians and audiologists) treating diabetic individuals.

4.2 Clinical implications of this study

From this study and numerous supporting reports in the literature it is evident that type 2 diabetes increases the prevalence and progression of hearing loss (Kakarlapaudi et al., 2003; Frisina et al., 2006; Fukushima et al., 2006; Bainbridge et al., 2008; Mitchell et al., 2009; Akinpelu et al., 2013; Hong et al., 2013). Audiologists should be aware of a diabetes (type 1 or type 2) diagnosis in their patients, and implement a hearing monitoring approach in order to track any possible changes in hearing (Xipeng et al., 2013). Annual testing can be recommended to track possible hearing changes and the progression of hearing loss. The treating clinicians, such as physicians, should also be aware of their patients' disease durations and HbA1c counts. These clinicians should advocate the importance of controlling the disease to their diabetic patients, as hearing loss has numerous detrimental implications resulting in decreased work productivity and income, limited social interactions, and poorer overall quality of life (Hong et al., 2013). The treating clinicians should inform their diabetic patients of current research on diabetes, and that inner ear changes and vestibular dysfunction are additional microvascular complications of the disease (Ward et al., 2015; Konukseven et al., 2015).

No audiological, vestibular, or fall risk assessment can clinically diagnose diabetes as a clinical diagnosis is required. Diagnoses can be made based on diagnostic criteria as stated by the Society for Endocrinology, Metabolism and Diabetes of South Africa and ADA (2016). However, in depth case histories and test results from audiological and vestibular testing can aid clinicians in making future recommendations, once auditory and vestibular pathologies have been ruled out. Once a clinician has performed audiometric tests and confirmed that there are no conductive pathologies such as otitis media or blocked ear canals due to excessive cerumen, vestibular testing can follow. If vestibular pathologies such as Benign Paroxysmal Positional Vertigo (BPPV), Meniere's disease, vestibular migraine, and superior semicircular canal dehiscence have been ruled out and vestibular symptoms still persist, clinicians should be on the lookout for possible indications of

diabetes related symptoms according to the ADA (2017), such as: constant fatigue, polyuria, extreme thirst, constant hunger, vision changes (blurry vision), injuries that take long to heal, weight loss (especially type 1 diabetes), and pain, tingling, and numbness in the hands and feet (especially with type 2 diabetes).

Test results and in-depth case history information can further guide these undiagnosed patients to seek help from medical doctors and to be tested for diabetes.

4.3 Critical evaluation of this study

The strengths and limitations of this research study were critically considered. This critical evaluation can aid in directing future research projects. The strengths and limitations are discussed below.

4.3.1 Strengths of this study

- The current study included the individual assessment of each bilateral vestibular end organ in a well-characterized population of 28 type 2 diabetic participants and 28 non-diabetic adults. Recent developments of modern vestibular testing permit the isolated assessment of each vestibular end organ, thus allowing for patterns of vestibular dysfunction to appear and to be identified (Curthoys, 2012; Ward et al., 2015).
- The research design controlled for age and gender with a matched experimental (diabetic group) and control group (non-diabetic group). Possible confounding influences were consequently minimised.
- This research study included a broad test protocol to determine and describe the audiovestibular function, risk of falling, and health-related quality of life in type 2 diabetics, compared to non-diabetic controls. Previous studies have not incorporated all three measures, but rather isolated testing in diabetic individuals.
- The hearing measure used to obtain hearing thresholds in this study is a set of standard clinical procedures regarding KUDUwave testing as validated by Swanepoel et al. (2013), and ensured accurate assessment of hearing thresholds 250 – 8000 Hz (Ma et al., 1998).
- This study is also in agreement with Ward et al. (2015) and Konukseven et al. (2015), as these researchers described and identified vestibular dysfunction as an additional microvascular complication of diabetes, since the inner ear functioning is compromised.

- This study explored the role of functional disability in diabetics as recommended by Ward et al. (2015). Three fall risk assessments and a HRQoL questionnaire were employed to determine the role of diabetes in risk of falling and overall quality of life. This study confirmed a definite increase in risk of falling as indicated by longer test times or lower scores. Overall quality of life also decreases in diabetics as a result of all of the emotional, psychological, physical, and financial implications of the disease.
- An additional strength of this study was that none of the participants had clinically diagnosed peripheral neuropathy that could further increase the risk of falling. All of the type 2 diabetic participants were assessed without the already established consequences that peripheral neuropathy has such as numbness or heaviness of the feet and postural instability increasing the risk of falling. These factors can be worsened by an already existing vestibular dysfunction (Kim et al., 2012).

4.3.2 Limitations of this study

- A possible limitation of this study was the small sample size of both groups (n=28). Further studies should aim to test and compare larger samples sizes. Age and gender control groups should also be matched according to hearing loss for the comparison against individuals with type 2 diabetes as hearing loss may have possible effects on VEMP test results.
- Future studies should also add the objective assessment of auditory brainstem responses to determine 8th cranial nerve functioning. Auditory brainstem responses along with VEMPs can further identify the site of the possible lesion in the vestibular system, whether the two otolith vestibular end organs or possible neuropathy of the vestibular nerve. It could then be determined which part of the vestibular system is more sensitive to diabetic changes and most likely to be affected (Sahu & Sinha, 2015).
- Cochlear functioning should also be measured by otoacoustic emissions in this population of diabetics, as normal inner ear functioning is compromised (Bainbridge et al., 2008). This test may be indicative of the most vulnerable part of the cochlea to the disease as previous studies indicate thickened walls of the vessels of the basilar membrane and greater loss of outer hair cells in the lower basal turn (Fukushima et al., 2006; Bainbridge et al., 2008).

- Future studies should determine if there are differences between male and female diabetics and disease progression with regard to hearing, vestibular functioning, risk of falling, and health-related quality of life.
- Lastly, future studies should look at the financial implications of the disease and the effects that it has on the overall emotional well-being of the diabetic participants. All financial expenses regarding the disease should be described.

4.3 Conclusion

The type 2 diabetic participants had a higher occurrence of audiovestibular dysfunction, higher risk of falling and poorer HRQL than the non-diabetic controls, and should be monitored as the disease progresses. If there are any auditory or vestibular involvements, further assessments should be considered to minimize the additional functional limitations of quality of life.

It is well established that diabetes has numerous deleterious effects on the vasculature of the eyes, kidneys, and peripheral nerves. The inner ear must also be added to the list of diabetes related complications (Smith et al., 1995). A hearing monitoring approach should be utilised for diabetic individuals, as additional interventions are critical in managing possible hearing losses and the functional changes within the inner ear, specifically changes affecting the cochlea (Xipeng et al., 2013). Furthermore, hemodynamic changes are important indicators of microcirculation disorders and have a pathological basis for hearing loss in this population of individuals. According to Xipeng et al. (2013), improving microcirculation is a crucial approach in treating possible hearing losses in these diabetic individuals. Moreover, additional studies need to develop effective treatments for inner ear diseases caused by hemodynamic changes and microcirculation disorders that are closely related to diabetes. The role that gender plays in the occurrence of hearing loss among diabetic individuals should also be studied further (Akinpelu et al., 2013).

In addition to inner ear changes, vestibular end organ damage in diabetic individuals is a prevalent condition and may reflect distinct disease-related complications. Additional studies should explore the role of rehabilitation in individuals with diabetes and vestibular dysfunction, and whether rehabilitative therapies may be beneficial in this population. According to Konukseven et al. (2015), diabetes affects vestibular functioning as seen in

various test results in diabetic individuals. Furthermore, these researchers identified 'subclinical vestibular neuropathy' as a new diabetes related complication which should be investigated further (Agrawal et al., 2010; Konukseven et al., 2015).

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Appendices

Ethical approval letters

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 28 August 2018.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

26/01/2017

**Approval Certificate
New Application**

Ethics Reference No.: 41/2017

Title: AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS [MA Audiology]

Dear Miss Danielle Minnaar

The **New Application** as supported by documents specified in your cover letter dated 22/01/2017 for your research received on the 23/01/2017, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 25/01/2017.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**41/2017**) 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).

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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 28 August 2018.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

16/02/2017

Approval Certificate

Amendment

(to be read in conjunction with the main approval certificate)

Ethics Reference No.: 41/2017

Title: Audiovestibular function in Adults with type 2 Diabetes Mellitus

Dear Miss Danielle Minnaar

The **Amendment** as described in your documents specified in your cover letter dated 16/02/2017 received on 16/02/2017 was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 16/02/2017.

Please note the following about your ethics amendment:

- Please remember to use your protocol number (**41/2017**) 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 amendment 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

Professor Werdie (CW) Van Staden
MBChB MMed(Psych) MD FCPsych FTCL UPLM
Chairperson: Faculty of Health Sciences Research Ethics Committee

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 2004 (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, Gezina, Pretoria



7 June 2017

Dear Ms Minnaar

Project: Audiovestibular function in adults with type 2 Diabetes Mellitus
Researcher: D Minnaar
Supervisor: Prof B Vinck
Department: Speech-Language Pathology and Audiology
Reference number: 13049985 (41/2017)

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

The Research Ethics Committee of the Faculty of Humanities acknowledges that your ethics application was reviewed and approved by Faculty of Health Science Ethics Committee on **16 February 2017**. We therefore give fully ethical clearance. Data collection may 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 B Vinck (Supervisor)

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

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
 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
 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.

Appendix E: Letter to Request Permission from the Hospital for Prof Paul Rheeder and Dr
Tanja Kemp



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

The Diabetic Clinic
Steve Biko Academic Hospital
Pretoria

Dear Prof Paul Rheeder and Dr Tanja Kemp,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Danielle Minnaar (Student number: 13049985; ID number: 9403110044085) will be doing my Master's-study in Audiology in 2017. I hereby request permission to conduct my research study at the Diabetic Clinic at Steve Biko Academic Hospital. If permission is granted, I intend to start with the data collection for the aforementioned from January 2017.

The title of my study is: **AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS.**

The aim of this study will be to explore and describe the audiovestibular functioning in adults who have had Type 2 Diabetes Mellitus for a period of 5 years and longer. The 30 participants that I will need to take part in my research study as the experimental group, will be required to complete two self-administered questionnaires regarding their vestibular symptoms (Dizziness Handicap Inventory) and their own perceived health status (EQ-5D-3L Health Questionnaire). Auditory (otoscopic, acoustic immittance measurements and pure tone audiometry) and vestibular (bedside assessments, dynamic visual acuity, vestibular evoked myogenic potentials, video head impulse test, head shake test and spontaneous nystagmus test) assessments will also be conducted on all of these participants.

Thank you for considering this request.

Sincerely,

A handwritten signature in black ink that reads 'Danielle Minnaar'.

Danielle Minnaar (Researcher)
BA Audiology Student (University of Pretoria)

My contact details are:
E-mail address: danielleminnaar1@gmail.com
Cellular number: 082 4150 158



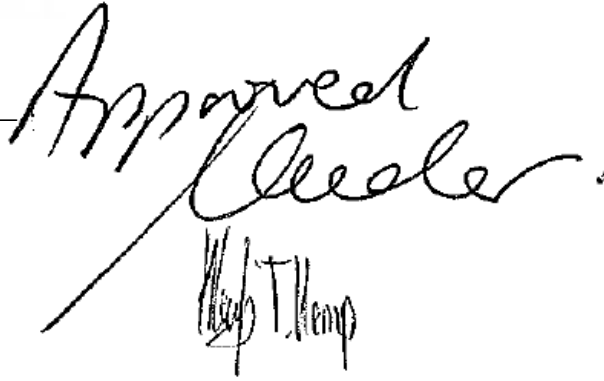
Supervisor: Prof Bart Vinck
E-mail: bart.vinck@up.ac.za



Co-supervisor: Dr Barbara Heinze
E-mail: barbara.heinze@up.ac.za

Prof Paul Rheeder

Dr Tanja Kemp



Approved
Clever



Tanja Kemp

Appendix F: Letter to Request Permission from the Hospital for the Chief Executive Officer of Steve Biko Academic Hospital

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

To: Chief Executive Officer
Steve Biko Academic Hospital
Dr M Kenoshi

From: Danielle Minnaar
The Department of Speech-Language Pathology and Audiology

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

Prof Bart Vinck, Dr Barbara Heinze, Prof Paul Rheeder and I are researchers and I am requesting permission on behalf of all of us to conduct a study on the patients of the Diabetic Clinic of Steve Biko Academic Hospital. We will also require access to the patient files, but we will additionally request their permission in the consent document.

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

The title of the study is: Audiovestibular function in adults with type 2 Diabetes Mellitus.

The researchers request access to the following information:
Type 2 Diabetes Mellitus patients as well as access to their clinical files.

We intend to publish the findings of the study in a professional journal and/ or 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 patient a random 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,

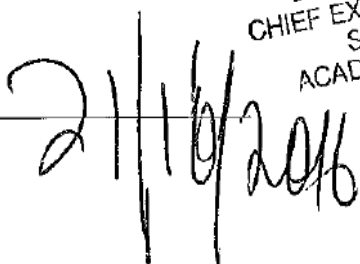


Danielle Minnaar (Researcher)
BA Audiology Student (University of Pretoria)

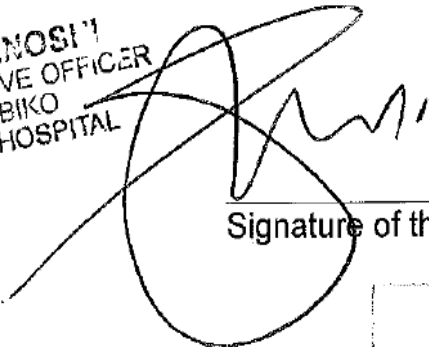
Permission to do the research study at this hospital and to access the information as requested is hereby approved.

Chief Executive Officer
Steve Biko Academic Hospital

Dr



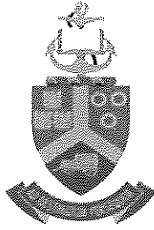
DR M KENOSHI
CHIEF EXECUTIVE OFFICER
STEVE BIKO
ACADEMIC HOSPITAL



Signature of the CEO

Hospital Official

Appendix G: Letter to Request Permission from Dr Mary Seeber at Mediclinic Heart Hospital



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

Room 304
Mediclinic Heart Hospital
Park/Hamilton Street
Sunnyside, 0002

Dear Dr Mary Seeber

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Danielle Minnaar (Student number: 13049985; ID number: 9403110044085) will be doing my Master's-study in Audiology in 2017. I hereby request permission to conduct my research study at the Diabetic Clinic at Mediclinic Heart Hospital, Room 304. If permission is granted, I intend to start with the data collection for the aforementioned from mid-February 2017.

The title of my study is: **AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS.**

The aim of this study will be to explore and describe the audiovestibular functioning in adults who have had Type 2 Diabetes Mellitus for a period of 5 years and longer. The 30 participants that I will need to take part in my research study as the experimental group, will be required to complete a self-administered questionnaire regarding their own perceived health status (EQ-5D-3L Health Questionnaire). Auditory (otoscopic, acoustic immittance measurements and pure tone audiometry), vestibular (vestibular evoked myogenic potentials and video head impulse test) and fall risk (Dynamic Gait Index, The Berg Balance Scale and Timed "Up & Go" test) assessments will also be conducted on all of these participants.


Thank you for considering this request.

Sincerely,

Handwritten signature of Danielle Minnaar in black ink.

Danielle Minnaar (Researcher)
BA Audiology Student (University of Pretoria)

My contact details are:
E-mail address: danielleminnaar1@gmail.com
Cellular number: 082 4150 158



Supervisor: Prof Bart Vinck
E-mail: bart.vinck@up.ac.za



Co-supervisor: Dr Barbara Heinze
E-mail: barbara.heinze@up.ac.za

M. Seeber

Dr Mary Seeber ~~Dr M Seeber~~

PR: 1493299
Medi-Clinic Heart Hospital Room 304
551 Park Street
Sunnyside, 0002
Tel: (012) 343 0872/3
Fax: (012) 343 2666

Appendix H: Permission to access Records / Files / Data base from Dr Mary Seeber at
Mediclinic Heart Hospital

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

To: Mary Seeber
Chief executive Officer/Information Officer
Mediclinic Heart Hospital
Room 304

From: Danielle Minnaar
The Department of Speech-Language Pathology and Audiology

Re: Permission to do research at Dr Mary Seeber's Rooms

Prof Bart Vinck, Dr Barbara Heinze, Prof Paul Rheeder and I are researchers and I am requesting permission on behalf of all of us to conduct a study on your patients with Type 2 Diabetes Mellitus. We will also require access to the patient files, but we will additionally request their permission in the consent document.

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

The title of the study is: Audiovestibular function in adults with type 2 Diabetes Mellitus.

The researchers request access to the following information:
Type 2 Diabetes Mellitus patients as well as access to their clinical files.

We intend to publish the findings of the study in a professional journal and/ or 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 patient a random 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,



Danielle Minnaar (Researcher)
BA Audiology Student (University of Pretoria)

**Permission to do the research study at this hospital and to access
the information as requested is hereby approved.**

Title and name of Chief Executive Officer: Dr Mary Seeber
Mediclinic Heart Hospital

Dr M. Seeber
~~Dr M Seeber~~

Date: 31/01/17

PR: 1493288
Mediclinic Heart Hospital Room 904
551 Park Street
Sunnyside, 0002
Tel: (012) 343 0972/8
Fax: (012) 343 3869



INFORMATION LEAFLET AND INFORMED CONSENT FOR TYPE 2 DIABETES MELLITUS PARTICIPANTS.

AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS.

Dear Participant,

1) INTRODUCTION

You are invited to participate in 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 will help you decide if you want to participate in my research study. Before you agree to take part you should fully understand what is involved. If you have any questions that this leaflet does not fully explain, please do not hesitate to ask me, Ms Danielle Minnaar in person or you can phone/sms me at 082 4150 158 for clarification.

2) THE NATURE AND PURPOSE OF THIS STUDY

The main aim of my study is to determine the hearing sensitivity and balance functioning of adults who have had type 2 diabetes mellitus for a period of 5 years or longer. There will also be a control group included into this study of participants without diabetes mellitus who will be matched according to age and gender for comparison purposes.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You are currently a patient at the Diabetic Clinic of the Steve Biko Academic Hospital or a patient of Dr Mary Seeber at the Mediclinic Heart Hospital, Room 304. I would like to do free hearing and balance assessments for you. Please be assured that my research study is not in any way related to the treatment you are receiving at the Diabetic Clinic and will not interfere with it.

For participation in this study I will collect all necessary information from your hospital file such as your blood glucose, HbA1c and Lipid profile (LDL, HDL and total cholesterol) and other clinical results such as your height, weight, BMI and duration of type 2 diabetes mellitus.

The main outcome of this study will be to have a better understanding of how type 2 diabetes mellitus affects hearing and balance.

All of tests will take approximately 90 minutes to complete:

You will also be required to complete two questionnaires:

1. *EQ-5D-3L Health Questionnaire:*

You will be required to complete 5 short questions as honestly as possible regarding your; (1) Mobility; (2) Self-care; (3) Usual activities; (4) Pain/Discomfort; and (5) Anxiety/Depression. You will also be required to complete the EQ Visual Analogue Scale (VAS) in order to record your self-rated health on a vertical, visual analogue scale according to 'Best imaginable health state' and 'Worst imaginable health state'. This questionnaire will measure your health related quality of life.

The following hearing tests will be done:

1. *Otoscopy:*

For this test, you will be required to be seated upright while I visually inspect your ear canal and your eardrum by using an otoscope (ear light).

2. *Middle ear test:*

For this test, you will be required to be seated upright while a soft probe is inserted into your ear canal in order to take measurements of middle ear pressure and movement.

3. *Hearing test:*

For this test, you will wear earphones on your ears. You will be required to respond to a soft sound by pushing a button. Your hearing sensitivity will be measured.

The following fall risk tests will be done:

1. *Dynamic Gait Index testing:*

You will be scored on a 24-point scale that will assess the following eight aspects of your walk: (1) walking on a flat surface level; (2) change of walk speed; (3) walk ability with your head turned horizontally; (4) walk ability with your head turned vertically; (5) your ability to turn around while walking; (6) your ability to step over obstacles; (7) your ability to step around obstacles; and (8) walking up the stairs, turning at the top of the staircase and then walking down the stairs.

2. *The Berg Balance Scale testing:*

This is a 14 item scale designed to measure your balance. You will be required to complete 14 different tasks while being timed. The 14 different tasks are: (1) sitting to standing movement; (2) standing unsupported; (3) sitting unsupported; (4) standing to sitting

movement; (5) transfers of positioning; (6) standing with eyes closed; (7) standing with feet together; (8) reaching forward with an outstretched arm; (9) retrieving an object from the floor; (10) turning to look backwards; (11) turning 360 degrees; (12) placing alternate feet on a chair; (13) standing with one foot in the front of the other; and (14) standing on one foot at a time.

3. *Timed “Up & Go” testing:*

This is a quick and easy measure of your balance and risk of falling. You will be required 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 test will be repeated twice.

The following vestibular (balance) tests will be done:

1. *Vestibular Evoked Myogenic Potentials:*

You will be required to be lying down on the bed with a soft probe placed in your ear canal while a sound stimulus is presented to you. Four different electrodes will be placed on your eyes, neck and chest. When the sound is presented, you will be required to lift your head and to look upwards towards the marked “X” on the roof for the duration of the sound.

2. *Video Head Impulse Test:*

You will be required to be seated upright while I move your head sideways and up-and-down while I measure your eye movements with a camera.

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study. You will however be expected to complete a few physical activities, rest time will be given as needed and support will continuously be available to prevent you from falling.

5) POSSIBLE BENEFITS OF THIS STUDY

Although you will not benefit directly from the study, the results of the study may help researchers to determine the occurrence and nature of hearing and balance problems in type 2 diabetes mellitus patients. Should I diagnose any hearing or vestibular problems, you will be referred to the Department of Speech-Language Pathology and Audiology at the University of Pretoria where you will further be examined and be treated for the identified problem.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this study is entirely voluntary. You may decline to participate or stop at any time during the examination. This will have no effect on your current treatment at the Diabetic Clinic of Steve Biko Academic Hospital.

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. The contact person of the Ethics Committee for the study is Mrs Manda Smith – 012 356 3085.

8) INFORMATION AND CONTACT PERSON

The contact person for the study is Me, Ms Danielle Minnaar. If you have any questions about the study please contact me at 082 4150 158 or danielleminnar1@gmail.com. Alternatively you may contact my supervisor, Prof Bart Vinck, at Bart.Vinck@up.ac.za or my co-supervisor, Prof Paul Rheeder, at paul.rheeder@med.up.ac.za or Dr Barbara Heinze, at Barbara.Heinze@up.ac.za.

9) COMPENSATION

You will not be paid to take part in this study. As my examination will be done during your routine clinical visit to one of the doctors in the Diabetic Clinic, no extra costs are expected to be concurred by you. There will however be refreshments that will be provided to you in the form of tea, coffee and/or water.

10) CONFIDENTIALITY

All your information will be kept confidential. Once the data sheet has been completed by me, a number will be allocated to your data sheet. Your name will not appear on the document. Research reports and articles in scientific journals will not include any information that may identify you.

All of the data collection sheets from this study will be stored for a period of 15 years in both hard copies and scanned electronic versions that will be stored on a CD and/or USB stick at the Department of Speech-Language Pathology and Audiology for future research by other researchers. However, before any further research will be done on the data, a proposal will be submitted to the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I have been given opportunity to ask questions and I am satisfied that they have been answered satisfactorily. I understand that if I do not participate it will not alter my medical treatment in any way. I am aware that the results of the study, including personal details, will be anonymously processed in research reports. I am participating willingly.

I have received a signed copy of this informed consent agreement.

Participant's name _____

(Please print)

Participant's signature: _____ Date _____

Investigator's name _____
(Please print)

Investigator's signature _____ Date _____

Witness's Name _____
(Please print)

Witness's signature _____ Date _____

VERBAL INFORMED CONSENT

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

The participant indicates that s/he understands that the results of the study, and that his/her personal details will be anonymously processed into a research report. The participant indicates that s/he has had an opportunity to ask questions and has no objection to participate in the research study. S/he understands that there is no penalty should s/he wish to discontinue with 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 _____



HEALTHY PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT.

AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS.

Dear Participant,

1) INTRODUCTION

You are invited to participate in 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 will help you decide if you want to participate in my research study. Before you agree to take part you should fully understand what is involved. If you have any questions that this leaflet does not fully explain, please do not hesitate to ask me, Ms Danielle Minnaar in person or you can phone/sms me at 082 4150 158 for clarification.

2) THE NATURE AND PURPOSE OF THIS STUDY

The aim of my study is to determine the hearing sensitivity and balance functioning of adults who have had type 2 diabetes mellitus for a period of 5 years or longer compared to healthy age and gender matched participants.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You have been asked to take part in this research study as you are a healthy participant. You will form part of the control group that has been matched according to age and gender with the type 2 diabetes mellitus group. I would like to do free hearing and balance assessments for you.

I merely want to understand how type 2 diabetes mellitus affects the hearing and balance functionality of diabetics in comparison to the healthy age and gender matched participants such as you.

All of tests will take approximately 90 minutes to complete:

You will also be required to complete two questionnaires:

1. *EQ-5D-3L Health Questionnaire:*

You will be required to complete 5 short questions as honestly as possible regarding your; (1) Mobility; (2) Self-care; (3) Usual activities; (4) Pain/Discomfort; and (5) Anxiety/Depression. You will also be required to complete the EQ Visual Analogue Scale (VAS) in order to record your self-rated health on a vertical, visual analogue scale according to 'Best imaginable health state' and 'Worst imaginable health state'. This questionnaire will measure your health related quality of life.

The following hearing tests will be done:

1. *Otoscopy:*

For this test, you will be required to be seated upright while I visually inspect your ear canal and your eardrum by using an otoscope (ear light).

2. *Middle ear test:*

For this test, you will be required to be seated upright while a soft probe is inserted into your ear canal in order to take measurements of middle ear pressure and movement.

3. *Hearing test:*

For this test, you will wear earphones on your ears. You will be required to respond to a soft sound by pushing a button. Your hearing sensitivity will be measured.

The following fall risk tests will be done:

1. *Dynamic Gait Index testing:*

You will be scored on a 24-point scale that will assess the following eight aspects of your walk: (1) walking on a flat surface level; (2) change of walk speed; (3) walk ability with your head turned horizontally; (4) walk ability with your head turned vertically; (5) your ability to turn around while walking; (6) your ability to step over obstacles; (7) your ability to step around obstacles; and (8) walking up the stairs, turning at the top of the staircase and then walking down the stairs.

2. *Berg Balance Scale testing:*

This is a 14 item scale designed to measure your balance. You will be required to complete 14 different tasks while being timed. The 14 different tasks are: (1) sitting to standing movement; (2) standing unsupported; (3) sitting unsupported; (4) standing to sitting

movement; (5) transfers of positioning; (6) standing with eyes closed; (7) standing with feet together; (8) reaching forward with an outstretched arm; (9) retrieving an object from the floor; (10) turning to look backwards; (11) turning 360 degrees; (12) placing alternate feet on a chair; (13) standing with one foot in the front of the other; and (14) standing on one foot at a time.

3. *Timed “Up & Go” testing:*

This is a quick and easy measure of your balance and risk of falling. You will be required 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 test will be repeated twice.

The following vestibular (balance) tests will be done:

1. *Vestibular Evoked Myogenic Potentials:*

You will be required to be lying down on the bed with a soft probe placed in your ear canal while a sound stimulus is presented to you. Four different electrodes will be placed on your eyes, neck and chest. When the sound is presented, you will be required to lift your head and to look upwards towards the marked “X” on the roof for the duration of the sound.

2. *Video Head Impulse Test:*

You will be required to be seated upright while I move your head sideways and up-and-down while I measure your eye movements with a camera.

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study. You will however be expected to complete a few physical activities, rest time will be given as needed and support will continuously be available to prevent you from falling.

5) POSSIBLE BENEFITS OF THIS STUDY

Although you will not benefit directly from the study, the results of the study may help researchers to determine the occurrence and nature of hearing and balance problems in healthy patients compared to the type 2 diabetes mellitus participants. Should I diagnose any hearing or vestibular problems you will be referred to the Department of Speech-Language Pathology and Audiology at the University of Pretoria where you will further be examined and be treated or referred for the identified problem.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this study is entirely voluntary. You may decline to participate or stop at any time during the examination.

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. The contact person of the Ethics Committee for the study is Mrs Manda Smith – 012 356 3085.

8) INFORMATION AND CONTACT PERSON

The contact person for the study is Me, Ms Danielle Minnaar. If you have any questions about the study please contact me at 082 4150 158 or danielleminnar1@gmail.com. Alternatively you may contact my supervisor, Prof Bart Vinck, at Bart.Vinck@up.ac.za or my co-supervisor, Prof Paul Rheeder, at paul.rheeder@med.up.ac.za or Dr Barbara Heinze, at Barbara.Heinze@up.ac.za.

9) COMPENSATION

You will not be paid to take part in this study. There will however be refreshments that will be provided to you in the form of tea, coffee and/or water.

10) CONFIDENTIALITY

All your information will be kept confidential. Once the data sheet has been completed by me, a number will be allocated to your data sheet. Your name will not appear on the document. Research reports and articles in scientific journals will not include any information that may identify you.

All of the data collection sheets from this study will be stored for a period of 15 years in both hard copies and scanned electronic versions that will be stored on a CD and/or USB stick at the Department of Speech-Language Pathology and Audiology for future research by other researchers. However, before any further research will be done on the data, a proposal will be submitted to the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I have been given opportunity to ask questions and I am satisfied that they have been answered satisfactorily. I am aware that the results of the study, including personal details, will be anonymously processed in research reports. I am participating willingly.

I have received a signed copy of this informed consent agreement.

Participant's name _____
(Please print)

Participant's signature: _____ Date _____

Investigator's name _____
(Please print)

Investigator's signature _____ Date _____

Witness's Name _____
(Please print)

Witness's signature _____ Date _____

VERBAL INFORMED CONSENT

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

The participant indicates that s/he understands that the results of the study, and that his/her personal details will be anonymously processed into a research report. The participant indicates that s/he has had an opportunity to ask questions and has no objection to participate in the research study. S/he understands that there is no penalty should s/he wish to discontinue with 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: Timed “Up and Go” Test

The “Timed Up and Go” (TUG)

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: _____

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 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 \geq 3 seconds
- 1 tries to lift leg unable to hold 3 seconds but remains standing independently.
- 0 unable to try or needs assist to prevent fall

TOTAL SCORE (Maximum = 56)



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 speed, 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 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.

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: $\leq 19/24$ = predictive of falls in the elderly, $\geq 20/24$ = 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 N: The EQ-5D-5L Questionnaire



Health Questionnaire

English version for the UK

Sample

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

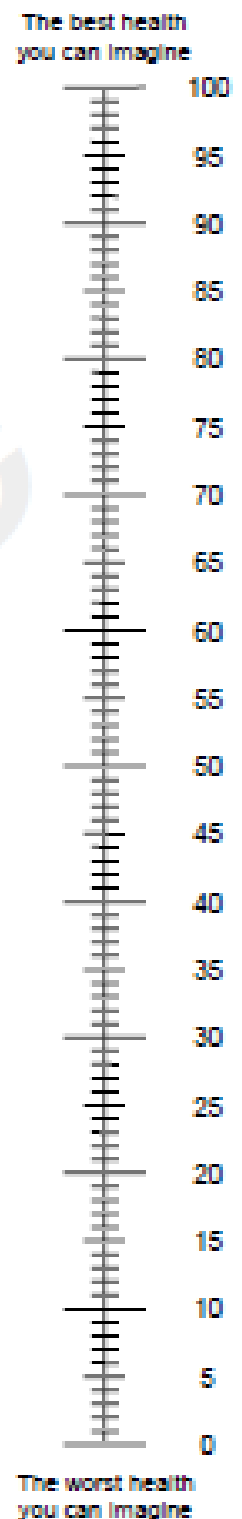
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

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 O: Principal Investigator(s) 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), Danielle Minnaar of the following trial/study titled:

AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS

will be storing all the research data and/or documents referring to the above mentioned trial/study at the following 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 commencement of this trial/study.

START DATE OF TRIAL/STUDY: January 2017

END DATE OF TRIAL/STUDY: September 2017

UNTIL WHICH YEAR WILL DATA WILL BE STORED: 2032

Name: Dr Barbara Heinze

Signature:



Date: 19 September 2016

Appendix P: Data Capturing Sheet for the Type 2 Diabetes Participant's



AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS

Data Capturing Sheet for the type 2 Diabetes Mellitus Participant's

Date of visit: _____

Randomized participant number: _____

Cell phone number 1: _____ Cell phone number 2: _____

Age: _____ Years

Height: _____ Meters

Weight: _____ Kg

BMI: _____ Kg/m²

Overweight: 25-29.9

Obese I: 30-34.9

Obese II: 35-39.9

Obese III: >40

Duration of type 2 Diabetes Mellitus: _____ Month/Years

Gender:

Male Female

Current:

Blood Pressure: _____ mmHg

Blood Glucose: _____ mmol/L

Microfilament Test: _____ /8

Blood results as in File:

Blood Glucose: mmol/L

HbA1c: %

Blood pressure: mmol/L

Total Cholesterol: mmol/L

LDL: mmol/L

HDL: mmol/L

Urea: mmol/L

Creatinine: mmol/L

T4: pmol/L TSH: mlu/L

Microvascular complications as in file:

Retinopathy: Yes No

Nephropathy: Yes No

Peripheral Neuropathy: Yes No

List of Medications used:

RESULTS

1. OTOSCOPY

Left ear:

Right ear:

2. ACOUSTIC IMMITTANCE MEASUREMENTS

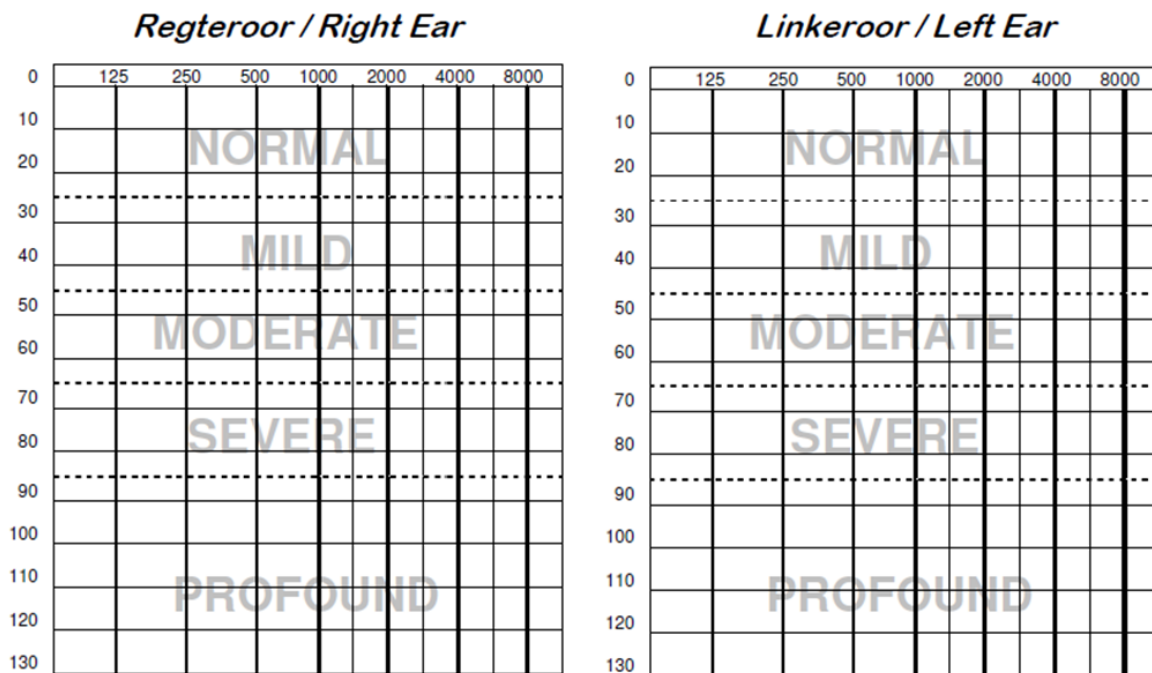
Tympanometry:

LEFT EAR:	RIGHT EAR:
Tympanogram type:	Tympanogram type:
Ear canal pressure:	Ear canal pressure:
Static compliance:	Static compliance:
Ear canal volume:	Ear canal volume:

Acoustic reflex measurements

LEFT EAR:	RIGHT EAR:
Reflex present at 500Hz:	Reflex present at 500Hz:
Reflex present at 1000Hz:	Reflex present at 1000Hz:
Reflex present at 2000Hz:	Reflex present at 2000Hz:
Reflex present at 4000Hz:	Reflex present at 4000Hz:

3. PURE TONE AUDIOMETRY



4. **Dynamic Gait Index**

Total score: _____/24

5. **The Berg Balance Scale**

Total Score: _____/56

6. **The Timed "Up & Go" Test**

Time for "Up & Go" test _____ sec

Unstable on turning?

Walking aid used? Type of aid: _____

7. **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					

8. **Video Head Impulse Test (vHIT):**

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

Appendix Q: Data Capturing Sheet for the Non-diabetic Age and Gender Matched Participants



AUDIOVESTIBULAR FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS

Data Capturing Sheet for the Participant's without type 1 or type 2 Diabetes Mellitus

Date of visit: _____

Randomized participant number: _____

Cell phone number 1: _____ Cell phone number 2: _____

Age: _____ Years

Height: _____ Meters

Weight: _____ Kg

BMI: _____ Kg/m²

Overweight: 25-29.9

Obese I: 30-34.9

Obese II: 35-39.9

Obese III: >40

Gender:

Male

Female

Current:

Blood pressure: _____ mmHg

Blood Glucose: _____ mmol/L

Microfilament Test: _____ /8

RESULTS

1. OTOSCOPY

Left ear:

Right ear:

2. ACOUSTIC IMMITTANCE MEASUREMENTS

Tympanometry:

LEFT EAR:	RIGHT EAR:
Tympanogram type:	Tympanogram type:
Ear canal pressure:	Ear canal pressure:
Static compliance:	Static compliance:
Ear canal volume:	Ear canal volume:

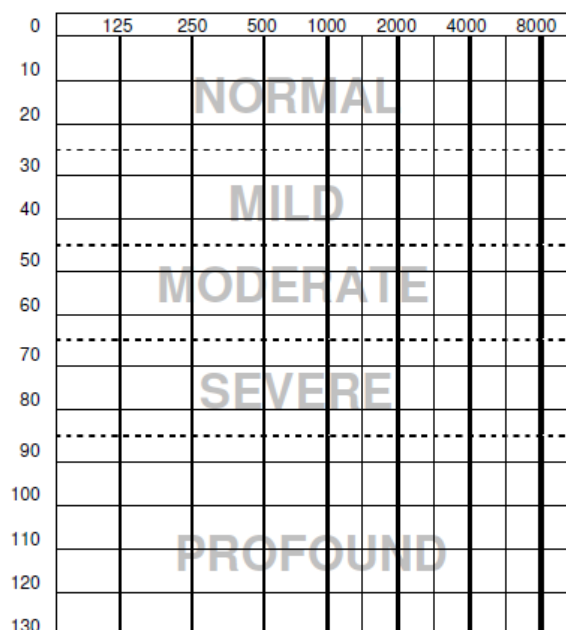
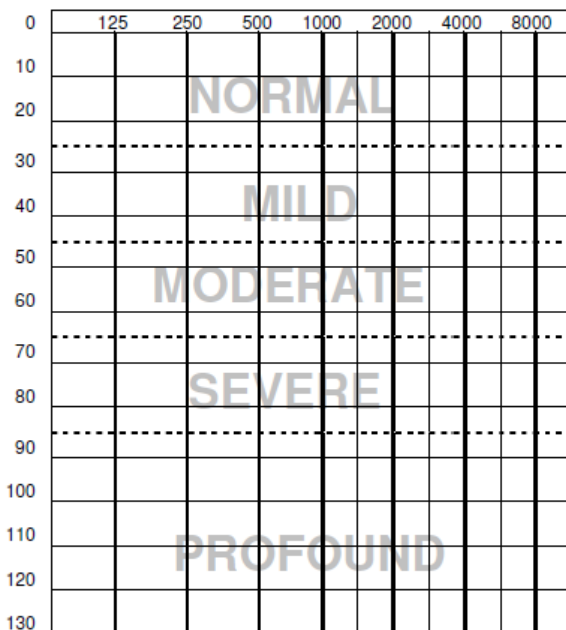
Acoustic Reflex Measurements:

LEFT EAR:	RIGHT EAR:
Reflex present at 500Hz:	Reflex present at 500Hz:
Reflex present at 1000Hz:	Reflex present at 1000Hz:
Reflex present at 2000Hz:	Reflex present at 2000Hz:
Reflex present at 4000Hz:	Reflex present at 4000Hz:

3. PURE TONE AUDIOMETRY

Regteroor / Right Ear

Linkeroor / Left Ear



4. **Dynamic Gait Index**

Total score: _____/24

5. **The Berg Balance Scale**

Total Score: _____/56

6. **The Timed "Up & Go" Test**

Time for "Up & Go" test _____ sec

Unstable on turning?

Walking aid used? Type of aid: _____

7. **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					

8. **Video Head Impulse Test (vHIT):**

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

Glossary

Cochlear microcirculation	The process that is responsible for providing the cochlea with energy and removes metabolic wastes (Nuttall, 1999; Wangemann, 2002; Shi, 2011; Xipeng et al., 2013). A reduction in this blood flow to the cochlea can result in numerous hearing disorders.
Covert Saccades	A corrective saccade or refixation eye movement, generated during the head movement (Tjernström, Nyström & Magnusson, 2012; McGarvie et al., 2015).
Diabetes mellitus	A group of metabolic diseases characterized as metabolic syndrome of chronic hyperglycaemia (high blood sugar) due to a relative insulin deficiency, insulin resistance or both (WHO, 2016; ADA, 2017). It is a lifelong disorder that affects your body's capability of using the energy found in food (Whiting, Guariguata, Weil & Shaw, 2011; Amod et al., 2012; WHO, 2016; ADA, 2017).
Diabetic microangiopathy	A disorder characterised by disease of the small blood vessels within the body (Zats & Brenner, 1986; Gärtner & Eigentler, 2008; Vojtková et al., 2012; Akinpelu et al., 2014). It is one of the major complications in chronic diabetes involving diabetic neuropathy, retinopathy and nephropathy (Vojtková et al., 2012; Akinpelu et al., 2014).
Dizziness	The subjective feeling of being lightheaded, unbalanced, feeling faint, pressure in the head, or can even be perceived as vertigo (Whitney et al., 2004).

Gestational Diabetes Mellitus	Can be defined as any form of glucose intolerance that occurs during pregnancy due to genetics, lifestyle factors and hormonal changes (WHO, 2016; ADA, 2017).
Hearing loss	Also known as hearing impairment and can be described as a partial or total inability to hear. It can also be further characterized according to the degree and the part of the auditory system that is affected (Kakarlapudi et al., 2003; Fukushima et al., 2006; Akinpelu et al., 2013; Al-Hariri, 2016).
Hemodynamic changes	Any changes in the blood flow that is pumped by the heart and circulates through the cardiovascular system through and within the tissues and organs of the body is controlled by homeostatic mechanisms (Zats & Brenner, 1986; Xipeng et al., 2013).
Hyperglycaemia	A surplus of glucose in the bloodstream as seen in patients with diabetes mellitus (WHO, 2016; ADA, 2017).
HbA1c	Refers to glycated haemoglobin (A1c) which identifies the average plasma glucose over a three month period and is known as a marker of disease regulation in diabetes (Alqahtani, Khan, Alhumaidi, & Ahmed, 2013; WHO, 2016; ADA, 2017). It develops when haemoglobin, a protein within the red blood cells that carries the oxygen throughout the body, joins with the glucose in the bloodstream and then becomes glycated.
Insulin	Insulin is a peptide hormone that is produced by the beta cells in the islets of Langerhans in response to a high glucose level (Amod et al., 2012; WHO, 2016; ADA,

2017). This then causes the glucose to be absorbed from the blood into fat, liver and skeletal muscle cells.

Increased vessel permeability	Vessel permeability is characterised as the capacity of a blood vessel to allow the flow of small molecules in and out. Increased vessel permeability describes the narrowing of blood vessels and consequently leads to less molecules flowing through these constricted blood vessels (Viberti, 1983; Adamis et al., 1994; Yuan et al., 2007; Xipeng et al., 2013).
Insulin Deficiency	Type 1 diabetes results mainly from insulin deficiency as the insulin producing pancreatic beta cells stop producing insulin as they become destructed or impaired (Amod et al., 2012; WHO, 2016; ADA, 2017). As a result, insulin deficiency leaves an excess of sugar in the blood and not enough in the cells of the body for energy.
Insulin Resistance	This is a condition in which the pancreas still produces insulin, but there seems to be a resistance to its actions as it is not used effectively (Amod et al., 2012; WHO, 2016; ADA, 2017). Consequently glucose builds up in the bloodstream instead of being absorbed by the cells leading to type 2 diabetes.
Macrovascular complications	Macrovascular complications affect the large blood vessels of the body and are usually as a result of arthrosclerosis (ADA, 2017). The main diabetic macrovascular complications are namely: a stroke, coronary artery disease and congestive heart failure (WHO, 2016; ADA, 2017; Chatterjee et al., 2017).

Microcirculation	The circulation of blood in the smallest blood vessels that is present within the vasculature that is embedded in various organs throughout the body (Xipeng et al., 2013).
Microvascular complications	Microvascular complications affect the small blood vessels within the body. The main diabetic microvascular complications are namely: retinopathy, nephropathy and peripheral neuropathy (Kumar & Clark, 2005; Agrawal, Carey, Della Santina, Schubert, & Minor, 2010; Vojtková, et al., 2012; Ward, et al., 2015; WHO, 2016; ADA, 2017).
Nephropathy	Diabetic kidney disease is caused by damage to the capillaries in the glomeruli of the kidneys (WHO, 2016; ADA, 2017). This is a progressive disease and can result in renal failure.
Overt saccades	A corrective saccade made at the end of the head movement. It is called “overt” as it is hidden and cannot be seen by simple visual observations (McGarvie et al., 2015).
Peripheral neuropathy	This results from damage to the peripheral nervous system and symptoms of weakness, numbness and pain are experienced in the hands and feet (WHO, 2016; ADA, 2017). The most common cause of peripheral neuropathy is diabetes.
Presbycusis	Refers to age-related hearing loss that occurs from the natural process of aging on the auditory system (Tay et al., 1995; Uchida et al., 2010; Ferrite & Santana, 2005; Hong et al., 2013). It is the most common type of sensorineural hearing loss that affects adults. It is bilateral in nature, occurs gradually and initially affects the high frequencies (1000Hz to 8000 Hz).

Retinopathy	This results from chronic high blood sugar and is associated with damage to the tiny vessels in the retina (WHO, 2016; ADA, 2017).The impairment of eyesight or loss of vision is a common complication associated with diabetes.
Type 1 Diabetes Mellitus	Type 1 diabetes can be described as an individual being insulin deficient as insulin can no longer be synthesised by the pancreatic beta cells and is usually as a result of an autoimmune process (WHO, 2016; ADA, 2017).
Type 2 Diabetes Mellitus	Type 2 diabetes results from an individual being insulin resistant. Their bodies are able to produce the insulin that is required, but the insulin is not used effectively. These individuals usually only require insulin treatment later on in life when their pancreas capacity to secrete insulin can no longer keep the blood glucose levels in normal range within the body (Amod et al., 2012; Chen et al., 2012; WHO, 2016; ADA, 2017; Chatterjee et al., 2017).
Vestibular Dysfunction	The vestibular system comprises of parts within the inner ear, namely the three semicircular canals and two otolith organs and along with the brain that helps to control balance and eye movements (Schubert & Shepard, 2008; Hewston & Deshpande, 2016). If this system is damaged due to aging, injury or diseases, vestibular dysfunction results and causes overwhelming dizziness, vertigo, nausea, imbalance, and an increased risk of falling (Horak, 2006).