THE IMPACT OF TYPE 2 DIABETES MELLITUS ON SYMPTOM PRESENTATION AND RESPONSE TO TREATMENT IN INDIVIDUALS WITH BENIGN PAROXYSMAL POSITIONAL VERTIGO

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Abstract

Diabetic complications, such as retinopathy and peripheral neuropathy, have been studied extensively and are known to impair balance and increase fall risk. However, the effect of diabetes on the vestibular system is not clear. The vestibular system plays an important role in maintaining static and dynamic balance, by providing spatially orienting information. Hence, damage to the vestibular system could potentially increase imbalance and risk of falls. The primary purpose of this work was to examine the effect of diabetes on the peripheral vestibular system, and the resulting impact on symptoms, mobility and balance.

In Chapter 1, we have presented a review of the literature on the pathophysiology of diabetes-related complications and their influence on balance and falls, with specific attention to emerging evidence of vestibular dysfunction due to diabetes. We have provided a perspective on the impact of vestibular complications, the need for a thorough vestibular evaluation, and recommendations for vestibular rehabilitation techniques, for people with diabetes.

Chapter 2 describes the results of our pilot investigation, where we focused our attention to identify if a specific vestibular disorder may be present in higher frequency in individuals with type 2 diabetes (T2D). In this retrospective analysis of electronic health records, we examined data from 3933 individuals with nine common vestibular disorders. Of the nine vestibular disorders commonly seen in the clinic setting, the prevalence of one condition, benign paroxysmal positional vertigo (BPPV), was significantly higher in individuals with diabetes. Factors that were predictive of BPPV included age, female sex, race and presence of hypertension. Hypertension was the mediating factor that increased the prevalence of BPPV in people with diabetes. Building upon this study, we identified benign paroxysmal positional

vertigo as our clinical condition of interest. We developed our specific aims to examine the direct effect of diabetes on the vestibular system using evoked potential studies, as well as the indirect effects on symptoms, mobility and balance, in people diagnosed with BPPV.

Chapter 2 showed that the prevalence of BPPV was higher in people with diabetes. BPPV results when otoconia fragments dislodge from the otolith organs of the inner ear, and cause symptoms of vertigo. The effect of diabetes on the saccule and utricle of the vestibular system is not clear, and the combined effect of BPPV and diabetes on the otolith organs, has not been studied. In Chapter 3, our main purpose was to analyze otolith function using vestibular evoked myogenic potential (VEMP) tests in people with diabetes and concurrent BPPV, and to examine the relationships between VEMP variables and diabetes-related variables. For this study, we recruited people who were 40 to 65 years of age, into four groups; 20 controls, 19 individuals with T2D without vestibular dysfunction, 18 individuals with BPPV, and 14 individuals with BPPV and diabetes (BPPV+DM). Results of this study showed that the frequency of delayed and absent saccule responses was significantly higher in people with T2D, BPPV, and BPPV+DM compared to healthy controls. Delayed latency of the saccule responses were associated with higher HbA1c levels. Utricle function did not appear to be as affected by diabetes as the saccule. Although, BPPV and diabetes independently affected utricle and saccule function, they did not appear to have a distinct cumulative effect.

The true impact of a disease is the resulting impairment to the affected individual, and the effect on daily activities. Chapter 3 revealed otolith dysfunction in people with T2D, BPPV and BPPV+DM. Because otolith dysfunction is associated with balance deficits and increased postural sway, in chapter 4, we examined postural sway. In this study, we compared the postural sway of people with BPPV and BPPV+DM who were between 40 to 65 years of age. We

expanded the scope of our data collection to include healthy controls and people with diabetes (without vestibular dysfunction) for comparison with BPPV and BPPV+DM, as normative values for postural sway using the specific accelerometry procedures and conditions we tested is not available. Not all participants from chapter 3 were included in this study due to equipment malfunction and other issues. Ultimately, we recruited 14 controls, 14 individuals with T2D only, 13 individuals with BPPV only and 11 individuals with BPPV+DM for this study. We measured postural sway using an accelerometer positioned over the L3 spine level, in five conditions that progressively challenged the vestibular system. Results of this study showed that participants with BPPV+DM had higher postural sway measures compared to controls and the T2D group, which was particularly evident in the anteroposterior direction. Standing on foam with eyes closed and tandem stance conditions were the most challenging conditions for people with BPPV+DM.

Besides causing symptoms of vertigo, BPPV is known to affect balance and functional mobility. However, BPPV can be effectively treated with canalith repositioning maneuvers. The effect of diabetes on symptom severity, mobility and balance and the response to treatment maneuvers in people with BPPV is unknown. In Chapter 5, we examined handicap due to dizziness, mobility, and balance in people between 40 to 80 years of age, in two groups, 34 individuals with BPPV and 16 with BPPV+DM, before and after treatment with the canalith repositioning maneuver. To identify these deficits, all individuals completed the Dizziness Handicap Inventory (DHI), the Functional Gait Assessment (FGA) and postural sway tests, in quiet stance with altered visual and proprioceptive feedback. We found no differences between people with BPPV and those with BPPV+DM, on the DHI or FGA scores, at baseline and after symptom resolution. Significant differences were seen in postural sway between the groups at

baseline. However, after resolution of dizziness, there were no differences between the two groups on any postural sway measures. The number of treatment maneuvers required for resolution of vertigo did not differ between groups. People with BPPV with or without diabetes, made significant improvements in symptoms, mobility, and balance after their vertigo had resolved.

In summary, this body of work makes significant contributions to the existing literature examining the vestibular complications due to diabetes. Our central hypothesis was that diabetes would affect the otolith organs of the vestibular system, thereby increasing symptom severity, functional deficits, and balance sway, compared to people without T2D. Our findings were that although the prevalence of BPPV was higher in people with diabetes, hypertension was the complete mediator in the relationship between BPPV and T2D. People with BPPV+DM did not have increased otolith dysfunction, compared to those with BPPV or T2D only; however, postural sway was higher in people with BPPV+DM. The higher postural sway in people with BPPV+DM may be due to the presence of diabetic peripheral neuropathy; however, we did not analyze the effect of neuropathy on mobility and balance. There was no difference in the severity of symptoms and mobility deficits of people with BPPV + DM compared to people with BPPV only. Of importance, we found that people with BPPV+DM do respond well to treatment maneuvers with significant improvements in symptoms, mobility, and balance, and do not require additional treatment maneuvers, when compared to people with BPPV. Although our results did not fully support our central hypothesis, it provides valuable information. This body of work emphasizes the need for early diagnosis and prompt treatment of vestibular dysfunction in individuals with BPPV+DM. Future studies examining falls in people with BPPV+DM

considering the influence of other diabetic complications, will help elucidate the relationship between diabetic complications and fall risk.

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Chapter 1 Preface

Diabetes causes many complications, including retinopathy and peripheral neuropathy, which are known to contribute to gait instability and falls. A less understood complication of diabetes is the effect on the vestibular system. In Chapter 1, we present evidence on the pathophysiology of diabetes-related complications and their influence on balance and falls, with specific attention to emerging evidence of vestibular dysfunction due to diabetes. This review of the literature has been published in the journal Physical Therapy as a "Perspectives article". This type of manuscript is described by the journal as follows: *"Perspectives contain new ideas, interpretations, and opinions and are intended to inform and advance practice in important ways. Perspectives are one of the most highly cited manuscript types, typically written by leaders in the field who set forth future direction."* We have made recommendations for examination as well as specific vestibular treatment interventions, which will benefit people with diabetes.

Introduction

Impact of Diabetic Complications on Balance and Falls: Contribution of the Vestibular System

D'Silva LJ, Lin J, Staecker H, Whitney SL, Kluding PM.

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1.1 Abstract

Diabetes causes many complications, including retinopathy and peripheral neuropathy, which contribute to gait instability and falls. A less understood complication of diabetes is the effect on the vestibular system. The vestibular system contributes significantly to balance in static and dynamic conditions by providing spatially orienting information. It is noteworthy that both animal and clinical studies have reported that diabetes affects vestibular function. Pathophysiological changes in peripheral and central vestibular structures due to diabetes have been noted. Vestibular dysfunction is associated with impaired balance and a higher risk of falls. As the prevalence of diabetes increases, so does the potential for falls due to diabetic complications. The purpose of this perspective article is to present evidence on the pathophysiology of diabetes-related complications and their influence on balance and falls, with specific attention to emerging evidence of vestibular dysfunction due to diabetes. Understanding this relationship may be useful for screening (by physical therapists) for possible vestibular dysfunction in people with diabetes as well as for further developing and testing the efficacy of interventions to reduce falls in this population.

1.2 Overview

Diabetes Mellitus affects 29.1 million people in the United States- about 9.3% of the US population.[1] Over the next 40 years, the prevalence of diabetes in the United States will increase from its current level of 1 in 10 to 1 in 3 because of the aging of the US population, longer life spans of adults with diabetes, and the increasing prevalence of obesity and physical inactivity.[2] The medical expenditures of people with diabetes are about 2.3 times higher than those of people without diabetes, with more than half of those expenditures being directly related to diabetes.[3] The high prevalence and chronicity of complications makes diabetes a health care concern around the world.[2]

People with diabetes often develop multiorgan anatomic, structural and functional changes due to microvascular and macrovascular complications.[4] Two common microvascular complications, peripheral neuropathy and retinopathy, are well established as contributors to increased postural sway and falls.[5, 6] Although vestibular system dysfunction is not commonly recognized as a microvascular complication of diabetes, a recent epidemiological study reported that vestibular dysfunction was 70% higher in people with diabetes than in people matched for age and serving as controls.[7] The prevalence of diabetes and vestibular dysfunction was higher in people with a longer duration of diabetes and with poor glucose control (i.e. higher serum glycated hemoglobin).[8] In addition, animal and clinical studies reported structural and functional changes in the vestibular system due to diabetes.[9-11]

If the vestibular system is adversely affected by diabetes, it will be important for physical therapists to consider the broad influence of diabetes on the risk of falls in older adults and other populations. Although most clinicians may be aware of the role of some diabetic complications

in increasing the risk of falls, the relationship between diabetes and vestibular dysfunction is not well known. The purpose of this perspective article is to present the pathophysiology of diabetic complications and their influence on balance and falls, with specific attention to emerging evidence of vestibular dysfunction due to diabetes. The clinical implications for physical therapists are discussed, as a comprehensive evaluation of the vestibular system may be necessary in people who have diabetes and balance impairment, and interventions that address all three sensory input systems (visual, vestibular and somatosensory), may be essential for reducing the risk of falls.

1.3 Pathophysiology of Diabetic Complications

Diabetes mellitus is a chronic metabolic condition characterized by elevated blood glucose levels resulting from the body's inability to produce insulin, resistance to insulin action, or both.[12] Chronic hyperglycemia plays a major role in the pathogenic mechanisms underlying microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (peripheral vascular disease, cardiovascular disease and cerebrovascular disease) complications in diabetes.

One mechanism of microvascular damage in diabetes is the result of chemical reactions between by-products of sugars and proteins, which forms irreversible cross-linked protein derivatives called advanced glycation end products.[13] These derivatives affect the surrounding tissues causing thickening of collagen and endothelium. Other mechanisms contributing to microvascular disease include the abnormal activation of signaling cascades, such as the protein kinase C pathway, which increases vascular permeability; the polyol pathway, a mechanism by which sorbitol accumulation results in osmotic and oxidative stress damage to the endothelium.[14] The elevated production of reactive oxygen species, by which oxygen-containing molecules

interact with other biomolecules and result in damage; and the abnormal stimulation of hemodynamic regulation systems, such as the renin-angiotensin system.[4]

Damage to the peripheral nerves may occur through the irreversible changes to myelin protein caused by advanced glycation end products, which results in segmental demyelination of the peripheral nerves.[13] Damage to the neuronal microvascular leads to impaired nerve perfusion.[15] Diabetic peripheral neuropathy affects up to two-thirds of people with diabetes, and is characterized by pain, paresthesia and sensory loss.[16]

Similar pathophysiological changes occur in the retinal vasculature in individuals with diabetes. In the United States, about 40% of people with type 2 diabetes and 86% with type 1 diabetes develop retinopathy.[17] Changes in the structure and cellular composition of the retinal vasculature are the hallmarks of early diabetic retinopathy. Damage to the endothelial cell lining causes an increase in vascular permeability, a breakdown of the inner blood–retinal barrier, and accumulation of extracellular fluid in the macula.[18] Damage to pericytes, which are responsible for maintaining capillary tone, leads to altered retinal hemodynamics and abnormal autoregulation of retinal blood flow, which cause the development of micro aneurysms.[19] Thickening of the capillary basement membrane and retinal leukostasis leads to capillary occlusion and nonperfusion in the retinal microcirculation.[20] These changes, in turn, stimulate pathologic neovascularization, which results in proliferative diabetic retinopathy and ultimately leads to retinal detachment and blindness.[21]

People with diabetes, neuropathy, and retinopathy have significant physical limitations because of decreased proprioception and vision. Loss of light touch, visual acuity, contrast

sensitivity, and depth perception may increase both the risk and the recurrence of falls in people with diabetes.[5]

1.4 Influence of Neuropathy and Retinopathy on falls

The presence and severity of diabetic peripheral neuropathy (DPN) have been shown to increase postural instability.[22, 23] People with DPN have a larger range of sway in the anterior-posterior and medial-lateral directions and a higher sway speed than people matched for age and serving as controls.[22] In quiet standing with eyes open, people with DPN have been shown to have 66% more sway than people who are of a similar age and healthy.[6] The greatest decrease in postural stability in people with DPN has been observed with eyes closed; this finding reveals a reliance on vision to compensate for sensory deficits.[6] In addition, decreased vibration sense and loss of pressure sensitivity are associated with recurrent falls.[24] Because of decreased proprioceptive feedback during walking, older adults with diabetes walk slower and have greater stride variability; these factors increase the risk of falls.[25] Similarly, strong associations are seen for diabetic retinopathy, the duration of diabetes and the risk of falls; with severe cortical cataracts being significantly associated with fractures.[26]

Besides having a higher risk of falls, adults who are more than 70 years of age and have diabetes have been found to have a higher risk of sustaining more severe injuries after a fall.[27] Both elderly men and elderly women with diabetes, have a higher risk of fractures compared to adults without diabetes, despite similar bone mineral densities.[28, 29] This compromised bone quality, which may be due to higher concentrations of advanced glycation end products in the bones because of diabetes,[30] increases the risk of fractures by 64% in people with diabetes compared with people who are healthy.[29] Pijpers et al[31] found that in people who were more

than 65 years old and had diabetes, 30.6% fell recurrently, whereas 19.4% of people without diabetes fell recurrently; in that study, recurrent falls were defined as at least two falls within a 6-month period.

Although the diabetic complications of neuropathy and retinopathy clearly increase the risk of falls, other pathways may affect balance and gait in people with diabetes. For example, Chiles et al[32] reported that after adjustment for age, sex, education, cognition, medications, and comorbidities (cardiovascular disease, hypertension, and kidney disease), people with diabetes had significantly decreased physical function ($\beta = -0.99$; $p < .01$), and decreased walking speed ($\beta = -0.1$ m/s; $p < .01$).[32] Even after adjustment for impaired nerve function in the lower extremities (higher neuropathy scores), significant differences in physical function, balance and gait speed between people with diabetes and people without diabetes persisted.[32] This evidence suggests that other pathways may affect balance and gait in people with diabetes.

Because the vestibular system plays a major role in maintaining balance in both static and dynamic conditions, it is important to consider this as a potential mechanism by which balance and gait may be affected. Here we provide a brief summary of the anatomy and physiology of the vestibular system and an overview of studies showing the relationship between diabetes and vestibular dysfunction.

1.5 Anatomy and Physiology of the Vestibular System

The vestibular system makes significant contributions to both sensory and motor systems. As a sensory system, it provides the central nervous system with information regarding motion of the head as well as its position in space. The central nervous system uses this information along with information from the visual and somatosensory system to create an internal map of

the position and movement of the entire body in relation to the environment. The vestibular system contributes directly to motor output by producing compensatory eye movements to maintain a stable gaze and to coordinate postural control during movement.

The peripheral sensory apparatus of the vestibular system comprises the semicircular canals and otolith organs. The three semicircular canals (anterior, posterior and horizontal) function as rate sensors by providing input regarding angular head acceleration. The saccule and the utricle, which are the otolith organs, register forces related to linear acceleration as well as static tilt with respect to the gravitational axis.

Specialized hair cells in each ampulla and otolith organ are the biological sensors that convert head position to neural firing. Type 1 hair cells are sensitive to rotations during large head accelerations, and type 2 hair cells are most effective during low frequency and small head accelerations. In addition, the maculae of the utricle and saccule contain otoconia, which are calcium carbonate crystals, embedded in a gelatinous matrix. The otoconia move in response to gravity and other accelerative movements, making the macula very sensitive to linear acceleration.[33]

Information from the peripheral vestibular organs is processed in the central nervous system with input from the proprioceptive and visual systems. Motor output through the vestibular-ocular reflex (VOR) generates eye movements for gaze stability, and the vestibulospinal reflex generates muscle activity to maintain balance.

The maintenance of balance depends on information provided by the somatosensory, visual and vestibular organs. These sensory systems provide information regarding body orientation within different frames of reference. Mirka and Black reported, “Vestibular input is

referenced to gravity, while somatosensory and visual inputs are referenced to the support surface and visual surrounds. Hence, the vestibular system provides orientation to earth vertical, while the other senses provide relative orientation references".[34] In people with impaired vision or somatosensory input, the vestibular system becomes very important for balance control.

1.6 Evidence for Vestibular Dysfunction in Diabetes

Morphological and physiological changes have been reported in the peripheral vestibular apparatus in animal models of diabetes. Myers and colleagues[11, 35] found morphological and structural changes in the peripheral vestibular system in animals with experimentally induced diabetes. These animals had an overproduction of extracellular matrix as well as a higher incidence of lysosomes and lipid droplets in the connective tissue of the utricle and the saccule.[35] These findings were considered the consequences of metabolic stress. The accumulation of excess extracellular matrix leads to impaired diffusion of oxygen, nutrients and waste products. Hair cell degeneration, noted in these animals, was suggested to be the result of impaired diffusion. The level of type 1 hair cell degeneration was higher in the saccule, suggesting that the saccule may be more susceptible to pathology in diabetes.[35] The vestibulocochlear nerve of rats with diabetes was observed to have large portions of disrupted myelin sheath lamellae as well as thinning of the myelin sheath and smaller axonal fiber diameters.[10, 36] Perez et al[37] observed physiological changes in the vestibular end organ due to diabetes in mice with diet-induced type 2 diabetes. The latency of evoked potential responses was delayed, amplitudes were smaller, and thresholds were higher compared with those in control mice. Because short vestibular evoked potentials were recorded in response to linear and angular accelerations, damage due to diabetes was shown to affect function of the vestibular system.[37] The Figure illustrates the potential mechanisms contributing to vestibular dysfunction in diabetes.

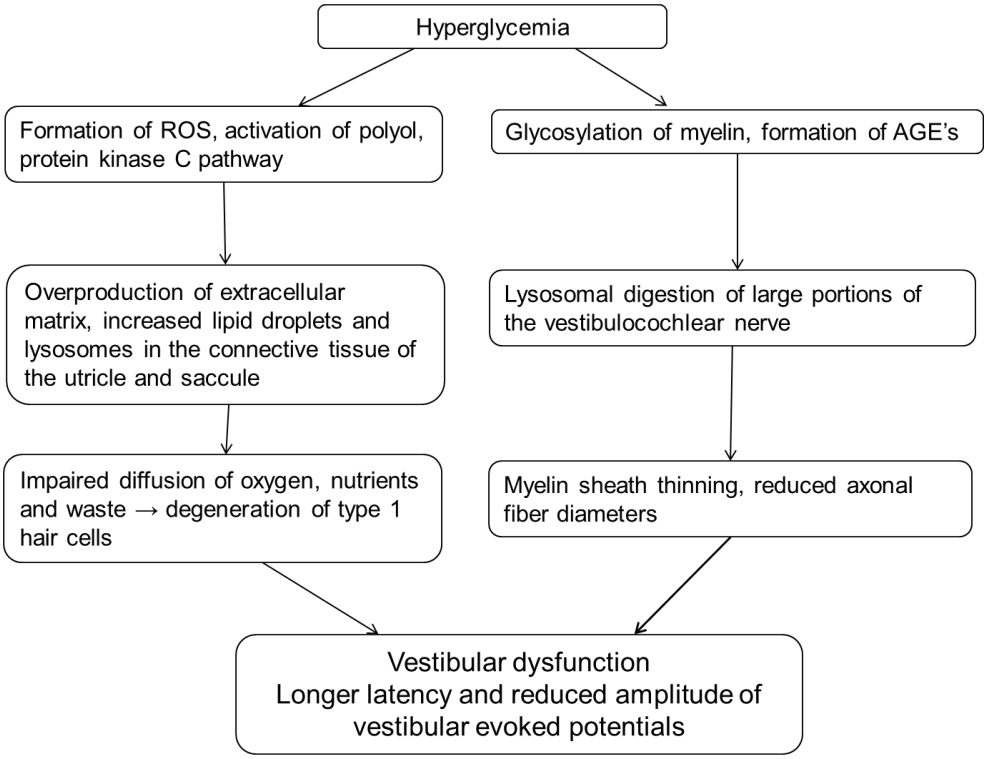

Figure 1: Potential mechanisms contributing to vestibular dysfunction in diabetes based on animal studies. Figure created from information derived from Myers et al.[10, 11, 35, 36] AGE= advanced glycation end products, ROS= reactive oxygen species.

There is clinical evidence of the presence of vestibular dysfunction in people with diabetes. Clinical examinations with oculomotor tests, videonystagmography and caloric testing have shown that children and young adults who are 6 to 28 years of age and have type 1 diabetes have central as well as peripheral vestibular dysfunction. Abnormal responses include impaired optokinetic responses and eye tracking,[9, 38] as well as reduced responses to caloric stimulation and positional nystagmus.[9, 39, 40] The frequency of abnormal responses was higher in the participants with a longer duration of diabetes, those with retinopathy and neuropathy, and those who had frequent hypoglycemic incidents.[9, 40] Despite the changes in central and peripheral structures, Biurrun et al reported no complaints of dizziness or imbalance[40] and Gawron et al reported only 6.3% of the participants had complaints of dizziness and imbalance.[9] In neither study was balance function in the participants examined. The minimal complaints of dizziness

could have been due to symmetrical impairment of function between the two inner ears.[37] In people with type 1 diabetes, vestibular system dysfunction was seen more often than auditory dysfunction (60% versus 30%), indicating that metabolic disturbances may affect the homeostasis of the vestibular organ more quickly than the homeostasis of the cochlea.[39]

Studies in people with type 2 diabetes have shown significant abnormalities in the phase of the vestibular ocular reflex (VOR) and the optokinetic reflex compared with those in people matched for age and serving as controls.[41] Due to VOR abnormalities as well as optokinetic reflex abnormalities, people with diabetes could have blurring of vision during head movements.[41] In adults with multiple chronic disorders, such as diabetes, hypertension, and dyslipidemia; cochlear and vestibular dysfunction was significantly prevalent, particularly in people more than 60 years of age and having 2 or more comorbidities.[42] Table 1 summarizes clinical studies examining vestibular dysfunction in people with type 1 and type 2 diabetes. Based on these studies, the strongest evidence presented is on VOR deficits, not balance problems- perhaps because direct assessment of the VOR is available during videonystagmography tests. Balance testing is more complex, and isolating the vestibular system is difficult because of proprioceptive feedback, as well as inherent compensatory strategies that patients use to avoid falling.

Table 1: Summary of Clinical Studies Examining Vestibular Dysfunction in People with Diabetes[a]

Study	Participants			Evidence of Vestibular Dysfunction
	Group	**N**	**Age (y), X (SD)**	
Biurrun et al[40]	Type 1 DM	46	25.9 (8.9)	21.8% of patients with DM had bilateral depressed caloric responses; oculomotor ENG tracings showed abnormal responses in 54.3% of participants with DM; abnormal responses were seen in participants with a longer duration of DM and with complications like retinopathy or nephropathy
	Control	33	26.2 (9.4)	
Gawron et al[9]	Type 1 DM	95	15.5 (5.1)	Impaired optokinetic responses and significant increases in spontaneous and positional nystagmus were seen in participants with severe hypoglycemic incidents, a longer duration of DM and uncontrolled diabetes
	Control	44	16.3 (6.1)	
Nicholson et al[41]	Type 1 DM	18	62.7 (21.1)	Gaze holding in darkness was worse for participants with DM than for controls; VOR gain was similar in the groups; however, phase velocity was decreased in participants with type 1 diabetes; OKR slow-phase velocity was decreased in both groups with DM, and postural sway was increased in both groups with DM
	Type 2 DM	23	65.4 (10.5)	
	Control	45	60.9 (8.2)	
Cohen et al[43]	Unilateral posterior canal BPPV	176	57 (13)	The prevalence of DM in participants with BPPV was significant ($p<.001$); equilibrium scores on condition 5 of the SOT were significantly lower in participants with BPPV and DM than in those without DM
Klagenberg et al[39]	Type 1 DM	30	25.7	Caloric test abnormalities were seen in 60% of participants; 40% had hyporeflexia, and 20% had hyperreflexia; spontaneous nystagmus, positional nystagmus, and optokinetic responses were within normal limits
Agarwal et al[7]	Adults >40 y old	4,743		The modified Romberg Test of Standing Balance on Firm and Compliant surfaces was used to determine vestibular dysfunction; odds of vestibular

				dysfunction were 70% higher in people with DM; the risk of falls in people with vestibular dysfunction and complaints of dizziness was increased 12-fold
Kim et al[44]	Type 2 DM	35	51.1 (15.5)	19 participants with DPN and complaints of vertigo received vestibular testing, which included a clinical examination for spontaneous and gaze-evoked nystagmus, positional testing, VNG and caloric tests; 11 participants (57.9%) had vestibular dysfunction, on the basis of abnormal caloric responses
Chavez-Delgado et al[42]	Type 2 DM, hypertension and dyslipidemia	385	62 (12.9)	40% of the study population had complaints of dizziness and received vestibular testing, spontaneous nystagmus was seen in 2.8% of the population; abnormal caloric responses were seen unilaterally in 73.4% of the participants and bilaterally in 26.6% of the participants
De Stefano et al[45]	Diabetes, hypertension	1,092	72.9 (6.14)	The number of recurrences of BPPV was related to the number of comorbidities; the combination of hypertension, diabetes, osteoarthritis, and osteoporosis increased the risk of recurrence 6.48 times.

[a] DM=diabetes mellitus, ENG=electronystagmography, VOR=vestibular-ocular reflex, OKR= optokinetic reflex, BPPV=benign paroxysmal positional vertigo, SOT=sensory organization test, DPN=diabetic peripheral neuropathy, VNG=videonystagmography.

The odds of developing vestibular dysfunction are 70% higher in adults with diabetes than in those without diabetes.[7] In a large epidemiological study, Agrawal et al[7] examined data from adults 40 years of age and older (N= 5,086), by using the modified Romberg Test of Standing Balance. Participants had to stand unassisted for 30 seconds in each of the following four positions: on firm ground with eyes open, on firm ground with eyes closed, on a foam surface with eyes open, and on a foam surface with eyes closed. Fifty-four percent of the participants with diabetes were identified as having vestibular dysfunction because they had to take a step or open their eyes when standing on foam with eyes closed. The risk of falls was 12

times higher in the participants who had vestibular dysfunction and complaints of dizziness than in those without either complaint.[7] Of interest, the participants with vestibular dysfunction but without complaints of dizziness also had a significantly higher risk of falls.[7] The prevalence of vestibular dysfunction was directly related to the duration of diabetes. Participants with a history of diabetes of up to 5 years had a 41% prevalence of vestibular dysfunction, whereas a 61% prevalence of vestibular dysfunction was seen both in participants with a history of diabetes of 6 to 10 years and in those with a history of diabetes of more than 10 years. Higher serum glycated hemoglobin levels ($\geq$ 7.0 U) increased the odds of vestibular dysfunction by 60%.[8] The prevalence of vestibular dysfunction was higher in participants with other diabetes-related complications, such as peripheral neuropathy (76% versus 49%) and retinopathy (71% versus 45%).[8]

The limitation of these studies[7, 8] was that the assessment of vestibular dysfunction was done using the modified Romberg Test of Standing Balance. There was no direct assessment of the vestibular system using calorics or evoked potential studies. The modified Romberg Test of Standing Balance has weak correlations with the Dizziness Handicap Inventory (r=0.26). However, when compared with caloric or vestibular evoked potential testing, the modified Romberg Test of Standing Balance has a sensitivity of 55% and a specificity of 65% for the detection of peripheral vestibular dysfunction, making it a poor screening tool for vestibular dysfunction.[46] Future studies of the relationship between direct assessment of the peripheral vestibular organs and balance and function in adults with diabetes are essential.

Degerman et al[47] examined the human saccule and identified the insulin receptor, insulin receptor substrate1, protein kinase B, and insulin- sensitive glucose transporter (GLUT4) in the sensory epithelium of the human saccule. These signaling mechanisms maintain ion and water

homeostasis in the saccule, and are important for oto-protection and neuronal survival. Chronic hyperglycemia and insulin resistance can affect these signaling pathways,[48] resulting in impaired inner ear function.

One particularly common vestibular condition, benign paroxysmal positional vertigo (BPPV), has been studied in adults with diabetes. In a histopathology study, Yoda et al[49] examined 28 temporal bones of people with type 1 diabetes and compared them with the temporal bones of 56 people, who were matched for age and healthy (controls). None of the individuals with type 1 diabetes had a documented medical history of vestibular or balance problems. Each temporal bone was sectioned at a thickness of 20μm, stained with hematoxylin and eosin, and studied under light microscopy. The cupulae were observed by light microscopy at a magnification of X400. A significantly higher prevalence of deposits of otoconia were seen in people with type 1 diabetes than in the controls, both in the posterior and lateral semicircular canals, as well as attached to the cupula.[49] Cohen et al[43] reported a significantly higher prevalence of diabetes in people with BPPV. In adults who were 65 to 74 years of age, 20% of those with BPPV had diabetes; in comparison, 9.2% of people in the general population have diabetes. In addition, comorbidities like diabetes and hypertension have been shown to increase the recurrence rate of BPPV.[50] The combination of hypertension, diabetes, and osteoarthritis increases the risk of recurrence of BPPV 4.55 times.[50] Once diagnosed, BPPV is effectively treated by appropriate repositioning maneuvers.[51] These results suggest that vestibular dysfunction could be considered an underreported complication of diabetes. Vestibular dysfunction independently increases the risk of falls, and may be considered an independent mediator of the association between diabetes and falls.[8]

Based on the literature presented, there appears to be a complex relationship between diabetes and vestibular dysfunction in people with both type 1 and type 2 diabetes. Damage to the inner ear may cause individuals with diabetes to have impaired gaze stability. In addition, there may be decreased sensory feedback from the peripheral vestibular organs due to hypofunction of the otolith organs and semi-circular canals. Hence, the high risk of postural instability and falls may be further increased because of vestibular dysfunction. The prevalence of BPPV also may be increased in people with diabetes. This information may be important to physical therapists that treat people with diabetes.

1.7 Clinical Implications for Examination and Treatment of People with Diabetes

Physical activity and exercise are essential components for managing diabetes and preventing complications,[52, 53] and clinical guidelines have been published to provide recommendations for starting and advancing an exercise program for people with type 2 diabetes.[54] However, the vestibular system is not included in these guidelines because vestibular dysfunction is not yet a widely recognized complication of diabetes. Here we present recommendations for physical therapy examinations and interventions that include an awareness of the possible role of vestibular dysfunction in people with type 2 diabetes.

1.7.1. Recommendations for Examination

For a clear understanding of the impact of diabetes on the vestibular system, a comprehensive examination of the vestibular system is necessary. The use of appropriate outcome measures can help identify deficits, provide direction for treatment, and improve outcomes for patients. Function and participation in daily activities can be assessed using standardized questionnaires.

The Dizziness Handicap Inventory is a measure of self-reported activity limitation and participation restriction due to either dizziness or unsteadiness.[55] It is a 25-item questionnaire with three subscales: functional, emotional and physical. The maximum score is 100 points (32 for the functional dimension, 40 points for the emotional dimension, and 28 points for the physical dimension). Higher scores indicate greater levels of self-perceived disability. People with scores of more than 60 points on the Dizziness Handicap Inventory have impaired functional mobility and a higher risk of falls.[56]

The Activities-specific Balance Confidence Scale is a 16-item measure of self-efficacy on a 10-point ordinal scale; people rate their confidence in maintaining their balance during various activities of daily living. Scores range from 0-100 points, where zero indicates no confidence. Scores of more than 80 points indicate high functioning, observed in physically active older adults;[57] scores of less than or equal to 67 points indicate an increased risk of falls.[58] The Activities-specific Balance Confidence Scale may be a useful tool for assessing people's level of confidence as a treatment plan is developed. Symptom severity can be assessed with a visual analog scale and the Vertigo Symptoms Scale, both of which can be used to monitor people's progress during the course of treatment.[59]

Because damage to the vestibular system is associated with increased postural sway and balance impairment,[60, 61] it is necessary to examine static balance as well as balance during dynamic activities. The Modified Clinical Test of Sensory Integration of Balance is a useful test that can be performed easily in the clinic setting to challenge the vestibular system while altering proprioceptive and visual feedback.[62] The Sharpened Romberg Test is particularly valuable in the clinic setting because people with type 2 diabetes have been shown to have higher medial-lateral sway.[23] In addition, we can assess the risk of falls with reliable tests that are validated in

individuals with DPN. Using modified cutoff scores of greater than or equal to 10.7 seconds on the Timed "Up & Go" Test, scores of less than or equal to 22 on the Dynamic Gait Index, and scores of less than or equal to 52 on the Berg Balance Scale, fallers may be accurately identified. Based on these cut-off scores, Jernigan et al identified the Timed "Up & GO" Test as most accurate to predict fallers; the Dynamic Gait Index and Berg Balance Scale were less accurate.[63] Even though the Functional Gait Assessment is not specifically validated in people with diabetes, it may be useful for identifying the risk of falls. People with vestibular dysfunction and scores less than or equal to 22 on the Functional Gait Assessment have been shown to report recurrent falls.[64]

Oculomotor and gaze-holding deficits are seen in people with diabetes; hence, assessment of the vestibular system should include gaze stability testing. The Dynamic Visual Acuity test provides information to clinicians regarding the degradation of visual acuity with rapid head movements. The patient reads a wall eye chart with the head stationary, followed by head oscillations at 2 Hz. A loss of the ability to read 3 or 4 lines on the chart suggests decreased gaze stability.[65] Making a diagnosis of BPPV in older adults with dizziness, multiple comorbidities, and coexisting cardiovascular disease is difficult, resulting in delayed interventions.[66] Hence, performing the Dix-Hallpike test to assess anterior and posterior canal BPPV, and the Roll test to assess the horizontal canal in patients complaining of dizziness or vertigo may help identify the presence of BPPV.[67] It is necessary to examine patients for diabetic complications such as peripheral neuropathy and lower extremity pain. The Michigan Neuropathy Screening Instrument can be easily completed in the clinic setting; scores of greater than or equal to two on the physical examination section indicate the presence of neuropathy.[68, 69] Pain due to neuropathy

can be assessed using the Brief Pain Inventory for DPN, a scale validated for people with DPN; it assesses pain severity as well as how the pain may affect various aspects of daily life.[70]

1.7.2. Suggestions for Interventions

Gaze stability exercises are effective in reducing the risk of falls in adults with vestibular dysfunction.[71] However, the role of gaze stability exercises in people with type 2 diabetes has not been explored. In people with diabetes, deficits in the VOR and the optokinetic reflex may make maintaining a stable gaze during dynamic activities difficult;[41] hence, we recommend the use of gaze stability exercises for maintaining a stable gaze and reducing the risk of falls in this population. Recommended gaze stability exercises include X1 viewing, X2 viewing, or both.[65]

Although studies have shown that BPPV may be more prevalent as well as recurrent in adults with diabetes,[43, 50] no studies have examined the response to repositioning maneuvers in patients with type 2 diabetes and concurrent BPPV. In patients with BPPV, providing appropriate repositioning maneuvers is essential for reducing patient complaints of vertigo and disequilibrium.[51, 72]

The roles of aerobic exercise, resistance exercise, and a combination of these exercises are well established; these exercises have been shown to improve glycemic control, overall physical function, balance, and gait speed in people will diabetes.[32, 53, 73-75] Balance training has been shown to improve postural control and clinical measures of balance; however, the intensity and duration of balance training as well as presence of diabetic complications may affect outcomes. Kruse et al[76] found no improvement in balance after a 12-month training program that included balance exercises; however, Allet et al[77] reported significant improvement in balance with similar exercises. The two studies differed in the frequency and mode of delivery of the

training program as well as the severity of neuropathy. For patients with diagnosed DPN, Kruse et al[76] prescribed balance training with a physical therapist once a week for 11 weeks. After this initial training period, subjects received regular phone calls encouraging them to continue the exercise program.[76] Allet et al[77] prescribed training 2 times per week for 12 weeks, for 60 minutes per session, in a physical therapy clinic; however, their patients had minimal neuropathy. Table 2 summarizes a few studies that used balance-training programs to improve balance and function in people with type 2 diabetes.

Beside weakness and imbalance, many factors contribute to falls in people with type 2 diabetes; these include glycemic control, fatigue, executive function, inappropriate footwear, polypharmacy, proprioceptive loss, and retinopathy.[32, 78-80] The American Diabetes Association clinical practice guidelines provide a comprehensive understanding of these risk factors and their management.[54]

Because of somatosensory and visual disturbances, adults with diabetes are limited in their ability to reweigh sensory information. Evaluation for an assistive device may be necessary, particularly in people who are not confident with walking outdoors or are limited in participation due to dizziness. The added stability of an assistive device may encourage older adults with diabetes to participate in a walking program.

Table 2: Table 2: Summary of balance training interventions in people with type 2 diabetes

Study	N	Type of exercise	Duration	Frequency	Outcome measures for Balance and Falls	Results
Richardson et al[81]	20(10 in IG, 10 CG)	For IG: strength and balance exercises to improve ankle function; for CG: Seated exercises	3 weeks	Daily	SLS, FRT, tandem stance time, ABC Scale	For IG: significant improvements in SLS, and tandem stance and FRT scores; for CG: no change in all measures
Kruse et al[76]	79 (41in IG, 38 in CG)	For IG: strengthening, balance, and walking program in Part1 and motivational phone calls in part 2; for CG: 8 sessions, diabetes care instruction, no exercises	Part 1: 1-3 mo; Part 2: 4-12 mo; total: 12 mo	8 individual sessions, 3 home visits	Ankle dorsiflexor strength, BBS, TUG, SLS, FES	No difference between groups in any measures
Allet et al[77]	71(35 in IG, 36 in CG)	For IG: gait, balance, and function oriented strengthening; for CG: no treatment, no advice	2x/ week	12 weeks	Walking speed, POMA, dynamic balance walking on a beam, static balance on the Biodex, FES-I	For IG: gait velocity increased 11.6%, dynamic balance improved by 34%, static balance improved by 31%, higher POMA and FES-I scores.
Morrison et al[82]	16	Balance and resistance training	3x/week	6 weeks	Fall history, fall risk assessment (PPA)	For IG: significant decrease in fall risk with improvements in proprioception and quadriceps and hamstring strength
Ahn and Song[83]	59 (30 in IG, 29 in CG)	Tai Chi	1 hour per session, 2x/week	12 weeks	SLS with eyes closed, SF-36	For IG: significant improvement in SLS and SF-36

						scores
Salsabili et al[84]	19	Biodex[b] stability system for training	10 sessions, 30 min each	3 weeks	OSI, APSI, MLSI on the Biodex	For IG: decreased OSI, APSI, MLSI scores with training
Song et al[85]	38 (19 in IG, 19 in CG)	Eyes open and eyes closed, on foam and on a trampoline	1 hour, 2x/week	8 weeks	SLS with eyes open and eyes closed, BBS, FRT, TUG, 10-min walk, postural sway	For IG: significant increase in BBS, FRT, and 10-min walk scores; improvements in SLS time; decrease in postural sway
Morrison et al[86]	37 (21 in no T2D, 16 in T2D)	Balance and strength training	3x/week	6 weeks	PPA, force plate test in mCTSIB conditions	Significant decrease in fall risk in both groups; decreased AP-ML coupling; higher range; decreased COP sway velocity
Mueller et al[87]	29 (15 in WB, 15 in NWB)	For WB group: balance, strength and progressive walking; for NWB group: strength, and progressive stationary bike	1 hour, 3x/week	12 weeks	6-minute walk distance, daily step counts	For WB group: improvement in 6 min walk distance and average daily steps

IG: intervention group, CG: control group, FRT: Functional Reach Test, ABC: Activities Specific Balance Confidence Scale, BBS: Berg Balance Scale, FES: Falls Efficacy Scale, POMA: Performance-Oriented mobility assessment, PPA: Physiological profile assessment, SLS: Single leg stance, EO: eyes open, EC: eyes closed, OSI: overall stability index, APSI: Anterior-posterior stability index, MLSI: Medio-lateral stability index, WB: weight bearing, NWB: non- weight bearing.

1.8 Conclusion

The relationship between diabetes, vestibular function and the risk of falls is complex. People with diabetes have many deficits, including neuropathy, retinopathy, and polypharmacy, all of which compromise their activity and daily functional status. Vestibular dysfunction is another possible complication of diabetes and may increase the risk of falls. Understanding this

relationship, identifying and treating BPPV, and working toward integrating all systems-- visual, vestibular and somatosensory-- to improve balance may be ways in which physical therapists can prevent falls.

Chapter 2 Preface

Chapter 1 provides an overview of what is currently known about the effect of type 2 diabetes on the vestibular system in general. It also gives insight into the potential impact diabetes may have on quality of life, balance and mobility. However, vestibular dysfunction is a very broad term, encompassing many vestibular disorders. In order to develop specific aims for the project, we designed a retrospective study to identify whether there was a difference in prevalence between different vestibular conditions in people with diabetes. One vestibular condition, benign paroxysmal positional vertigo (BPPV), has been reported in higher frequency in people with diabetes; however, the relationship between diabetes and BPPV, in the presence of known contributors like age, gender and hypertension, is not clear.

Results of our study confirmed that BPPV was present in higher frequency in people with type 2 diabetes, compared to the other conditions. As we examined the different predictors of BPPV, we found hypertension to be a significant predictor that mediated the relationship between diabetes and BPPV. Based on the results of this study, we developed the aims for this dissertation project and focused on BPPV as our clinical condition of interest.

Chapter 2

Retrospective Data suggests that the Higher Prevalence of Benign Paroxysmal Positional Vertigo in Individuals with Type 2 Diabetes is mediated by Hypertension

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2.1 Abstract

Objective: Benign Paroxysmal Positional Vertigo (BPPV) has been linked to comorbidities like diabetes and hypertension. However, the relationship between type 2 diabetes (DM) and BPPV is unclear. The purpose of this retrospective study was to examine the relationship between DM and BPPV in the presence of known contributors like age, gender and hypertension.

Methods: A retrospective review of the records of 3933 individuals was categorized by the specific vestibular diagnosis and for the presence of type 2 DM and hypertension. As the prevalence of BPPV was higher in people with type 2 DM compared to those without DM, multivariable logistic regressions were used to identify variables predictive of BPPV. The relationship between type 2 DM, hypertension and BPPV was analyzed using mediation analysis.

Results: BPPV was seen in 46% of individuals with type 2 DM, compared to 37% of individuals without DM ($p<0.001$). Forty two percent of the association between type 2 DM and BPPV was mediated by hypertension, and supported hypertension as a complete mediator in the relationship between type 2 DM and BPPV.

Conclusions: Hypertension may provide the mediating pathway by which diabetes affects the vestibular system. Individuals with complaints of dizziness, with comorbidities including hypertension and diabetes, may benefit from a screening for BPPV.

2.2 Introduction

Benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder, affecting about 1.6% of the adult population per year.[88] The main symptom of BPPV is vertigo which is position dependent and transient.[67] Patients typically develop vertigo when looking overhead, getting in or out of bed, and bending. When symptomatic, 86% of individuals with BPPV have been shown to restrict daily activities, while 18% avoided leaving their homes.[88] Fortunately, BPPV is easily treated with appropriate repositioning maneuvers, which are very effective.[51, 89, 90]

Known factors associated with a higher prevalence of BPPV include age, female sex, history of head trauma, other inner ear disease including Meniere's disease and vestibular neuritis, osteoporosis, and migraines.[88, 91-94] Vasospasm of the labyrinthine arteries may cause detachment of otoconia from the macula, seen in conditions like migraine.[95] BPPV is associated with hypertension and hyperlipidemia, due to possible vascular damage to the inner ear, and is a known sequel of labyrinthine ischemia that precipitates detachment of the otoconia.[42, 88] The relationship between diabetes (DM) and BPPV is not well understood. However, in people with type 2 DM, the risk of diabetic complications have been shown to increase significantly when systolic blood pressure is high.[96] The prevalence of hypertension is 40-60% higher in people with type 2 DM between 45-70 years of age, compared to the nondiabetic population.[97] Cohen et al[43] reported DM as being unusually prevalent in patients with BPPV, and comorbidities like hypertension and diabetes, have been shown to significantly increase the recurrence rate of BPPV,[45] however Warninghoff et al[98] did not detect an increased prevalence of DM or hypertension in individuals with vertigo. By the year 2030, the prevalence of DM globally is estimated to rise to 366 million people [99], with type 2 DM accounting for 95% of all cases of DM

diagnosed in adults.[100] It is necessary to understand the relationship between BPPV, hypertension and type 2 DM because making a diagnosis of BPPV in older adults, with multiple comorbidities is difficult.[101] In fact, the prevalence of unrecognized BPPV in elderly people with multiple chronic diseases is as high as 9%,[66] which could potentially delay treatment maneuvers.

This study was a retrospective, observational study that investigated the interaction between type 2 DM and vestibular disorders as they naturally occur within individuals managing chronic disease through their adult lifespan. Because animal research has shown morphological changes in the saccule of diabetic rats, [35] and clinical research has shown a higher prevalence of BPPV in type 1 and type 2 DM,[43, 49] our hypothesis was that in people with type 2 DM, the prevalence of BPPV may be higher. We examined the role of known contributing factors such as age, gender, and hypertension; as well as the potential mediating relationship between type 2 DM, hypertension, and BPPV.

2.3 Materials and Methods

Following Institutional Review Board approval from the University of Kansas Medical Center (KUMC), data was collected using the Healthcare Enterprise Repository for Ontological Narration (HERON), which is a medical records system. HERON is built upon the i2b2 integrated clinical data repository software.[102] This database integrates data from electronic medical records, as well as the billing system to provide de-identified medical data pieces, preserving patient privacy.[103] Using a query search in Heron, data for this study was extracted from the University of Kansas Hospital inpatient and emergency room records as well as from area outpatient clinics affiliated with KUMC, that use the electronic medical record system.

Data was obtained on individuals 18 years and older. Our population of interest was patients with a vestibular diagnosis for their complaints of dizziness (ICD9 code 386.1- 386.5) between October 2006 and December 2012. We collected data on age at the time of the vestibular diagnosis, sex, race, smoking history, and specific vestibular diagnosis. The presence or absence of type 2 diabetes and hypertension were collected within the data query, making sure to identify the date of first diagnosis of diabetes and hypertension. This was used to determine if diabetes and hypertension were present before or after the vestibular diagnosis, thus helping us classify the cases as having type 2 diabetes and hypertension or not. Our query included a population inclusive of a range of vestibular diseases with and without diabetes. We excluded individuals with type 1 DM from the analysis.

2.4 Statistical Analysis

Chi-square tests were used to compare the frequency of specific vestibular diagnoses in people with and without type 2 DM. Descriptive statistics describe the presence of comorbidities in individuals with BPPV.

Univariate logistic regression was used to identify the variables with significant relationship to BPPV. Variables with significant relationship to BPPV were included in a multivariable logistic regression analysis. Factors included in the model were age, sex, race, presence of hypertension and diabetes, which were entered in a backward stepwise regression model.

We tested the mediating effect of hypertension on the relationship between type 2 DM and BPPV using multiple regression analyses. According to Baron and Kenney,[104] mediation is demonstrated when the following relationships are observed: 1) the main independent variable

(type 2 DM) is significantly associated with the main dependent variable (BPPV), 2) the independent variable (type 2 DM) is significantly associated with the mediator variable (hypertension), 3) the mediator variable (hypertension) is significantly associated with the dependent variable (BPPV) when the independent variable (type 2 DM) is controlled. All analyses were conducted at the 0.05 level of significance a priori, using SPSS 20.0 for Windows (Chicago, IL).

2.5 Results

The HERON search results identified 3933 electronic medical records, of which, 12 individuals had type 1 DM and were excluded from the analysis. There were nine vertiginous conditions frequently diagnosed, BPPV was the most common among people with and without type 2 DM (n=1518). BPPV was present in 46% of the sample who had concurrent DM (n=322), and in 37% of individuals who did not have concurrent DM (n=1196), this proportion was significantly higher than expected ($p< 0.001$) (Table 1).

Table 1: Frequency of vertiginous diagnoses in people with and without type 2 DM

	With Type 2 DM (n= 699)	**Without Type 2 DM (n= 3222)**	**p**
BPPV	46.1%	37.1%	p<0.001*
Peripheral vertigo unspecified	12.7%	16.7%	p=0.01*
Meniere's disease	28.3%	35.4%	p< 0.001*
Other disorders of labyrinth	1.8%	4.7%	p<0.001*
Labyrinthine fistula	0.4%	0.5%	p= 0.82
Labyrinthine dysfunction	3.4%	2.3%	p=0.07

Vestibular neuronitis	4.0%	3.7%	p=0.69
Central vertigo	7.7%	8.7%	p=0.39
Labyrinthitis	10.7%	8.9%	p=0.29

Chi-square tests were used to examine differences in frequency between groups. * Significant difference between groups is based on $p<0.05$ DM=diabetes

2.5.1 Descriptive Statistics of Individuals with BPPV:

The mean age of people with BPPV was 59 ± 15.8 years, while those with BPPV and type 2 DM was 66 ± 12.8 years. The female to male proportion in both groups was 68% female and 32% male. The frequency of hypertension and type 2 DM in people with BPPV was stratified by age group (Table 2). Two percent of patients (n=79) had BPPV and coexisting Meniere's disease, 1% (n=45) had BPPV and a diagnosis of central vertigo, 0.6% (n=23) had BPPV and vestibular neuronitis, while 0.9% (n=36) had BPPV and a diagnosis of labyrinthitis.

Table 2: Presence of hypertension and type 2 diabetes in people with BPPV (n=1518)

People with BPPV	Hypertension: yes	Hypertension: no
Between 18- 40 years		
Diabetes: yes (n=10)	50% (n=5)	50% (n=5)
Diabetes: no (n=161)	11.2% (n=18)	88.8% (n=143)
Between 41- 65 years		
Diabetes: yes (n=131)	80.2% (n=105)	19.8% (n=26)
Diabetes: no (n=611)	30.6% (n=187)	69.4% (n=424)
People > 65 years		
Diabetes: yes (n= 181)	90.1% (n=163)	9.9% (n=18)
Diabetes: no (n= 424)	56.6% (n= 240)	43.4% (n= 184)

BPPV=benign paroxysmal positional vertigo

2.5.2 Analysis of Variables with Logistic Regression:

Variables with a significant relationship to BPPV included age (independent sample t-test, $p<0.001$), sex (chi square test, $p=0.008$), race (chi square test, $p< 0.001$), diabetes (chi square test, $p<0.001$) and hypertension (chi square test, $p<0.001$). Using a backward stepwise regression model, we found that age, sex, race and hypertension were the significant variables predictive of BPPV (Table 3).

Table 3: Logistic linear regression model showing the variables predictive of and odds of developing benign paroxysmal positional vertigo

Factors	B	Odds Ratio (95% CI)	p-value
Age (by decade)	0.01	1.10(1.06-1.15)	0.01
Gender (female- reference) n= 2603	0.18	1.19(1.04-1.38)	0.01
Race (White-reference) n= 2977			
Race (African American) n= 396	0.24	1.3 (1.05-1.63)	0.02
Race (Hispanic) n= 13	-0.01	0.98 (0.32-3.06)	0.98
Race (Asian) n= 50	0.94	2.56 (1.44-4.54)	0.001
Race (other/ unknown) n= 485	0.24	1.27 (1.04- 1.55)	0.02
Hypertension (no) n= 2418	-0.55	0.58 (0.49-0.66)	0.00

95% CI= 95% confidence interval, significant p-value is <0.05

The prevalence of BPPV was higher with increasing age and female gender. African-American were 1.3 times more likely to present with BPPV, while Asians were 2.6 times more likely to present with BPPV, compared to their Caucasian counterparts. In people with hypertension, the frequency of BPPV was 1.7 times higher; diabetes did not influence the presence of BPPV in the multivariate analysis.

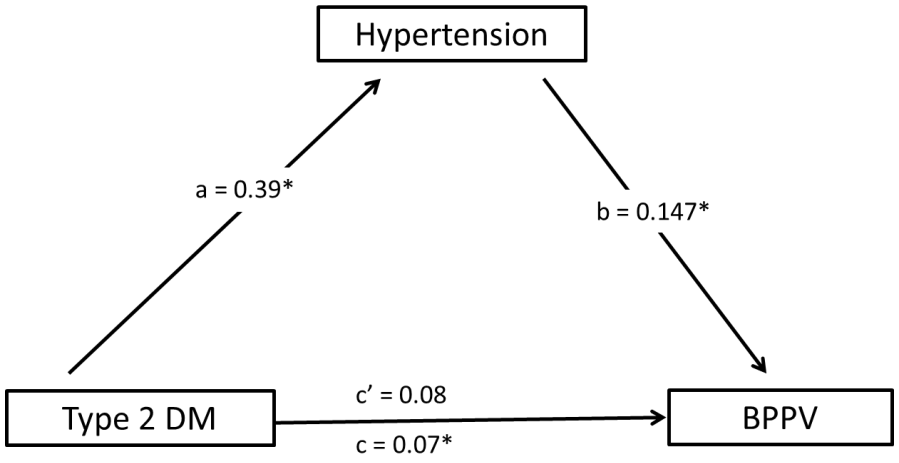

Figure 1: Hypertension is the mediator of the association between type 2 diabetes and benign paroxysmal positional vertigo. a= coefficient relating type 2 DM to hypertension, b=coefficient relating hypertension to BPPV, c= coefficient relating type 2 DM to BPPV, c'= coefficient relating type 2 DM to BPPV while adjusting for hypertension.

Figure 1 illustrates the mediation effect and shows that hypertension mediated the association between type 2 DM and BPPV. The effect can be expressed as (0.39 x 0.15)/ [(0.39 x 0.15) + 0.08] = 42.2%. In the presence of hypertension, the association between type 2 DM and BPPV is no longer significant, showing that hypertension is a complete mediator in the relationship between type 2 DM and BPPV. Hypertension was present in 86.8% of individuals with type 2 DM, compared to 37.2% with BPPV without type 2 DM. This relationship between type 2 DM and hypertension was present in all age groups.

2.6 Discussion

Results of this study show that hypertension was a strong predictor of BPPV and completely mediated the effect of diabetes on BPPV. The close association between type 2 DM and hypertension is well known and they are often referred to as "the bad companions." [105] The

overall prevalence of hypertension in people with DM is as high as 71%, of which only 12% have their hypertension controlled (<130/85 mm of Hg).[106] Microvascular and macrovascular complications are significantly higher in people with type 2 DM and hypertension.[107] Some mechanisms by which hyperglycemia increases vascular resistance is by inhibiting nitric-oxide related vasodilation, by disrupting nitric oxide signaling as well as by forming reactive oxygen species (ROS). Formation of advanced glycation end products through the polyol pathway increases formation of ROS, [108] which further depletes nitric oxide. In addition, activation of the protein kinase pathway leads to cell proliferation, leading to increased stiffness of arterial walls.[109] These mechanisms are responsible for vasoconstriction of small arterioles leading to tissue ischemia. The vascular effects of hypertension and diabetes may be possible mechanisms leading to tissue hypoxia and cochleovestibular degeneration.[110, 111] Results of our study are in agreement with other studies of hypertension in vestibular dysfunction.[42, 88] Chavez-Delgado et al[42] report that hypertension, type 2 DM and dyslipidemia resulted in the highest percentage of cochlear and vestibular dysfunction, with hypertension present in 74% of their study population (n=385). Besides microvascular damage, macrovascular damage is seen in people with diabetes and hypertension. Arteriosclerotic changes were seen in the carotid arteries of 71% of people with BPPV compared to 43% of people with other vestibular disorders,[112] while stenosis or occlusion of the vertebrobasilar artery was seen in 21% of people with BPPV, compared to 6.8% of people without BPPV.[113] Elderly people (mean age 57.36±15.44 years) with BPPV and comorbidities like hypertension and diabetes have a higher risk of ischemic stroke (4.5% compared to 2.9% without BPPV).[114]

The effect of diabetes on the peripheral vestibular organs has been examined in animal models. Morphological changes were noted in the utricle and saccule of rats with experimentally

induced diabetes[11, 35] with type 1 hair cell degeneration seen, particularly in the saccule. These changes were considered signs of metabolic stress due to hyperglycemia,[35] however the impact of diabetes on the dislodgement of otoconia has not been reported. However, in a histopathological study examining the temporal bones of patients with type 1 diabetes, Yoda et al. noted a higher prevalence of otoconia deposits in the semicircular canals as well as adhered to the cupula, compared to age matched controls.[49]

We examined other known factors associated with a higher prevalence of BPPV like age, gender and race. Aging has been shown to cause changes in the protein and gelatinous matrix of the otolith membrane, as well as weakening of the linking filaments among otoconia with fragmentation of the otoconia.[115] This results in displacement of the otoconia into the semicircular canals. Our study showed that the presence of BPPV increased by 10% for every advancing decade of life. Twice as many females were diagnosed with BPPV as compared to males. This is aligned with current literature showing that there is a marked female preponderance in BPPV;[88] this female preponderance may be linked, among other factors, to migraines or hormonal factors.[92-94] Estrogen deficiency is known to disturb the internal structure of the otoconia and their interconnection, and attachment to the matrix.[94, 116] Regarding race, we found that African-Americans were more likely to have BPPV compared to Caucasians. This finding could be because the age adjusted prevalence of diagnosed diabetes is higher in African-American individuals compared to Caucasians, and is highest in general, in African-American women.[117] Of interest, our study showed that BPPV was present in higher frequency in the Asian community. Previous research has shown a higher prevalence of DM and its complications in the Asian population.[118] In our study, the mean age in the Asian population was younger (56 ± 14

years) than the mean for the overall population, more commonly female (72%) and comorbidities included hypertension and diabetes 37.9% and 20.7% of the time respectively.

Another result of this study was that unspecified peripheral vertigo and other disorders of the labyrinth, conditions whose etiology is unclear, was seen more commonly in people without type 2 DM. It is possible that in people with comorbidities like diabetes and hypertension, referrals to specialists are higher, which may not be the case for people without DM. Referrals to specialists in tertiary care centers usually result in revised and specific diagnoses.[119] Thirty-four percent of our cases had a diagnosis of Meniere's disease. This may be because KUMC is a tertiary care center with specialists in the field of neuro-otology, resulting in a higher referral rate to this center. These are interesting observations that require further investigation.

Results of our study suggest a multifactorial and interrelated risk that may influence the presence of BPPV in people with DM. Being aware of the relationship between BPPV, type 2 DM and hypertension may benefit clinicians. Since hypertension, diabetes and BPPV can independently cause dizziness, it is important for the clinician to examine all potential causes of dizziness carefully. Asking specific questions, to determine if BPPV could be a source of the dizziness, may help with early diagnosis and treatment.[120]

Limitations

One limitation of this study is the retrospective nature of data collection. Every effort was made to exclude type 1 DM and ensure that the diagnosis of diabetes and hypertension predated the vestibular diagnosis. We found that the prevalence of BPPV was 9% higher in those with type 2 DM compared to those without DM. Although this difference was statistically significant, we cannot establish if this is a clinically meaningful difference. This was an observational study

hence the cause/ effect relationship between diabetes and BPPV cannot be established. In this study, indicators of DM severity (e.g. HbA1c levels, fasting glucose) were not consistently available. Future studies examining relationships between DM, glycemic control, and severity of vertiginous symptoms will assist clinicians in the management of these patients.

2.7 Conclusion

In summary, this study shows that hypertension is the mediating factor contributing to the increased prevalence of BPPV in individuals with type 2 DM. Hypertension may cause vascular damage to the macula of the utricle and saccule, resulting in dislodgement of the otoliths. Improved understanding about the role of hypertension and DM as risk factors for the presence of BPPV can help generate new pathophysiological hypotheses that may ultimately help to improve patient care.

Specific Aims

As illustrated in the first two chapters, diabetes affects the vestibular system and the prevalence of benign paroxysmal positional vertigo is higher is people with diabetes. BPPV results when otoconia fragments dislodge from the saccule and utricle, and fall into the semicircular canals, causing movement of the endolymph, after head movements have ceased. Both disease processes independently increase postural sway and risk of falls, while limiting mobility and daily function. The prevalence of BPPV increases with age, hence as the population ages the coexistence of both disease processes will increase. Fortunately, because of effective repositioning maneuvers, BPPV is very successfully treated. The effect of diabetes on the saccule and utricle, in people with BPPV, is not known. The severity of symptoms as well as mobility and balance deficits due to the presence of both disease processes needs further examination. The prognosis of patients with BPPV and diabetes treated with repositioning maneuvers is not clear and the recovery of function after treatment is not clear. *The main objective of this body of work was to examine differences in symptom severity, functional mobility and balance in people with BPPV and diabetes compared to people with BPPV only. We examined the efficacy of treatment and change in function after repositioning treatment maneuvers in both groups.* The specific aims proposed for this study are as follows:

<u>Specific Aim 1: To determine if there are differences in symptom severity, mobility and balance in people with posterior canal BPPV and diabetes compared to people with BPPV only.</u>

People with diabetes suffer from diabetic complications like neuropathy and retinopathy, which impair balance and mobility. In addition, there may be a possible direct effect of diabetes on the otolith organs of the inner ear. *We hypothesized that people with both BPPV and diabetes would*

have higher deficits on the Dizziness Handicap Inventory, which is a self-report measure relating to daily activities (Hypothesis 1). T*hey would have greater impairment in functional mobility measured by the Functional Gait Assessment (Hypothesis 2), and they would have increased postural sway in conditions that challenge the vestibular system (Hypothesis 3), when compared to people with BPPV only.*

Specific Aim 2: To examine the effect of type 2 diabetes on the otolith organs, namely the saccule and the utricle of the inner ear.

Vestibular evoked myogenic potential tests have shown that BPPV and diabetes independently affect the responses of the saccule and utricle. The combined effect of BPPV and diabetes on the saccule and utricle is not clear. *We hypothesized that the latency, amplitude, and threshold of the cVEMP will be affected reflecting impairment in saccule function (Hypothesis 4), and the latency and amplitude of the oVEMP will be affected showing impairment in utricle function (Hypothesis 5) in people with BPPV and diabetes compared to people with BPPV only, T2D only and controls.*

Specific Aim 3: Identify differences in efficacy of treatment and recovery of function after resolution of vertigo in people with BPPV and diabetes compared to people with BPPV only.

T2D has been shown to increase the prevalence and recurrence of BPPV. Degenerative changes in the otolith organs are seen in people with diabetes. Hence, people with BPPV and diabetes may require repeat treatments for symptom resolution. *We hypothesized that more canalith repositioning maneuvers would be required for resolution of vertigo in people with BPPV and diabetes (Hypothesis 6). We hypothesized that after complete resolution of vertigo; daily function (Hypothesis 7), mobility (Hypothesis 8) and postural sway (Hypothesis 9) would not*

improve to the same extent in people with BPPV and diabetes compared to people with BPPV only.

Based on the results of the specific aims above, we have three experimental papers. Chapter 3 describes the effect of diabetes on the otolith organs and the results of the vestibular evoked potential studies (Aim 2; hypothesis 4 and 5). In Chapter 4, we included data from hypothesis 3 of Aim 1, where we examined postural sway in people with BPPV and those with BPPV+DM. The scope of the study was expanded to include controls and people with T2D (from Aim 2), so that we could compare postural sway among controls, people with T2D, people with BPPV and those with BPPV+DM. In Chapter 5, we provide the combined results of Aim1 (hypothesis 1, 2, 3) and Aim 3 (hypothesis 6, 7, 8 and 9), so that we could succinctly show differences in symptom severity, mobility and balance, between people with BPPV and BPPV+DM at baseline and after treatment.

Chapter 3 Preface

Benign paroxysmal positional vertigo is a vestibular condition resulting from degeneration of the otolith organs. Diabetes has been shown to cause degeneration of the saccule and utricle. However, the combined effect of BPPV and diabetes on the saccule and utricle is not clear. In Chapter 3, which is our first experimental chapter related to Aim 2 of the study, we examined the otolith organs, using vestibular evoked myogenic potential (VEMP) tests. In this study, we analyzed and compared otolith function in people with BPPV and diabetes (BPPV+DM), to those with BPPV only, diabetes only, and controls. Our hypothesis was that people with BPPV+DM would have a higher frequency of abnormal responses, longer latency and smaller amplitude of cVEMP and oVEMP responses compared to all other groups. We examined the relationships between VEMP variables and diabetes-related variables.

Results of this study showed that people with type 2 diabetes, BPPV and BPPV+DM had a higher frequency of abnormal saccule responses compared to controls. Higher HbA1c levels were associated with prolonged saccule latency. We did not see a higher frequency of abnormal responses on the oVEMP across all four groups. Although, BPPV and T2D independently affected utricle and saccule function, they did not appear to have a distinct cumulative effect. Results of this study and the clinical implications comprise Chapter 3.

Chapter 3

Both Diabetes and Benign Paroxysmal Positional Vertigo Cause Otolith Dysfunction

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3.1 Abstract

Objective: Vestibular dysfunction is a newly recognized complication of type 2 diabetes (T2D) that is known to increase fall risk. The prevalence of benign paroxysmal positional vertigo (BPPV) is higher in people with T2D. The impact of T2D on the otolith organs of the vestibular system in people with BPPV is unknown. The purpose of this study was to analyze otolith function using vestibular evoked myogenic potential (VEMP) tests in people with T2D and concurrent BPPV (BPPV+DM), and to examine the relationships between VEMP variables and diabetes-related variables.

Study Design: Prospective, cross-sectional study.

Setting: Tertiary academic medical center

Subjects and Methods: Participants 40-65 years, were recruited in four groups: controls (n=20), people with T2D (n=19), BPPV (n=18), and BPPV+DM (n=14). Saccule and utricle function were examined using cervical VEMP (cVEMP) and ocular VEMP (oVEMP), respectively. Diabetes related variables such as HbA1c, duration of diabetes and presence of diabetic peripheral neuropathy were collected.

Results: The frequency of abnormal cVEMP responses were higher in the T2D ($p=0.005$), BPPV ($p=0.003$), and BPPV+DM ($p<0.001$) groups compared to controls. In the participants with diabetes, higher HbA1c levels were correlated with prolonged P1 ($p=0.03$) and N1 latencies ($p=0.03$). The frequency of abnormal oVEMP responses was not different between groups ($p=0.2$).

Conclusion: Although, BPPV and T2D may independently affect utricle and saccule function, they do not appear to have a distinct cumulative effect. Examining the extent of otolith dysfunction may increase our understanding of factors contributing to fall risk in adults with diabetes.

3.2 Introduction

Presently, type 2 diabetes affects 9.3% of the United States population[1] and is predicted to affect 1 in 3 people by the year 2050.[2] Diabetic complications such as peripheral neuropathy and retinopathy contribute significantly to balance deficits, increasing fall risk.[26, 121] Emerging evidence has shown that vestibular dysfunction may be considered another possible complication of diabetes.[7, 8, 122] In people with diabetes and vestibular dysfunction, the risk of falls increases more than two times, even after adjusting for peripheral neuropathy and retinopathy.[8] Fall prevention is a major clinical focus for people with diabetes, hence examining the effect of diabetes on the vestibular system merits attention.

Within the peripheral vestibular system, animal studies have shown that diabetes affects the saccule, causing morphological changes, such as type 1 hair cell loss.[10, 35] In addition, clinical research has shown that in people with type 2 diabetes (T2D), utricle and saccule function is significantly impaired compared to age matched, healthy controls.[123, 124] Microangiopathy and arteriosclerosis due to hyperglycemia and hypertension are known to cause degeneration of the macula of the utricle and saccule.[125, 126] Degeneration of the maculae of the utricle and saccule can cause otoconia fragments to dislodge, which is the cause of one common peripheral vestibular condition, benign paroxysmal positional vertigo (BPPV).[67, 127] Recent studies have shown that BPPV is present in higher frequency in people with both type 1 and type 2 diabetes compared to healthy controls.[43, 49]

Vestibular evoked myogenic potentials (VEMP) are objective, clinically reproducible, and reliable electrophysiological tests that measure otolith function.[128] The cervical VEMP (cVEMP) is a short latency muscle response to acoustically evoked saccular stimulation,[129, 130]

while the ocular VEMP (oVEMP) arises from acoustic stimulation of the utricle and the superior branch of the vestibular nerve.[131, 132] VEMP studies have been used to identify abnormal responses in people with BPPV, where a significantly higher frequency of abnormal cVEMP responses,[133-136] as well as oVEMP responses[137-139] are seen, compared to age matched controls. A few studies have also shown VEMP abnormalities in people with diabetes.[123, 124, 140, 141] To date, there have been no studies that have examined the effects of BPPV and type 2 diabetes (BPPV+DM) on the utricle and saccule.

The primary objective of this study was to analyze differences in otolith organ function in people with BPPV+DM compared to controls, people with diabetes only and people with BPPV only, using VEMP testing. Our hypothesis was that people with BPPV+DM would have a higher frequency of abnormal responses, longer latency, smaller amplitude, and higher threshold of cVEMP and oVEMP responses compared to all other groups. A secondary aim was to examine the association between otolith dysfunction and variables that indicate severity of diabetes such as glycemic control (HbA1c), duration of diabetes, and the presence of diabetic peripheral neuropathy.

This study examines the extent of damage to the otolith organs in people with BPPV+DM. Otolith organ dysfunction has been shown to increase postural instability;[61] hence, examination of the otolith organs may help with understanding fall risk factors in adults with diabetes.

3.3 Methods

3.3.1 Study Design:

This was a single center, prospective study with a sample of convenience, conducted at a University neuro-otology clinic. The research protocol was approved by the Human Subjects Committee at the University of Kansas Medical Center. All participants signed the institutionally approved written informed consent prior to participation in the study.

3.3.2 Participants:

Participants who were 40 to 65 years of age were recruited into four groups: healthy controls (n=20), people with type 2 diabetes without vestibular problems (T2D) (n=19), people with unilateral, posterior canal BPPV canalithiasis without type 2 diabetes (BPPV) (n=18), and those with unilateral posterior canal BPPV canalithiasis and type 2 diabetes (BPPV+DM) (n=14). Our recruitment strategies included physician referral, study advertisements, and two registry programs for research participants. Participants were excluded if they had (1) a history of neurological disease including stroke, multiple sclerosis, Parkinson's disease, intracranial tumor, (2) a history of Meniere's disease, had bilateral BPPV, anterior or horizontal canal BPPV, or cupulolithiasis, (3) received chemotherapy or ototoxic and/or neurotoxic medications, (4) traumatic head injury, or (5) conductive hearing loss. Participants with T2D did not have a prior medical diagnosis of a vestibular condition, while controls did not have a recorded medical history of a vestibular disorder or T2D.

A detailed medical history was collected and BMI, presence or absence of diabetes and hypertension, and medication list were confirmed through electronic health records, if available. Glycosylated hemoglobin (HbA1c) via a disposable finger stick testing kit (Metrika A1cNow^{+} Bayer, Tarrytown NY) was collected. In participants with T2D, additional history regarding duration of diabetes and history of diabetic peripheral neuropathy was collected. In addition, all

participants were screened for the presence of diabetic peripheral neuropathy (DPN) using the Michigan Neuropathy Screening Instrument (MNSI), and were classified as neuropathic if their physical exam score was ≥ 2.0.[69]

For participants with BPPV, inclusion was determined based on a diagnosis of unilateral posterior canal BPPV canalithiasis, made by a physician and confirmed by a physical therapist (LD). The diagnosis of BPPV was made using videonystagmography (Micromedical, Visual Eyes 2002), and was based on the presence of torsional, up-beating nystagmus in the Dix-Hallpike position, which had a brief latency, lasted less than 60 seconds and reversed with sitting, with associated complaints of vertigo.[67]

3.3.3 Procedures:

All participants were examined using air conducted cVEMP and oVEMP (Biologic Auditory Evoked Potentials Navigator Pro- Version 6.2.1), using self-adhesive, silver/ silver chloride ECG monitoring electrodes (Tracer rite Bio-Detek Inc.). We scrubbed the skin to maintain the impedance of the recording electrodes below five kOhms. Responses to 150 sweeps were averaged and two trials were performed to verify the reproducibility of the waveform. For consistency, one investigator (LD) performed all the VEMP tests and a second evaluator (CM) confirmed absent responses.

Cervical VEMP testing (cVEMP):

The cVEMP was performed with the participant seated in an upright position. During testing, participants turned their head away from the ear being tested, while they pushed their chin against a blood pressure cuff that had been inflated to 20 mm of Hg. They were required to push against the cuff, until the pressure reached 40 mm of Hg, while holding the dial so that they

could maintain the pressure, in order to monitor muscle contraction.[142, 143] The primary electrode was placed over the mid-point of the ipsilateral sternocleidomastoid muscle, the secondary on the upper forehead and ground electrode on the lower forehead. The acoustic stimulus (tone burst, 500 Hz, 95 dB HL, rate 4.3/sec, rise/fall: 2 ms, plateau: 0 ms), was delivered using insert earphones. The EMG signal was amplified (1000x), and band-pass filtered (10-1500 Hz). The first positive deflection was marked P1 and first negative deflection N1. Threshold was determined next by decreasing the sound volume, and noting the lowest level at which a reproducible waveform was recorded.

Ocular VEMP testing (oVEMP):

For the oVEMP test, participants were sitting upright; and they were instructed to maintain an upward gaze of approximately 30 degrees, on a pre-marked visual target. The primary electrode was placed below the lower lid margin of the contralateral eye; the secondary electrode above the eyebrow and the ground at the sternum. The acoustic stimulus (tone burst, 500 Hz, 125 dB SPL, rate 5.0/sec, rise/fall: 1 ms, plateau: 2 ms), was delivered using insert earphones. The EMG signal was amplified 5000x and band-pass filtered 1-1000 Hz. The first negative deflection was labeled as n10 and first positive deflection p16.

3.3.4 Data Processing:

Latencies of the VEMP components were defined as the time from stimulus onset to the peak of the waveform. The amplitude was defined as peak-to-peak distance of P1-N1 for cVEMP, and n10-p16 for oVEMP. The mean± 2 standard deviation for healthy controls was defined as a normal range of responses for the equipment and procedures used in this study.

Responses were defined as abnormal if latencies were greater than this normal range, or if responses were absent (i.e. if there was no recognizable or reproducible waveform).

Testing was completed on both ears for all participants. For participants with BPPV or BPPV+DM, the affected ear was defined as the ear that caused symptoms of vertigo and nystagmus with the Dix-Hallpike testing. For T2D and control groups, the right and left ears were both considered unaffected. After excluding absent VEMP responses, we examined differences in latency, amplitude, and threshold between right and left ears and affected/unaffected ears using ANOVA. As no differences in latency, amplitude, and threshold were found between the right and left ears in all groups as well as between the affected/ unaffected ears of participants with BPPV and BPPV+DM, data from each ear were treated as individual data points in the analysis.

3.4 Statistical Analysis

Descriptive statistics (mean, standard deviation, %) were used to examine participant demographics in each group. Group differences in participant demographics were tested using ANOVA for significant variables and Tukey's procedures for post-hoc pairwise comparisons between groups. Chi-square tests were used to determine differences in the frequency of abnormal responses between groups. Differences in HbA1c and duration of diabetes between participants with normal responses and those with absent or delayed responses in the diabetes groups were examined using ANOVA. After excluding absent VEMP responses, we examined the latency, amplitude, and threshold of VEMP responses for normality and equality of variances, and compared them across groups using ANOVA for normally distributed variables and Kruskal-Wallis test for P1 and N1 latency and the amplitude of oVEMP. In the two groups

of participants with diabetes (T2D and BPPV+DM), the relationships between age, sex, BMI, hypertension, HbA1c, years with T2D, and MNSI physical scores and each cVEMP and oVEMP variable were examined using multiple linear regression models. A p-value <0.05 was considered statistically significant. We used SPSS for Windows version 20.0 (SPSS Inc., Chicago, USA) for statistical analysis.

3.5 Results

Seventy-one individuals participated in the study in four groups: healthy controls (n=20), T2D (n=19), BPPV (n=18) and BPPV+DM (n=14). HbA1c, BMI, and the prevalence of hypertension were significantly higher in the groups with diabetes (Table 1).

Table1: Descriptive statistics of the groups

	Control (n=20)	T2D (n=19)	BPPV (n=18)	BPPV+DM (n=14)	p-value
Age (years)	57.5 ± 5.3	58.6 ± 5.3	54.9 ± 5.9	58.5 ± 5.6	p=0.17
Gender (M/F)	6/14	5/14	4/14	5/9	p=0.84
HbA1c (unit-%)	5.3 ± 0.3	7.8 ± 1.7	5.6 ± 0.4	7.1 ± 1.5	p<0.01*
BMI (kg/m^2)	26.9 ± 5.3	35.4 ± 6.3	29.5 ± 8.1	37.4 ± 5.2	p<0.01*
Hypertension (%)	5 (25%)	13 (65%)	8 (44.4%)	13 (92.9%)	p<0.01*
Diabetic peripheral neuropathy	-	11 (58%)		7 (50%)	

Years with T2D	-	10 ± 8.8	-	10.6 ± 11

HbA1c= glycosylated hemoglobin, BMI= body mass index. Continuous variables are described as mean ± SD, categorical variables as count (percentages). p values are based on chi square tests for frequencies and ANOVA for continuous variables.

3.5.1. Frequency of abnormal VEMP responses:

cVEMP responses:

In the healthy control group, thirty-eight ears showed a normal cVEMP response. The normal range for P1 latency (mean±2SD) was 13.5-19.4ms, and N1latency was 21.8- 27.52ms. Based on these findings, the P1 and N1 responses in all four groups were classified as normal, delayed, or absent. We observed significant differences in the frequency of abnormal responses between the T2D, BPPV and BPPV+DM groups, when compared to controls (Table 2). There were no differences in the frequency of abnormal responses between any of the other groups (T2D, BPPV, and BPPV+DM).

Table 2: Frequency of abnormal cVEMP responses in each group based on P1 and N1 latency

	P1 delay	N1 delay	P1 and N1 delay	cVEMP not recordable	cVEMP abnormal
Control (n= 40 ears)	1	0	0	1	2 (5%)
Type 2 diabetes (n= 38 ears)	3	3	0	5	11 (28.9%) p=0.005*
BPPV (n=36 ears)	1	1	3	6	11 (30.6%) p=0.003*
BPPV+DM (n=28 ears)	2	1	3	5	11 (39%) p<0.001*

chi square tests were conducted. * Significant differences between controls and the three other groups noted. BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and type 2 diabetes

In the two diabetes groups examined (T2D and BPPV+DM, n=33), 15 participants had absent or delayed responses in at least one ear (45.5%). In these participants, the mean HbA1c was 8.3 ± 1.7% compared to 6.8 ± 1.2% in participants with normal responses (p=0.006); the mean time since diagnosis of diabetes was 8.0 ± 10.2 years compared to 4.7 ± 6.2 years in those with normal responses (p=0.27). Figure 1 illustrates the cVEMP responses of a participant in each group, matched by age and sex.

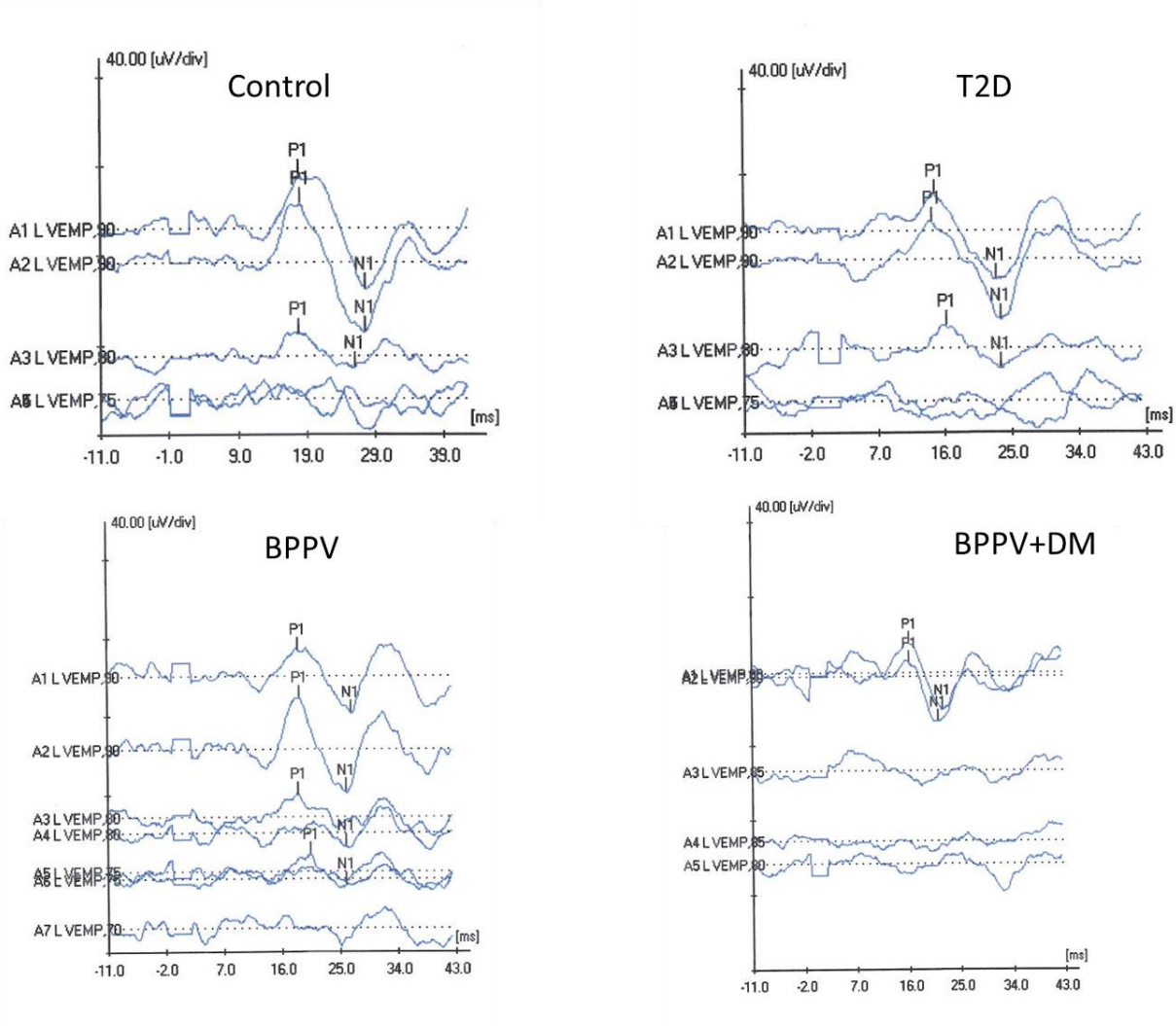

Figure 1: Tracings of the cVEMP responses in the left ear of four participants, one from each group, matched by age and sex. T2D- type 2 diabetes, BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and diabetes

oVEMP responses:

In the healthy control group, thirty-four ears showed a normal oVEMP response. The normal range for n10 latency was 8.6-13.3ms and p16 latency was 14.0-18.7ms. No differences were noted in the frequency of abnormal responses between any groups (p=0.2) (Table 3).

Table 3: Frequency of abnormal oVEMP responses in each group based on n10 and p16 latency

	n10 delay	p16 delay	n10 and p16 delay	oVEMP not recordable	oVEMP abnormal
Control (n= 40 ears)	1	1	0	4	6 (15%)
Type 2 diabetes (n= 38 ears)	2	1	1	9	13 (34%) (p=0.05)
BPPV (n=36 ears)	0	0	2	10	12 (33%) (p=0.06)
BPPV+DM (n=28 ears)	3	0	0	6	9 (32%) (p=0.08)

Chi-square tests were used to compare frequency of abnormal responses across groups. BPPV-benign paroxysmal positional vertigo, BPPV+DM- BPPV and type 2 diabetes

In the two groups of participants with diabetes (T2D and BPPV+DM, n=33), 17 had delayed or absent oVEMP responses (51.5%), in at least one ear. The mean HbA1c in these participants was 8.0 ± 1.8% compared to 6.9 ± 1.2% (p=0.06); mean time since diagnosis of

diabetes was 7.9 ± 9.6 years compared to 4.4 ± 6.4 years, in participants with normal responses (p=0.24). Figure 2 illustrates the oVEMP responses from a participant in each group.

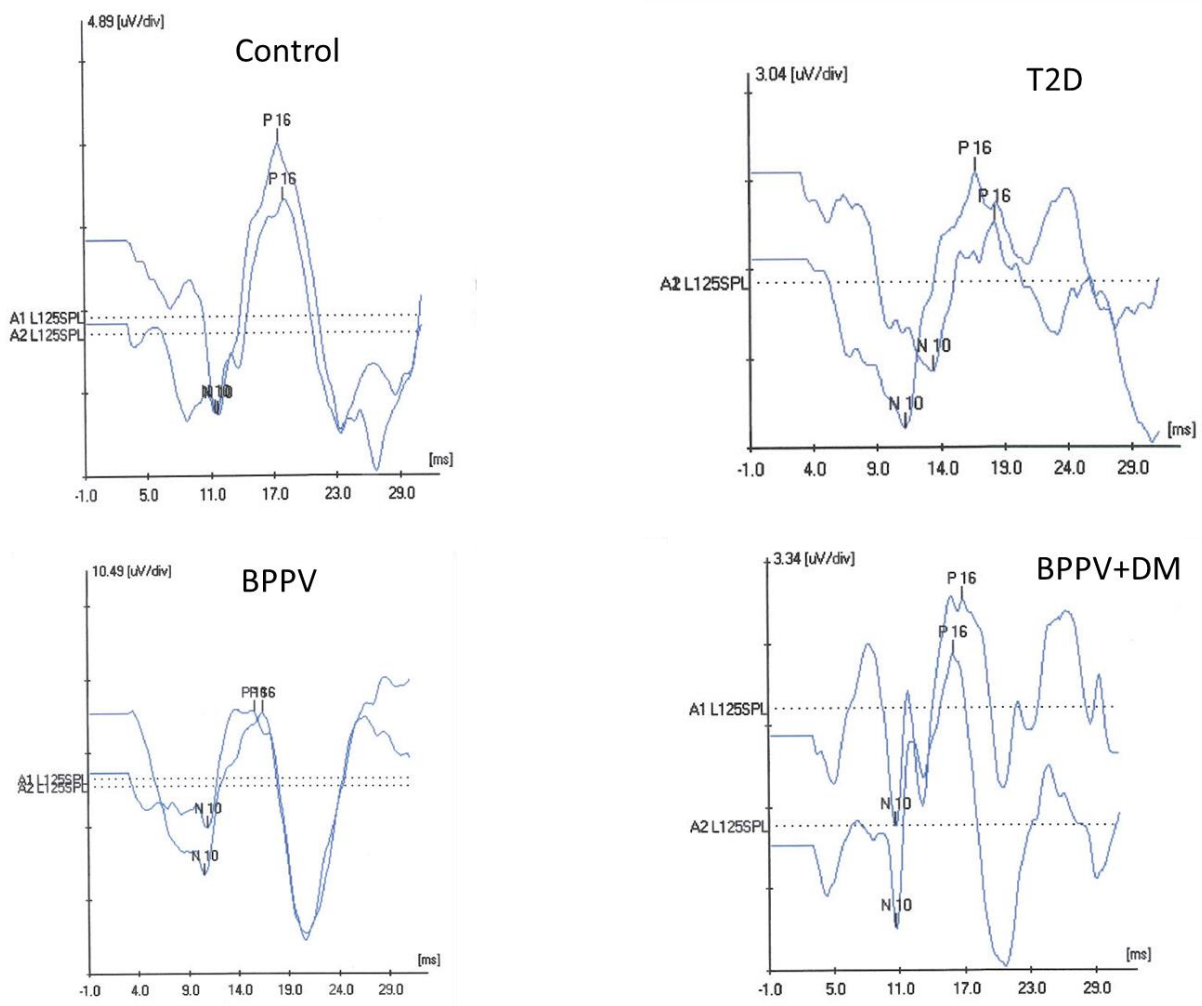

Figure 2: Tracings of the cVEMP responses in the left ear of four participants, one from each group, matched by age and sex. T2D- type 2 diabetes, BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and diabetes

3.5.2 Comparison of VEMP variables across groups:

After excluding participants with absent responses, there were no differences in the cVEMP P1 and N1 latency, amplitude, or threshold between the four groups. Significant differences were found in oVEMP n10 latency between groups (p=0.03); post hoc tests showed that the T2D group had prolonged n10 latency compared to the control group. Significant differences were seen in amplitude between groups (p=0.01), with a smaller amplitude in the T2D group compared to the BPPV group (Table 4).

Table 4: Comparisons of the oVEMP variables

	n10 latency (ms)	p16 latency (ms)	Amplitude (μV)
Control (n=36 ears)	10.9 (1.1)	16.4 (1.2)	9.5 (7.5)
T2D (n=29 ears)	11.8 (1.0)	16.9 (1.3)	8.1 (3.4)
BPPV (n=26 ears)	11.4 (1.3)	17.3 (1.5)	13.5 (7.3)
BPPV+DM (n=22 ears)	11.3 (0.8)	16.9 (1.1)	12.1 (7.2)
p	p=0.03[a]	p=0.10	p=0.01[b]

[a] Bonferroni procedure showed significant difference between the control and the T2D group. [b] Kruskal-Wallis test showed significant differences in amplitudes between the BPPV group and the T2D group
T2D- type 2 diabetes, BPPV-benign paroxysmal positional vertigo, BPPVDM- type 2 diabetes and concurrent BPPV

3.5.3 Relationships between VEMP variables and diabetes variables:

cVEMP variables: In the two groups of participants with diabetes (T2D and BPPV+DM), cVEMP responses were recorded in 56 ears. We examined the relationship between age, sex, BMI, HbA1c, hypertension, MNSI physical score, years with diabetes and cVEMP variables. P1 latency (r=0.44) was associated with BMI (p=0.001) and HbA1c level (p=0.05), while N1

latency (r=0.5) was associated with HbA1c level (p=0.01). Threshold (r=0.49) was associated with HbA1c level (p=0.04) and MNSI physical score (p=0.003).

oVEMP variables: In the diabetes groups (T2D and BPPV+DM, n= 51 ears with responses), we examined the relationship between age, sex, BMI, HbA1c, hypertension, MNSI physical scores, years with diabetes, and oVEMP variables. Significant associations were seen between the amplitude of oVEMP (r=0.61) with age (p=0.009), and hypertension (p=0.04).

3.6 Discussion

The results of this study reveal a higher prevalence of abnormal cervical VEMP responses in people with T2D, BPPV, and both BPPV and T2D as compared to healthy people of similar age. Contrary to our hypothesis, people with BPPV+DM did not have a higher frequency of abnormal cVEMP responses compared to people with either T2D or BPPV only. The frequency of abnormal cVEMP responses in BPPV (30.6%) is similar to observations made by others.[134, 135] After excluding absent VEMP responses from the analysis, our study found no differences in latency, amplitude, or threshold between the groups. This finding differs from Hong et al[133] who found that 75% of their participants with BPPV had prolonged P1 latencies, compared to healthy controls. This difference may be due to the participants recruited for their study, who had BPPV in any canal in a wide age range (20 to 81 years); advancing age is associated with prolonged VEMP latencies.[144]

Our findings of a 28.9% abnormal cVEMP response rate in people with T2D are similar to other studies,[123, 124] however, unlike those studies, we did not see prolonged latencies or reduced amplitude when we compared people with diabetes who had cVEMP responses to our control group. The main difference between this study, and the one by Ward et al,[123] is that their

participants were older with a 10-year or longer history of T2D. We did see a relationship between prolonged latency of P1 and N1 with higher HbA1c levels.

When participants with T2D and BPPV+DM were examined, we found that 45.5% had absent or delayed responses, with a significantly higher HbA1c level in people with abnormal responses. Degeneration of the macula of the saccule, with hair cell loss, is one suggested cause for detachment of the otoconia, causing BPPV,[145, 146] while degeneration of the vestibulocochlear nerve; particularly the inferior vestibular nerve has been observed in BPPV. These pathophysiological mechanisms of damage have been seen in experimentally induced diabetic rats, where histopathological changes due to metabolic stress may be the cause of degeneration of type 1 hair cells in the saccule.[35] Diabetic rats have been shown to have demyelination of the vestibulocochlear nerve with smaller axonal fiber density.[10] These morphological changes may explain both delayed and absent VEMP responses. Of importance, several studies have shown that absent cVEMP responses are indicative of extensive neuronal damage, seen in people with chronic and resistive BPPV,[136] and in people with recurrent BPPV.[138]

Our study did not find a difference in abnormal cVEMP responses between the T2D, BPPV, and BPPVDM groups. This finding is particularly interesting because the individuals with T2D did not have a diagnosis or any symptoms of vestibular disease. Other researchers have noted a higher frequency of vestibular dysfunction in people with diabetes, who are asymptomatic, compared to healthy controls.[9, 40] Gawron et al[9] found a higher frequency of spontaneous and positional nystagmus in children with type 1 diabetes, particularly in those with uncompensated diabetes and a longer duration of diabetes, however, only 6.3% of their participants complained of vertigo, imbalance, or both. Ward et al[123] found that in people with T2D, there was no relationship between the frequency of abnormal vestibular responses and the

dizziness handicap inventory, which is a questionnaire that assesses the person's perception of handicap due to dizziness. Likewise, even though vestibular dysfunction was evident with VEMP testing, Konukseven et al[124] reported no complaints of dizziness in 70% of people with T2D; and in the 30% who did have dizziness the complaints of dizziness were attributed to chronic autonomic neural degeneration due to diabetes. Based on these results, it is speculated that people with diabetes may have symmetrical involvement of both inner ears with minimal complaints of dizziness, as clinical symptoms may be seen only when damage to the vestibular system is severe.[37] Therefore, VEMP studies may be sensitive to diagnose subclinical vestibular involvement.

Analysis of the oVEMP showed no differences in the frequency of abnormal oVEMP responses between any groups. This was surprising since utricle dysfunction is prevalent in people with BPPV,[137, 139] and Nakahara et al[137] found that 66.7% of ears affected with BPPV had abnormal responses compared to healthy age-matched controls. However, in their study, participants were selected from a wide age range (34 to 82 years), and they took amplitude of the oVEMP into account when they examined the frequency of abnormal responses. We classified abnormal responses based on the latency of the oVEMP only, because the equipment we used did not have the electromyography capability to correct for baseline variations in ocular muscle activity.

Comparisons of oVEMP latency across groups showed significantly prolonged n10 latency in the T2D group compared to controls. Our results are similar to two recent studies that have examined the oVEMP in people with T2D showing prolonged latency of n10[123, 124] compared to healthy, age matched controls. Our study also found a significant decrease in the amplitude of the oVEMP in the T2D group compared to people with BPPV. Seo et al[139] have

reported that 46% of their participants with BPPV had augmented oVEMP amplitudes, and have speculated that because the otoconia are detached, the same sound volume may cause greater oscillation of the otolith membrane, producing a larger oVEMP response. It is possible that T2D may cause a decrease in amplitude of the oVEMP; however, the literature on the effect of T2D on the amplitude of the oVEMP is conflicting.[123, 124]

We did not find associations between oVEMP and diabetes variables in participants with T2D and those with BPPV+DM. T2D did not appear to affect the utricle as clearly as it did saccule, a result that is supported by a recent study by Konukseven et al,[124] who speculated that hyperglycemia may not affect the superior vestibular nerve, or the oVEMP compensation may be quicker.

The main limitation of this study is the small sample size, particularly in the BPPV+DM group; however, because of the strict inclusion criteria we were able to focus our attention to people with BPPV in a single canal, with canalithiasis only. Based on the study design, we cannot determine the causal relationship between diabetes and vestibular dysfunction in people with BPPV, because the presence of other medical conditions like migraine and post-menopausal status, which are known to increase the degeneration of the otolith organs, was not matched between groups. We did not perform a neurootologic examination of the healthy controls and people with T2D only. Although, they did not report complaints of dizziness and their medical records did not indicate vestibular disease, they could have had subtle vestibular deficits.

Ultimately, the interest in examining otolith function is to determine how this finding may affect a person's mobility and quality of life. Of all the vestibular organs, the otolith organs provide the primary vestibular contribution to postural control.[147] People with BPPV have been

shown to have otolith organ dysfunction,[134, 137] which is bilateral and does not improve even after successful repositioning.[148] Otolith dysfunction is associated with postural instability and higher risk for falls.[66, 149, 150] Our study showed that otolith dysfunction was present in people with diabetes. In people with diabetes, who have vestibular dysfunction and complaints of dizziness, the risk of falling is two times higher, independent of peripheral neuropathy and retinopathy.[7] In addition, people with diabetes are prone to developing diabetic complications, of which diabetic peripheral neuropathy and retinopathy increase the risk of falls.[24, 26, 121] Understanding the impact of multiple sensory deficits i.e. visual, vestibular and somatosensory, and their relative contribution to fall risk could help in developing strategies to prevent falls.

3.7 Conclusion

T2D is a common comorbidity that affects the vestibular system in addition to other body systems and organs. This study showed that both adults with BPPV and those with T2D have abnormalities in otolith responses; but diabetes may have a stronger effect on the saccule than the utricle. Future studies examining the incidence of falls in people with BPPV+DM who have abnormal VEMP responses, will help elucidate the relationship between otolith dysfunction and fall risk.

Chapter 4 Preface

In Chapter 3, we examined otolith organ function to determine the effect of BPPV and diabetes on the otolith organs of the vestibular system. Otolith dysfunction is associated with postural instability and a higher fall risk. Hence, the primary objective of the study described in Chapter 4 was to examine postural sway in people with BPPV and diabetes (BPPV+DM), in different visual and standing support conditions, using accelerometry. This study was initially conceived as hypothesis 3 of Aim 1, to examine sway in people with BPPV and BPPV+DM only. We expanded the scope of our data collection to include healthy controls and people with diabetes (without vestibular dysfunction). This study design allowed us to compare people 40 to 65 years of age, with BPPV and BPPV+DM to healthy controls and people with diabetes, using our specific accelerometry study procedure and the conditions that we were interested in examining.

As both, diabetes and BPPV are known to increase postural sway in challenging conditions, our original hypothesis was that people with BPPV+DM, would have higher sway values compared to people with BPPV only. After we added the control and diabetes groups, our hypothesis was that people with BPPVDM, would have higher sway values compared to patients with BPPV only, type 2 diabetes only and healthy controls. Our second objective was to identify which specific conditions of postural stability would be more challenging for people with BPPV+DM.

Results of this experimental study showed that the range and velocity of postural sway measures were significantly higher in people with BPPV+DM compared to people with diabetes and controls, particularly in the anteroposterior direction. In people with BPPV+DM,

significantly higher sway was seen when standing on foam with eyes closed and in tandem stance. Results of this study and the clinical implications of the results comprise Chapter 4.

Chapter 4

Postural sway is significantly higher in Individuals with Type 2 diabetes and Concurrent Benign Paroxysmal Positional Vertigo

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4.1 Abstract

Background and Purpose: Diabetes has been shown to affect the peripheral vestibular end organs and is associated with an increase in the frequency of benign paroxysmal positional vertigo (BPPV). People with diabetes have higher postural sway; however, the impact of concurrent BPPV on postural sway, in these individuals is unclear. The purpose of this prospective study was to examine postural sway in people with type 2 diabetes and concurrent BPPV (BPPV+DM).

Methods: Fifty-two participants (mean age 56.9 ± 5.6 years) were enrolled: controls (n=14), diabetes (n=14), BPPV only (n=13) and BPPV+DM (n=11). We used an inertial motion sensor to detect pelvic acceleration across five standing conditions with eyes open/closed on varied surfaces. Range of acceleration ($cm/s^{2)}$, peak velocity (cm/s), and variability of sway (RMS), in anterior-posterior (AP) and medial-lateral (ML) directions were used to compare postural sway between groups across the conditions.

Results: Participants with BPPV+DM had higher range of acceleration in AP ($p=0.003$) and ML ($p=0.006$) directions, as well as higher peak velocity ($p<0.001$) and RMS values ($p=0.006$) in the AP direction compared to the control and diabetes groups. Standing on foam with eyes closed and tandem stance conditions were the most challenging conditions for people with BPPV+DM.

Discussion and Conclusion: Clinicians may consider using standing on foam with eyes closed and tandem stance positions to assess postural control in people with BPPV+DM. Education on increasing the use of visual or sensory feedback, particularly on uneven surfaces, may help to reduce falls.

4.2 Introduction

In people with type 2 diabetes, complications such as peripheral neuropathy and retinopathy are frequently cited as the cause of increased postural sway and falls.[24, 26, 121] Although vestibular dysfunction is not commonly recognized as a microvascular complication of diabetes, there is substantial evidence of reduced central and peripheral vestibular function in people with type 1 and type 2 diabetes.[9, 39, 41, 123, 151] In people with diabetes, the presence of vestibular dysfunction has been shown to increase fall risk more than two times, even after adjusting for peripheral neuropathy and retinopathy.[8]

Among the peripheral vestibular organs, the otolith organs of the inner ear, namely the utricle and saccule, have shown morphological changes and loss of hair cells in experimentally induced diabetic rats,[35] while clinical research has shown that 50% of people with type 2 diabetes have otolith organ impairment.[123] The prevalence and recurrence of one specific vestibular condition, benign paroxysmal positional vertigo (BPPV), has been shown to be higher in people with diabetes.[43, 49, 50] BPPV results when otoconia, which are calcium carbonate crystals, detach from the utricle and saccule, and end up either free floating in the semicircular canals or attached to the cupula.[152, 153] Degeneration of the otolith organs is one reason for the detachment of the otoconia.[88, 94] BPPV causes vertigo which is dependent on the position of the head relative to gravity, has a short latency, and is transient; and is associated with loss of balance and frequent falls.[154-156] People with BPPV have been shown to have increased postural sway compared to healthy controls, particularly in conditions with altered proprioception and vision.[157, 158] In addition, dynamic balance is affected, where people with BPPV have slower walking speed during tandem walking, compared to age matched healthy controls.[157]

Kinetic analysis of posture has been used to quantify postural stability in healthy individuals, older adults, as well as people with orthopedic, neurologic and vestibular disease.[159-162] These studies usually include quiet standing in single or double stance on a force platform while the different sensory systems (visual, vestibular and somatosensory) of these individuals are perturbed.[22, 163-166] More recently, studies have used an accelerometer positioned near the center of mass, to measure postural sway quantitatively.[167-169] Accelerometry has high criterion validity (r=0.92), and excellent test-retest reliability (r=0.80) when compared to center of pressure measures, using force platforms.[170-172] One-30 second trial of accelerometry has been shown to be as useful as three trials, to capture postural sway. [171] Accelerometry has the ability to discriminate between various test conditions, as the complexity of the task increases[169, 173] and is able to differentiate between fallers and non-fallers with a sensitivity of 58.3% and specificity of 80%.[174] Time sensitive accelerometry measures that are used to characterize postural sway include range of acceleration, root mean square of acceleration and peak velocity.[171, 174, 175]

The primary objective of this study was to examine postural sway in people with type 2 diabetes and concurrent BPPV (BPPV+DM), in different visual and standing support conditions, using an accelerometer. Our hypothesis was that people with BPPV+DM, would have higher sway values compared to people with BPPV only, type 2 diabetes only and healthy controls. Our second objective was to identify which specific conditions of postural stability would be more challenging for people with BPPV+DM. We hypothesized that people with BPPV+DM would have greater difficulty maintaining a stable position in conditions with reduced visual and somatosensory information, due to a co-existing disturbance in the vestibular system. Results of this study will be important to help clinicians understand the effect of underlying sensory deficits and their impact on postural stability in people with BPPV+DM. Making patients aware of their

postural instability in challenging conditions could serve as an effective education tool. For example, they may learn to avoid situations of daily life that are challenging due to reduced somatosensory and visual feedback. This may help reduce falls in this high-risk patient population.

4.3 Methods

4.3.1 Study Design:

This was a single-center, prospective study with a sample of convenience. The research protocol was approved by the Human Subjects Committee at the University of Kansas Medical Center. Institutionally approved written informed consent was obtained from all individuals prior to participation in the study.

4.3.2 Participants:

Participants between 40 to 65 years were recruited and allocated to four groups: healthy controls, individuals with type 2 diabetes without vestibular problems (type 2 DM), individuals with BPPV without diabetes (BPPV), those with both type 2 diabetes and BPPV (BPPV+DM). Participants were recruited through physician referral, study advertisements, and two research participant registry programs. For the BPPV and BPPV+DM groups, only people with unilateral posterior canal BPPV canalithiasis were included in the study. The diagnosis of BPPV was made based on the presence of up beating torsional nystagmus in the Dix-Hallpike position with a brief latency, nystagmus lasting less than 60 seconds and reversed upon sitting, with associated complaints of vertigo,[67] determined by a physician and confirmed by a physical therapist, using videonystagmography.

The presence or absence of diabetes was confirmed through the individual's medical records. In addition, glycosylated hemoglobin (HbA1c) information was collected via a disposable finger stick testing kit (Metrika A1cNow^{+} Bayer, Tarrytown NY). Participants with type 2 diabetes did not have a medical diagnosis of vestibular problems and no complaints of dizziness. The control group did not have a medical history of vestibular disease or diabetes.

All participants were screened for the presence of diabetic peripheral neuropathy (DPN), using the Michigan Neuropathy Screening Instrument (MNSI), which has a questionnaire and physical exam components. Participants were classified as neuropathic if their physical exam score was ≥ 2.0.[69]

Participants in all groups were excluded if they had a (1) history of neurological disease including stroke, multiple sclerosis, Parkinson's disease, or intracranial tumor, (2) history of Meniere's disease, (3) received chemotherapy or ototoxic and/or neurotoxic medications, (4) traumatic brain injury, or (5) musculoskeletal or integumentary conditions that would impair balance testing.

4.3.3 Materials and Procedure:

In a single testing session, participants were assessed in quiet standing in the feet together position for 30 seconds. The 5 testing conditions were: (1) standing on a firm surface with eyes open, (2) on a firm surface with eyes closed, (3) on a foam pad (Alimed balance pad elite) with eyes open, (4) on a foam pad with eyes closed, and (5) tandem stance with eyes open on a firm surface (Figure 1). A physical therapy student guarded all participants during the testing. Each condition was explained and demonstrated to participants, and were performed in the same order

for all participants. The recording was started at the signal "ready, set, and go" and stopped after counting backwards from 3. All participants wore their regular shoes during testing to avoid provoking their dizziness due to bending down to remove their shoes. Whitney et al[176] have shown that balance testing can be performed with or without shoes on, with no significant change in sway measures. One 30-second trial was conducted in each testing position. Participants were advised to open their eyes or reach for the person guarding them, if they lost their balance. If a participant lost their balance or opened their eyes during a particular condition, they were given another opportunity to retest that position. During the tests, pelvic accelerations were measured using an inertial motion sensor (Xsens North America, USA) sized 5.25 x 3.75 x 2 cm. The sensor was held firmly in place over the posterior aspect of the third vertebra of the lumbar spine using an elastic belt provided by the manufacturer (Figure 1).

Figure 1: The five experimental conditions used to examine postural sway. The inertial sensor was positioned at L3 spine level, displayed in the inset picture.

4.4.4 Data Processing:

Data was acquired using the MT Manager software (Xsens North America, USA) at a sampling frequency of 120 Hz. The three-axial (X, Y, and Z) acceleration data was recorded during the 30 seconds of data collection. The accelerations in Y and Z directions, corresponding to medial-lateral (ML) and anterior-posterior (AP) directions respectively, were used to calculate the variables that represented postural sway. The data was filtered using a second order, Butterworth low-pass filter at 20 Hz and corrected for offset.

The following variables were calculated and used for statistical analysis: (1) Range (cm/s^2) – the peak-to-peak amplitude of acceleration, in AP (Range-AP) and ML directions (Range –ML). (2) Peak velocity (cm/s) in AP (PV-AP) and ML (PV-ML) directions, velocity was calculated by integrating the acceleration. (3) Root mean square (RMS) which is the dispersion of the acceleration traces in AP (RMS-AP) and ML (RMS-ML) directions. All variables were calculated using customized Matlab code (The Mathworks Inc., Natick, MA).

4.5 Statistical Analysis

Descriptive statistics (mean, standard deviation, %) were used to present participant demographics in each group. Group differences in participant demographics were tested using ANOVA for significant variables and Tukey's procedures for post-hoc pairwise comparisons between groups. Range-AP, range-ML, PV-AP, PV-ML, RMS-AP and RMS-ML were examined using a general linear mixed model method. We used compound symmetric correlation structure to take into account within subject correlation due to repeated measures. The conditions were entered as within subject factor, while groups were entered as between subject factor. The condition by group interaction was to evaluate the group differences within conditions. For a

significant model, post hoc comparisons were done using Tukey's method for multiple comparisons. In those trials in which participants were unable to complete the test, we used an intention to treat model, and values were assigned based on the group mean ± 2SD. Statistical analysis was performed using SPSS 20.0 (SPSS, Inc., Chicago, IL) with significance level set at $p<0.05$.

4.6 Results

We screened 151 individuals and enrolled 52 in the four participant groups: 1) controls (n=14), 2) type 2 diabetes (n=14), 3) BPPV (n=13) and 4) BPPV+DM (n=11). The reasons for exclusion from the study are outlined in Figure 2.

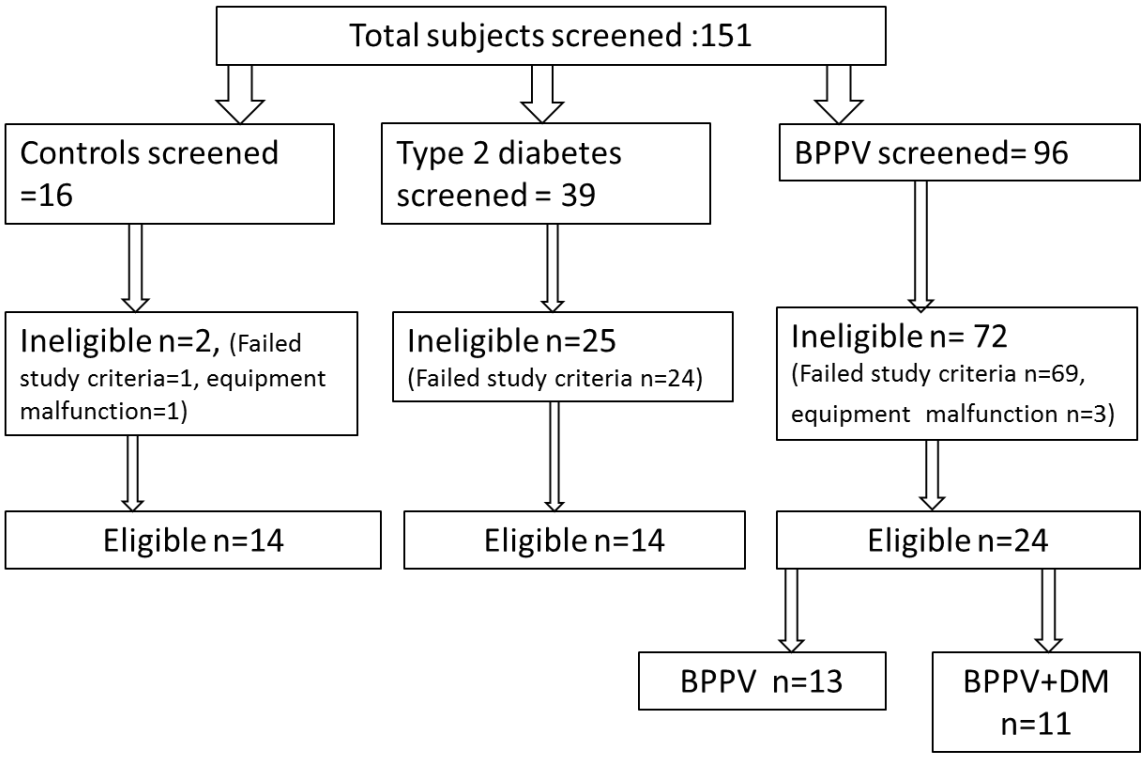

Figure 2: Participant enrollment flow chart.

4.6.1 Descriptive statistics:

Participant characteristics are summarized in Table 1. HbA1c (p=0.03) and BMI (p<0.01) were significantly different in subjects with and without type 2 diabetes. Eight participants in the diabetes group and four in the BPPV+DM group had MNSI physical scores ≥ 2.0.

Table 1: Participant characteristics

	Controls (n-14)	Type 2 DM (n=14)	BPPV (n=13)	BPPV+DM (n=11)	p-value
Age (years)	58.07 (4.9)	57.4 (5.5)	54.5 (6.0)	57.6 (5.7)	p= 0.34
HbA1c (%)	5.4 (0.4)	7.8 (1.9)	5.6 (0.4)	6.9 (1.6)	p< 0.001
BMI (kg/m^2)	27.2 (6.3)	34.0 (5.5)	28.2 (6.5)	36.3 (4.2)	p<0.001
DPN	0	57% (n=8)	0	36% (n=4)	

Values are presented as mean ± SD or frequency. DM- diabetes, BPPV- benign paroxysmal positional vertigo, BPPV+DM- diabetes and concurrent BPPV, DPN-diabetic peripheral neuropathy, BMI-body mass index, HbA1c- glycosylated hemoglobin

4.6.2 Postural Sway variables:

One participant in the BPPV+DM group could not stand on foam, eyes closed or tandem stance (condition 4 and 5), while another in the BPPV+DM group was unable to complete tandem stance, due to loss of balance.

Range of acceleration:

Range-AP had a significant main effect of group ($F_{1, 52:}$ 3.5, p=0.02), condition ($F_{1, 52:}$ 34.6, p<0.001), and interaction between group and condition ($F_{1, 52:}$ 2.6, p=0.003). The BPPV+DM and BPPV groups had significantly higher range of sway in the AP direction

compared to controls and the diabetes group on foam, eyes closed (condition 4) and tandem stance (condition 5) (Figure 3).

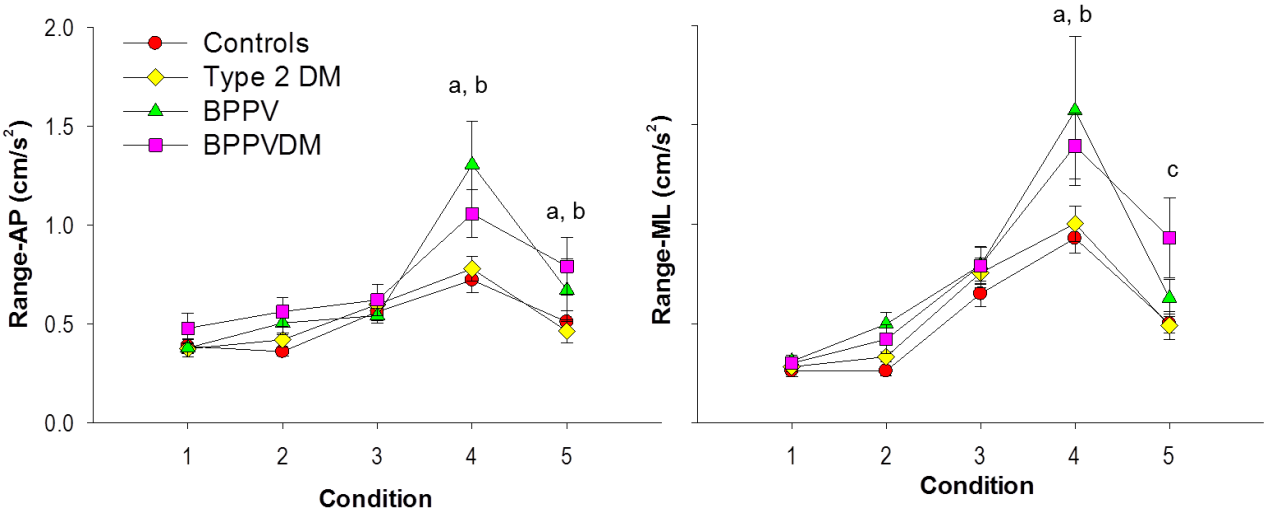

Figure 3: Mean range and standard errors in anteroposterior (AP) and mediolateral (ML) directions for the four groups across the five testing conditions. a and b indicate the significant difference between the BPPV+DM and BPPV groups compared to the control and diabetes groups, respectively based on testing conditions. c represents the significant difference between the BPPV+DM group and the other three groups.

Range-ML had a significant main effect of group ($F_{1, 52}$: 4.7, p=0.01), and condition ($F_{1, 52}$: 45.3, p<0.001), there was no interaction between group and condition ($F_{1, 52}$: 1.5, p=0.13). The BPPV+DM and BPPV group had significantly greater ML range on foam with eyes closed compared to controls and the diabetes groups, additionally the BPPV+DM group had greater range of sway in the ML direction in tandem stance (Figure 3).

Peak velocity:

PV-AP showed a significant main effect of group ($F_{1, 52:}$ 7.2, p<0.001), and condition ($F_{1, 52:}$18.1, p<0.001), no interaction was seen between group and condition ($F_{1, 52}$: 1.5, p=0.11). PV-AP was higher in the BPPV+DM group compared to the control, diabetes, and BPPV groups,

when standing on a firm surface with eyes closed and tandem stance. Higher peak velocity of AP sway was seen in both the BPPV and BPPV+DM groups when standing on foam with eyes closed compared to control and the diabetes groups (Figure 4).

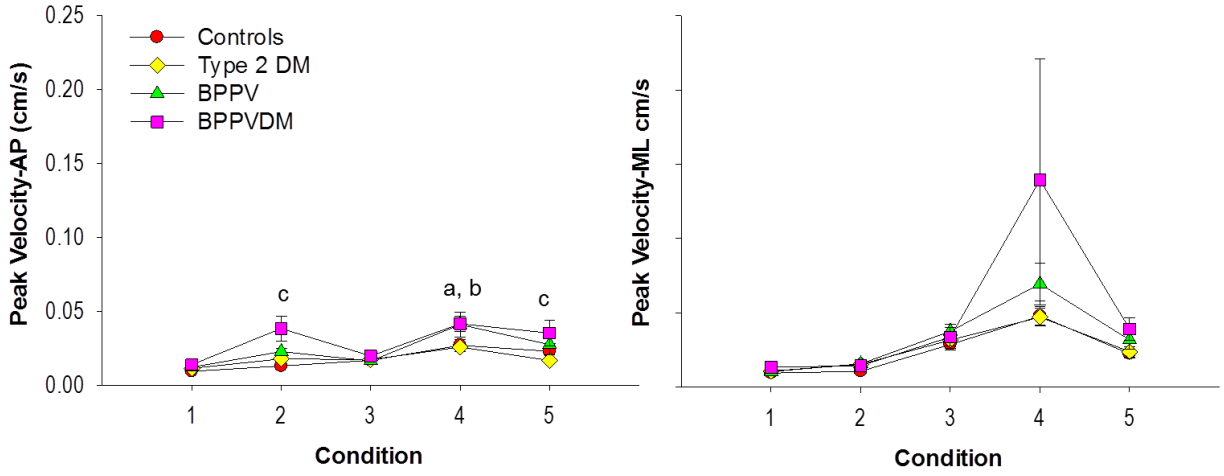

Figure 4: Mean and standard errors of peak velocity in anteroposterior (AP) and mediolateral (ML) directions for the four groups across the five testing conditions. a and b indicate the significant differences between the BPPV+DM and BPPV groups and the control and diabetes groups, respectively. c indicates the significant difference between the BPPV+DM group and the 3 other groups.

PV-ML showed a main effect of condition ($F_{1, 52:}$ 10.5, $p<0.001$). The main effect of group ($F_{1, 52}$: 1.9, $p=0.1$), and interaction between group and condition ($F_{1, 52:}$ 1.2, $p=0.3$) was not significant. Subsequent analysis showed that the peak velocity of sway was greater when standing on foam with eyes closed (Figure 4).

Root Mean Square:

RMS-AP showed a significant main effect of condition ($F_{1, 52:}$ 14.73, $p<0.001$) and interaction between group and condition ($F_{1, 52:}$ 2.43, $p=0.006$). There was no effect of group ($F_{1,}$

$_{52:}$ 1.32, p=0.28). RMS values were greater in the BPPV group when standing on foam with eyes closed, and greater in the BPPV+DM group in tandem stance (Figure 5).

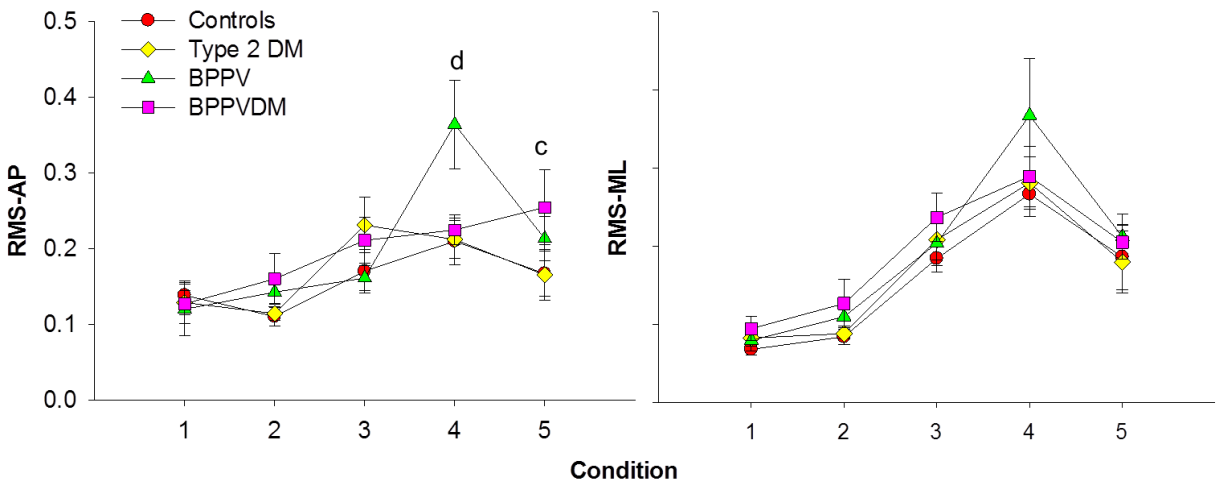

Figure 5: Mean and standard errors of RMS of acceleration in anteroposterior (AP) and mediolateral (ML) directions for the four groups across the five testing conditions. c and d indicate the significant difference between the BPPV+DM and BPPV groups compared to the three other groups, respectively.

RMS-ML showed a main effect of condition ($F_{1, 52}$: 37.4, p<0.001). There was no effect of group ($F_{1, 52}$: 1.2, p=0.26), and no interaction between group and condition ($F_{1, 52}$: 0.49, p= 0.92). Significantly greater RMS in the ML direction was seen when standing on foam with eyes closed (Figure 5).

4.7 Discussion

The present study was designed to examine balance sway in individuals with type 2 diabetes and concurrent BPPV in various conditions of postural stability. The conditions examined are used frequently in the clinic setting to assess the contribution of the vestibular, visual and somatosensory systems towards postural stability.[62] We analyzed pelvic accelerations

to detect balance performance, where higher range, peak velocity and variability of sway, are indicative of impaired postural stability.[172] The main findings of our study supported our primary hypothesis that individuals with type 2 diabetes and concurrent BPPV would exhibit increased postural sway, suggestive of decreased postural stability. Our second objective was to identify the specific conditions that would be challenging for people with BPPV+DM. Our hypothesis was supported by our study findings, which showed that standing on a complaint surface without visual input and tandem stance were the most challenging positions for people with BPPV+DM.

The vestibular system, along with the visual and somatosensory systems provides information about the position and motion of the body with respect to earth's vertical. In normal conditions, information from all sensory systems complement each other, however, if one of the sensory inputs is unavailable or deprived, it is critical for the central nervous system to be able to extract sensory information from the other available sensory systems (sensory reweighting) to maintain postural stability and avoid a fall.[177] Thus, results of our study suggest that distorted inputs from the vestibular system in individuals with BPPV, both with and without diabetes, changes the sensory reweighting. This increases postural sway, particularly in conditions in which the somatosensory and visual systems are not operating optimally. These results are similar to the findings of previous studies using static posturography, which have shown higher range and velocity of sway in people with posterior canal BPPV when standing on foam, eyes closed.[157, 158]

People with BPPV+DM also experienced difficulty maintaining tandem stance (condition 5). Tandem stance inherently utilizes the hip strategy rather than ankle strategy for balance control. However, use of the hip strategy might possibly be limited in people with BPPV+DM since the information being integrated from the somatosensory system does not match the

vestibular inputs. People with vestibular problems may also be unable to maintain tandem stance due to coexisting somatosensory deficits. Participants with BPPV+DM in this study (36%) presented with DPN (see Table 1); hence, it is possible that they were not able to compensate for their vestibular deficits due to the reduced somatosensory inputs. In contrast, our group of participants with BPPV only, did not have problems balancing in tandem stance, which means they could compensate well in tandem standing for their vestibular deficits.

There is a possibility that people with BPPV+DM may have greater impairment of their vestibular system due to a direct effect of diabetes on the vestibular system.[123, 124] Animal studies have shown morphological and physiological changes specifically in the saccule of rats in experimentally induced diabetes due to metabolic stress.[10, 35, 37] Of all the vestibular organs, the otolith organs provide the primary vestibular contribution to postural control;[178] and damage to the otolith organs has been shown to affect postural control.[61] Serrador et al[179] demonstrated that age related loss of otolith function increased postural sway. A recent study by Ward et al[123] has shown that adults with type 2 diabetes of longer durations (>10 years), have decreased function of the peripheral vestibular apparatus, compared to healthy age-matched controls. Hence, it is plausible that increased sway seen in people with BPPV+DM is not only due to the effect of diabetes and BPPV independently, but also the effect of diabetes on the vestibular apparatus directly. The present study was not designed to examine the impact of diabetes directly on the vestibular system, but it can stimulate future studies to investigate the relationship between postural sway and direct measures of vestibular function such as calorics or evoked potential tests. Altogether, the results of our study provide useful information when screening people with BPPV with or without type 2 diabetes. It is likely that both groups of people will have increased sway when standing on foam with eyes closed, but people with BPPV+DM will also have

significant difficulty maintaining the tandem stance position. In fact, Vereeck et al. have noted that tandem walking was much more difficult for older people with vestibular loss than the Timed Up &Go (TUG) test and the dynamic gait index.[180]

In our study, no differences were found in any measure of balance in individuals with type 2 diabetes compared to controls. Previous studies have shown that individuals with type 2 diabetes, particularly those with diabetic peripheral neuropathy (DPN), have greater range and velocity of sway compared to age matched controls, when standing on a firm surface with and without visual input.[6, 22, 23, 181] We found no differences in sway measures in our group with diabetes compared to our control population. This difference may be due to the fact, that not all of our participants with diabetes had neuropathy as determined by MNSI physical exam scores. Although the MNSI is a well-established clinical screening tool to identify people at risk for DPN, it is not a gold standard diagnostic test.[182]

Ultimately, the significance of finding increased postural sway in people with BPPV+DM is related to its potential association with functional mobility and fall risk. Although the present study cannot answer this question, one study has shown that sway values calculated from accelerometry were higher in older adults with lower scores on the Berg balance scale (BBS), and those who walked slower on the TUG.[174] Whitney et al. have shown that people with vestibular dysfunction, who score more than 11 seconds on the TUG were five times more likely to have had a fall in the previous 6 months.[183] The BBS assesses balance and postural control and is useful to identify people with vestibular dysfunction at a higher risk for falling.[184] Therefore, we can reasonably suggest that people with BPPV+DM may have a higher risk of falling especially in conditions where the somatosensory and visual feedbacks are deprived, as in certain daily activities like walking in the yard or on plush carpet without adequate lighting.

BPPV may be considered a complication of type 2 diabetes, and it is frequently encountered in clinical settings. Fall prevention is a major focus of the care provided to people with diabetes with or without BPPV, since they are prone to fractures and more severe injuries after a fall.[27, 28, 30] Information from this study is pertinent to clinicians working with people with diabetes to identify daily life activities that could increase risk of falls, and to make patients aware of their balance deficits during balance screening in the clinic. After successful resolution of BPPV with the appropriate treatment maneuver, treatment plans need to be developed for people with BPPV+DM that include walking programs and balance training on compliant and narrow surfaces with and without visual feedback to improve balance performance.

Limitations

Admittedly, there are limitations to this study that need to be considered when interpreting the results. Our groups did differ significantly in BMI, and higher BMI is known to affect postural stability.[185] However, people with diabetes are known to have higher BMI.[186] Due to small sample sizes, we did not further break down the analysis of the groups with diabetes on the basis of diabetic peripheral neuropathy. Future studies examining how DPN may influence postural stability in people with BPPVDM are essential.

4.8 Conclusion

Fall prevention is a major focus of the care provided to people with diabetes. This study showed that people with type 2 diabetes and concurrent BPPV had significantly higher sway on compliant surfaces, vision deprived environments, and in situations with a narrow base of support. Information from this study is pertinent to clinicians working with people with diabetes

to identify daily life activities that could increase risk of falls, and to make patients aware of their balance deficits.

Chapter 5 Preface

Diabetes and benign paroxysmal positional vertigo independently affect mobility and increase postural sway. In Chapter 5, we examined the functional status of people with BPPV+DM compared to those with BPV only, at baseline and after resolution of vertigo. Chapter 5 includes the combined results of Aim 1 and 3. The main objective of Aim 1 was to examine if the combined effect of BPPV and diabetes increased symptom severity, functional mobility deficits and postural sway prior to treatment, compared to people with BPPV only. Our hypotheses were that people with BPPV+DM would present with greater symptom severity, have higher mobility deficits and higher postural sway compared to people with BPPV only. The main objective of Aim 3 was to examine symptom severity, mobility and balance after resolution of vertigo; as well as the number of treament maneuvers required for resolution of vertigo, in people with BPPV+DM compared to those with BPPV only. Our hypotheses were that following treatment, people with BPPV+DM would continue to have more symptoms, and higher mobility and balance deficits and would require more repositioning maneuvers for symptom resolution compared to people with BPPV only.

Results of this study showed that at baseline, there were no differences in symptom severity or mobility deficits between people with BPPV and those with BPPV+DM. People with BPPV+DM had higher range and velocity of sway in tandem stance at baseline, compared to those with BPPV only. After resolution of symptoms, there were no differences between the groups in symptom severity, mobility or postural sway. The repositioning maneuver was effective in both groups, and people with BPPV+DM did not require additional treatment manuevers compared to those with BPPV only.

Chapter 5

The Influence of Type 2 Diabetes on Symptom Presentation and Response to Repositioning Maneuvers in Individuals with Benign Paroxysmal Positional Vertigo

Manuscript in preparation, to be submitted to the *Journal of Neurologic Physical Therapy*

5.1 Abstract

Background and Purpose: Type 2 diabetes affects the otolith organs of the vestibular system and the prevalence of benign paroxysmal positional vertigo (BPPV) is higher in people with diabetes. The combined effect of BPPV and type 2 diabetes (BPPV+DM) on symptom presentation, mobility, and balance, and the response to canalith repositioning maneuvers (CRM) is unknown. In this prospective study, we compared symptom severity, mobility and postural sway before and after treatment, as well as the number of treatment maneuvers needed for resolution of vertigo, in people with BPPV and BPPV+DM.

Methods: Fifty participants completed the study in two groups, people with BPPV (n=34) and with BPPV+DM (n=16). The Dizziness Handicap Inventory (DHI) and Functional Gait Assessment (FGA) examined symptom severity and mobility, and an accelerometer examined postural sway in five different conditions, before and after the CRM. We compared the number of maneuvers required for resolution of vertigo, between groups.

Results: At baseline, there was no difference in DHI scores ($p=0.52$) or FGA scores ($p=0.28$) between the BPPV and BPPV+DM groups, however there were significant differences in range, and peak velocity of sway in the anteroposterior and mediolateral directions, seen in tandem standing. After resolution of vertigo, both the DHI and FGA score showed a main effect of time ($p<0.001$), there was no effect of group ($p=0.28$; $p=0.08$), and no interaction between group and time ($p=0.59$; $p=0.14$). After symptom resolution, significant change was seen in postural sway in the mediolateral direction in people with BPPV+DM in the tandem stance position. There were no differences in the number of maneuvers needed between the two groups ($p=0.37$).

Conclusions: People with BPPV and BPPV+DM have significant difficulty with mobility and function when symptomatic with vertigo; however, they both respond well to treatment maneuvers. Early identification of BPPV in people with diabetes, as well as prompt treatment may help restore activity levels and reduce falls in this high-risk population.

5.2 Introduction

Type 2 diabetes (T2D) currently affects 29.1 million people in the United States,[1] and is projected to affect 1 in 3 people by the year 2050.[2] Diabetes causes microvascular complications such as peripheral neuropathy and retinopathy, which increase the risk of falls.[24, 26, 121] Vestibular dysfunction is being recognized as a complication of T2D, and has been reported to be 70% higher in people with T2D, compared to age matched controls.[7] In people with diabetes, vestibular dysfunction, and complaints of dizziness, the risk of falls is two times higher after accounting for peripheral neuropathy and retinopathy.[8]

Increasing evidence is showing both central and peripheral vestibular dysfunction in type 1 and 2 diabetes.[9, 10, 35, 39, 41, 123, 151] Metabolic stress due to hyperglycemia has been shown to cause loss of type 1 hair cells in the saccule[35] and demyelination of the vestibulocochlear nerve,[10] in experimentally induced diabetic animal models; as well as peripheral vestibular organ dysfunction, of both the otolith organs and semicircular canals [123, 124] in clinical studies. One common vestibular condition, benign paroxysmal positional vertigo (BPPV) is prevalent and recurrent in people with type 2 diabetes.[43, 45] One reason for the detachment of the otoconia is underlying degeneration of the otolith organs.[88, 94] Posterior canal BPPV canalithiasis is the most common variant of BPPV, seen when otoconia fragments detach from the utricle and saccule and enter the posterior semicircular canal causing movement of the endolymph, even after head movements have ceased.[67, 152, 153] BPPV causes a position dependent vertigo and nystagmus, and is associated with loss of balance and frequent falls.[154-156] Due to vertigo, individuals with BPPV restrict their daily activities with increased missed days at work resulting in decreased

productivity.[88, 187] Fortunately, the canalith repositioning maneuver (CRM) is very effective in treating posterior canal BPPV.[51, 89, 90]

Presently, we do not have a clear understanding of how T2D may affect the clinical presentation of people with BPPV when they are symptomatic, or the efficacy of the CRM to resolve BPPV symptoms, in people with diabetes. The main objectives of this study were to compare symptom severity, mobility and postural sway in people with BPPV to those with both BPPV and type 2 diabetes (BPPV+DM) when symptomatic, and after the resolution of vertigo with the CRM. Our hypotheses were that: People with BPPV+DM would have 1) higher symptom severity measured by the Dizziness Handicap Inventory (DHI), 2) impaired functional mobility measured by the Functional Gait Assessment (FGA), and 3) higher postural sway when symptomatic with vertigo, compared to people with BPPV only. After the resolution of vertigo following CRM, our hypotheses were that people with BPPV+DM would continue to have 4) higher symptom severity, 5) greater impairments in functional mobility, 6) and higher postural sway. Because the prevalence and recurrence of BPPV is higher in the presence of T2D, we also hypothesized that 7) people with BPPV+DM would require more treatments with the CRM for symptom resolution compared to those with BPPV only.

As the population ages, the prevalence of both BPPV and T2D is predicted to increase. Clinicians will encounter both disease conditions frequently during the evaluation and treatment of their patients. The findings of this study would provide knowledge about how the presence of diabetes in a person with BPPV may affect their function and prognosis for recovery after treatment.

5.3 Methods

5.3.1 Study Design

This was a single center, prospective study with a sample of convenience, which included two groups of participants, those with BPPV and with BPPV+DM. In this single-blinded study, the primary investigator (LD) was blinded to the diabetes status of participants during both data collection time points. The Human Subjects Committee at the University of Kansas Medical Center approved the research protocol. Each individual provided institutionally approved written informed consent prior to participation in the study.

5.3.2 Participants

Individuals between 40 and 80 years with a diagnosis of unilateral posterior canal BPPV canalithiasis, as determined by a physician and confirmed by a physical therapist, were allocated to two groups, based on whether or not they had type 2 diabetes: BPPV and BPPV+DM. Participants were recruited through physician referral from the University of Kansas Medical Center neuro-otology clinic, as well as internal medicine, and family medicine clinics in the area.

The diagnosis of posterior canal BPPV was based on the presence of torsional up beating nystagmus in the Dix-Hallpike position with a brief latency, nystagmus lasting less than 60 seconds, which reversed upon sitting, with associated complaints of vertigo, [67] using videonystagmography (Micromedical, Visual Eyes 2002). Participants were excluded if they presented with any of the following: (1) history of neurological disease including stroke, multiple sclerosis, Parkinson's disease, intracranial tumor, (2) history of Meniere's disease, (3) received chemotherapy or ototoxic and/or neurotoxic medications, (4) traumatic head injury, (5) BMI greater than 45kg/m^2, (6) musculoskeletal or integumentary conditions that would impair

balance. In addition, participants were excluded if videonystagmography revealed anterior or lateral canal BPPV canalithiasis, cupulolithiasis in any canal, or bilateral BPPV.

After the resolution of symptoms, a detailed medical history, list of medications, the presence or absence of diabetes, hypertension and BMI were collected from the electronic health records. In addition, glycosylated hemoglobin (HbA1c) was tested via a disposable finger stick testing kit (Metrika A1cNow^{+} Bayer, Tarrytown NY). Participants were classified as BPPV+DM if they had a physician diagnosis of T2D in their health records. Participants were screened for the presence of diabetic peripheral neuropathy (DPN), using the Michigan Neuropathy Screening Instrument (MNSI), which has a questionnaire and physical exam components.[55] Participants were classified as having DPN if their physical exam score was ≥ 2.0.[69]

5.3.3 Study Procedures

Once inclusion/ exclusion criteria and the diagnosis of unilateral posterior canal BPPV was confirmed, informed consent was obtained from participants and baseline outcome measures were collected.

After collection of baseline outcome measures, all participants received treatment for posterior canal BPPV, with the canalith repositioning maneuver (CRM).[67] All participants received restrictions to follow for 48 hours, including no bending, no looking overhead, and no sleeping on the affected side.

Participants returned for follow up between 7 to10 days of the initial evaluation, and the Dix-Hallpike was repeated using videonystagmography, to test if the BPPV had resolved. If participants had no nystagmus or vertigo with Dix-Hallpike testing, they were considered symptom-free, and post-treatment outcome measures were collected. If nystagmus and vertigo

persisted, they received another CRM, and were scheduled to follow up in 7 to10 days, until resolution of symptoms. Once symptoms were resolved, the assessor was un-blinded with regard to diabetes status, at which time the MNSI physical was completed and HbA1c level was collected (Refer to Figure 1).

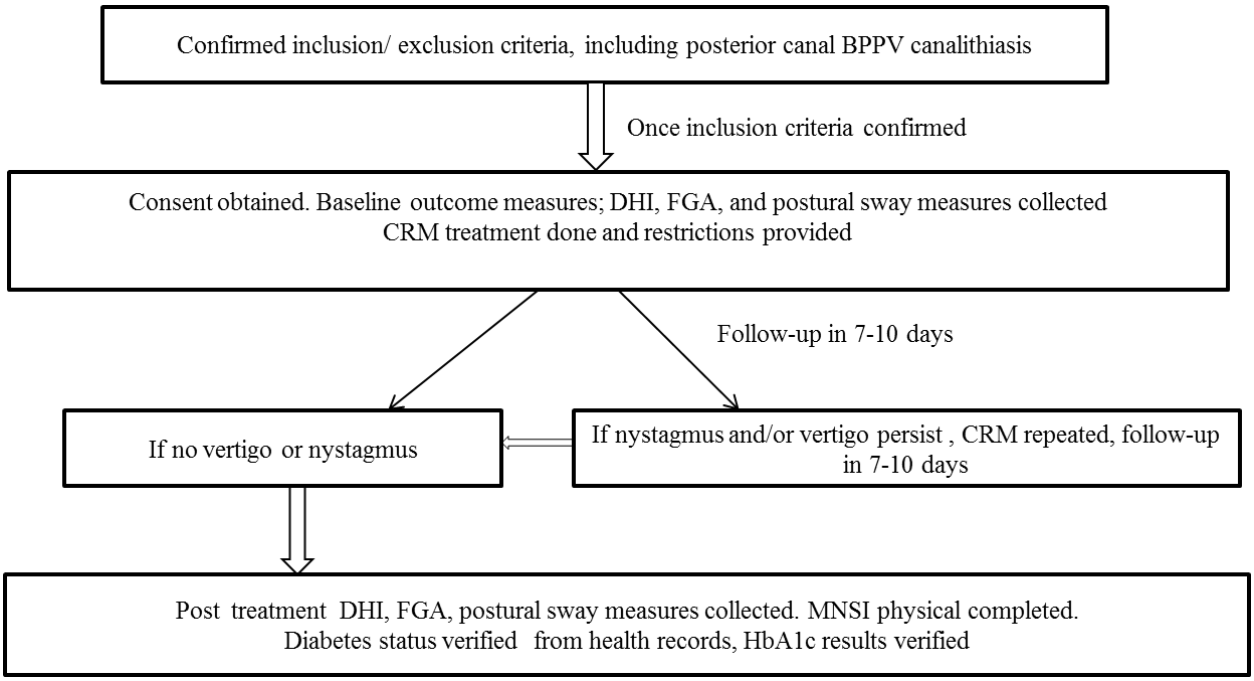

Figure 1: Study sequence flow sheet. DHI- Dizziness Handicap Inventory, FGA- Functional Gait Assessment, CRM- canalith repositioning maneuver, MNSI- Michigan neuropathy screening instrument, HbA1c- glycosylated hemoglobin level

5.3.4 Outcomes

The following outcome measures were collected at baseline and after resolution of vertigo

Dizziness Handicap Inventory (DHI): This is a standardized measure of self-report activity limitation and participation restriction due to either dizziness or unsteadiness [55]. It is a 25-item questionnaire with three subscales: functional, emotional and physical. It has a high test-retest reliability, good internal consistency, [55] and it is responsive to change in the vestibular

population,[188] with an 18-point change on the DHI considered clinically meaningful.[55] A DHI total score of 0-14 indicates no activity limitation and participation restriction; 16-26 as mild activity limitation, 28-44 as moderate and a total score of 46 or greater as severe activity limitation.[55]

Functional Gait Assessment (FGA): The FGA is a 10-item functional mobility test,[64, 189] that is scored on a four point ordinal scale (0-3) with a higher score indicating greater control during functional mobility. The FGA has moderate to strong correlations with other standard tests of balance.[64] A cut-off score of 22/30 on the FGA provides optimum validity for classifying fall risk in older adults.[64]

Postural sway: Participants were assessed in quiet standing in five conditions: (1) standing on a firm surface with eyes open; (2) standing on a firm surface with eyes closed, (3) standing on a foam pad with eyes open, (4) standing on a foam pad with eyes closed, and (5) tandem standing with eyes open on a firm surface. Details of postural sway assessment are described in detail in Chapter 4. The following variables were analyzed: 1) Range (cm/s^2), 2) peak velocity (cm/s), and 3) root mean square (RMS). All sway variables were examined in the anteroposterior (AP) and mediolateral (ML) directions.

Number of treatment maneuvers: Every repositioning maneuver performed was counted, with usually one repositioning maneuver done per session. In some participants, who were able to tolerate the procedure, the Dix-Hallpike was repeated in the same session and if the person was symptomatic, they received another CRM. No more than two CRM were done in one treatment session. All maneuvers that a participant required to achieve complete resolution of symptoms were added, to get a total count.

5.4 Statistical Analysis

Descriptive statistics (mean, standard deviation, %) were used to present participant demographics in each group. Differences in demographics between groups were examined using ANOVA and for significant differences, Tukey's pairwise comparisons were completed. After examining data for normality and homogeneity of variance, ANOVA was used to compare baseline DHI, and FGA scores between groups, and a general linear mixed model was used to examine postural sway measures before treatment between the two groups. Repeated measures ANOVA were used to examine change in DHI and FGA scores with treatment between groups. Change in range-AP, range-ML, PV-AP, PV-ML, RMS-AP and RMS-ML were examined using a general linear mixed model, with the change score on each condition entered as within subject factor, while group as between subject factor. The condition by group interaction was used to evaluate the group differences within conditions. For a significant model, we performed post hoc comparisons using Tukey's least significant difference for multiple comparisons. We compared number of treatment maneuvers required between groups using Mann-Whitney U tests. Data was analyzed using SPSS 20.0 (SPSS, Inc., Chicago, IL) with significance level set at 0.05.

5.5 Results

The screening and enrollment numbers for this study are presented in Figure 2. Two participants with BPPV dropped out from initial evaluation to final collection of outcome measures due to due to transportation difficulties. One participant with BPPV+DM dropped out because of shoulder pain that interfered with correct CRM technique. All three participants were excluded from the study, including baseline analysis. Due to equipment malfunction, we were only able to complete posture analysis on 42 out of 50 total participants.

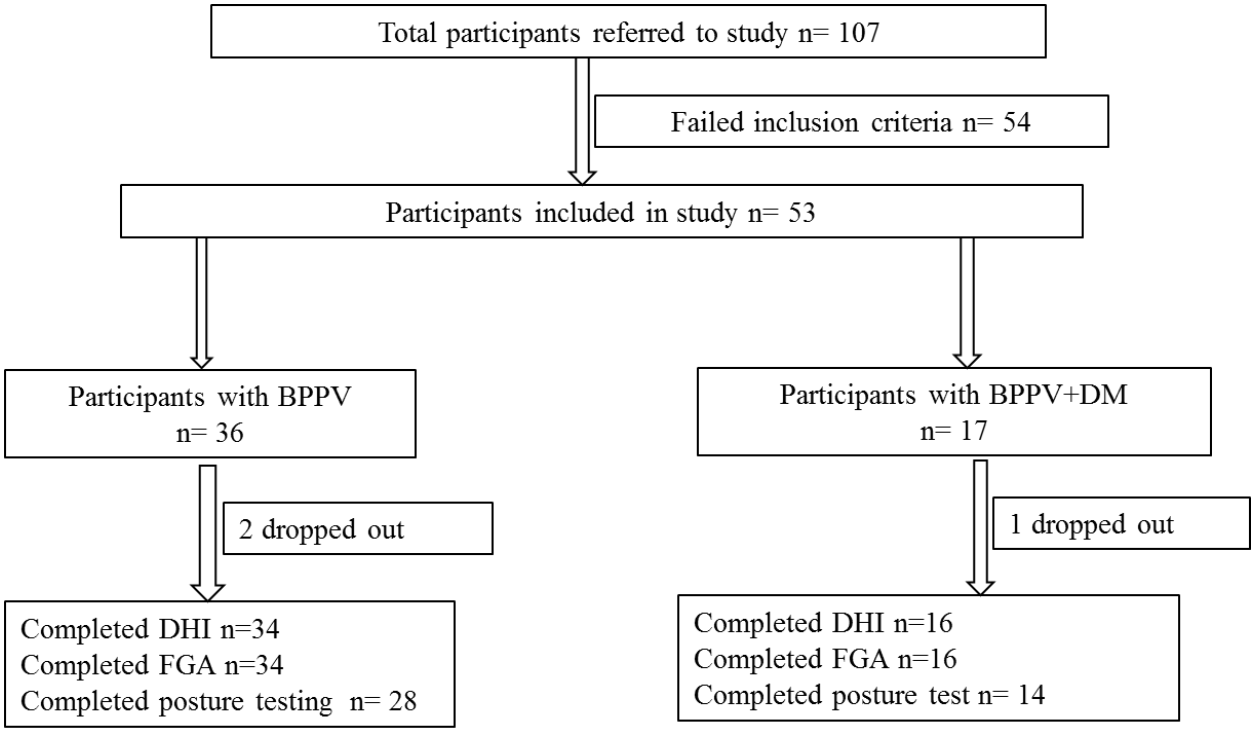

Figure 1: Participant enrollment chart. BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and type 2 diabetes

Participant demographics are presented in Table 1, as expected, significant differences were seen in HbA1c ($p<0.001$) and BMI ($p=0.002$) between the groups.

Table 1: Participant Characteristics

	BPPV (n=34)	**BPPV+DM (n=16)**	**p**
Age (years)	58.85 ± 10.65	62 ± 7.8	p=0.29
Gender (Female/ male)	29/5	10/6	
HbA1c (unit-%)	5.66 ± 0.41	6.93 ± 1.4	p<0.001
BMI (kg/m^2)	29.56 ± 7.6	36.27 ± 4.4	p=0.002
Peripheral neuropathy	6 (17%)	8 (50%)	

HbA1c- glycosylated hemoglobin, BMI- body mass index, BPPV-benign paroxysmal positional vertigo, BPPV+DM- BPPV and concurrent type 2 diabetes

Dizziness Handicap Inventory:

At baseline, there was no difference in DHI scores between groups (p=0.52). The DHI score changed significantly (pre to post treatment), with a main effect of time (p<0.001). There was no effect of group (p=0.28), and no interaction between group and time (p=0.59). Figure 3a shows DHI scores before and after treatment in both groups.

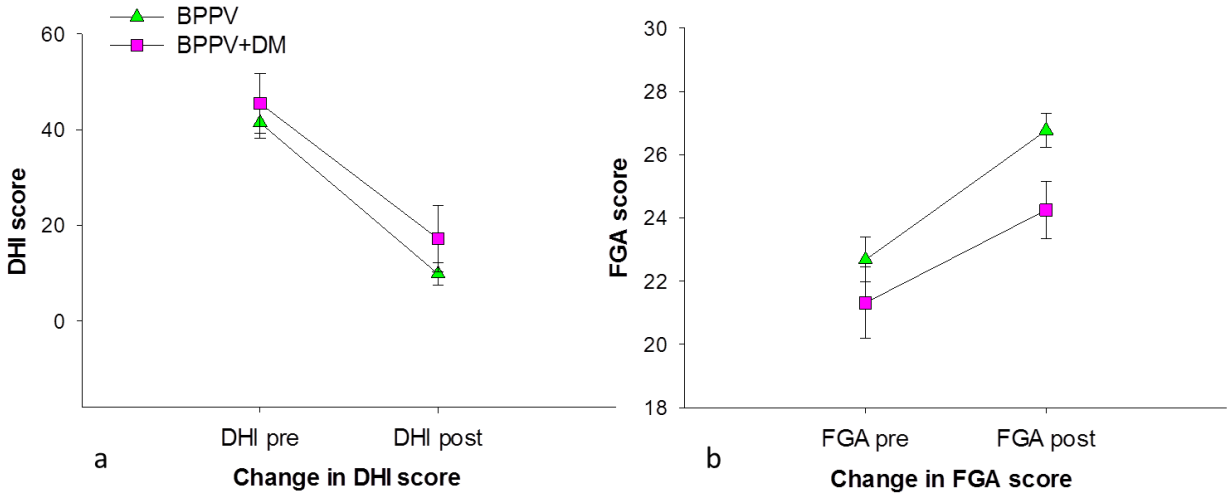

Figure 3: Change in 3a) DHI and 3b) FGA scores in both groups before and after treatment DHI- Dizziness Handicap Inventory, FGA- Functional Gait Assessment, BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and type 2 diabetes.

Functional Gait Assessment:

At baseline, there was no difference in FGA scores between groups (p=0.29). FGA scores changed significantly with treatment showing a main effect of time (p<0.001). There was no effect of group (p=0.08), and no interaction between group and time (p=0.14). Figure 3b shows FGA scores in both groups before and after treatment.

Po*stural sway variables:*

Results of postural sway comparison at baseline are presented in another manuscript and summarized here (Chapter 4, in review).

Range of acceleration:

At baseline, the postural sway variables of range of acceleration (AP and ML direction) and peak velocity (AP and ML direction) showed a significant interaction between group and condition. Post hoc analysis revealed that the BPPV+DM group had higher sway in condition 5, tandem stance, compared to the BPPV group (Figure 3). No effect of condition, group, or interaction between group and condition was noted for RMS at baseline.

Analysis of data following the treatment (change scores) revealed no effect of condition, group, or interaction between group and condition for any of the AP postural sway change scores (range, velocity, or RMS).

Change scores for range-ML showed a main effect of condition ($p=0.002$), and interaction between group and condition ($p=0.003$). The BPPV+DM group showed significant change in range-ML in condition 5, tandem stance (Figure 3).

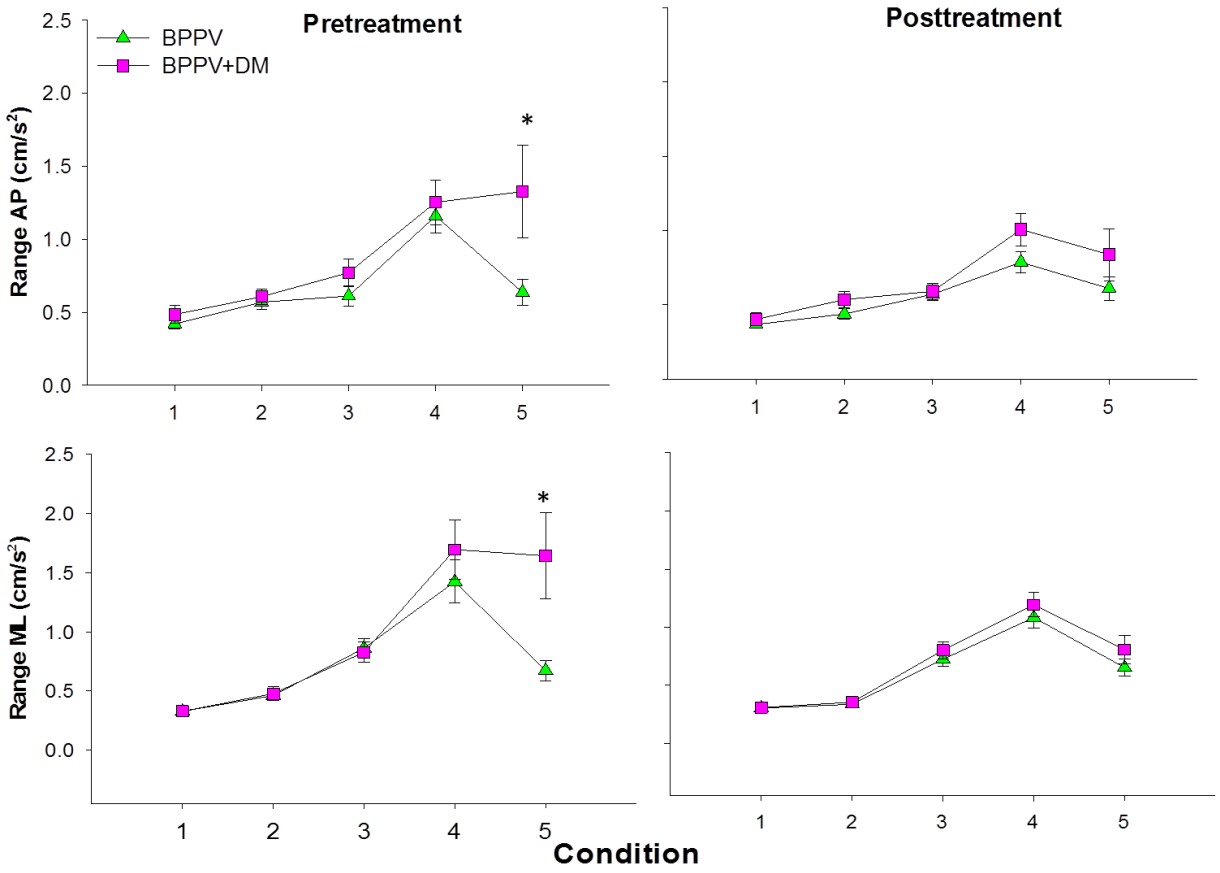

Figure 3: Means and standard errors of range in the anteroposterior (AP) and mediolateral (ML) direction in the two groups across the five testing conditions, before and after treatment. BPPV-benign paroxysmal positional vertigo, BPPV+DM- BPPV and concurrent type 2 diabetes

Change scores for PV-ML showed a significant main effect of condition (p=0.001), group (p=0.03), and interaction between group and condition (p=0.003). The BPPV+DM group showed change in PV-ML score in tandem stance (Figure 4).

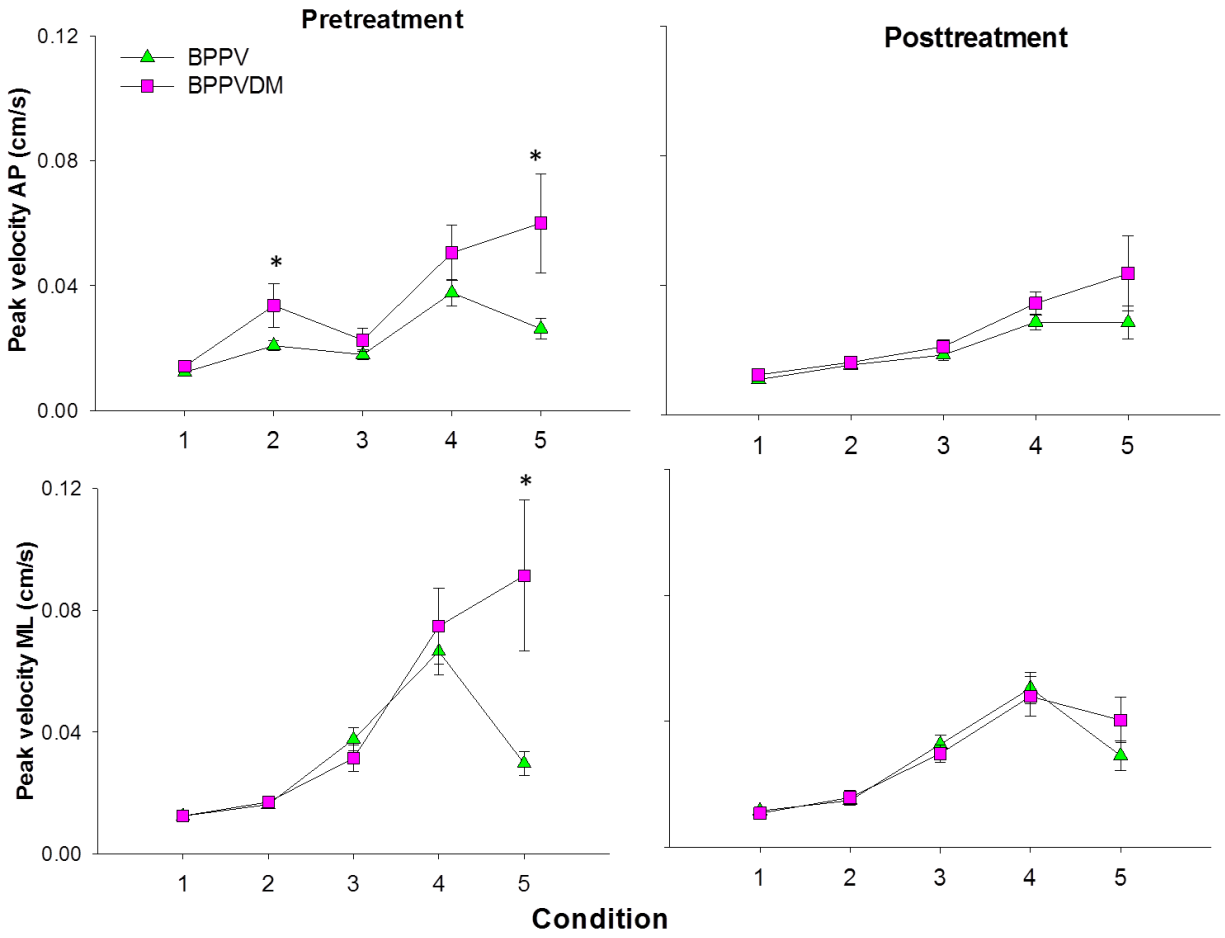

Figure 4: Means and standard errors of peak velocity in the anteroposterior (AP) and mediolateral (ML) direction in the two groups across the five testing conditions, before and after treatment. BPPV-benign paroxysmal positional vertigo, BPPV+DM- BPPV and type 2 diabetes

Change score for RMS showed no effect of condition, group, or interaction between group and condition in the AP or ML directions.

Treatment Maneuvers:

In the BPPV group, the average number of CRM performed was 1.8 ± 1.4, with a range between 1 and 7. In the BPPV+DM group, the average number of CRM performed were 2.0 ± 1.2, with a range between 1and 5. The difference was not statistically significant (p= 0.37).

5.6 Discussion

The main purpose of this study was to examine if the presence of diabetes increased BPPV symptoms, mobility and balance deficits or changed the efficacy of CRM treatments. Because T2D affects the neural and muscular structures, and the otolith organs directly, we hypothesized that people with BPPV and T2D would have more symptoms and mobility deficits when symptomatic, as well as after CRM treatment. Results of the study showed that diabetes did not increase symptom severity or decrease functional mobility before or after treatment. Both, people with BPPV and those with BPPV and T2D, improved significantly after successful resolution of the vertigo with CRM; and people with BPPV+DM did not require additional treatment maneuvers for symptom resolution when compared to those with BPPV only.

People with BPPV and BPPV+DM showed significant improvement in the Dizziness Handicap Inventory scores after the treatment maneuver. Both groups improved by more than 18 points, which is a clinically meaningful change,[55] showing that both people with BPPV and those with BPPV+DM benefitted significantly from treatment. However, we found that residual symptoms persisted in both groups, at levels that would indicate mild restriction of physical activity due to dizziness.[55] Results of our study are similar to others that have shown significant improvement in DHI scores after resolution of vertigo in people with BPPV,[190] with persistence of residual symptoms.[191, 192]

Functional mobility based on the Functional Gait Assessment improved significantly after treatment in both the BPPV and BPPV+DM groups, showing lower risk of falls.[64] Although, we could not find studies that have examined the FGA after treatment of BPPV, a recent study showed improvement in the Dynamic Gait Index after treatment of BPPV with the CRM.[191]

As we have previously reported, people with BPPV and BPPV+DM had higher postural sway values before treatment, particularly in conditions with altered proprioception, vision, or both; namely when standing on foam with eyes closed. These findings are similar to those of other researchers who have examined balance in people with BPPV.[149, 154, 158, 193] After successful resolution of vertigo, all participants showed a decrease in postural sway measures that was particularly evident in condition four, standing on foam with eyes closed. Results of our study are similar to Celebisoy et al[157] who showed that sway velocity was higher when standing on foam with eyes closed, compared to healthy controls, and a significant reduction in sway was observed after the canalith repositioning maneuver, approaching control sway. Our study showed that people with BPPV+DM made significant improvement in postural sway after the CRM; this improvement was seen in the mediolateral direction, when standing on foam with eyes closed as well as in tandem stance (condition 4 and 5). There were no differences between the groups in sway measures in the anteroposterior directions. Although we did not have a comparison with a healthy age matched control group for this study, the results of Chapter 4, show that neither the BPPV or BPPV+DM groups achieved levels of sway post treatment noted in the control group of our previous study, when standing on foam with eyes closed and tandem standing. Other researchers have found that postural sway did not improve completely immediately after the CRM in people with BPPV,[149, 154] and balance training was essential to improve postural control.[193, 194]

Based on the results of this study, we can conclude that people with BPPV (with or without diabetes) have significant deficits in daily activity, functional mobility and balance, and they respond well to treatment with the repositioning maneuver. This information underscores the importance of making an accurate vestibular diagnosis in people with T2D who present with

dizziness. Fife et al[195] found that it took 92 weeks for people with BPPV to obtain successful treatment of their vertigo, and once diagnosed 75% recovered from their symptoms in just one session. Oghalai et al. reported that 9% of adults with multiple comorbidities like T2D and hypertension go undiagnosed, with higher rates of falls and poor quality of life.[66]

Another important result of this study is that although people with BPPVDM respond well to treatment maneuvers, just like people with BPPV, they may require additional gait and balance training to recover fully.[154, 191, 192]

Limitations:

The main limitation of this study is the small sample size, particularly in the BPPV+DM group. This is likely due in part to our strict inclusion criteria, which did allow us to focus our attention to people with BPPV specifically in the posterior canal, of the canalithiasis variant. Participants in this study were from a wide age range, and age is known to affect balance and mobility. However the difference in age between groups was not statistically significant. Our study was conducted at a tertiary care center, where a large majority of our participants particularly in the BPPV group, had a history of recurrent episodes of BPPV, and hence, they may have been more complex and difficult to treat than people with BPPV recruited from the general community. We did not have a control group to compare postural sway measures with our participants after treatment, hence we could not assess if the postural sway measures returned to normal sway levels.

5.7 Conclusion

People with both BPPV and type 2 diabetes have functional deficits in daily activity, mobility, and balance similar to those seen in people with BPPV. Fortunately, these deficits respond well to treatment maneuvers in both groups.

Chapter 6

Discussion and Conclusion

6.1 Summary of Findings

This body of presented work extends the known impact of the complications of type 2 diabetes on the proprioceptive system and visual system, to another sensory system, the vestibular system. In this body of work, we explored the impact of vestibular dysfunction due to diabetes on a person's functional abilities and balance. Overall, our findings validate the results of other studies that have shown vestibular dysfunction due to diabetes. This is the first body of work to look at a specific vestibular condition, benign paroxysmal positional vertigo (BPPV), and the effect of diabetes in this patient population. The findings of this work have implications for the evaluation and treatment of individuals with type 2 diabetes and concurrent BPPV in clinical settings.

Chapter 2 Retrospective Data suggests that the Higher Prevalence of Benign Paroxysmal Positional Vertigo in Individuals with Type 2 Diabetes is Mediated by Hypertension.

The purpose of this study was to identify if diabetes increased the prevalence of specific vestibular conditions. Using a retrospective study design, we examined the charts of 3933 individuals, with results showing that the frequency of BPPV was significantly higher in people with diabetes. This study validated the results of one other study,[43] but was instrumental in showing how hypertension was the mediator in the relationship between diabetes and BPPV. This study contributes to science by identifying potential pathological mechanisms that may influence the prevalence of BPPV. Understanding underlying mechanisms can help in the development of new treatment strategies that may help to delay or prevent BPPV.

Chapter 3: Both Diabetes and Benign Paroxysmal Positional Vertigo affect Otolith Function

While many studies have shown impaired otolith function in people with BPPV, none of them had evaluated if their participants with BPPV had comorbidities like diabetes, which could have affected otolith function. A few, recent studies, have examined otolith function in people with T2D,[123, 124] but our study is the first to examine and compare otolith function in people with BPPV+DM to controls, people with T2D, and people with BPPV. Results of this work shows that saccule dysfunction was higher in people with T2D, BPPV and BPPV+DM compared to controls, with prolonged saccule latencies associated with higher HbA1c levels. In people with BPPV+DM, we did not see a distinct cumulative effect of BPPV and T2D on the otolith organs.

Chapter 4: Postural Sway is Significantly Higher in Individuals with Type 2 Diabetes and Concurrent Benign Paroxysmal Positional Vertigo

The purpose of this study was to extend the findings of Chapter 3 to look at postural control in individuals with BPPV+DM. Because otolith organ dysfunction is associated with postural instability, our next step was to examine postural sway in people with BPPV+DM and compare the findings with people with BPPV, T2D and controls. In Chapter 4, we examined postural sway using an accelerometer, and found that postural sway was significantly higher in people with BPPV+DM compared to people with T2D and healthy controls, particularly when standing on a compliant surface with eyes closed and in tandem stance. This study makes a significant contribution to the existing body of literature by showing that during everyday activities, there are certain positions in which people with BPPV+DM may feel unstable, which could increase their risk of falling.

Chapter 5: The Impact of Type 2 Diabetes on Symptom Presentation and Response to Treatment in Individuals with Benign Paroxysmal Positional Vertigo

Based on the preceding chapters, we found impairments in otolith function and postural control in people with BPPV+DM, which could potentially affect daily function, mobility and recovery after treatment with the canalith repositioning maneuver. In this study, we compared symptom severity, functional mobility and postural control in people with BPPV+DM to those with BPPV only. We examined if diabetes influenced the number of repositioning maneuvers required for resolution of vertigo, as well as function after treatment to evaluate if people with BPPVDM recovered to the same extent as those with BPPV only. Results of this study showed that people with BPPV regardless of their diabetes status, improved significantly with repositioning maneuvers in all aspects of daily life. People with BPPV+DM did not require additional maneuvers and there were no differences between the groups on measures of handicap, mobility, or balance after resolution of symptoms. Results of this study underscore the importance of early diagnosis and effective treatment of people with BPPV+DM.

6.2 Potential Mechanisms by which type 2 diabetes affects gait and balance- what is the significance of the vestibular system?

Balance is a motor skill that emerges from the interaction of multiple sensory systems to meet functional goals. The proprioceptive, visual, and vestibular systems, work together to provide the body with optimal feedback to ensure appropriate motor planning and execution. In people with diabetes and BPPV, all three sensory systems may be affected, thereby, affecting mobility and function.

Peripheral neuropathy due to diabetes

Diabetic peripheral neuropathy (DPN) affects up to two-thirds of individuals with diabetes, and is characterized by pain, paresthesia and sensory loss.[16] Postural sway is higher in

people with DPN who have a longer duration of diabetes, and poorly controlled hyperglycemia.[22, 23] The greatest decrease in postural stability in individuals with DPN, is seen with eyes closed, showing a reliance on vision to compensate for sensory deficits.[6] People with DPN fall more often and the cause of the recurrent falls are decreased vibration sense and loss of pressure sensitivity due to DPN.[24] Because of decreased proprioceptive feedback during walking, older adults with diabetes walk slower and have greater stride variability, increasing the risk of falls.[25] Although aerobic exercise has been shown to increase intra-epidermal nerve fiber branching in people with DPN,[73, 196] currently, there are no therapeutic interventions that can reverse DPN.

Diabetic Retinopathy

In the United States, about 40% of individuals with type 2 diabetes and 86% with type 1 diabetes develop retinopathy.[17] There are strong associations between diabetic retinopathy, the duration of diabetes and the risk of falls; with severe cortical cataract significantly associated with fractures.[26]

Vestibulopathy due to diabetes

The odds of developing vestibular dysfunction are 70% higher among adults with diabetes compared to those without diabetes,[7] especially in people with a longer duration of diabetes, higher serum HbA_{1C} levels ($\geq$ 7.0%),[8] and in those people who have other diabetes-related complications like peripheral neuropathy and retinopathy.[8] In people with diabetes, the odds of falling are two times higher, even after taking retinopathy and neuropathy into account.[8]

Based on the review of existing literature, diabetes can impair gait and balance by affecting all three sensory systems: proprioception, vision, and vestibular. The results of our study showed that people with BPPV+DM had a higher frequency of abnormal saccule responses

compared to healthy age matched controls. However, abnormal VEMP responses in the BPPV+DM group were not different from the BPPV only or the T2D only groups. Given this information, we would have expected that postural sway would be similar in people with T2D, BPPV, and BPPV+DM. However, we found significantly increased postural sway in people with BPPV+DM, particularly when standing on foam with eyes closed and tandem stance. In conditions of daily life, where vision and somatosensation are available and dependable sources of sensory information, people with BPPV+DM perform well. In compromised situations like compliant or uneven surfaces and with a narrow base of support, they had higher sway compared to all other groups. It appears that factors other than otolith dysfunction may contribute to this increased sway; peripheral neuropathy, which was seen in 50% of people with BPPVDM, could be one possible factor. In addition, other factors like weakness, decreased endurance due to sedentary lifestyles, and obesity may have contributed to increased sway. We did not examine these factors; however, it would be interesting to examine the relative contributions of these factors, mainly because they are all modifiable with diet, exercise, and education.

People with BPPV and diabetes may be unable to reweight their sensory systems to meet the demands of daily life. Participating in walking programs may be difficult for people with BPPV+DM, especially if they have to walk outdoors and on uneven sidewalks. Identifying and treating the BPPV is essential, but even after successful treatment of vertigo, balance deficits persist. Balance training may be necessary to teach people how to use their available sensory capabilities more effectively. Even if the function of the peripheral vestibular organs does not improve, we need to identify if we can improve balance by influencing central mechanisms. This study provides the framework by which we can move ahead to identify the role of vestibular rehabilitation. We need to develop exercises that target the otolith organs, to benefit all people

with BPPV. We need to identify outcome measures that are sensitive to deficits and change in people with BPPV. We need to identify exercises that may help to prevent BPPV and prescribe them efficiently to delay recurrences. We need to disseminate the information gleaned from this body of work to physicians and other health care providers to promote early diagnosis and treatment of BPPV. In addition, education regarding the risk of potential falls, particularly in professionals such as painters, and construction workers, where people are working at heights, will help to reduce falls.

6.3 Limitations

6.3.1 Setting of Study

All of the testing for this study was completed in the Otolaryngology-Head and Neck Surgery clinic at the University of Kansas Medical Center. We had a quiet room to conduct the examinations and posture testing and a soundproof room to complete the VEMP testing. However, KUMC is a tertiary care center; hence, a majority of the participants in this study had recurrent episodes of BPPV. This may have influenced recovery patterns since people with recurrent episodes of BPPV are more difficult to treat.

6.3.2 Participant Characteristics and Sample Size

The participants with BPPV, both with and without diabetes, who were recruited for this study, were in good health. We did not have a variety of participants with poor and uncontrolled T2D; hence, this study may not be representative of the diabetic population at large. In addition, majority of our T2D control group participants were employees from the medical center. They all had well controlled diabetes and we did not see a variety of participants with poor or uncontrolled blood glucose levels.

Another limitation of our sample was the modest sample size per group. Although, we had adequate participants in the BPPV group, we could not recruit enough participants in our BPPV+DM group, despite our extensive recruitment efforts. We lost three subjects to follow-up, which is a small number, but affected our total subjects analyzed. Due to the small sample, we could not analyze mobility and function based on the presence of DPN, even though we had completed the MNSI on all participants.

Our participants were 40-80 years of age; hence, they did have other comorbidities like osteoarthritis, osteoporosis, joint arthroplasty, mild visual impairments, migraine, and other such conditions. We included them in the study if they were ambulating independently without physical impairment. In addition, all participants took a variety of medications, and those with BPPV+DM were taking ant-diabetic medications and/or exogenous insulin. We collected the list of comorbidities and medications, but did not control for them in the study.

6.3.3 Study Design:

Our study was designed to confirm the diagnosis of BPPV in the participant and collect outcome measures immediately after the diagnosis was confirmed. Likewise, at the end of the study, if VNG did not show torsional nystagmus, the BPPV was considered resolved and outcomes were collected immediately. Because of this design, several participants were unsure when answering the Dizziness Handicap Inventory after treatment, as they did not have enough time to evaluate how much daily activity still bothered them.

We used the MNSI to make a diagnosis of diabetic peripheral neuropathy; however, this test is not the gold standard for diagnosing peripheral neuropathy.

6.3.4 Tests and Measures:

The VEMP is a sensitive test of otolith function, however, evoked potential tests are responses derived from muscle contraction. Our equipment did not have the electromyography feature built into the machine. Hence, we could not control for baseline variations of muscle activity during the oVEMP or account for increased muscle activity, which directly affects the cVEMP response. We used the blood pressure manometer technique, which is a validated technique to control for contraction of the sternocleidomastoid.[142] Since we could not control for variations in amplitude of oVEMP, results related to amplitude of the oVEMP have to be viewed with caution.

Studies in people with unilateral BPPV have shown that both ears have abnormal VEMP responses, which persist after successful repositioning,[148] indicating a permanent change in function of the saccule. The subjective visual vertical (SVV) is a test that has been shown to be useful to identify utricle dysfunction in people with BPPV.[197] Responsiveness of the SVV in people with BPPV has not been examined, it may be a useful test to show if utricle function improves after the canalith repositioning maneuver.

The Functional Gait Assessment (FGA), used in this study to assess mobility has been validated in the vestibular population in people with unilateral and bilateral vestibular hypofunction. However, people with BPPV are high functioning and not all items of the FGA are difficult for them to perform. Hence, the overall score on the FGA may not be sensitive enough to detect their deficits. Analyzing individual items on the FGA, i.e. looking at change in gait speed or specifically examining items that depend heavily on the vestibular system, like walking with eyes closed, may be more sensitive to deficits and change with treatment in this patient population, compared to the total score.

We examined accelerometry before and after treatment in people with BPPV and BPPV+DM, however, we did not compare accelerometry results after treatment to a control group, in the same age range. Having a comparison of this nature, would be particularly useful at the end of the treatment to examine if people with BPPV and BPPV+DM returned to the same baseline level as healthy, age matched controls.

6.4 Future Directions

This body of work addresses several key areas showing the effect of type 2 diabetes on the vestibular system and the impact it has on daily life. The future directions proposed arise from questions that remain unanswered.

6.4.1 Comprehensive Assessment of the Vestibular System:

Vestibular Tests:

In this study, we focused our attention on the otolith organs because our patient population had an identified otolith problem. However, they could also have had semicircular canal involvement as well as central vestibular structures involved. Studies in people with type 1 diabetes have implicated the involvement of both central[9] and peripheral[39] vestibular structures. Hence, future studies need to extend the examination of people with BPPV to include the semicircular canal. Including the caloric test and examination of the vestibular-ocular reflex, which includes the vestibular head thrust test, and the dynamic visual acuity test, will provide information about the semicircular canals and their functional status. Using videonystagmography to examine nystagmus with position changes, the optokinetic reflex, as well as rotary chair tests, will allow for a comprehensive examination of central and peripheral

vestibular structures. We need to examine differences in all these measures in people with BPPV with and without T2D, before and change after treatment.

Future studies need to examine the VEMP immediately after treatment as well as 12 weeks after treatment, which is the time period at which balance improves in people with BPPV. We need to see if there are improvements in balance in people with BPPV+DM, and if there are changes in the VEMP, and the time point at which the changes are noted. In addition, examining the utricle using the subjective visual vertical test would be a good addition to assess otolith function.

6.4.2 Physical Therapy tests and measures of vestibular function:

Future studies are needed to identify tests and measures that are sensitive to functional deficits and responsive to change, in people with BPPV. The Functional Gait Assessment was developed with additional items that challenged the vestibular system, because the Dynamic Gait Index had a ceiling effect in some vestibular patient populations. Although, we found that the FGA was sensitive to change after treatment, the total score was not able to reflect the activities that continued to be difficult after treatment. It is necessary to identify the specific items of the FGA that do not improve after the vertigo has resolved, so that they can be incorporated into exercise programs for individuals with BPPV+DM, to improve treatment outcomes.

Future studies that examine fall risk in people with BPPVDM are essential. People with diabetes are known to have a higher fall risk, become recurrent fallers, and sustain more severe injuries compared to those without diabetes. In our study, we did not include measures to assess falls. However, in people with T2D, with diabetic complications like neuropathy and retinopathy, having the additional burden of vestibular dysfunction could increase risk of falls significantly.

Examining fall risk will help in the development of education tools and fall prevention programs that could benefit this patient population tremendously.

6.4.3 Management of People with BPPV:

This study demonstrates that the canalith repositioning maneuver was very effective for the management of BPPV and improved the quality of life in all individuals treated. This underscores the importance of making an early and accurate diagnosis of the canal involved, so that the appropriate treatment maneuver can be performed. It is essential to educate health care professionals who work with people with diabetes regarding the prevalence of BPPV. Asking only a few pointed questions about the dizziness, can help identify BPPV so that an appropriate referral can be made for treatment. Recent studies continue to show that the Dix-Hallpike test, which is the gold standard to diagnose BPPV, is performed in only 3.9% of people who come to the emergency department with complaints of dizziness.[198] To disseminate the information to rural areas with limited number of vestibular therapists, future studies looking at tele-medicine as a viable option to diagnose and treat individuals with BPPV would be beneficial.

Most importantly, we need to identify which balance exercises will benefit people with BPPV+DM. If we identify semicircular dysfunction, we need to explore the usefulness of gaze stability exercises, which is not part of a standard exercise prescription currently for people with diabetes. For otolith dysfunction, we need to develop exercises that target the otolith organs. Presently, balance exercises on compliant surfaces and with eyes closed are shown to improve balance. However, we need to examine which movements specifically stimulate the otolith organs, and the frequency and duration of exercise, which would make the most meaningful

change, so that we can include them in our exercise prescription. We need to examine change with standard exercises, and change with a more focused vestibular prescribed program.

We need to examine the recurrence rate in people with BPPV+DM. We need to conduct longitudinal studies that look at the recurrence rates of BPPV in people with T2D as well as evaluate the benefit of preventative exercises so that we can effectively prescribe preventative exercises for people with BPPV+DM.

6.4.4 Other Patient Populations:

Vestibular dysfunction is commonly seen in veterans who have returned from wars, after being exposed to either direct or indirect blast trauma. Evaluating the extent of damage to the vestibular organs in veterans, and examining the prevalence as well as recurrence of BPPV could provide valuable information on the pathophysiology of BPPV. As the veteran population ages, and they present with comorbidities like hypertension and diabetes, it is necessary to examine their symptom presentation, examine how vertigo affects their daily activities, and proactively evaluate what we can do to avoid falls and injury.

6.5 Conclusion

This body of work provides evidence that vestibular dysfunction is a complication of type 2 diabetes. The prevalence of BPPV is higher in people with type 2 diabetes, with the saccule more affected by diabetes compared to the utricle. Postural sway is higher in the presence of type 2 diabetes and BPPV, especially in challenging conditions. However, the canalith repositioning maneuver was effective in treating vertigo and people with type 2 diabetes and concurrent BPPV, recovered just as well as those with BPPV without diabetes. Overall, our findings reinforce the importance of making an early and accurate diagnosis of BPPV in people with

coexisting comorbidities, so that they can be treated effectively. This study highlights the need for further research investigating physiological and functional factors, in patient populations that have vestibular dysfunction, like our veterans. It also emphasizes the need to develop focused exercise programs that will stimulate the otolith organs that are affected in people with both BPPV and T2D.

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