

FOOTSTEPS TOWARD UNDERSTANDING FALL RISK AND QUALITY OF LIFE IN
PEOPLE WITH DIABETIC PERIPHERAL NEUROPATHY

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Abstract

As of 2010, diabetes affected nearly 25.8 million people in the United States, an increase of 25% from 2005. Nearly half of these individuals experience diabetic peripheral neuropathy (DPN), a serious complication of diabetes. DPN influences how these individuals experience the world around them. Sensory abnormalities and sometimes motor dysfunction in the lower extremities are known to increase fall risk and decrease quality of life in these individuals. However, little is known about whether or not current fall risk assessment tools are effective or useful for identifying fall risk in people that have DPN. In addition, relatively few studies have attempted to identify factors that may relate to this increased fall risk and decreased quality of life in people with DPN.

Chapter 2 details the research conducted to compare the ability of 4 fall risk assessment tools to accurately discriminate between fallers and nonfallers, who were categorized according to recent fall history. The 4 tools that were compared included the Functional Reach Test (FRT), Timed Up and Go (TUG), Berg Balance Scale (BBS) and the Dynamic Gait Index (DGI). These tools performed poorly when traditional cut-off scores were used; however, the use of modified cut-off scores substantially improved the discriminative ability of these tools. The TUG performed the best, followed by the DGI, BBS and then the FRT. Additional research validating the use of these tools and/or new tools that are more specific to people with DPN needs to be conducted.

Fall risk is a complex, multifaceted issue that has been extensively studied in populations other than people with DPN. Chapter 3 details research conducted with the aim of identifying factors that relate to fall history, which may also relate to risk for future falls, specifically in people with DPN. The data suggest that physical activity levels, fear of falling, and balance and

gait deficits relate to fall history and may play a role in fall risk for people with DPN. Additional studies that use larger samples of people with DPN need to be conducted to confirm these new findings and to more fully understand the nature of the relationship between these factors and fall risk.

Health related quality of life (HRQOL) is a targeted outcome measure because it is meaningful to patients. The aim of the research associated with Chapter 4 was to identify specific factors that relate to HRQOL in people with DPN. This research confirmed previous findings that pain relates to HRQOL but did not support findings that neuropathy severity relates to HRQOL in people with DPN. The current body of work also extended previous findings in other populations to people with DPN, namely, that fear of falling and physical activity levels also relate to HRQOL. As with the factors related to fall history in Chapter 3, additional research needs to be conducted to more fully understand how these factors influence HRQOL in people with DPN.

This body of work has added new knowledge to the previously understudied areas of fall risk and quality of life in people with DPN. Although this new knowledge is important, it does not fully explain all aspects of these issues for people with DPN. Additional research is needed to more fully understand fall risk and quality of life in people with DPN and, ultimately, to effectively prevent falls and improve quality of life for these individuals.

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Chapter 1

Introduction

1.1 Diabetes and Peripheral Neuropathy

Diabetes, a disease characterized by inadequate production or improper use of insulin that results in high levels of blood sugar, affects nearly 25.8 million people in the United States.(CDC, 2011) This disease has many serious complications including diabetic neuropathy, which presents clinically in many different ways.(Vinik, Park, Stansberry, & Pittenger, 2000) The diabetic neuropathies can be classified into 3 different categories: 1) focal neuropathies, 2) diffuse neuropathies, and 3) autonomic neuropathies.(Vinik, et al., 2000) The proposed study addresses one of the diffuse neuropathies, distal symmetric polyneuropathy, which is the "most common and widely recognized form of diabetic neuropathy"(Vinik, et al., 2000, p. 961). Prevalence rates are as high as 50% in people with diabetes.(Dyck et al., 1993) Others cite 30-40% with a general increase in prevalence as duration of diabetes lengthens.(Harris, Eastman, & Cowie, 1993) This type of diabetic neuropathy is often referred to as diabetic peripheral neuropathy (DPN).

DPN is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".(Boulton et al., 2005) Clinically, DPN presents as abnormalities in sensory and sometimes motor function in the lower legs and the hands. Generally, sensory abnormalities in the lower leg present earlier in the progression of DPN than motor abnormalities and the hands are usually involved only in more severe cases of DPN.(Vinik & LeRoith, 2008) Symptoms of DPN are often stocking-like in nature and may include burning or aching pain in about 50% of individuals with DPN; however, others may report painless, numb feet.(Boulton, et al., 2005; Feldman, Russell, Sullivan, & Golovoy, 1999; Vinik & LeRoith, 2008) Clinical signs of DPN are more consistent than symptoms and usually include some degree of bilateral lower extremity loss of touch, pressure,

vibratory, position, and temperature sensory perception and decreased ankle reflexes.(Boulton, et al., 2005; Feldman, et al., 1999; Vinik & LeRoith, 2008) Which signs and symptoms a DPN patient presents with depends on whether large and/or small nerve fibers are affected by the disease.(Vinik, et al., 2000)

Why people with diabetes develop DPN is not entirely clear, however, research indicates that persistent hyperglycemia in people with diabetes leads to a cascade of events that ultimately damage peripheral nerve tissue.(Feldman, et al., 1999) Boulton and colleagues suggest that aggressive glycemic control is important for the treatment of diabetic neuropathy as it appears that optimal blood glucose control helps to prevent DPN.(Boulton, et al., 2005) Regardless of the mechanisms that lead to DPN, the signs and symptoms associated with this complication of diabetes can influence a person's ability to safely stand, walk and maintain their balance during daily activities, which can lead to falls.(Menz, Lord, St George, & Fitzpatrick, 2004; van Schie, 2008)

How to arrive at the diagnosis of DPN is also a bit unclear. The American Diabetes Association's position statement "Standards of Medical Care in Diabetes - 2008" suggest that electrophysiological testing is not necessary except when a patient presents with atypical signs and symptoms.("Standards of medical care in diabetes--2008," 2008) However, it is suggested that clinical screening for DPN consist of "tests such as pin-prick sensation, vibration perception (using a 128-Hz tuning fork), 10-g mono-filament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of ankle reflexes".("Standards of medical care in diabetes--2008," 2008) Vinik suggests that a comprehensive clinical examination is essential to diagnosing DPN and that using at least two different clinical tests of sensation (e.g. pinprick, vibration sensation, monofilament pressure perception) increased the ability to detect

DPN.(Vinik & LeRoith, 2008) Others suggest that a diagnosis of DPN should include a minimum of 2 abnormalities in signs or symptoms often associated with DPN and that for research, at least one of these should include a quantitative deficit in nerve function as measured by, for example, nerve conduction study.(Boulton, Malik, Arezzo, & Sosenko, 2004; Dyck, 1988) The use of the Michigan Neuropathy Screening Instrument(Feldman & Stevens, 1994) (MNSI) which assesses vibration perception, mono-filament pressure sensation and ankle reflexes has also been supported as a complimentary tool for the diagnosis of DPN. According to the Mayo Clinic Proceedings, "Consensus Guidelines: Assessment, Diagnosis, and Treatment of Diabetic Peripheral Neuropathic Pain", the MNSI is an acceptable and valid tool used to establish the presence of neuropathy.(Argoff et al.) Feldman and colleagues, the creators of the MNSI, and the results of recent validation studies by other researchers suggest an MNSI cut-off score of 2 for detecting the presence of DPN.(Feldman & Stevens, 1994; Moghtaderi, Bakhshipour, & Rashidi, 2006)

1.2 Falls and Diabetic Peripheral Neuropathy

Falls have been studied extensively in older persons and it is estimated that 30% of people over the age of 65 fall every year.(Tinetti, Speechley, & Ginter, 1988) It is also clear that this increased fall risk holds true for older, community-dwelling people with diabetes as well and that diabetes is an independent risk factor for falls.(Hanlon, Landerman, Fillenbaum, & Studenski, 2002; Schwartz et al., 2008; Tilling, Darawil, & Britton, 2006) Diabetic peripheral neuropathy, as mentioned previously, influences sensory and, depending on severity, motor nerve function in the distal lower extremities. Intuitively, one would think that sensory and/or motor changes in the distal legs may influence balance and gait in individuals with DPN which

may increase fall risk; studies have demonstrated that DPN does indeed increase fall risk.

Cavanaugh and colleagues (Cavanaugh, Derr, Ulbrecht, Maser, & Orchard, 1992) conducted a study comparing safety, injury, changes in gait and posture, and worry about falls during walking and standing between neuropathic and non-neuropathic groups of insulin-dependent diabetes mellitus (Type 1) subjects (age range, 29-35). The neuropathic group demonstrated significantly poorer ($p < 0.001$) nerve conduction velocity and vibratory threshold scores as compared to the non-neuropathic group. It was found that subjects in the neuropathic group were 15 times more likely to report an injury related to falls during walking and standing than those in the non-neuropathic group. (Cavanaugh, et al.)

Powell, Carnegie, and Burke (Powell, Carnegie, & Burke, 2006) found that 29% of older subjects that had been diagnosed with DPN had fallen in the previous year with 73% having fallen 2 or more times during that period. These investigators were studying the affect of monochromatic near-infrared photoenergy therapy (MIRE™), a treatment for DPN, on falls in older persons. To be enrolled in the study, all subjects ($n=252$, age range 64-101) had to have demonstrated clinical improvements in sensation after the MIRE™ treatment. During the 9 months after MIRE™ treatment for DPN, these same subjects reported a 55% reduction in falls compared to the year prior to treatment; this reduction in the number of patients reporting a fall after phototherapy was significant ($p < 0.0001$) using paired two-tailed t-tests for statistical analysis. (Powell, et al., 2006) Even though the subjects were older, the reduction in fall rate due to DPN treatment suggests that DPN influences fall incidence independent of older age.

Another study by Richardson, Ching, and Hurvitz (Richardson, Ching, & Hurvitz, 1992) investigated the relationship between peripheral neuropathy (diabetic and non-diabetic) and falls. This study involved a neuropathy group and a control group, defined by abnormal and normal nerve conduction study results, respectively. The two groups were age-

and sex-matched. The results of this study indicated that peripheral neuropathy was a significant risk factor for and significantly associated with falling and repetitive falling.(Richardson, et al., 1992) Even though this study also included persons with peripheral neuropathy due to reasons other than diabetes, it demonstrates that peripheral neuropathy, in general, increases fall risk. While research evidence for increased fall risk in people with DPN exists, there appears to be greater amounts of research evidence for gait and balance problems in people with DPN.

In the early 1990's, researchers investigated balance and gait changes in people with DPN noting slower reaction times, decreased ankle strength and mobility, altered walking patterns, and greater postural instability when compared to control groups without DPN.(Boucher, Teasdale, Courtemanche, Bard, & Fleury, 1995; Courtemanche et al., 1996; Mueller, Minor, Sahrman, Schaaf, & Strube, 1994; Richardson, et al., 1992; Simoneau, Ulbrecht, Derr, Becker, & Cavanagh, 1994) Mueller and colleagues compared the gait characteristics of a group of subjects with DPN (defined by a history of a neuropathic foot ulcer, n=10) and a group of age-matched non-diabetic subjects; all subjects were able to ambulate independently without an assistive device. The subjects in the DPN group demonstrated decreased ankle range of motion, decreased ankle power, and decreased stride length as compared to the non-diabetic subjects.(Mueller, et al., 1994) Another study that also compared people with DPN and non-diabetic controls reported significantly increased sway range ($p<0.001$), sway speed ($p<0.05$), sway dispersion ($p<0.001$) of subjects' center of pressure during quiet, barefoot standing for those in the DPN group.(Boucher, et al., 1995) These changes indicate impaired postural stability, which the authors suggest may put these subjects at higher risk of falling. More recently, LaFond, Corriveau, and Prince(Lafond, Corriveau, & Prince, 2004) also found significantly greater ($p<0.05$) center of pressure displacement during quiet standing in subjects

with DPN (defined by the Valk scale score(Valk, et al., 1992)) as compared to an age-matched control group of healthy subjects. In this study, the DPN group demonstrated significantly poorer vibratory sense and mono-filament testing results when compared to the control group, further confirming the DPN diagnosis. Both of the aforementioned studies address postural stability in a static position, but do not address stability when falls would most likely occur, during walking. Menz and colleagues(Menz, et al., 2004) compared walking stability between people with DPN and age-matched healthy controls. Walking stability was assessed by measuring head and pelvis accelerations and harmonics (e.g. "smoothness" or "rhythm" of walking pattern) while walking on a 20-meter walkway. Even though DPN subjects demonstrated significantly slower walking speeds than control subjects, head and pelvis acceleration were not significantly different, suggesting a decreased ability of DPN subjects to lessen the accelerations experienced during walking. In addition, the DPN subjects demonstrated significantly smaller harmonic ratios, indicating a decreased ability to "smooth" accelerations as compared to the control groups, in spite of walking more slowly. Menz et al.(Menz, et al., 2004) also reported a significantly decreased foot pedal reaction time for the DPN group, demonstrating a decreased ability to rapidly generate torque at the ankle which they suggest may have implications for falls in people with DPN. It is clear from these studies that DPN results in balance and gait problems.

The top two reasons cited for falls, from a review of 12 of the largest retrospective fall-related studies in the elderly, are environment-related accidents and gait and balance disorders or weakness.(Rubenstein, 2006) Gait and balance problems alone are responsible for a 3-fold increase in risk of falling.(Rubenstein & Josephson, 2002) Rubenstein states that these balance and gait problems may "stem from simple age-related changes", "from specific dysfunctions of

the nervous, muscular, skeletal, circulatory and respiratory systems or from simple deconditioning following a period of inactivity".(Rubenstein, 2006) In the case of DPN, it is clear that this dysfunction of the peripheral nerves negatively affects balance and gait, and increases fall risk. Whether due to sensory loss, muscle weakness, balance and gait problems or other factors not yet identified, it is clear that falling is an issue for people with DPN that needs to be addressed.

1.3 Fall Risk Assessment

Due to the negative consequences of falls, a number of fall risk assessment tools have been developed to identify people who are at risk of falling, in hopes that early identification combined with fall reduction interventions would lead to a decrease in the incidence of falls.("Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention,") Some commonly used fall risk assessment tools include the Functional Reach Test (FRT), the Timed Up and Go (TUG), the Berg Balance Scale (BBS), and the Dynamic Gait Index (DGI). Each of these tools measures some degree of static or dynamic balance and/or gait. After conducting each test, a tester is able to determine whether or not the person tested is at risk for falling based on the score received and how it compares to an established cut-off score related to fall risk. Generally speaking, the result of the assessment can be considered accurate if the specific tool has been validated for persons similar to the person being tested; it is important to only use fall risk assessment tools that have been validated for the population being tested.(O'Sullivan & Schmitz, 2005) For example, all of the aforementioned tools appear to be valid for use with healthy older persons(K. Berg, Wood-Dauphinee, & Williams, 1995; Bogle

Thorbahn & Newton, 1996; Duncan, Studenski, Chandler, & Prescott, 1992; O'Sullivan & Schmitz, 2005; Podsiadlo & Richardson, 1991; Weiner, Duncan, Chandler, & Studenski, 1992). The utility of these tools has led to their validation in people with a known increased risk of falls due to problems such as Parkinson's disease(Dibble, Christensen, Ballard, & Foreman, 2008), vestibular dysfunction(Marchetti, Whitney, Blatt, Morris, & Vance, 2008), and after stroke(Blum & Korner-Bitensky, 2008). However, no literature indicates that any of these tools have been validated for people with DPN. Considering the increased risk of falling and impaired gait and balance often present with DPN, the ability of these fall risk assessment tools to discriminate between fallers and nonfallers needs to be assessed for people with DPN so that those at risk of falling can be identified and enrolled in fall prevention programs.

Validation

Validity is defined as "the meaningfulness of test scores as they are used for specific purposes".(Domholdt, 2005) Validity assessments are conducted to determine the usefulness of screening and/or diagnostic tools for clinical purposes. The current work set forth to assess the ability of fall risk assessment tools to accurately discriminate, in people with DPN, between fallers and nonfallers. In order to assess the usefulness of the tools, there needs to be some measure to which the assessment results can be compared; this is often called the gold standard.(Domholdt, 2005) This gold standard allows a researcher to determine whether or not the tool being assessed accurately measures what it is intended to measure. Depending on the nature of the study, investigators use either fall history or future fall incidence as the gold standard by which the discriminative accuracy of fall risk assessment tools is assessed. To date,

no researchers have assessed the usefulness of the aforementioned fall risk assessment tools in people with DPN.

Ideally, these types of studies would use prospective methods to determine whether or not fall risk assessment tools accurately identify people at risk of falling.(Dibble & Lange, 2006; Rubenstein, 2006) However, prospective studies that record fall incidence require significantly more time and resources to conduct than studies that inquire about fall history. If a prospective study is not conducted, an assessment of fall history is often employed(Rubenstein, 2006) and has been used by many researchers to assess the discriminative ability of fall risk assessment tools in other populations.(Dibble, et al., 2008; Dibble & Lange, 2006; Shumway-Cook, Baldwin, Polissar, & Gruber, 1997; Smithson, Morris, & Iansek, 1998) Researchers have successfully used self-reported, recent fall history as the gold standard for validation purposes.(Dibble, et al., 2008; Dibble & Lange, 2006; Morris, Iansek, Smithson, & Huxham, 2000; Smithson, et al., 1998; J. Visser et al., 2003) There is concern that a person's recent fall history and present physical ability may not be the same. This is a legitimate concern for people whose physical function is expected to improve significantly due to natural disease course or direct intervention during the period of time over which fall history is assessed. In DPN, significant improvement in nerve function and physical ability is not expected unless the individual has received directed and proven care to address the nerve-related changes, such as with MIRE™.(Powell, et al., 2006) Also related to this concern, in a recent publication by the American Geriatrics Society, the British Geriatrics Society, and the American Academy of Orthopaedic Surgeons, “history of falls” was listed as the second-ranked, most common risk factor for falls.(“Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on

Falls Prevention," 2001) It is clear that an individual that has fallen in the recent past, meaning within the past 6 months or year(Dibble, et al., 2008; Muir, Berg, Chesworth, & Speechley, 2008), has an increased risk of falling again(Brians, Alexander, Grota, Chen, & Dumas, 1991; Dibble, et al., 2008; Rubenstein & Josephson, 2002; Russell, Hill, Blackberry, Day, & Dharmage, 2006; Schmid, 1990; Shumway-Cook, et al., 1997); thus, a person's recent fall history is most likely an accurate reflection of that individual's present fall risk. For persons with DPN because of the nature of this dysfunction, if a difference in fall risk exists, it would more likely increase rather than decrease.

Fall History Assessment

If fall history is used as the "gold standard" for an investigation of fall risk assessment tools, there are some measures that can be taken to minimize concern with this approach. Specifically, these measures relate to the definition used for "fall", the fall history assessment, and the classification scheme used to categorize participants as fallers or nonfallers.

For the current work and as has been done with multiple other fall-related studies(Tilling, et al., 2006; Tinetti, et al., 1988; J. Visser, et al., 2003; M. Visser et al., 2003), a "fall" will be defined as “an event that resulted in a person coming to rest unintentionally on the ground or other level, not as the result of a major intrinsic event or overwhelming hazard”. A major intrinsic event may include, but is not limited to, a heart attack or seizure. An overwhelming hazard may include, but is not limited to, being hit by a car and falling as the result of the failure of an external structure (chair, walkway, bridge, etc.). This definition is more specific than definitions used by some researchers(Dibble, et al., 2008; Dibble & Lange, 2006; Powell, et al., 2006; Richardson, et al., 1992; Schwartz et al., 2002; Schwartz, et al., 2008; Wallace et al., 2002)

leaving less room for subjective interpretation of what constitutes a fall. This definition also helps emphasize falls that stem from intrinsic factors (e.g. decreased ankle mobility, decreased muscle strength, poor balance, etc.) rather than extrinsic factors (e.g. environmental barriers, etc.).

Clinically, a fall history assessment should involve a description of the circumstances surrounding each fall to understand the cause of each fall and aid with fall prevention and/or treatment. ("Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention," 2001; Rubenstein, 2006) In research, the same detailed assessment is encouraged and has been used in a number of fall-related studies (Arnold & Faulkner, 2007; Richardson, et al., 1992; Tinetti & Speechley, 1989; M. Visser, et al., 2003; Wallace, et al., 2002) in an effort to obtain an accurate fall history. If a subject cannot recall any circumstances surrounding a fall, that specific fall occurrence will not be counted as a fall. (Richardson, et al., 1992) This classification scheme should be sufficiently rigorous to allow for a true distinction between the faller and nonfaller groups when assessing the discriminative ability of fall risk assessment tools.

In fall risk studies that use recent fall history as the "gold standard", the classification scheme used to categorize subjects is important. The number of falls reported during the fall history assessment is used to categorize a subject as a faller or a nonfaller. A few studies have classified a person that had fallen at least once in either the previous 6 months (Behrman, Light, Flynn, & Thigpen, 2002) or year (Arnold & Faulkner, 2007; Thrane, Joakimsen, & Thornquist, 2007) as a faller. Other studies have used 2 or more falls in either the previous year (Ashburn, Stack, Pickering, & Ward, 2001; Dibble, et al., 2008; Dibble & Lange, 2006) or the previous 6 months (Shumway-Cook, et al., 1997) to classify an individual as a faller. Ashburn and

colleagues(Ashburn, et al., 2001) conducted a prospective study related to predicting falls in people with Parkinson's disease and concluded that persons that have fallen 2 or more times in the previous 12 months should be considered for fall prevention programs. For the current study, a person was classified as a faller if s/he had fallen 2 or more times during the previous year.

Fall Risk Assessment

As mentioned previously, the use of a "gold standard" is necessary when investigating the usefulness of diagnostic tools. This "gold standard" allows for the calculation of indices that characterize the ability of the tools to accurately discriminate, in the current study, between fallers and nonfallers. These indices allow researchers to compare the results of a new test against those of the "gold standard".(Domholdt, 2005) Some indices that are used include sensitivity and specificity(Dibble, et al., 2008; Dibble & Lange, 2006; Shumway-Cook, et al., 1997; J. Visser, et al., 2003), positive and negative predictive value(Portney & Watkins, 2009), and overall accuracy(Shumway-Cook, Brauer, & Woollacott, 2000). All of these indices give valuable information when assessing usefulness of a tool in question and have been used in other fall related studies.(Behrman, et al., 2002; Mackintosh, Hill, Dodd, Goldie, & Culham, 2006; Shumway-Cook, et al., 2000)

Sensitivity is defined as "the proportion or percentage of individuals with a particular diagnosis who are correctly identified as positive by the test".(Domholdt, 2005) As it relates to fall risk assessment tools and the proposed study, sensitivity is the percentage of individuals with a recent fall history (fallers) who are correctly identified as being "positive" for fall risk. Based on this definition, if a fall risk assessment tool accurately identifies all individuals that are fallers as being at risk for falls, sensitivity of the tool is high, which is desired. If fallers are not

identified by a tool as being at risk for falls, then sensitivity of this tool is low. Particularly with fall risk assessment, low sensitivity of a tool is of significant concern in that it corresponds to false negatives. It is important that everyone who is evaluated for fall risk and is truly at risk of falls is identified as such so that appropriate fall prevention measures can be taken; false negatives correspond to these at-risk individuals being identified as not having fall risk. This is more concerning, from an individual patient perspective, than having false positives which relates to low specificity.(Dibble, et al., 2008)

Specificity is defined as "the proportion or percentage of individuals without a particular diagnosis who are correctly identified as negative by the test".(Domholdt, 2005) As it relates to fall risk assessment tools and the proposed study, specificity is the percentage of individuals without a recent fall history (nonfallers) who are correctly identified as being "negative" for fall risk. Based on this definition, if a fall risk assessment tool accurately identifies all individuals that do not have a recent history of falls (nonfallers) as not having fall risk, specificity of the tool is high, which is desired. If individuals are identified incorrectly that they have fall risk when they actually do not have a history of falls (nonfallers), then specificity of the tool is low, which corresponds to more false positives. As mentioned previously, false positives are not as concerning as false negatives; however, false positives would still encourage the enrollment of someone who does not have fall risk in a fall prevention program which would incur time and financial cost for both the individual and the fall prevention experts.

If fall prevention is the goal, then we want fall risk assessment tools to correctly identify all fallers as having fall risk (true positives) and to avoid identifying fallers as not having fall risk (false negatives), this would correspond to high sensitivity. In addition, we want fall risk assessment tools to correctly identify all nonfallers as not having fall risk (true negatives) and to

avoid identifying nonfallers as having fall risk (false positives), which would correspond to high specificity. While high sensitivity is emphasized in some fall-related studies(Dibble & Lange, 2006), overall accuracy of a fall risk assessment tool warrants a balance between sensitivity and specificity. The outcome of using a tool that has 100% sensitivity but 0% specificity would result in all persons tested being identified as having fall risk and would therefore have no ability to discriminate between fallers and nonfallers. Conversely, a tool with 0% sensitivity but 100% specificity would result in all persons tested being identified as not having fall risk and would therefore, again, have no ability to discriminate between fallers and nonfallers. A balance of sensitivity and specificity is advantageous in that it allows for greater overall accuracy of any tool. Overall accuracy has been used in some studies to compare fall risk assessment tool utility.(Shumway-Cook, et al., 2000)

While sensitivity and specificity indicate the ability of a tool to discriminate between fallers and nonfallers, positive and negative predictive value indicate the probability that positive and negative test results will be accurate. For example, positive predictive value is calculated by dividing the number of true positives by the number of true and false positives. This value, in the context of the current study, gives the probability that a person that tests as having fall risk will actually be a faller. The converse is true for negative predictive value. Negative predictive value is calculated by dividing the number of true negatives by the number of true and false negatives. This value gives the probability that a person that tests as not having fall risk will actually be a nonfaller. Sensitivity, specificity and negative and positive predictive value have been used to assess the usefulness of the Functional Reach Test for identifying fall risk in people with Parkinson's disease(Behrman, et al., 2002) and the Berg Balance Scale for identifying recurrent fallers in people that have had a stroke(Mackintosh, et al., 2006).

A fall risk assessment tool identifies an individual as having or not having fall risk based on how their score on the test compares to a pre-established cut-off score. This cut-off score can greatly influence the aforementioned indices because it ultimately designates what scores categorize a tested individual as having or not having fall risk. In studies where tool accuracy is being investigated, especially when tools do not demonstrate high sensitivity or specificity, an assessment of the effects of different cut-off scores on sensitivity and specificity can be performed to determine if a cut-off score other than the pre-established cut-off score might be useful. This can be visualized through a receiver operating characteristic (ROC) curve.(Domholdt, 2005) ROC curves are created by plotting sensitivity against 100 - specificity for different possible cut-off scores and have been used in other fall risk related studies.(Alzayer, Beninato, & Portney, 2009; Belgen, Beninato, Sullivan, & Narielwalla, 2006; Dibble & Lange, 2006; Leddy, Crowner, & Earhart, 2011; Muir, et al., 2008) For each ROC curve, there is point that is the closest to the upper left-hand corner of the graph; this point corresponds to the cut-off score that maximizes both sensitivity and specificity for the sample of data(Domholdt, 2005) and has been used by others for establishing a new cut-off score(Alzayer, et al., 2009; Leddy, et al., 2011; Muir, et al., 2008). The distance between that point and the upper left-hand corner of the graph is the smallest Euclidian (or geometric) distance. If two points have the same smallest Euclidian distance, researchers are encouraged to choose the point that maximizes the index (sensitivity or specificity) that is most important for the clinical scenario(Domholdt, 2005; Portney & Watkins, 2009). As has already been stated, maximizing sensitivity (avoiding false negatives) is more important than maximizing specificity (avoiding false positives) for fall risk related studies and therefore, the point with the greatest sensitivity would be selected.

Fall Risk Assessment Tools

The 4 fall risk assessment tools that were used for the current study were chosen based partly on their validity and reliability as reported in the literature but also because of other studies that conducted similar analyses.(Dibble & Lange, 2006 1997; Shumway-Cook, et al., 1997) Dibble and Lange conducted a comprehensive investigation of how valid these same fall risk assessment tools were for predicting falls, using recent fall history as their criterion, in people with Parkinson's disease.(Dibble & Lange, 2006) They used the same cut-off scores based on their review of previous literature and found the sensitivity of each measure to be low (FRT = 0.54, TUG = 0.39, BBS = 0.41, and DGI = 0.57). They then analyzed the results to determine different cut-off scores that maximized the sensitivity of the fall risk assessment tools and suggested a reconsideration of cut-off scores when clinically evaluating people affected by Parkinson's disease.(Dibble & Lange, 2006) Shumway-Cook and colleagues(Shumway-Cook, et al., 1997) also used the BBS and the DGI in a similar analysis for community-dwelling older adults and found that sensitivity was maximized with a BBS cut-off score (49/56) slightly higher than and a DGI cut-off (19/24) score identical to what had been reported in previous literature.

Functional Reach Test (FRT)

This test assesses the “maximal distance one can reach forward beyond arm's length while maintaining a fixed base of support in the standing position”.(Duncan, et al., 1992; O'Sullivan & Schmitz)^{30,31} This tool was created by Duncan and colleagues and demonstrated excellent precision and interobserver reliability (ICC = 0.98) when testing 3 groups of volunteers ranging in age from 21 to 87 years.(Duncan, Weiner, Chandler, & Studenski, 1990) In the creation of this tool, it was compared to a center of pressure measurement and electronic

functional reach measurement and was found to have better test-retest reliability than either of the other measures (ICC = 0.92 vs. 0.52 and 0.81, respectively). In addition, validity of the test was confirmed by a strong association with center of pressure excursion ($r = 0.71$). The author noted that this test relates to functional activity and uses a continuous outcome measure which allows for better sensitivity than non-continuous measures.(Duncan, et al., 1990) This tool was assessed for its fall risk validity in a group of elderly inpatient subjects and demonstrated sensitivity, negative predictive value, and overall rate of agreement values of 76%, 77%, and 46%, respectively.(Eagle et al., 1999) Duncan conducted a prospective study in a sample of elderly male veterans and found a significant difference between fallers' (both one-time and recurrent fallers) and nonfallers' FRT scores.(Duncan, et al., 1992)

Timed Up and Go (TUG)

This test has been described as a test of balance and functional mobility(Shumway-Cook, et al., 2000) and is a timed test.(Podsiadlo & Richardson, 1991) Subjects are required to stand from a seated position, walk about 10 feet, turn around, walk back to the chair, and then sit down.(Podsiadlo & Richardson, 1991) It was initially created by Mathias et al.(Mathias, Nayak, & Isaacs, 1986) and then modified to improve psychometric properties by Podsiadlo and colleagues.(Podsiadlo & Richardson, 1991) A study conducted by Shumway-Cook et al.(Shumway-Cook, et al., 2000) assessed the validity of the TUG for identifying fallers and non-fallers in 30 older, community-dwelling individuals and found it to be sensitive and specific for this population. A more robust study by Gunter and colleagues found the TUG to differentiate between fallers (one-time and frequent fallers) and nonfallers in a group of 157 community dwelling older individuals.(Gunter, White, Hayes, & Snow, 2000) One study reported that the

TUG was not predictive of falling and concluded that it should not be used to assess falls risk; however, this validity assessment was conducted on a population of individuals that were acutely ill and admitted to a hospital ward.(Lindsay, James, & Kippen, 2004) The individuals that will participate in the proposed study will be community-dwelling individuals rather than acutely ill patients in a hospital.

Berg Balance Scale (BBS)

This test is used to rate a person's ability to maintain balance while performing movements associated with different activities encountered during daily living.(Berg, Wood-Dauphinee, Williams, & Maki, 1992) The test involves 14 different tasks that are related to activities one might experience during daily life. Each item is scored between 0 and 4 based on pre-established criteria for the performance of each task, with a total possible score of 56. This scale has demonstrated validity for predicting falls in individuals who are elderly (Berg, et al., 1992) and has demonstrated validity related to physical function and excellent correlation with other tests of mobility and balance in persons after stroke.(Blum & Korner-Bitensky, 2008; Mao, Hsueh, Tang, Sheu, & Hsieh, 2002) Thorbahn and colleagues found that individuals scoring higher than 45/56 were less likely to fall than those who scored lower than 45/56; however, sensitivity of the tool was only 53%.(Bogle Thorbahn & Newton, 1996) Shumway-Cook and colleagues(Shumway-Cook, et al., 1997) used a bivariate analysis and found that the BBS was the most sensitive predictor of fall status in community-dwelling older adults. However, two other authors conclude that the BBS is not useful for predicting fallers in community-dwelling elderly or after stroke.(Blum & Korner-Bitensky, 2008; Muir, et al., 2008) As mentioned previously, no validity studies have been conducted with any of these fall risk assessment tools

in people with DPN. This specific tool's validity as it relates to physical function and mobility combined with conflicting reports on its validity for fall risk assessment in different populations warrant further investigation. If sensitivity and specificity for the BBS are poor using the traditional cut-off score that we intend to use, a ROC curve analysis may help to clarify if any score on the BBS would result in higher sensitivity and specificity.

Dynamic Gait Index (DGI)

This test was developed to measure the ability to perform movement tasks while walking and to determine risk of falling in community-living older people.(Marchetti & Whitney, 2006) This test has 8 items, each of which is scored on a scale from 0 to 3 based on pre-established criteria for the performance of each task. The DGI has a total possible score of 24. It has been demonstrated to be valid and reliable.(Shumway-Cook & Woollacott, 2000) Whitney and colleagues have conducted a number of studies related to the DGI, two of which found that it is a valid tool for assessing fall risk in individuals with vestibular dysfunction. One of the studies investigated DGI score relationship to self-reported fall history(Whitney, Hudak, & Marchetti, 2000) and the other compared its validity concurrently with the BBS and found that the DGI was the more sensitive tool for identifying people with vestibular dysfunction that have increased fall risk(S. Whitney, Wrisley, & Furman, 2003).

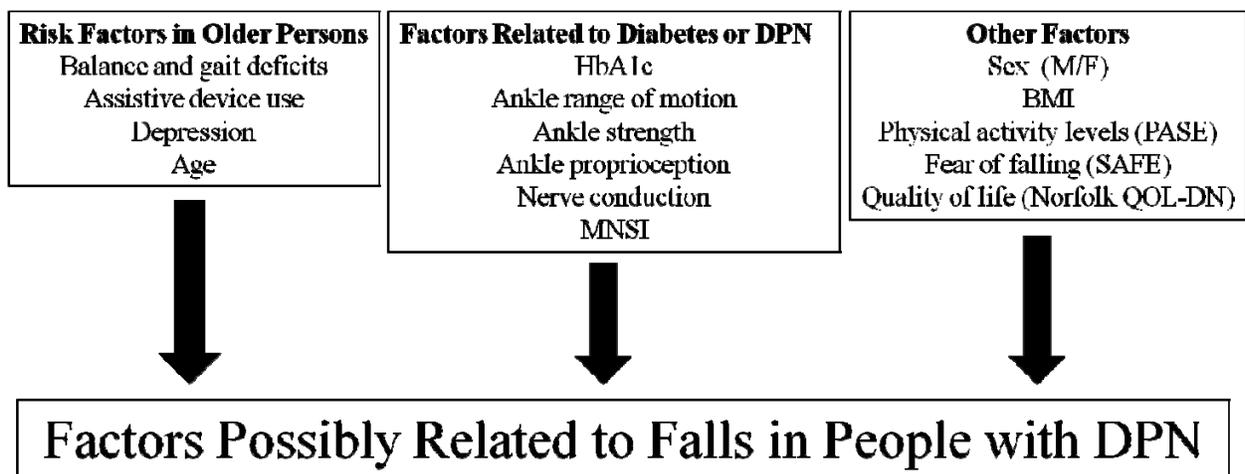
Even though each of the 4 fall risk assessment tools have been validated for use in people with Parkinson's disease, stroke, vestibular disorders and older persons, some researchers also question their validity. Behrman and colleagues(Behrman, et al., 2002) concluded that the FRT was not sensitive for identifying fall risk in people with Parkinson's disease. Thrane and colleagues(Thrane, et al., 2007) suggest that the ability of the TUG to classify fallers is poor for

older persons and Lindsay et al.(Lindsay, et al., 2004) conclude that it is not predictive of fallers in acutely unwell older patients in a medical ward. Muir and colleagues(Muir, et al., 2008) suggest that BBS threshold scores used to dichotomously identify a faller or nonfaller need to be adjusted for community-dwelling elderly. Besides the fact that, to our knowledge, no assessment of the usefulness of these tools for people with DPN has been conducted, these studies that question their validity provide additional reason for these tools to be addressed in persons with DPN. In addition, DPN presents with unique manifestations that justify an analysis of whether or not these tools are appropriate for persons affected by this condition. Unlike Parkinson's disease, DPN is a peripheral nerve dysfunction that cannot be mediated with central nervous system interventions. Unlike stroke, DPN primarily affects both lower extremities equally which has different implications for gait and balance dysfunction than single-leg deficits that are often associated with a unilateral stroke. Unlike vestibular disorders, DPN results in a loss of sensory and motor nerve function in the lower extremities. The current study aimed to compare the discriminative ability of these fall risk assessment tools for people with DPN using traditional cut-off scores and to use ROC curves to determine if modified cut-off scores would improve the tools' sensitivity, specificity, positive and negative predictive value, and overall accuracy.

1.4 Factors Related to Falls in People with Diabetic Peripheral Neuropathy

A comprehensive understanding of falls in people with DPN requires knowledge of factors that increase fall risk in these individuals. Identifying these factors would allow for additional avenues, besides effective fall risk assessment tools, for identifying those that are at risk of falling. In addition, knowledge of risk factors for falling would provide insight into areas that could potentially be addressed through fall prevention programs and/or treatment. The

current study was the first, to our knowledge, to specifically investigate factors that relate to falls (fall history) in people that have DPN. When initially investigating factors that might relate to falls, it is important to take into consideration factors that have already been supported by previous research and to consider factors unique to the participant sample being studied. Factors for the current study were primarily selected based on abundant literature related to fall risk in older adults, logic related to clinical manifestations of diabetes and/or DPN, and the interest of the research team. The figure below depicts these factors for ease of reference.



Rubenstein reviewed 16 controlled studies related to falls in older persons and reported the following risk factors for falls: muscle weakness, a history of falls, balance and gait deficits, use of an assistive device, visual deficits, arthritis, depression, impairment in activities of daily living and age >80 years.(Rubenstein & Josephson, 2002) The American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention published an article titled "Guideline for the Prevention of Falls in Older Persons" that included these same risk factors for falls, with Rubenstein's article as a reference.("Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention," 2001) Although knowledge of these risk factors for falls in older persons is valuable, it cannot be

assumed that what is true for older persons is also true of individuals with DPN, especially considering that DPN does not only affect older persons. As mentioned previously, DPN is a complication of diabetes that affects sensorimotor ability of affected individuals and contributes to balance and gait problems; the nature of this complication is different than those changes solely associated with increasing age.

Factors associated with diabetes and/or DPN that might influence fall risk include glycemic control, ankle function, nerve function and severity of neuropathy. Schwartz et al.(Schwartz, et al., 2002) investigated fall risk in older women with diabetes and found that fall risk was increased in women who use insulin to control their diabetes and suggest that glycemic control may influence fall risk. A follow-up study found that in those using insulin, low A1C levels were associated with falling.(Schwartz, et al., 2008) Arkkila and Gautier reported(Arkkila & Gautier, 2003) that connective tissue changes related to hyperglycemic complications of diabetes may contribute to gait problems in people with diabetes, perhaps through range of motion limitations at the ankle. Studies have indeed demonstrated that ankle range of motion and strength are negatively affected by DPN(Mueller, et al., 1994) and that these influence balance and gait. Ankle proprioception has not been assessed directly but studies related to postural instability in people with DPN(Boucher, et al., 1995; Lafond, et al., 2004; Menz, et al., 2004) suggest that this measure of ankle function may also play a role in balance and gait problems. The manifestations of nerve dysfunction in people with DPN, many of which seem to negatively affect balance and gait, are variable and therefore actual nerve function should be assessed to determine its role in fall risk, separate from its variable effects. This can be done through nerve conduction study. Richardson and colleagues found that nerve conduction study results, concomitant with peripheral neuropathy, are significantly associated with both "falls" and

"repetitive falls" in people with peripheral neuropathy of various origins.(Richardson, et al., 1992) Schwartz et al.(Schwartz, et al., 2008) found that low peroneal nerve response amplitude was associated with fall risk in older people with diabetes. Lastly, a clinical assessment specific to neuropathy, such as the Michigan Neuropathy Screening Instrument (MNSI), gives useful information about the presence and severity of neuropathy. Part of the MNSI involves assessing light touch sensation, a loss of which has been associated with fall risk.(Schwartz, et al., 2008)

Other factors that are not necessarily associated with diabetes or DPN but may influence fall risk include sex (male or female), body mass index (BMI), physical activity levels, fear of falling, and health-related quality of life. It seems clear that obesity, in particular, a BMI over 30 kg/m² is associated with increased fall risk and incidence(Fjeldstad, Fjeldstad, Acree, Nickel, & Gardner, 2008). Studies indicate that increasing body weight is strongly correlated and associated with decreasing balance stability(Hue et al., 2007). A study by Teasdale and colleagues(Teasdale et al., 2007) demonstrated that weight loss was strongly related to an improvement in balance stability. Physical activity and exercise interventions that target improving balance and strength have shown a decrease in the incidence of falls in older individuals.(Hauer et al., 2001; Robertson, Campbell, Gardner, & Devlin, 2002) This would suggest that physical activity levels may influence fall risk. A study by Mertz et al.(Mertz, Lee, Sui, Powell, & Blair, 2010) found that physical inactivity (exercise participation measured as METs per week) was significantly associated with walking-related falls in men between the ages of 20 and 87. Another study investigated the effects of physical activity including household activities, sports activities, and leisure activities, not just exercise, on falls in older persons and found a non-linear relationship between levels of physical activity and fall history.(Graafmans, Lips, Wijnhuizen, Pluijm, & Bouter, 2003) In particular, they found that only those with the

highest levels of physical activity seemed to be protected from falls, suggesting that fall risk is increased in older persons with low to moderate levels of physical activity. A questionnaire called the Physical Activity Survey in the Elderly(Washburn, Smith, Jette, & Janney, 1993) (PASE) has been used to assess physical activity levels and is considered to be a valid(Hagiwara, Ito, Sawai, & Kazuma, 2008; Washburn, et al., 1993) and reliable(Washburn, et al., 1993) tool for this purpose. In a study by Tinetti and colleagues that assessed fear of falling in community-living elders, 24% of those who had fallen reported activity restriction due to fear of falling.(Tinetti, Mendes de Leon, Doucette, & Baker, 1994) In a larger sample (n=3,474) of adults over 65 years of age, 22% reported fear of falling over the past year and it was noted that fear of falling increased with age.(Bertera & Bertera, 2008) A prospective study demonstrated that, again in elderly individuals, 30% of those who fell developed a fear of falling.(Vellas, Wayne, Romero, Baumgartner, & Garry, 1997) Although most of the studies related to fear of falling are conducted in older individuals and seem to indicate that the fear developed after falls had taken place, it would be interesting to determine if fear of falling plays a role in fall risk, directly, or indirectly through fear-based activity restriction. The Survey of Activities and Fear of Falling in the Elderly(Lachman et al., 1998) (SAFE) is a valid tool(Jorstad, Hauer, Becker, & Lamb, 2005; Lachman, et al., 1998) for assessing fear of falling. Lastly, one author reports strong correlations between risk factors for falls and quality of life(Ozcan, Donat, Gelecek, Ozdirenc, & Karadibak, 2005). If quality of life is associated with fall history, and even if it is not, this outcome measure is important to assess as it relates to determining how fall prevention programs for people with DPN may influence their quality of life.(Benbow, Wallymahmed, & MacFarlane, 1998) The Norfolk QOL-DN is a unique tool, specific to people that have diabetic

neuropathy, that has been developed and is considered valid for assessing quality of life in people with DPN.(Vinik & LeRoith, 2008; Vinik et al., 2005)

It is important to be more inclusive of possible factors when first attempting to identify factors that relate to falls in a population for which this, to our knowledge, has not previously been assessed. Some factors that previous literature reported to be risk factors for falls in older adults (i.e. visual deficits) were part of this study's exclusion criteria and were therefore not assessed as possible fall-related factors for these individuals. The current study aimed to comprehensively assess the aforementioned factors as possible factors related to falls (fall history) in people with DPN, in hopes that this additional knowledge will ultimately improve fall-related care for these individuals who experience increased fall risk secondary to DPN.

1.5 Factors Related to Quality of Life in People with Diabetic Peripheral Neuropathy

Health related quality of life (HRQOL) is defined as "a personal sense of physical and mental health and the ability to react to factors in the physical and social environments".(U.S. Department of Health and Human Services, 2000) Many feel that HRQOL is an important outcome measure to assess in health care, in addition to typical physiologic or biomedical measures of health, because it reflects a patient's perception of his/her health and is therefore meaningful to the patient.(Hays, Hahn, & Marshall, 2002; Huang et al., 2008; Magwood, Zapka, & Jenkins, 2008) For example, in people with DPN, an improvement in nerve conduction velocity (a physiologic measure) may not be meaningful to the patient unless it equates to improved function in daily activities or participation in life roles; a HRQOL survey would capture these changes in function or participation. The most recent version of the World Health Organization's International Classification of Functioning, Disability and Health (ICF) model

includes 3 categories of primary levels of human functioning, body functions and structures, activities, and participation. Unlike clinical measures used to assess physiologic status, HRQOL surveys are thought to measure function at the "participation" level of the ICF model(WHO, 2002), with participation defined as "involvement in a life situation".(WHO, 2002)

It is clear that DPN affects HRQOL of those that are affected by the disease.(Benbow, et al., 1998; Currie et al., 2006; Lewko et al., 2007; Lloyd, Sawyer, & Hopkinson, 2001; van Schie, 2008) One of the largest studies (n=185) that investigated quality of life burden of diabetic neuropathy demonstrated a significant worsening of HRQOL as severity of neuropathy increased.(Happich, John, Stamenitis, Clouth, & Polnau, 2008) This study measured HRQOL with two different quality of life assessment tools, one generic tool (Short Form -12 Health Survey) and one tool specific to diabetic neuropathy(Norfolk QOL-DN). The Short Form-12 Health Survey, a shorter version of the Short Form Health Survey (SF-36), and the Norfolk QOL-DN are discussed below.

Norfolk QOL-DN

There are many different tools used to assess HRQOL; some are generic in nature while others are more disease-specific. Generic HRQOL surveys have been used to compare the impact of different diseases on quality of life of individuals.(Garratt, Schmidt, & Fitzpatrick, 2002) The Short Form Health Survey (SF-36) is an example of one of the most commonly used generic HRQOL surveys in the United States.(Hays, et al., 2002) This survey has been used by some to assess HRQOL in people with DPN.(Currie, et al., 2006; Lewko, et al., 2007; Lloyd, et al., 2001) However, many support the idea that a disease-specific HRQOL survey is most appropriate when assessing HRQOL in a sample of persons affected by a specific disease,

especially as it relates to detecting a change in or differences in HRQOL.(El Achhab, Nejjari, Chikri, & Lyoussi, 2008; Garratt, et al., 2002; Hays, et al., 2002; Huang, et al., 2008; Magwood, et al., 2008) In an effort to capture HRQOL in people with diabetes, a number of different diabetes-specific measures have been created. A systematic review article by El Achhab and colleagues describes the psychometric properties of 16 different diabetes-specific HRQOL instruments that have been used in research.(El Achhab, et al., 2008) They concluded that 6 of the 16 had adequate psychometric properties, including the Diabetes-39 (D-39); others have confirmed these results.(Garratt, et al., 2002; Huang, et al., 2008; Watkins & Connell, 2004)

Even though diabetes-specific HRQOL surveys were designed to be more sensitive than generic measures, some suggest that using both a generic and disease-specific HRQOL survey is best. A study was conducted with 280 patients to compare the psychometric properties of a generic measure, the SF-36, and the diabetes-specific measure, the D-39.(Peek, Cargill, & Huang, 2007) They found that each scale demonstrated better validity than the other scale when considering different aspects of the surveys. The authors concluded that the combined use of a disease-specific and generic survey would be beneficial when assessing HRQOL of people with diabetes. Another author who investigated disability-related HRQOL also recommended the same.(Hays, et al., 2002)

Recently, a unique HRQOL tool, the Norfolk QOL-DN, was developed.(Vinik, et al., 2005) This tool is unique because it combines generic and disease-specific HRQOL questions into one survey. The authors of this tool received permission from the originators of the SF-36, a generic HRQOL survey, to include some of the items from that survey in this not only diabetes specific, but diabetic neuropathy specific HRQOL survey. This tool is comprised of 48 items, 35 of which are scored using various scales. The first 7 scored items address symptoms related to

nerve fiber function; one point is scored for each type of symptom experienced. The next 23 items address how physical problems associated with small-fiber, large-fiber and autonomic neuropathy cause problems with daily activities; each of these items is scored using a Likert scale from 0 ("not a problem" or "not at all") to 4 ("severe problem" or "severely"). The last 5 items are generic HRQOL questions. Two of these items assess general health and are scored with different point values; the remaining 3 items use the 0 to 4 Likert scale as previously described. This tool is valid (Vinik & LeRoith, 2008) and has demonstrated internal consistency and reliability (Vinik, et al., 2005) and has recently been used as a primary quality of life measure in large-scale studies assessing the impact of DPN on HRQOL. (Currie, et al., 2006; Happich, et al., 2008) In this study by Currie and colleagues, HRQOL scores decreased significantly as symptom severity of DPN increased. (Currie, et al., 2006) The Norfolk QOL-DN tool was used as the HRQOL outcome measure for the current study.

Factors that Influence Health-related Quality of Life

It is clear that DPN negatively influences HRQOL (Currie, et al., 2006; Happich, et al., 2008; Vinik, et al., 2005), even when compared to diabetic patients without neuropathy and non-diabetic control patients (Benbow, et al., 1998); however, relatively few studies have attempted to identify specific factors that influence HRQOL in people with DPN. Similar to the guidance provided to clinicians from an understanding of factors that influence fall risk in people with DPN, identifying factors that likewise influence HRQOL could serve a very important purpose for clinicians who desire to treat patients in ways that patients consider to be meaningful. For the current study, factors were selected as possible mediators of HRQOL based on guidance from

current literature. These factors included pain, neuropathy severity, fear of falling and physical activity levels.

Pain and neuropathy severity have been found to relate to HRQOL in people with DPN.(Davies, Brophy, Williams, & Taylor, 2006; Van Acker et al., 2009). A study by Van Acker and colleagues(Van Acker, et al., 2009), used a visual analogue scale to assess pain, which is comparable to the method that was used for the current study. Many studies indicate that increasing severity of DPN is related to worsening quality of life.(Currie, et al., 2006; Happich, et al., 2008) There are a number of different ways to measure severity of neuropathy. One of the tools used in these studies was the Neuropathy Total Symptom Score (Currie, et al., 2006) while another grouped participants into 5 pre-defined mutually exclusive categories based on degree of diabetic neuropathy(Happich, et al., 2008). The creator of the Norfolk QOL-DN found a relationship between Norfolk QOL-DN score and severity of neuropathy based on an extensive assessment of both signs and symptoms of neuropathy.(Vinik, et al., 2005) Although less extensive than the methods used by Vinik et al.(Vinik, et al., 2005) in the aforementioned study, the Michigan Neuropathy Screening Instrument (MNSI) is similar in that it combines assessment of both signs and symptoms of neuropathy. The MNSI is a valid tool(Feldman et al., 1994; Moghtaderi, et al., 2006) and was used in the current study to assess neuropathy.

Fear of falling and physical activity and their relationships to HRQOL have been studied but only in older adults and people with diabetes, respectively. Fear of falling was found to be significantly negatively correlated with quality of life.(Ozcan, et al., 2005) No studies however, have investigated fear of falling in people with DPN and how it relates to HRQOL. Unfortunately, fear of falling is thought to lead to activity avoidance(Bertera & Bertera, 2008), which, for people with DPN who might benefit from physical activity, is not optimal. It is also

apparent that severe activity restriction that stems from fear of falling results in increased ADL disability and worsening of lower extremity performance as it relates to mobility.(Deshpande et al., 2008) These effects of fear of falling are undesirable considering that people with DPN, according to the literature, already demonstrate gait and balance problems. In comparison to similar measures of fear of falling, the SAFE is reported as having the most acceptable content validity and was the fear of falling measure used in the current study.(Jorstad, et al., 2005) Some literature indicates that quality of life is also related to physical activity levels, including exercise, employment and disability.(Glasgow, Ruggiero, Eakin, Dryfoos, & Chobanian, 1997; Vickrey, Hays, & Beckstrand, 2000) Glasgow and colleagues(Glasgow, et al., 1997) assessed physical activity levels in terms of the number of times exercise was performed in the past week and the frequency over the past month and found that in a large sample (n = 2000+) of adults with diabetes, self-reported physical exercise was the only assessed self-management behavior that predicted quality of life. A study investigating diabetic neuropathy and quality of life found that more disability days (work or school) were strongly associated with worse quality of life on a majority of the domains assessed.(Vickrey, et al., 2000) Methods used to assess physical activity levels have varied; for the current study we chose to use the Physical Activity Survey for the Elderly (PASE) largely because this survey encompasses many aspects of physical activity, including exercise (aerobic and resistance training), sports play and household activities. Even though it does not ask about disability days specifically, it does inquire about physical activity associated with work for pay or as a volunteer. The PASE is considered to be a reliable(Hagiwara, et al., 2008; Washburn, et al., 1993) and valid(Washburn & Ficker, 1999) tool for assessing physical activity levels in older adults and has also been used to assess physical activity in younger populations(Pollak, Kushnir, & Goldberg, 2011).

A number of other factors could also be associated with HRQOL of people with DPN and has been taken into consideration; however, we selected the aforementioned 4 factors as the primary focus for the investigation for the reasons previously stated. In addition, literature does not support the idea that specific measures of physiologic function are related to quality of life. In fact, a study by Vickrey and colleagues(Vickrey, et al.) found no relationship between quality of life and neurologic examination and electrophysiological scores in people with DPN when using a generic quality of life survey. Even when using the Norfolk QOL-DN, a more specific tool, Currie and colleagues also found that physiologic measures, such as nerve conduction velocity, did not relate to the HRQOL.(Currie, et al., 2006) It is hoped that by elucidating factors that relate to HRQOL in a sample of persons that have DPN, the paucity of knowledge on this topic can be expanded and further inform and guide health care practitioners in their treatment of patients with DPN in ways that are meaningful to the patients.

1.6 Significance of Research

DPN is known to increase fall risk and decrease quality of life. To our knowledge, the current study is the first to take a closer look at fall risk assessment and factors related to falls and quality of life in people that have DPN. If adequately equipped with the necessary knowledge, health care practitioners could more effectively decrease fall risk and increase quality of life for patients with DPN. The current study aimed to take steps towards establishing the knowledge necessary to improve patient care as it relates to fall risk and quality of life in people with DPN. The current work can be a springboard for additional, more robust and specific studies related to fall risk and quality of life in people with DPN.

Because DPN can increase fall risk, it is important to both accurately identify those that are at risk of falling and to identify factors that may contribute to this increased fall risk. In doing so, patients with DPN who are identified as having fall risk can be enrolled in fall prevention programs and/or receive interventions that target the factors associated with the increased fall risk. Similarly, it is important to identify factors associated with decreased quality of life in people with DPN so that treatment, if the factors are modifiable, can be directed towards these aspects of patients' lives that could affect them in meaningful ways.

1.7 Specific Aims and Statement of Hypotheses

Falls can have devastating effects on a person's health and quality of life. It is clear that fall risk increases with age and the presence of certain diseases. Diabetes is a disease that affects nearly 25.8 million people in the United States, 50% of whom develop diabetic peripheral neuropathy (DPN), a serious complication of diabetes that leads to physical impairments that are thought to increase fall risk. However, to our knowledge, little research has been conducted to understand falls in people with DPN. Specifically, no studies have been conducted to determine the usefulness of commonly used fall risk assessment tools for people with DPN. The identification of useful fall risk assessment tools would allow for early recognition of at-risk individuals and would be an appropriate starting point for reducing falls and their subsequent negative consequences. In addition, little is known about factors that relate to falls in people with DPN. Identifying these factors would ultimately allow for greater specificity of interventions that aim to reduce fall risk in these individuals.

Health-related quality of life (HRQOL) is a priority outcome in clinical research because it reflects patients' perceptions of their health which is inherently meaningful to them.

Unfortunately, the presence of DPN appears to negatively affect HRQOL. To our knowledge, a dearth of research has been conducted to identify factors that are related to quality of life in people with DPN. Once these factors are identified, more targeted means to improving this important aspect of health could be realized.

The present study aimed to add substantial knowledge to the inadequately understood topics of fall risk and HRQOL in people with DPN, in hopes that related care for people with DPN can ultimately be improved.

Specific Aim 1: Compare the ability of selected fall risk assessment tools to accurately discriminate between fallers and nonfallers that have DPN.

Because no studies have previously examined the usefulness of fall risk assessment tools in people with DPN, we aimed to compare the discriminative accuracy of 4 different tools: the Functional Reach Test (FRT), the Timed Up and Go (TUG), the Berg Balance Scale (BBS) and the Dynamic Gait Index (DGI). We hypothesized that the DGI would demonstrate the highest overall discriminative accuracy based on literature in other populations and the high level of difficulty inherent to this tool. The DGI demonstrated the highest overall discriminative accuracy when traditional cut-off scores were used but did not demonstrate adequate sensitivity to be useful clinically. When more appropriate cut-off scores were used, the DGI was replaced by the TUG as the most useful tool for accurately discriminating between faller and nonfallers in our sample of participants with DPN.

Specific Aim 2: Identify factors related to fall history in people with DPN.

Because this is an understudied area and could influence care for people with DPN who have increased fall risk, we aimed to use bivariate and then simple logistic regression analyses to identify factors that relate to self-reported fall history in people with DPN. Variables analyzed were selected based on previous fall risk literature in older adults, logic related to clinical manifestations of diabetes and/or DPN, and the interest of the research team. Variables related to older adults included 1) balance and gait deficits, 2) assistive device use, 3) depression and 4) age. Variables related to diabetes and/or DPN included 5) glycemic control (HbA1c) 6) ankle range of motion, 7) ankle strength, 8) ankle proprioception, 9) nerve conduction and the 10) Michigan Neuropathy Screening Instrument (MNSI). Other variables of interest included 11) sex, 12) body mass index, 13) physical activity levels, 14) fear of falling, and 15) HRQOL specific to people with diabetic neuropathy. We hypothesized that assistive device use and MNSI physical exam scores would be significant explanatory variables for fall status (faller or nonfaller) based on the regression analyses. Preliminary bivariate analyses demonstrated that neither of these factors was significantly different between fallers and nonfallers. However, separate regression analyses revealed that fear of falling, physical activity levels, and balance and gait performance contributed significantly to the explanation of fall status in our sample of participants with DPN.

Specific Aim 3: Identify factors that relate to HRQOL in people with DPN.

Because HRQOL is inherently meaningful to patients and understudied in people with DPN, we aimed to use multivariable linear regression to identify factors that relate to HRQOL in a sample of people with DPN. The Norfolk QOL-DN was the dependent variable. Based on previous work in HRQOL in other populations and some in people with DPN, the independent

variables that were selected for this analysis included 1) pain levels, 2) severity of neuropathy as assessed by the MNSI, 3) fear of falling, and 4) physical activity levels. We hypothesized that all of these variables would be significant explanatory variables for Norfolk QOL-DN scores in the final regression model. Pain levels, fear of falling, and physical activity levels, but not MNSI scores, were found to be significant predictors of HRQOL in our sample of participants with DPN.

Chapter 2

Discriminative Accuracy of Fall Risk Assessment Tools in People with Diabetic Peripheral Neuropathy: A Comparison of the Functional Reach Test, Timed Up and Go, Berg Balance Scale and Dynamic Gait Index.

2.1 Introduction

Diabetes is a disease that affects nearly 25.8 million people in the United States(CDC, 2011), with a prevalence rate at nearly 50% for diabetic peripheral neuropathy (DPN).(Dyck, et al., 1993) DPN is a serious complication of diabetes that, irrespective of age, leads to physical impairments, such as slower reaction times, decreased ankle strength and mobility, altered walking patterns, and greater postural instability.(Boucher, et al., 1995; Courtemanche, et al., 1996; Mueller, et al., 1994; Richardson, et al., 1992) Balance and gait problems alone are responsible for a 3-fold increase in risk of falling(Rubenstein & Josephson, 2002). Powell, Carnegie, and Burke found that 29% of older people that had been diagnosed with DPN had fallen in the previous year with 73% of those having fallen 2 or more times during that period.(Powell, et al., 2006) This identified fall risk is not true only of older persons with DPN; Richardson, Ching, and Hurvitz(Richardson, et al., 1992) demonstrated that neuropathy affecting the lower extremities was a significant risk factor for and significantly associated with falling and repetitive falling, independent of age. In 2008, a report by the Quality Standards Subcommittee of the American Academy of Neurology indicated that persons with peripheral neuropathy have probable (Level B evidence) risk of falling and that those with disorders of balance and gait have established (level A evidence) risk of falling.(Thurman, Stevens, & Rao, 2008) Given this information, it is imperative that fall risk is accurately assessed in people with DPN in order to effectively address this risk.

Fortunately, a number of different clinical tools are available to assess fall risk; however, the usefulness of these tools for identifying fall risk in specific populations has been questioned.(Dibble & Lange, 2006; Muir, et al., 2008; Thrane, et al., 2007) Some have determined that traditional cut-off scores used to classify a person's fall risk need to be modified

for people with specific diagnoses in order to accurately assess fall risk. For example, Dibble and colleagues(Dibble & Lange, 2006) found that when using the Timed Up and Go test in people that have Parkinson's disease, a cut-off score of 8.5 seconds, as opposed to the 13.5 seconds traditionally suggested, increases the validity of this tool for those with Parkinson's disease. Others have found that cut-off scores of 49 in older adults(Shumway-Cook, et al., 1997), 52 in persons with chronic stroke(Alzayer, et al., 2009) or 54 in those with Parkinson's disease(Belgen, et al., 2006; Dibble & Lange, 2006) instead of the more traditional cut-off score of 45, have also improved the accuracy of this fall risk assessment tool. To our knowledge, no studies have been conducted to compare the accuracy of clinically used fall risk assessment tools for people that have DPN.

The four fall risk assessments tools that were selected for this study include the Functional Reach Test (FRT), Timed Up and Go (TUG), Berg Balance Scale (BBS) and Dynamic Gait Index (DGI). These tools were selected because each measures some degree of static and/or dynamic balance and gait and are easily conducted in a clinical setting. Of the 4 tools, the DGI presents the greatest level of dynamic challenge in that not only do all test items require ambulation but some require ambulation with visual and vestibular modifications (head turns). We expected this altered visual and vestibular input to increase the overall accuracy of the DGI over the other tools because people with impaired sensory input from the periphery, such as is the case with DPN, may be more reliant on visual and vestibular inputs. All of these tools appear to be valid for use with older persons(K. Berg, et al., 1995; Bogle Thorbahn & Newton, 1996; Duncan, et al., 1992; O'Sullivan & Schmitz, 2005; Podsiadlo & Richardson, 1991; Weiner, et al., 1992) and some for diagnoses that are associated with increased fall risk, such as Parkinson's disease(Dibble, et al., 2008), vestibular disorders(Marchetti, et al., 2008) and

stroke(Blum & Korner-Bitensky, 2008). In addition, previous studies have conducted similar comparisons using all or some of these tools for other diagnoses.(Dibble & Lange, 2006; Shumway-Cook, et al., 1997)

The primary purpose of this study was to identify which of these 4 commonly-used fall risk assessment tools, in people with DPN, is best able to accurately discriminate between fallers and nonfallers. A secondary purpose was to determine if modified cut-off scores would improve the discriminative accuracy of these fall risk assessment tools for these individuals. It was hypothesized that of the 4 fall risk assessment tools, the Dynamic Gait Index (DGI) would be the most accurate tool.

2.2 Methods

Participants

Prior to recruitment, the study was approved by the Institutional Review Board. Interested persons could participate if they 1) had signs and symptoms of DPN (confirmed through clinical assessment), 2) were between the ages of 40 and 65, and 3) were able to ambulate without the help of another person. Individuals were excluded if they had untreated major medical depression, open wounds on the weight-bearing surfaces of either foot, or any musculoskeletal, visual, vestibular or neurological conditions that could significantly alter gait and/or balance (such as stroke, knee replacement, uncorrected visual deficits or diagnosed vestibular disorders). Of the 37 participants that were recruited for the study, 36 met the inclusion criteria. The excluded participant did not have signs and symptoms consistent with DPN. Participant demographics are listed in Table 2.1.

Procedures

After informed consent, participants underwent a single testing session that included nerve conduction study, screening for neuropathy using the Michigan Neuropathy Screening Instrument (MNSI), 4 fall risk assessments, and a fall history assessment. All assessments, except the nerve conduction studies, were conducted by the same physical therapist with 10 years of experience, including experience with all of the assessments. Nerve conduction studies were conducted by an experienced technician. Fall risk assessments for every participant were conducted in a randomized order (using randomly generated numbers in SPSS v. 16.0 for Windows) and always preceded the fall history assessment. This order of the fall risk assessments followed by the fall history assessment was intentional so as to avoid any fall history knowledge bias on the part of the examiner during the fall risk assessments. Rest was allowed as needed during testing and a gait belt was used at all times.

The nerve conduction study was conducted for the peroneal, tibial and sural nerves of the right lower extremity, to confirm the presence of peripheral neuropathy. Nerve conduction velocity, amplitude and latency were measured for the tibial and peroneal nerves, and amplitude and latency were assessed for the sural nerve. This assessment was used to confirm each participant's previously reported symptoms and/or diagnosis of DPN, which was necessary to be included in the study. If the results of the nerve conduction study and/or MNSI raised questions about the presence of DPN, a collaborating neurologist was consulted to determine the absence or presence of DPN. The MNSI is a tool that was created to screen for diabetic neuropathy and is comprised of two parts, a history portion and a physical exam portion.(Feldman, et al., 1994) The history portion is comprised of 15 questions that address patient neuropathy-related symptoms in the legs or feet. The maximum score one can achieve on the history portion is 13

(2 of the 15 questions are not used in the score calculation). The physical exam portion includes foot inspection, monofilament sensation, vibration sensation and reflex testing. The maximum score one can achieve on the physical portion is 10. For both the history and physical exam portions, higher scores indicate increased presence of neuropathic signs and symptoms. A physical exam score of 2 or greater has been shown to indicate neuropathy.(Feldman & Stevens, 1994; Moghtaderi, et al., 2006) The participants' mean MNSI scores are listed in Table 2.1.

The 4 fall risk assessments included the Functional Reach Test (FRT), Timed Up and Go (TUG), Berg Balance Scale (BBS), and Dynamic Gait Index (DGI). The FRT(Duncan, et al.) is a test of anterior and posterior dynamic stability(Duncan, et al., 1990) and assesses the "maximal distance one can reach forward beyond arm's length while maintaining a fixed base of support in the standing position"(Duncan, et al., 1992). The test was performed 5 times, including 2 practice trials and 3 test trials, which is consistent with the procedure used by the creators of this tool.(Duncan, et al., 1992) The TUG(Podsiadlo & Richardson, 1991) has been described as a test of balance and functional mobility(Shumway-Cook, et al., 2000) and is a timed test. The participant started in the seated position resting against the back of the chair. During the test, the participant stood up from the chair, walked 3 meters, turned around, returned to the chair and sat down against the back of the chair. The test was performed 3 times, including 1 practice trial and 2 test trials. This TUG procedure is consistent with that used by Shumway-Cook and colleagues(Shumway-Cook, et al., 2000) in their assessment of fall risk in older adults. The BBS(Berg, et al., 1992) is a tool used to rate a person's ability to maintain balance while performing movements associated with different activities encountered during daily living.(Berg, et al., 1992) This test is a multiple item (14) test and was conducted once with each participant. Each item was scored on a 4-point scale with a total possible score of 56. The DGI was

developed to measure the ability to perform movement tasks while walking and to determine fall risk in community-living older people.(Shumway-Cook & Woollacott, 1995) Like the BBS, it is a multiple item (8) test and was conducted once with each participant. Each item was scored on a 3-point scale with a total possible score of 24. Both the BBS and DGI were conducted according to standard procedure as outlined by each test. No more than a total of 45 minutes was needed to conduct all of these fall risk assessments. All participants were allowed to rest as needed during the assessments. A lower test score indicates greater impairment for all of these fall risk assessment tools, except for the TUG, for which a higher test score indicates greater impairment.

Fall history was assessed to determine participant fall status (faller or nonfaller). A participant was classified as a "faller" if s/he reported falling 2 or more times within the previous year based on the following definition of a fall. Similar to other studies(Tilling, et al., 2006; Tinetti, et al., 1988; M. Visser, et al., 2003) a fall was defined as "an event that resulted in a person coming to rest unintentionally on the ground or other level, not as the result of a major intrinsic event or overwhelming hazard". This definition is more specific than definitions used by other researchers(Dibble, et al., 2008; Dibble & Lange, 2006; Richardson, et al., 1992; Schwartz, et al., 2002; Schwartz, et al., 2008; Wallace, et al., 2002) leaving less room for subjective interpretation of what constitutes a fall. During the fall history assessment, individuals were read the definition of a fall and then asked if they had fallen during the past year based on that definition. If they responded in the affirmative, they were asked how many times they had fallen. They were then asked if they could recall the exact or approximate dates of any of the falls and any of the circumstances surrounding any of the falls, including where they fell, how they fell, why they thought they fell, when they fell (time of day, before or after certain

activities, etc.) and if they were injured by the fall. For a fall to count towards the fall status classification, the participant had to recall at least an approximate date and specific circumstances surrounding the fall.

Data Analysis

All data was analyzed using Microsoft Office Excel 2007 and PASW Statistics 18.0 (SPSS, Inc., Chicago, IL, 2009). Directly after each participant was tested, tests were scored and these scores were entered into a Microsoft Office Excel spreadsheet. For quality assurance, after all testing for the study was completed, a 100% audit was conducted to ensure accurate data entry. In addition, boxplots were created for each outcome variable to visually inspect the data for outliers. If an outlier was noted, accurate entry for that outlier was verified against the source documents.

Descriptive statistics of all participant demographic variables were calculated. These included means, standard deviations, and ranges for continuous measures. Descriptive statistics of demographic variables and fall risk assessment tool scores for the faller and nonfaller groups were calculated, including frequencies for categorical data and means and standard deviations for continuous data. For the FRT and TUG, the mean score of repeated test trials was used for analysis; for the BBS and DGI, the sums of all individual items were used for data analysis.

In studies where tool accuracy is being investigated, receiver operating characteristic (ROC) curves can be used to visualize this accuracy.(Domholdt, 2005) ROC curves are created by plotting sensitivity against 100 - specificity for different possible cut-off scores and have been used in other fall risk related studies.(Alzayer, et al., 2009; Belgen, et al., 2006; Dibble & Lange, 2006; Leddy, et al., 2011; Muir, et al., 2008) These curves can also be used to determine which

cut-off scores maximize the sensitivity and specificity of the fall risk assessment tools, which was the secondary purpose of this study. The cut-off score that maximizes the sensitivity and specificity for each tool corresponds to a point on the ROC curve that is the smallest Euclidian (or geometric) distance from the upper left-hand corner of the graph.(Domholdt, 2005) This approach was used to establish modified fall risk assessment tool cut-off scores for this study and has been used by others conducting similar research(Alzayer, et al., 2009; Leddy, et al., 2011; Muir, et al., 2008).

Five indices were calculated and then used to compare the usefulness of the fall risk assessment tools for discriminating between fallers and nonfallers, including sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy. Other researchers have used these same indices when assessing the usefulness of fall risk assessment tools for other populations.(Behrman, et al., 2002; Mackintosh, et al., 2006; Shumway-Cook, et al., 2000) In order to calculate these indices, cut-off scores for each tool that are used to classify participants according to fall risk (at risk or not at risk) need to be selected. The cut-off scores selected initially were ones that have been established by the authors of these assessment tools and reported in the literature (FRT <25.4 cm(Behrman, et al., 2002; Dibble & Lange, 2006; Duncan, et al., 1990), TUG \geq 13.5 seconds(Dibble & Lange, 2006; Shumway-Cook, et al., 2000), BBS < 45/56(Berg, et al., 1992; Bogle Thorbahn & Newton, 1996), DGI \leq 19/24(Dibble & Lange, 2006; Marchetti & Whitney, 2006; Shumway-Cook, et al., 1997)). For the FRT, BBS, and DGI, higher scores indicate less impairment; the opposite is true for the TUG.

The following diagram depicts detailed information about the 5 indices used in this study, including how each was calculated. The uppermost row in the diagram refers to the results of the fall history assessment (YES, faller; NO, nonfaller) and was the “gold standard” used to

determine the usefulness of the fall risk assessment tools. The leftmost column refers to the results of the fall risk assessments using the predetermined cut-off scores (YES, fall risk; NO, no fall risk). All 5 indices were calculated for each fall risk assessment tool using the traditional cut-off scores and the modified cut-off scores that were determined from the ROC curve analyses. The fall risk assessment tool that demonstrated the highest overall accuracy index was designated as the most discriminatively accurate tool.

	Fall History YES	Fall History NO	
Fall Risk YES	A (+,+) True Positives	B (-,+) False Positives	Positive Predictive Value $A / (A+B)$
Fall Risk NO	C (+,-) False Negatives	D (-,-) True Negatives	Negative Predictive Value $D / (C+D)$
	Sensitivity $A / (A+C)$	Specificity $D / (B+D)$	Overall Accuracy $A+D / (A+B+C+D)$

The sensitivity of each fall risk assessment tool was calculated as the proportion of participants with a fall history (fallers) that were correctly identified by the tool as having fall risk, $A/(A+C)$. The specificity of each fall risk assessment tool was calculated as the proportion of participants who did not have a history of falls (nonfallers) that were correctly identified as not having fall risk, $D/(B+D)$. While sensitivity and specificity indicate the ability of a tool to discriminate between fallers and nonfallers, positive and negative predictive values give the probability that positive (YES) and negative (NO) fall risk assessment tool results, respectively, will be accurate. Positive predictive values were calculated by dividing the number of true

positives by the total number of true and false positives, $A/(A+B)$. Negative predictive values were calculated by dividing the number of true negatives by the total number of true and false negatives, $D/(C+D)$. Overall accuracy was calculated for each tool by summing the number of true positives and true negatives and then dividing by the total sample size ($n=36$). In addition, 95% confidence intervals for binomial proportions (Agresti, 2007) were calculated for all 5 indices.

2.3 Results

Of the 36 participants, 10 (27.8%) were classified as fallers (≥ 2 falls) and 26 (72.2%) as nonfallers (< 2 falls). Of the 26 nonfallers, 12 (46.2%) had fallen 1 time and 14 (53.8%) had fallen 0 times. The faller and nonfaller descriptive statistics for demographic variables and fall risk assessment scores are listed in Table 2.2.

The indices used to compare the discriminative accuracy of each fall risk assessment tool using the traditional cut-off scores and the modified cut-off scores are listed in Table 2.3. Using the traditional cut-off scores, the DGI and the FRT demonstrated the highest sensitivities at 30% but the DGI had higher specificity (96.2% vs. 88.5%) and had the highest overall accuracy (77.8%). The DGI also demonstrated the highest negative predictive value whereas the BBS demonstrated the highest positive predictive value.

The ROC for each fall risk assessment tool is depicted in Figure 2.1. The points on each curve that correspond to the sensitivity and 1- specificity values associated with the traditional and modified cut-off scores are labeled. Figure 2.2 depicts a graph of all fall risk assessment tool ROC curves and the points on each curve that maximized sensitivity and specificity, which correspond to the modified cut-off scores for each tool.

The modified cut-off scores that were used to identify fallers are as follows: FRT (≤ 31.7 cm), TUG (≥ 10.7 sec), BBS (≤ 52), and DGI (≤ 22). When using the modified cut-off scores, the TUG, BBS and DGI all demonstrated the highest sensitivity at 90% with the TUG demonstrating the highest specificity of the 3 (88.5% vs. 76.9% and 84.6%); therefore the TUG had the highest overall accuracy (88.9%). The TUG also demonstrated the highest positive and negative predictive values.

When comparing the differences between the two groups (traditional vs. modified cut-off scores) there was an increase in sensitivity of between a 50% and 80% and a reduction in specificity of between 7.7% and 23.1%. Positive predictive values increased by 25% for the TUG but decreased by 3%, 40%, and 5.8% for the FRT, BBS, and DGI, respectively. Negative predictive values increased the most for the TUG (22.3%) followed by the BBS (20.9%), DGI (17.6%), and FRT (12.9%). Overall accuracy increased the most for the TUG (16.7%), followed by the DGI (8.3%) and BBS (5.6%), whereas the overall accuracy of the FRT decreased by 2.8%.

2.4 Discussion

It is clear from the results of this study that, in this sample of participants with DPN, the modified cut-off scores proved to more useful for accurately identifying fallers than did the traditional cut-off scores and, in most cases, improved the ability of the tools to discriminate accurately between fallers and nonfallers. The DGI demonstrated the highest overall accuracy when traditional cut-off scores were used but was replaced by the TUG when modified cut-off scores were used. The TUG was also the only tool to demonstrate the highest scores across all 5

indices assessed, which indicates that it may be the most useful fall risk assessment tool of the 4 studied.

The use of traditional cut-off scores with the 4 fall risk assessment tools resulted in the accurate identification of only 1(10%) to 3(30%) out of the 10 fallers in the study. If these tools and traditional cut-off scores were to be used clinically as guidance for when fall prevention needs to be addressed, 7 to 9 of the 10 participants who actually needed fall-risk related interventions would not have received this important aspect of care. Although some have found much higher sensitivities ($> 60\%$) for these tools in other populations(Andersson, Kamwendo, Seiger, & Appelros; Gunter, et al., 2000; Shumway-Cook, et al., 2000), many have found similar results using the traditional cut-off scores. Muir and colleagues(Muir, et al., 2008) found that the BBS had a sensitivity of 42% for identifying community-dwelling older adults that had multiple falls (≥ 2) over one year. Thrane and colleagues(Thrane, et al., 2007) found that the TUG had a sensitivity of between 26% and 35% for older adults, where as Dibble and colleagues(Dibble & Lange, 2006) found a TUG sensitivity of 39% for persons with Parkinson's disease. Dibble et al.(Dibble & Lange, 2006) also found low sensitivity for the FRT (54%) and DGI (57%). Shumway-Cook(Shumway-Cook, et al., 1997) found a DGI sensitivity of 59% for community-dwelling older adults. These authors postulated that the low sensitivities may be due to the differences in populations tested or test procedures(Thrane, et al., 2007), specific characteristics of the samples tested(Dibble & Lange, 2006), or because a dichotomous view of impaired balance does not fully explain fall risk.(Muir, et al., 2008) Muir et al.(Muir, et al., 2008) goes on to articulate that the previously reported cut-off score of 45 for the BBS was not originally intended to be a dichotomous cut-off point. All of these potential explanations can be applied to

this study in which a specific sample of people, who have relatively mild DPN that presents with a unique clinical manifestation when compared to an older adult without disease, were tested.

Receiver operating characteristic (ROC) curves were used in this study to determine cut-off scores that would increase the utility of these tools for clinicians that treat patients similar in presentation to the participants in this study. A variety of methods have been used by fall researchers to determine these modified cut-off scores. All fall researchers seem appropriately concerned more with increasing sensitivity than specificity, as were we. However, we also chose to balance our desire to have high sensitivity with the importance of also maximizing specificity. To focus on only achieving 100% sensitivity would allow one to accurately capture all those that have fall risk but at the same time may result in very low specificity such that everyone, even those who do not have fall risk, would be targeted with fall risk interventions. A balanced approach allows one to identify true positives and true negatives as accurately as possible when assessing fall risk. While we appreciate the different and more complex approaches for determining cut-off scores that have been used by others (Behrman, et al., 2002; Dibble, et al., 2008; Dibble & Lange, 2006), we opted instead for a simpler approach that has also been reported in the literature (Alzayer, et al., 2009; Leddy, et al., 2011; Muir, et al., 2008) for reasons similar to those we stated.

The modified cut-off scores that have been identified for this study are comparable to those determined by other fall researchers, which they found also improved tool sensitivity. The FRT cut-off score of 31.7 cm is almost identical to that suggested by Dibble et al. (Dibble & Lange, 2006) (31.75 cm) and very similar to that suggested by Behrman and colleagues (Behrman, et al., 2002) (30.1 cm). The TUG cut-off score of 10.7 seconds falls between the traditional cut-off score (13.5 seconds) and that suggested by Dibble et al. (Dibble &

Lange, 2006) (7.95 seconds). The BBS cut-off score of 52 is identical to those suggested by Belgen et al.(Belgen, et al., 2006) (52) and Alzayer et al.(Alzayer, et al., 2009) (52), and similar to that suggested by Dibble et al.(Dibble & Lange, 2006) (54). The DGI cut-off score of 22 is the same as that suggested by Dibble and colleagues(Dibble & Lange, 2006) as well. Previously, it was mentioned that low sensitivity using traditional cut-off scores is not uncommon, possibly because of the differences in populations tested. Although the aforementioned revised cut-off scores were determined for populations other than DPN, such as stroke and Parkinson's disease, it should be noted that most of the participants in these other studies have relatively high levels of function (unlimited community ambulation(Belgen, et al., 2006), between no balance impairment to some impairment but physically independent(Dibble & Lange, 2006)). This high level of function was also characteristic of the participants in our study in that all were able to ambulate in the community without person-assistance and only 4 used assistive devices of any kind.

While the tool with the highest overall accuracy was designated as the most useful tool for accurately discriminating between fallers and nonfallers in the current study, when it comes to indices that are relevant to fall-related clinical outcomes, some would suggest that sensitivity and negative predictive value are most important. When sensitivity and negative predictive value are maximized, false negatives are minimized. False negatives correspond to people that need fall-related interventions because they are fallers but do not receive the intervention because they are inaccurately identified by a fall risk assessment tool as not having fall risk. When one weighs the potential cost of a false negative (future falls and fall-related injuries) against the potential cost of a false positive (fall prevention program), maximizing sensitivity and negative predictive value warrants consideration. Even though our approach to choosing

modified cut-off scores emphasized overall accuracy instead of maximizing sensitivity and negative predictive value, the tool with the highest overall accuracy, the TUG, also demonstrated the highest sensitivity and negative predictive value. The TUG demonstrated an overall false negative rate of only 2.8% (1/36) for our sample of participants with DPN.

The primary purpose of this study was to identify which of 4 commonly-used fall risk assessment tools is best able to accurately discriminate between fallers and nonfallers that have DPN. When using the modified cut-off scores, the TUG shares the highest sensitivity with the BBS and DGI, and has the highest specificity, positive and negative predictive value and overall accuracy. Our hypothesis that the DGI would best discriminate between fallers and nonfallers was true using the traditional cut-off scores; however, this was not the case when using the modified cut-off scores. It should be noted though that for the most important indices from a clinical perspective, the DGI was nearly equivalent to the TUG in that it had the same sensitivity and had a lesser negative predictive value by only 0.1%. While our hypothesis was based on the potential difficulty people with DPN might experience on certain DGI items, the scoring differences between the two tests may have influenced these results. Each item on the DGI is scored on an ordinal scale where as the TUG is measured in seconds (ratio scale) and may therefore be more sensitive to differences in our participants' performances. Comparable results were found by Dibble and colleagues (Dibble & Lange, 2006) in a slightly larger sample (n=45) of persons with Parkinson's disease (mean Hoehn and Yahr level 2.60 ± 0.66). When comparing these same 4 fall risk assessment tools, they found that the TUG had the highest sensitivity (93%) followed by the DGI (89%), although both demonstrated much lower specificities (30% and 48%) than those found in the current study (88.5% and 84.6%). This difference is likely due to the differences in our methods for selecting the modified cut-off scores. Dibble et al. (Dibble

& Lange, 2006) focused on maximizing sensitivity and minimizing negative likelihood ratio where as we emphasized maximizing sensitivity and specificity.

Falling is a complex and multi-faceted issue and requires a comprehensive approach to both assessment and intervention. Many researchers in the field of fall risk emphasize that clinicians should not fully rely on one fall risk assessment tool as the definitive case for a patient's fall risk secondary to the multifactorial nature of falls.(Bogle Thorbahn & Newton, 1996; Muir, et al., 2008) While the aim of this study was to compare fall risk assessment tools and identify modified cut-off scores for each tool that maximize discriminative accuracy, it should not be misinterpreted that the use of only a single tool is the best approach for identifying fall risk. Some researchers have investigated the use of multiple tools to more accurately identify patient fall risk and found promising results. Shumway-Cook et al.(Shumway-Cook, et al., 1997) found improved sensitivity (by 14%) when using both a history of imbalance and the BBS to identify fallers in a group of community dwelling older adults, over using just the BBS alone. Dibble and colleagues(Dibble, et al., 2008) found that interpreting multiple fall risk assessment tool scores collectively resulted in fewer false negatives compared to using only a single tool for the same purpose in people with Parkinson's disease. While we would have liked to conduct a similar analysis in our sample of people with DPN, our small sample size and the narrow margin of possible improvement using the modified cut-off scores precluded this type of analysis. However, this should be considered as a possible area for future investigation.

Limitations of this study include the use of fall history as the "gold standard" for assessing usefulness of the tools and the small sample size. In order to minimize the potential inaccuracies associated with a fall history assessment, care was taken use a very specific "fall" definition, require recall of specific circumstances surrounding a reported fall for it to be

counted, which is more stringent than fall history assessment methods used by other researchers.(Behrman, et al., 2002; Dibble, et al., 2008; Mertz, et al., 2010; Thrane, et al., 2007) In addition, we chose to require 2 or more reported falls to be classified as a faller, as opposed to only 1 or more falls(Arnold & Faulkner, 2007; Behrman, et al., 2002; Tinetti & Speechley, 1989), considering that a single fall may simply be the result of a unique unfortunate situation and may not be indicative of genuine fall risk(Graafmans, et al., 2003). The small sample size limits the inference from and generalizability of the study; however, the proportion of fallers to nonfallers for the sample of participants tested for this study (27.8%) is comparable to that of another study in people with DPN. The number of persons that had fallen ≥ 2 times in the "Feet First" study, a larger study investigating the effects of exercise on ulceration and balance in people with DPN (mean age 65 years), was 30.4%.(Kruse, Lemaster, & Madsen, 2010) Due to the small sample size of this study, inference from the results to all people with DPN is not recommended because the sample tested may not be a representative sample of all people with DPN. The sample of participants in this study were rather homogenous in that all had relatively mild DPN, were community ambulators, and had no significant non-diabetes related lower extremity musculoskeletal conditions that might influence balance and gait. It is clear that additional research needs to be conducted with this understudied population as it relates to fall risk, in particular, studies that use larger sample sizes and more heterogeneous samples of participants with DPN need to be conducted to validate the modified cut-off scores. Due to our small sample size, the modified cut-off scores likely overfit the particular sample tested; these cut-off scores would likely shift if a different sample of participants with DPN were tested. In addition, studies that are prospective in nature would minimize limitations associated with our fall history assessment.

2.5 Conclusion

This study was the first to compare the discriminative accuracy of 4 commonly used fall risk assessment tools for a sample of participants with DPN. The majority of fallers were not accurately identified as having fall risk by any of the fall risk assessment tools when traditional cut-off scores were used but this improved with the use of modified cut-off scores. The use of modified cut-off scores that are more specific to the patient population being tested may allow for a more accurate identification of fall risk. Validation studies need to be conducted to confirm these preliminary findings in order to advance the opportunity for improved fall-related care in people that have DPN.

Tables and Figures

Table 2.1 Descriptive Statistics

Means, standard deviations and ranges for selected variables except sex, for which frequencies are listed. (n = 36)

	Mean	SD	Range
Sex	Males = 21 (58.3%) Females = 15 (41.7%)	-----	-----
Age (years)	57.3	6.1	42-65
Years with DPN	4.3	3.2	0.25-10
Body Mass Index (kg/m ²)	34.6	7.5	22-55
MNSI History (max=13)	5.5	2.5	1-10
MNSI Physical Exam (max=10)	3.2	2.3	0-9

Table 2.2 Descriptive Statistics: Fallers and Nonfallers

Means and standard deviations for all variables except sex, for which frequencies are listed.

	Faller (n = 10)	Nonfaller (n = 26)
Sex	Males = 3 (30%) Females = 7 (70%)	Males = 18 (69.2%) Females = 8 (30.8%)
Age (years)	57 ± 7.3	57.5 ± 5.7
Years with DPN	4.2 ± 3.5	4.4 ± 3.2
BMI (kg/m ²)	34.4 ± 5.4	34.7 ± 8.2
MNSI History (max = 13)	4.8 ± 2.4	5.9 ± 2.9
MNSI Physical Exam (max=10)	4.9 ± 2.4	3.2 ± 2.5
FRT (cm)	28.8 ± 5.2	33.0 ± 5.4
TUG (sec)	11.7 ± 2.3	8.8 ± 2.2
BBS (max=56)	49.1 ± 3.2	54.0 ± 2.5
DGI (max=24)	20 ± 2.2	23.2 ± 1.5

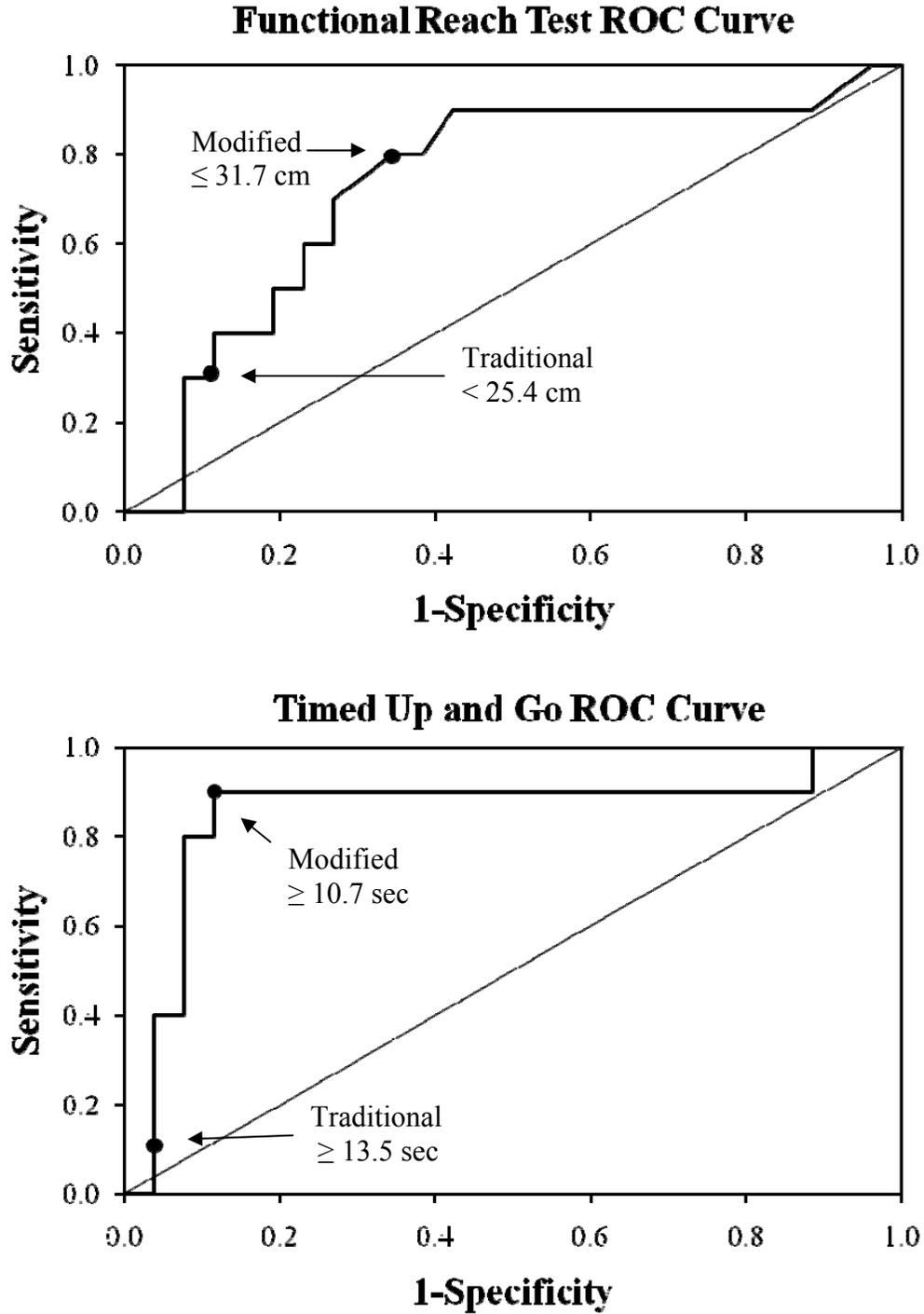
Table 2.3 Indices of Discriminative Accuracy for Fall Risk Assessment Tools Traditional versus Modified Cut-off Scores

Sensitivities, specificities, positive predictive values (+PV), negative predictive values (-PV), overall accuracy and associated 95% binomial proportion confidence intervals for the traditional (Trad) and modified (Mod) cut-off scores associated with each fall risk assessment tool (FRT = Functional Reach Test, TUG = Timed Up and Go, BBS = Berg Balance Scale, DGI = Dynamic Gait Index).

	Sensitivity% (95% CI)	Specificity% (95% CI)	+PV% (95% CI)	-PV% (95% CI)	Overall Accuracy %
FRT					
Trad <25.4 cm	30 (1.6,58.4)	88.5 (76.2,100.7)	50 (10,90)	76.6 (61.4,91.8)	72.2 (57.6,86.9)
Mod ≤31.7 cm	80 (55.2,104.8)	65.4 (47.1,83.7)	47 (23.2,70.7)	89.5 (75.7,103.3)	69.4 (54.4,84.5)
TUG					
Trad ≥13.5 sec	10 (-8.6,28.6)	96.2 (88.8,103.6)	50 (-19.3,119.3)	73.5 (58.7,88.4)	72.2 (57.6, 86.9)
Mod ≥10.7 sec	90 (71.4,108.6)	88.5 (76.2,100.7)	75 (50.5,90.5)	95.8 (87.8,103.8)	88.9 (78.6,99.2)
BBS					
Trad <45	10 (-8.6,28.6)	100 (0, 0)	100 (0,0)	74.3 (59.8,88.8)	75.0 (60.9,89.2)
Mod ≤52	90 (71.4,108.6)	76.9 (60.7,93.1)	60 (35.2,84.8)	95.2 (86.1,104.4)	80.6 (67.6,93.5)
DGI					
Trad ≤19	30 (1.6,58.4)	96.2 (88.8,103.6)	75 (32.6,117.4)	78.1 (63.8,92.5)	77.8 (64.2,91.4)
Mod ≤22	90 (71.4,108.6)	84.6 (78.8,98.5)	69.2 (44.1,94.3)	95.7 (87.3,104)	86.1 (74.8,97.4)

**Figure 2.1 Fall Risk Assessment Tool ROC Curves
Traditional versus Modified Cut-off Scores**

This figure depicts the ROC curve for each fall risk assessment tool. The labeled points correspond to the sensitivity and 1-specificity values associated with the traditional or modified cut-off scores.



(Figure 2.1 continued)

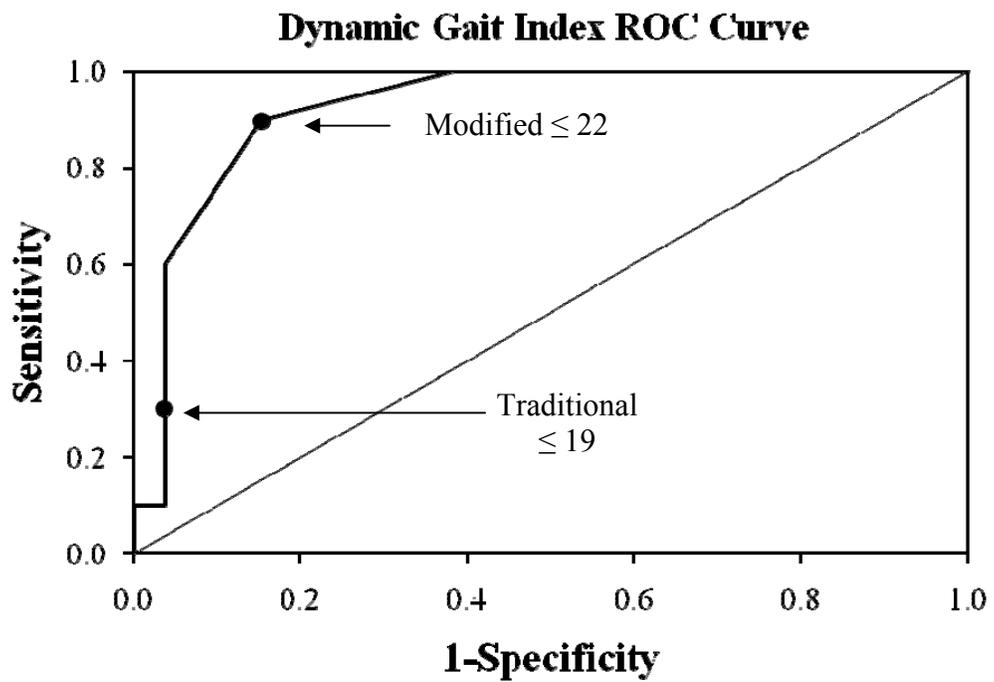
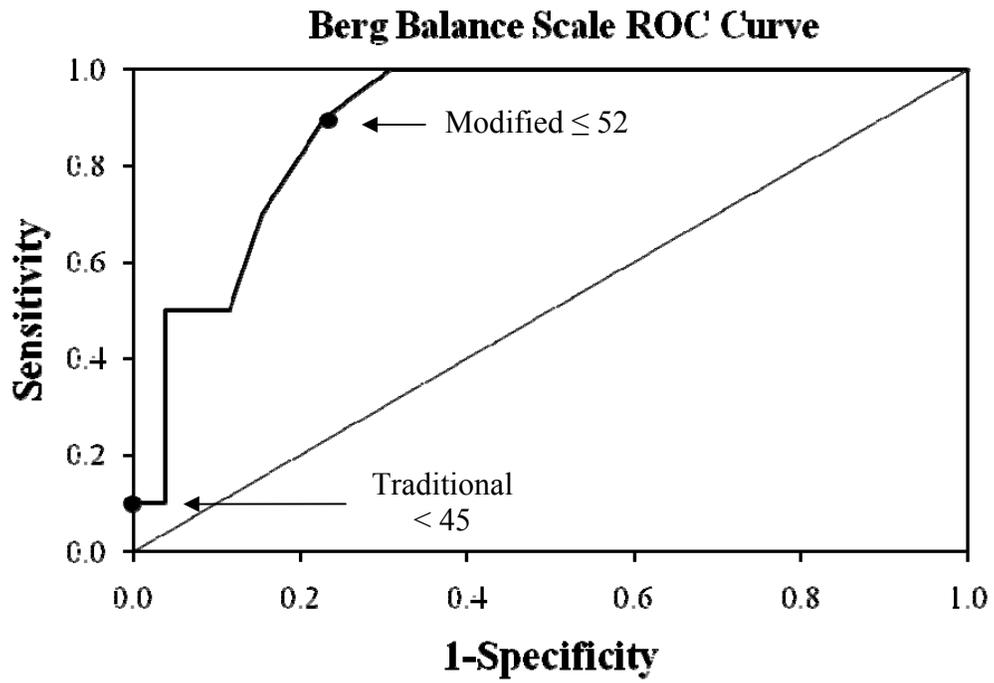
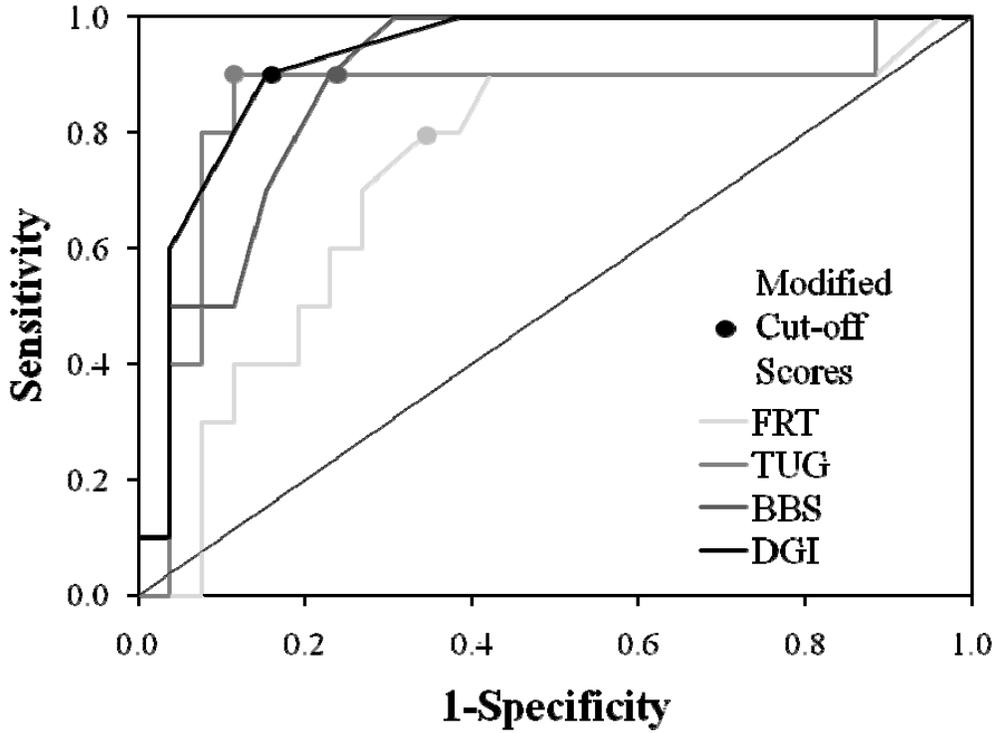


Figure 2.2 Composite Graph of all Fall Risk Assessment Tool ROC Curves

This figure depicts all 4 fall risk assessment tool ROC curves on one graph, to allow for a comparison between the tools of the points where sensitivity and specificity were maximized. Each of these points corresponds to the modified cut-off score for each respective tool as labeled.



Chapter 3

*The Identification of Factors That Relate to Fall History in
People With Diabetic Peripheral Neuropathy.*

3.1 Introduction

Approximately 50% of people with diabetes experience diabetic peripheral neuropathy (DPN), a serious complications of diabetes that is thought to contribute to increased fall risk. This diffuse neuropathy is the "most common and widely recognized form of diabetic neuropathy"(Vinik, et al., 2000) and is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".(Boulton, et al., 2005) Signs and symptoms of DPN may present as abnormalities of sensory and sometimes motor impairments of the lower extremities and in more severe cases, the upper extremities as well.(Boulton, et al., 2005; Feldman, et al., 1999; Vinik & LeRoith, 2008)

Research studies indicate that fall risk is increased in people that have DPN. Schwartz et al.(Schwartz, et al., 2008) found reduced peripheral nerve function to be associated with increased risk of falls in people with diabetes. Powell, Carnegie, and Burke(Powell, et al., 2006) found that 29% of older subjects that had been diagnosed with DPN had fallen in the previous year with 73% of those that had fallen having fallen 2 or more times during that period. The sensory and motor impairments associated with DPN have been found to result in disorders of balance and gait, which are one of the second most cited reasons for falls from a review of 12 of the largest retrospective fall-related studies in the elderly.(Rubenstein, 2006) Studies have implicated DPN for slowed reaction times, decreased ankle strength and mobility, altered walking patterns, and greater postural instability, all of which may increase fall risk. (Boucher, et al., 1995; Courtemanche, et al., 1996; Mueller, et al., 1994; Richardson, et al., 1992; Simoneau, et al., 1994) Research has established increased fall risk in people with DPN and investigated the effects of DPN on physical function but, unlike the extensive investigation into risk factors for falls in older adults ("Guideline for the prevention of falls in older persons.

American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention," 2001; Moreland et al., 2003; Rubenstein & Josephson, 2002), very few studies have specifically attempted to identify factors related to falls in people with DPN.

Understanding factors related to falls in people with DPN is imperative especially when one considers that people with DPN are 15 times more likely to report an injury (falls, fractures or cuts/bruises) during standing and walking than their diabetic, non-neuropathic counterparts (Cavanagh, et al., 1992) and that the ramifications of injuries in people with diabetes are often more severe and costly than those without diabetes. Although it appears that costs associated with falls in people with DPN have not been reported, the high costs of fall injury (Findorff, Wyman, Nyman, & Croghan, 2007; Tiedemann, Murray, Munro, & Lord, 2008), in general, warrant the conduct of fall-related research specific to people with DPN. A study by Gordois et al. (Gordois, Scuffham, Shearer, Oglesby, & Tobian, 2003) investigated the cost of DPN and its complications in the United States and reported that they may have underestimated the cost because they did not include falls in their analysis.

The aim of this study was to identify factors related to fall history in people with DPN. Factors that were selected for this study were primarily chosen based on the abundant fall risk literature in older adults, reasoning based on the clinical manifestations of diabetes and/or DPN, and the interest of the research team. Of all the factors assessed, it was hypothesized that assistive device use and the Michigan Neuropathy Screening Instrument physical exam scores would be significant explanatory factors for fall status. The identification of factors related to fall history could ultimately equip health care providers with the knowledge necessary to reduce falls in people with DPN.

3.2 Methods

Participants

All participants gave consent prior to participating in this study that was approved by the Institutional Review Board. Participants were required to have signs and symptoms of DPN, be between the ages of 40 and 65, and be able to walk without person-assistance. Participants were excluded from participating in the study if during the screening they reported having untreated major medical depression, open wounds on the weight-bearing surfaces of either foot, uncorrected visual deficits or any musculoskeletal, neurological or vestibular dysfunction that results in balance or gait problems. Of the 37 people that were recruited, only 1 was excluded secondary to the absence of DPN. Four of the participants used assistive devices during ambulation at home and/or in the community; two used ankle foot orthoses and 2 used single-tip canes.

Of the 36 participants, 10 were identified as fallers and 26 as nonfallers based on a fall history assessment. A participant was classified as a "faller" if s/he reported falling 2 or more times within the previous year based on the following definition of a fall. Similar to other studies (Tilling, et al., 2006; Tinetti, et al., 1988; M. Visser, et al., 2003) we defined a fall as "an event that resulted in a person coming to rest unintentionally on the ground or other level, not as the result of a major intrinsic event or overwhelming hazard". This definition is more specific than definitions used by other researchers (Dibble, et al., 2008; Dibble & Lange, 2006; Richardson, et al., 1992; Schwartz, et al., 2002; Schwartz, et al., 2008; Wallace, et al., 2002) leaving less room for subjective interpretation of what constitutes a fall. During the fall history assessment, individuals were read the definition of a fall and then asked if they had fallen during

the past year based on that definition. If they responded in the affirmative, they were asked how many times they had fallen. They were then asked if they could recall the exact or approximate dates of any of the falls and any of the circumstances surrounding any of the falls, including where they fell, how they fell, why they thought they fell, when they fell (time of day, before or after certain activities, etc.) and if they were injured by the fall. For a fall to count towards fall status classification, the participant had to recall at least an approximate date and specific circumstances surrounding the fall.

Procedures

An extensive clinical exam was conducted. With the exception of nerve conduction studies, all data collection was conducted by the same person who is a physical therapist with 10 years of physical therapy experience, including experience with the tools used for this study. Nerve conduction studies were conducted by a technician who had many years of experience with these assessments. A neurologist was consulted for any questions related to nerve conduction study results. In an effort to minimize bias towards fall status, all fall-related surveys (Fall History Assessment, Survey of Activities and Fear of Falling in the Elderly, Assistive Device Use Assessment) were completed with each participant after all fall risk assessments were conducted.

General Clinical Measures. Participant sex was recorded. Height and weight were measured to calculate Body Mass Index (BMI). Each participant's glycosylated hemoglobin (HbA1C) was measured using the BAYER A1CNow+ Multi-Test A1C System.

Neuropathy Related Measures. The Michigan Neuropathy Screening Instrument(Feldman, et al., 1994) (MNSI) is a valid tool(Feldman, et al., 1994; Moghtaderi, et al., 2006) and consists of two parts, a subjective history portion related to symptoms of neuropathy and a physical exam portion related to signs of neuropathy. Maximum possible scores on the history and physical portions of the MNSI were 13 and 10, respectively. The nerve conduction study was performed on the right lower leg by a technician trained and experienced in nerve conduction studies. Tibial and peroneal nerve conduction study measures of conduction velocity, amplitude and latency were measured in meters per second, milliVolts and milliseconds, respectively. Sural nerve amplitude and latency were measured in microVolts and milliseconds, respectively.

Balance and Gait Assessment. The balance and gait assessment was conducted using 4 clinical fall risk assessment tools that collectively measure static and dynamic aspects of balance and gait. The Functional Reach Test (FRT) assesses the “maximal distance one can reach forward beyond arm’s length while maintaining a fixed base of support in the standing position”(Duncan, et al., 1992) and is a reliable(Duncan, et al., 1990) and valid tool for assessing fall risk(Duncan, et al., 1992; Duncan, et al., 1990; Eagle, et al., 1999). It was performed 5 times with the last 3 trials averaged to result in a final score in centimeters. The Timed Up and Go(Podsiadlo & Richardson, 1991) (TUG) has been described as a test of balance and functional mobility(Shumway-Cook, et al., 2000) and is a valid tool(Gunter, et al., 2000; Shumway-Cook, et al., 2000). It was performed 3 times; the last 2 trials were averaged for a final score in seconds. The Berg Balance Scale(Berg, et al., 1992) (BBS) is used to rate a person's ability to maintain balance while performing movements associated with different activities encountered during daily living(Berg, et al., 1992) and is valid for assessing fall risk in different

populations.(Berg, et al., 1992; Mao, et al., 2002; Shumway-Cook, et al., 1997) The Berg Balance Scale (BBS) consists of 14 individually scored tasks with each individual score ranging between 0 and 4 for a total possible score of 56. The Dynamic Gait Index (DGI) was developed to measure the ability to perform movement tasks while walking and to determine fall risk in community-living older people.(Shumway-Cook & Woollacott, 1995) and has been found to be a reliable and valid tool in older adults(Shumway-Cook & Woollacott, 1995) and people with vestibular dysfunction(S. Whitney, et al., 2003; Whitney, et al., 2000). The DGI consists of 8 individually scored items with each individual score ranging from 0 to 3 for a total possible score of 24.

Ankle Measures. All ankle range of motion measurements were conducted using a goniometer. Ankle strength and proprioception measurements were conducted on the right ankle using a Biodex System 4 (Biodex Medical Systems, Inc., Shirley, NY) isokinetic dynamometer. Although reliability and validity of this device for ankle strength testing specifically in people with DPN has not been assessed, this device has demonstrated reliability for isometric ankle strength assessment in other healthy and diseased populations.(Callaghan, McCarthy, Al-Omar, & Oldham, 2000; Webber & Porter, 2010) Ankle strength was measured during 3 isometric dorsiflexion and plantarflexion trials. Peak dorsiflexion and plantarflexion torque was averaged across the 3 trials of each and their sum comprised the total ankle strength score. Ankle proprioception measures (joint position sense) required a participant to, with the eyes closed, feel a target position of the ankle and then during passive movement of the ankle, indicate by the push of a button when the previously felt target position was reached. For each of 2 target positions, error in degrees was averaged across 3 trials for the final outcome scores. Joint

movement threshold required each participant to, with the eyes closed, push a button immediately when any ankle movement was felt and was measured in degrees from the start position. This was conducted 3 times, with the average of the three trials used for the final outcome score.

Surveys. The Beck Depression Inventory II (BDI) is a screen for depression and consisted of 21 items with a maximum score of 63 (maximum 3 points per item); the higher the score, the greater the likelihood of depression. This tool is an effective screening tool for major medical depression in people with diabetes.(Lustman, Clouse, Griffith, Carney, & Freedland, 1997) The Norfolk QOL-DN(Vinik, et al., 2005) is a health-related quality of life (HRQOL) survey that address both general HRQOL and HRQOL related specifically to diabetic neuropathy; the higher the score, the poorer the HRQOL. This tool is valid(Vinik & LeRoith, 2008) and reliable(E. J. Vinik, et al., 2005). The Physical Activity Survey for the Elderly(Washburn, et al., 1993) (PASE) was used to assess physical activity levels and is considered to be a valid(Hagiwara, et al., 2008; Washburn, et al., 1993) and reliable(Washburn, et al., 1993) tool for this purpose. The PASE inquires about physical activity related to walking outside of the home or yard for any reason, light, moderate and strenuous sport or recreational activities, exercise (aerobic and resistance training), light and heavy housework, home repair, lawn care/gardening, caring for another person and work or volunteer activity. The PASE uses an algorithm to score the activity level; the higher the score the higher the activity level. The Survey of Activities and Fear of Falling in the Elderly(Lachman, et al., 1998) (SAFE) is a valid tool(Jorstad, et al., 2005; Lachman, et al., 1998) and inquires about 11 different activities and whether or not the respondent participates in these activities and if a fear of falling influences their participation.

Outcomes associated with this survey included activity level (number of activities performed), activity restriction (number of activities not performed), and 3 fear of falling measures (fear of falling associated with all 11 activities, fear of falling associated with activities the respondent does and fear of falling associated with activities the respondent does not do). A distinction between fear of falling for activities a respondent does and a fear of falling for activities a respondent does not do has been made previously by the creators of this tool.(Lachman, et al., 1998) Maximum SAFE activity level, activity restriction and fear of falling scores are 11, 11, and 3, respectively; higher values indicate greater amounts of that domain. Information was gathered about assistive device use, including the amount of time participants used assistive devices at home and in the community. A survey was created to score assistive device use with a maximum score of 4 indicating use of an assistive device at least 50% of the time both at home and in the community.

Data Analysis

The aim of this analysis was to determine factors that were significant explanatory variables for the differences in fall status (faller and nonfaller) in our sample of participants with DPN. All analyses were conducted with PASW Version 18.0 (SPSS, Inc., Chicago, IL, 2009). For quality assurance, after all testing for the study was completed, a 100% audit was conducted to ensure accurate data entry. Descriptive statistics (means and standard deviations) were first calculated and an exploratory bivariate analysis was then conducted to determine if there was a difference in performance between fallers and nonfallers for each of the outcome measures. Two-sample independent t-tests were used for the bivariate analysis with all factors except sex, for which a Fisher's Exact test was used since an expected cell count was less than 5. For

variables that had inequality of variance, as indicated by Levene's test [Levene, 1960], t-tests were conducted with equal variances not assumed [Field, 2005]. No statistical adjustments for multiplicity were made to the results presented here because they were secondary analyses for the parent study. Variables that demonstrated significant differences ($p < 0.05$) from the bivariate analysis were then used, individually, as independent variables for logistic regression analyses with faller status as the dependent variable. Unconditional logistic regression was the primary analysis associated with this study. Logistic regression was performed using only 1 independent variable at a time due to the small number of fallers and the Wald test was used to determine if the b coefficient for each variable was significantly different from zero [Field, 2005]. Hosmer and Lemeshow's goodness-of-fit test was used to assess whether or not each model differed significantly from the observed data. Odds ratios and their associated 95% confidence intervals were then used to interpret the results of the logistic regression analyses.

3.3 Results

Group means and standard deviations for each factor are listed in Table 3.1, along with the results of the bivariate analysis. The bivariate analysis demonstrated a significant difference ($p < 0.05$) between fallers and nonfallers for 8 factors. These included the PASE ($p = 0.012$) and 2 components of the SAFE, the activity level score ($p = 0.041$) and the fear of falling ($p = 0.023$) score for activities the participant reported not doing. Significant differences were also found with the 4 fall risk assessments (FRT, $p = 0.042$; TUG, $p = 0.001$; BBS, $p < 0.001$; DGI, $p < 0.001$) and active ankle dorsiflexion range of motion measured in the supine position ($p = 0.023$).

Five of the 8 factors that demonstrated significant differences from the bivariate analysis were also identified as significant ($p < 0.05$) individual predictors of faller status (faller or

nonfaller); these factors included the PASE ($p=0.024$), the SAFE (fear of falling for the activities not done, $p=0.041$), and the TUG ($p=0.01$), BBS ($p=0.003$) and DGI ($p=0.004$). Please see Table 3.2 for a comprehensive list of the logistic regression analyses results, including odds ratios, and Table 3.3 for the Hosmer and Lemeshow results.

3.4 Discussion

To our knowledge, this is the first study to investigate factors related to recurrent fall history in people with DPN. The results indicate that physical activity levels, fear of falling, and impaired balance and gait (as measured by the fall risk assessment tools) were independent predictors of fall status (faller or nonfaller). A more complete understanding of these factors and how they influence fall risk may improve clinicians' efforts to reduce fall risk and ameliorate the negative ramifications of falls for people with DPN.

The primary physical activity measure associated with this study was the Physical Activity Survey of the Elderly (PASE). This outcome measure demonstrated a significant difference between fallers and nonfallers, and made a significant contribution to the prediction of faller status as indicated by the logistic regression analysis. Based on the odds ratios, a 1 point decrease in the PASE score increased the odds of being a faller by 1.8%. When extrapolating this to a 68-point smaller PASE score, which is equivalent to the difference in mean PASE scores between fallers and nonfallers, the odds of being a faller increase by 3.5 times. Physical activity and in particular, exercise, has often been touted as important for people with diabetes to help control blood sugars and minimize or prevent diabetic complications.(Nyenwe, Jerkins, Umpierrez, & Kitabchi, 2011) The PASE assesses many different types of physical activity, not just exercise, which needs to be taken into account when interpreting these results. The results

indicate that many different types of physical activities combined, not just exercise alone, play a significant role in predicting fall status (faller or nonfaller) in our sample of participants with DPN.

Participants' fear of falling associated with activities that they reported not doing was also significantly different between fallers and nonfallers and made a significant contribution to the prediction of fall status. Based on the odds ratio, a 1 point increase in the fear of falling score, which is equivalent to the average participant response moving from "a little worried" to "somewhat worried", corresponds to a 2.5 times greater odds of that person being a faller. Interestingly, even though the average SAFE activity restriction levels were nearly identical for fallers and nonfallers, the fallers' activity restriction was due, more specifically, to a fear of falling than the nonfallers' activity restriction. It is possible that this fear of falling could be expanded to partially explain why the physical activity levels as measured by the PASE are significantly lower in the fallers, although this would need to be substantiated by additional research. However, a study by Bertera et al.(Bertera & Bertera, 2008) did demonstrate that fear of falling resulted in significant reductions in physical activities in older adults, including bending, stooping, reaching overhead, walking and going outside. This was also substantiated by Deshpande and colleagues(Deshpande, et al., 2008) in a large-scale prospective study of older adults. It should also be noted that the SAFE activity level, although significantly different between fallers and nonfallers, did not make a significant contribution to the prediction of fall status whereas the PASE, also a measure of physical activity levels, did. We believe this was the case because the SAFE lacked the sensitivity to do so. The SAFE assesses whether a respondent does or does not do 11 specific activities whereas the PASE covers a broader range of activities and allows for a range of responses for each activity assessed.

As is expected of valid fall risk assessment tools, all 4 tools used in this study demonstrated significant differences between fallers and nonfallers. However, logistic regression analyses indicated that the TUG, BBS, and DGI, but not the FRT, were significantly predictive of fall status. These findings are consistent with our previous work comparing the discriminative accuracy of these same tools, which indicated that the FRT demonstrated the poorest overall accuracy for discriminating between fallers and nonfallers. We suggest that the primary reason the FRT was not found to be predictive of fall status relates to the relatively static state of the participant's lower extremities when being tested, compared to the other tools. The other 3 tools primarily assess balance and gait activities associated with moving the base of support whereas the FRT measures a single reaching task with no movement of the base of support (Duncan, et al., 1992). As mentioned previously, literature indicates that people with DPN demonstrate slowed reaction times, decreased ankle strength and mobility, altered walking patterns, and greater postural instability (Boucher, et al., 1995; Courtemanche, et al., 1996; Mueller, et al., 1994; Richardson, et al., 1992; Simoneau, et al., 1994), all of which would likely be challenged to a greater degree by the more dynamic TUG, BBS, and DGI.

The odds ratios associated with the TUG, BBS, and DGI help to interpret the logistic regression results as they relate to people with DPN. For every second longer it takes a person to complete the TUG, there is a 1.7 times increase in the odds of being a faller. For every point decrease in the BBS score, there is a 1.7 times increase in the odds of being a faller. For every point decrease in the DGI score, there is a 2.3 times increase in the odds of being a faller. In a converse capacity, one can interpret these findings such that improved scores would decrease the odds of that person being a faller. It follows then that interventions that target specific aspects of these tools or even domains of balance and gait activities measured by these tools may decrease

the odds of being a faller. Many of these interventions may require an increase in physical activity, which may be beneficial considering that higher levels of physical activity were associated with nonfallers.

It was hypothesized that assistive device use score and MNSI physical exam scores would be significant predictors of fall status; this hypothesis was not supported by this research. Even though assistive device use is thought to improve independence and decrease fall incidence(Aminzadeh & Edwards, 1998; Dean & Ross, 1993), it has been associated with fallers both in older persons with and without diabetes(Shumway-Cook, et al., 1997; Tilling, et al., 2006). In the current study, only 4 participants (11.1%) reported using an assistive device of any kind; 3 of the 4 were fallers. A majority of the subjects had mild DPN (still had a sural nerve response with nerve conduction study), which may not necessitate the use of an assistive device. In addition, we excluded participants that had any significant lower extremity non-diabetes impairments, which could also explain the minimal use of assistive devices in our sample of participants. We anticipated that more participants in our sample would need to use an assistive device; our sample of participants did not present as we expected with regards to this variable. Due to the small number of participants that actually used an assistive device, our power was not sufficient to detect the presence of a difference. Richardson and colleagues(Richardson, et al., 1992) found that nerve conduction study results, concomitant with peripheral neuropathy, are significantly associated with both "falls" and "repetitive falls" in people with peripheral neuropathy of various origins. MNSI physical exam scores reflect severity of neuropathy-related dysfunction and we expected that this variable would contribute to the explanation of faller status. Although this variable was not significantly different ($p < 0.05$) between fallers and nonfallers ($p = 0.084$), the MNSI physical exam scores trended in the direction anticipated. As

with assistive device use, a small sample size of fallers limited the power associated with the bivariate analysis and may have precluded finding a significant difference for this variable. These two variables were therefore not included as factors in the logistic regression analyses. Additional research with a larger number of more heterogeneous (level of DPN severity) participants would allow for more robust analysis as it pertains to assistive device use and MNSI physical exam scores.

Inferences from the results of this study need to be made carefully secondary to some of the limitations associated with this study. None of the DPN-specific factors nor many of the more general factors demonstrated significant differences between the faller and nonfaller groups. We were not entirely surprised by this finding considering the small sample size of fallers. Had a larger sample been tested, significant findings may have been more abundant especially when one considers that all non-significant outcomes, like the MNSI physical exam scores, for fallers trended in the direction one would expect. For example, fallers had higher HbA1c scores, greater depression and fear of falling, less ankle range of motion and strength, worse proprioception and nerve conduction, and poorer quality of life when compared to nonfallers. The small sample size of fallers in particular also precluded the use of multivariable logistic regression which would have been more informative as to the relative contribution of the outcome measures to the prediction of fall status. The non-significant findings may also be due to the characteristics of the participant sample; the sample was rather homogenous in that all participants were community ambulators and walked without person assistance. As mentioned previously, only 4 (11.1%) reported using an assistive device of any kind. Although increasing the potential for confounding variables, less stringent exclusion criteria would have allowed for a more heterogeneous sample of participants and improved generalizability. In particular,

additional studies that use larger, more heterogeneous samples of individuals need to be conducted.

While physical activity levels, fear of falling and balance and gait, as measured by the fall risk assessment tools, contributed significantly to the prediction of fall status (faller or nonfaller), it should not be interpreted that these factors caused the falls experienced by the fallers or prevented falls in the nonfallers. There are relationships between fall status and these factors but the nature of these relationships cannot be inferred from the results of this study. The decreased physical activity levels in the fallers may have preceded their falls or the falls may have resulted in decreased activity levels. Likewise, fear of falling may stem from recurrent falls or a fear of falling may precede falls. Balance and gait impairments are known risk factors for falls, as previously described, but when falls occur, the resultant fear of falling may lead to decreased physical activity and ultimately, a reduction in lower extremity performance (Deshpande, et al., 2008). Even though we know that the fallers in the study demonstrated decreased physical activity levels, increased fear of falling for activities they do not do and more pronounced balance and gait impairments when tested, it cannot be assumed that this was true of these participants prior to their history of recurrent falls. A prospective study in which these outcome measures could be assessed prior to and after an ongoing recording of fall incidence would allow for a more robust inference about the nature of these relationships. Understanding the relationships of these fall-related variables would help to inform healthcare practitioners how to better prevent or reduce falls in people with DPN.

3.5 Conclusion

This study was the first to investigate factors that relate to falls in people with DPN, in an effort to better understand what might influence fall risk so that falls can be prevented more effectively. It appears that balance and gait impairment, level of physical activity, and fear of falling may play a role in fall risk but how these factors influence fall risk has yet to be determined. Additional prospective studies with larger, more heterogeneous samples of people with DPN need to be conducted to confirm and expand on these new findings.

Tables

Table 3.1 Bivariate Analysis of Fallers versus Nonfallers

This table contains the faller and nonfaller group descriptive statistics (mean ± SD) for each factor, in addition to the results of the bivariate analysis. Significance was determined using an α -level of 0.05. No corrections for multiplicity were made because this was not the primary end-point analysis.

	Faller, n=10 (mean ± SD)	Nonfaller, n=26 (mean ± SD)	p-value
Age (years)	57 ± 7.3	57.5 ± 5.7	0.842
Sex (M/F)	M = 3, F = 7	M = 18, F = 8	0.058
BMI (kg/m ²)	34.4 ± 5.4	34.7 ± 8.2	0.919
HbA1c	8.1 ± 2.3	7.7 ± 1.8	0.522
Beck Depression Inventory - II (max=63)	12.3 ± 6.3	9.8 ± 6.9	0.321
Norfolk QOL-DN (max=115)	34.2 ± 23.4	26.8 ± 22.7	0.390
PASE	78.7 ± 46.0	146.5 ± 74.6	0.012*
SAFE, Activity Level (max=11)	7.5 ± 1.1	8.5 ± 1.4	0.041*
SAFE, Activity Restriction (max=11)	3.5 ± 3.5	3.4 ± 3.2	0.925
SAFE, Fear of Falling (ALL) (max=3)	0.80 ± 0.6	0.46 ± 0.6	0.117
SAFE, Fear of Falling (YES) (max=3)	0.72 ± 0.6	0.53 ± 0.6	0.379
SAFE, Fear of Falling (NO) (max=3)	0.95 ± 1.0	0.24 ± 0.7	0.023*
MNSI History (max=13)	4.8 ± 2.4	5.9 ± 2.9	0.256
MNSI Physical Exam (max=10)	4.9 ± 2.4	3.2 ± 2.5	0.084
Assistive Device Use ^ (max=4)	0.48 ± 0.8	0.08 ± 0.4	0.178
FRT (cm)	28.8 ± 5.2	33.0 ± 5.4	0.042*
TUG (seconds)	11.7 ± 2.3	8.8 ± 2.2	0.001*
BBS (max=56)	49.1 ± 3.2	54.0 ± 2.5	< 0.001*
DGI (max=24)	20.0 ± 2.2	23.2 ± 1.5	< 0.001*
Ankle ROM, Active Supine DF (degrees)	-0.90 ± 11.0	5.1 ± 4.4	0.023*
Ankle ROM, Active Supine PF (degrees)	58.9 ± 9.1	53.4 ± 8.8	0.100
Ankle ROM, Total Supine DF and PF (degrees)	58.0 ± 11.8	58.5 ± 9.9	0.914
Ankle ROM, Active Seated DF (degrees)	4.9 ± 10.9	8.4 ± 5.8	0.213
Ankle ROM, Active Seated PF (degrees)	53.6 ± 4.5	51.3 ± 7.9	0.387
Ankle ROM, Total Seated PF and DF (degrees)	58.5 ± 10.9	59.7 ± 8.9	0.738
Ankle Strength, DF (torque)	19.6 ± 6.6	21.6 ± 8.9	0.532
Ankle Strength, PF (torque)	26.5 ± 17.3	28.5 ± 13.0	0.718
Ankle Strength, Total (torque)	46.1 ± 21.4	50.1 ± 20.7	0.619
Ankle JPS, 15° (error in degrees)	4.1 ± 1.8	3.7 ± 2.7	0.683
Ankle JPS, 30° (error in degrees)	4.1 ± 1.7	3.6 ± 2.4	0.497
Ankle JMT (degrees)	2.8 ± 1.8	2.4 ± 1.5	0.573

* significant difference

^ Levene's test indicated inequality of variance so t-test was conducted with equal variances not assumed.

(Table 3.1 continued)

Tibial Nerve CV (m/s) ^	27.6 ± 16.4	39.2 ± 5.1	0.067
Tibial Nerve Latency (ms) ^	3.7 ± 2.2	4.4 ± 0.8	0.384
Tibial Nerve Amplitude (mV)	3.6 ± 4.1	7.1 ± 5.3	0.078
Peroneal Nerve CV (m/s)	33.8 ± 14.8	36.9 ± 14.7	0.588
Peroneal Nerve Latency (ms)	4.2 ± 1.7	4.3 ± 1.8	0.873
Peroneal Nerve Amplitude (mV)	2.9 ± 2.8	3.4 ± 2.5	0.646
Sural Nerve Latency (ms)	2.2 ± 2.4	3.0 ± 3.7	0.305
Sural Nerve Amplitude (µV)	3.0 ± 3.7	5.2 ± 5.7	0.270

* significant difference

^ Levene's test indicated inequality of variance so t-test was conducted with equal variances not assumed.

Table 3.2 Unconditional Logistic Regression Analyses

This table contains the results from the logistic regression analyses. Each variable was entered separately into the regression analysis. Significance was determined using an α -level of 0.05.

Variable	<i>B</i>	Wald χ^2	p-value	Odds Ratio (Confidence Interval)
PASE	-0.018	5.109	0.024*	0.982 (0.967,0.998)
SAFE, Activity Level	-0.652	3.602	0.058	0.521 (0.266,1.022)
SAFE, Fear of Falling (NO)	0.927	4.166	0.041*	2.53 (1.038,6.150)
FRT	-0.143	3.746	0.053	0.867 (0.750, 1.002)
TUG	0.543	6.648	0.010*	1.721 (1.139, 2.600)
BBS	-0.529	8.880	0.003*	0.589 (0.416,0.835)
DGI	-0.849	8.410	0.004*	0.428 (0.241,0.759)
Active ROM, Active Supine DF	-0.149	3.041	0.081	0.862 (0.729,1.019)

*significant association

Table 3.3 Hosmer and Lemeshow Test Results

This table contains the goodness-of-fit statistics for each of the variables that were significant with the unconditional logistic regression analyses.

Variable	Chi-square	df	Significance
PASE	8.265	7	0.310
SAFE, Fear of Falling (NO)	2.602	1	0.107
TUG	10.525	7	0.161
BBS	9.774	5	0.082
DGI	6.102	3	0.107

Chapter 4

*Health Related Quality of Life in People with Diabetic Peripheral Neuropathy.
Which Factors Play a Role?*

4.1 Introduction

Health related quality of life (HRQOL) is an outcome of interest in clinical research because it reflects a patient's perception of his/her health which is inherently meaningful to the patient.(Hays, et al., 2002; Huang, et al., 2008; Magwood, et al., 2008) HRQOL has been defined as "a personal sense of physical and mental health and the ability to react to factors in the physical and social environments".(U.S. Department of Health and Human Services, 2000) The most recent version of the World Health Organization's International Classification of Functioning, Disability and Health (ICF) model includes 3 categories of primary levels of human function, namely, body function and structures, activities, and participation; HRQOL surveys are thought to measure function at the "participation" level of the ICF model, with participation defined as "involvement in a life situation".(WHO, 2002). In 1997, Glasgow and colleagues (Glasgow, et al., 1997) concluded that "quality of life is an important and understudied topic in diabetes". More recently in 2008, Magwood and colleagues wrote a review of intervention outcome studies in diabetes(Magwood, et al., 2008) and stated that quality of life continues to be insufficiently addressed and that health care providers should consider using HRQOL as a "priority outcome".

It is estimated that as of 2010, diabetes affects 25.8 million adults in the United States, an increase of approximately 25% from 2005.(CDC, 2011) There were about 1.9 million new cases of diabetes diagnosed in 2010 alone.(CDC, 2011) Complications of diabetes include cardiovascular problems, blindness and other eye problems, kidney disease, nervous system damage, limb amputation, dental disease, and pregnancy complications.(CDC, 2011) The nervous system damage affects many different areas of the body and it has been estimated that approximately 65% of people with diabetes have some form of nervous system damage, with

almost half of these having some form of peripheral nerve damage.(CDC, 2011) Diabetic peripheral neuropathy (DPN) is one of the most common forms of nervous system damage associated with diabetes(Vinik, et al., 2000) and is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".(Boulton, et al., 2005) DPN often presents as abnormalities in sensory and sometimes motor function in the lower legs and hands, including the presence of pain and/or numbness and tingling.(Boulton, et al., 2005; Feldman, et al., 1999; Vinik & LeRoith, 2008) The presence of these symptoms can often influence a person's participation in daily activities and has been reported to influence quality of life.(Benbow, et al., 1998; Currie, et al., 2006; Lewko, et al., 2007; Lloyd, et al., 2001; van Schie, 2008)

It is clear that DPN negatively influences HRQOL (Currie, et al., 2006; Happich, et al., 2008; Vinik, et al., 2005), even when compared to diabetic patients without neuropathy and non-diabetic patients(Benbow, et al., 1998). Not only has decreased HRQOL been identified in people with DPN, but studies have demonstrated that HRQOL worsened significantly as severity of DPN increased.(Currie, et al., 2006; Happich, et al., 2008) Relatively few studies have gone beyond determining the presence of reduced HRQOL in people with DPN to determine factors that influence HRQOL in these individuals. The few studies that have, have found that HRQOL was related to the degree of acceptance of illness(Lewko, et al., 2007) and the presence of neuropathic pain(Davies, et al., 2006; Van Acker, et al., 2009). It also appears, although not studied in people with DPN, that fear of falling(Ozcan, et al., 2005) and physical activity levels(Glasgow, et al., 1997; Vickrey, et al., 2000) influence HRQOL as well. The goal of this study was to contribute to the growing body of knowledge related to HRQOL in people with DPN.

To accomplish this goal, we set forth to understand the contribution of selected factors to HRQOL in people with DPN. We hypothesized that severity of neuropathy, neuropathic pain, fear of falling, and physical activity levels would contribute significantly to the explanation of the measured HRQOL in our sample of participants with DPN. Understanding the factors that influence HRQOL in people with DPN, especially if these factors are modifiable, would allow for targeted means to improve this important aspect of health in these individuals.

4.2 Methods

Participants

Prior to participant enrollment, the study was approved by the Institutional Review Board at the University of Kansas Medical Center. Thirty-five persons participated in this cross-sectional study, all of whom had signs and symptoms of DPN. Participants were included if they had DPN, were between the ages of 40 and 65, and were able to walk without assistance from another person. This research was part of another study that investigated fall risk in people with DPN and therefore, participants were excluded if they had any significant non-diabetes related musculoskeletal, neurologic, or vestibular dysfunction that might influence balance and/or gait.

Health Related Quality of Life

The primary measure used to assess HRQOL for the study was the Norfolk QOL-DN(Vinik, et al., 2005). This tool is comprised of 48 items, 35 of which are scored using various scales. The first 7 scored items address symptoms related to nerve fiber function; one point is scored for each type of symptom experienced. The next 23 items address how physical problems associated with small-fiber, large-fiber and autonomic neuropathy cause problems with daily

activities; each of these items is scored using a Likert scale from 0 ("not a problem" or "not at all") to 4 ("severe problem" or "severely"). The last 5 items are generic HRQOL questions. Two of these items assess general health and are scored with different point values; the remaining 3 items use the 0 to 4 Likert scale as previously described. A higher score on this tool indicates lesser quality of life. This tool is unique in that it targets both disease-specific and generic quality of life domains, which has been suggested (Peek, et al., 2007) as advantageous because the disease-specific questions are clinically relevant to the population being tested and might be sensitive to change, and the generic questions comprehensively assess quality of life. (Vickrey, et al., 2000) It has demonstrated internal consistency and reliability (Vinik, et al., 2005) and has recently been used as a primary quality of life measure in a large-scale study assessing the impact of DPN on HRQOL. (Currie, et al., 2006; Happich, et al., 2008) The Norfolk QOL-DN is a valid tool for assessing quality of life in people with diabetic neuropathy (Vinik & LeRoith, 2008) and may be an effective means for making decisions about how to best alter health and functional status in these individuals (Vinik, et al., 2005).

Explanatory Variables

Pain. Visual analogue scales were used to assess neuropathy-related pain. (Van Acker, et al., 2009) Participants were asked to rate their current, average and worst pain in the last month on separate scales by marking a vertical line across a horizontal line that represented "no pain" at the left end to "worst imaginable pain" at the right end. Participants were asked to rate only their pain associated with DPN, not generalized pain like low back pain or general joint pain or muscle soreness. The horizontal line for each pain scale was 10 cm in length and each pain rating score was obtained by measuring the distance from the left side of the horizontal line to

the point where a participant's marked vertical line bisected the horizontal line. The pain scores from each of the 3 scales were summed and this total pain score (range, 0 to 30 cm) was used for analysis purposes.

Severity of DPN. The Michigan Neuropathy Screening Instrument (MNSI) was used to assess neuropathy severity to determine how it relates to HRQOL in people with DPN. The MNSI is a two-part (history and physical exam) tool. The history portion assesses the patient's subjective experience of DPN symptoms and the physical exam portion involves foot inspection, monofilament sensation, vibration sense and reflex testing. A higher score indicates more severe DPN. The maximum scores one can achieve on the history and physical exam portions are 13 and 10, respectively. The total MNSI score was calculated by summing the scores from each portion of the tool; this total score was used for data analysis. The MNSI tool has been shown to be a sensitive and reliable screening tool for people with DPN.(Feldman, et al., 1994; Lunetta, Le Moli, Grasso, & Sangiorgio, 1998; Moghtaderi, et al., 2006)

Fear of Falling. The Survey of Activities and Fear of Falling in the Elderly(Lachman, et al., 1998) (SAFE) was used to measure fear of falling for this study and has been used previously in studies with healthy older adults(Deshpande, et al., 2008; Fuzhong et al., 2002). This survey was conducted as an interview and involved asking the participants if they perform 11 different activities and whether or not they have a fear of falling (and the degree of fear) with each of these activities. The degree of fear with each activity was rated on a scale from 1 (very worried) to 4 (not at all worried) but scored on a scale from 0 (not at all worried) to 3 (very worried). Outcomes associated with this survey included activity level (number of activities performed),

activity restriction (number of activities not performed) and fear of falling. Activity level and activity restriction scores were calculated as the total number of activities the participant answered "yes" and "no" to, respectively. Fear of falling scores were averaged across all 11 activities. A higher fear of falling score indicates greater average fear across all 11 activities. The SAFE was created specifically to assess the role that fear of falling plays in activity restriction and has been shown to be reliable and valid when used in community-dwelling older adults.(Lachman, et al., 1998) In comparison to similar measures of fear of falling, the SAFE is reported as having the most acceptable content validity.(Jorstad, et al., 2005)

Physical Activity Levels. The Physical Activity Survey for the Elderly (PASE) was used to assess physical activity levels. The PASE inquires about physical activity related to walking outside of the home or yard for any reason, light, moderate and strenuous sport or recreational activities, exercise (aerobic and resistance training), light and heavy housework, home repair, lawn care/gardening, caring for another person and work or volunteer activity. Participants were asked to answer the questions as they considered their activity over the past 7 days. An algorithm is used to score the PASE; a higher score corresponds to a higher level of physical activity. The PASE is considered to be a reliable(Hagiwara, et al., 2008; Washburn, et al., 1993) and valid(Washburn & Ficker, 1999) tool for assessing physical activity levels in older adults and has also been used to assess physical activity in younger populations(Pollak, et al., 2011).

Other data was collected for descriptive purposes, including depression as measured by the Beck Depression Inventory-II(Lustman, et al., 1997) (BDI), the use of assistive devices at home and in the community, body mass index(BMI), and glycosylated hemoglobin (A1Cnow+, Metrika).

Data Analysis

All data analysis was conducted with PASW Statistics 18.0 (SPSS, Inc., Chicago, IL, 2009). For quality assurance, a 100% audit was conducted to ensure accurate data entry after all testing for the study was completed. Descriptive statistics (means, standard deviations, ranges) were calculated for age, body mass index (BMI), years with DPN, Norfolk QOL-DN scores, total pain scores, MNSI total scores, SAFE fear of falling scores and PASE scores. Multivariable linear regression was used to achieve the aim of the study which was to determine the contribution of 4 independent variables (pain, neuropathy severity, fear of falling, physical activity levels) to the dependent variable (HRQOL). As has been suggested (Field, 2005), a theoretical basis, based on previous research findings, was used to determine which factors should be included in the regression analysis. Variables were included in the final multivariable linear regression model if the significance of the coefficients was less than 0.05. A backwards elimination approach was used to build a model for regression analysis with significance for exit set at 0.10. The assumption of normality was assessed by plotting a frequency histogram of the standardized residuals. The assumption of linearity was assessed using P-P plots of the standardized residuals. The assumption of homoscedasticity was assessed with a scatterplot of the studentized deleted residuals against the standardized predicted values. Collinearity diagnostics (tolerance and VIF) were conducted to assess for collinearity in the final model. Overall model fit was assessed using residual plots. Bivariate scatter plots were also generated to display the relationship of each independent variable to the dependent variable, and simple linear regression models were used to derive R-square values for these relationships.

4.3 Results

Twenty one (60.0%) of the 35 participants were male and 4 of the 35 participants used assistive devices (2 ankle foot orthoses, 2 canes). The descriptive statistics (means and standard deviations) are listed in Table 4.1. The multivariable linear regression analysis demonstrated that total pain scores, SAFE fear of falling scores and PASE scores (model 2), but not MNSI total scores were significantly associated with Norfolk QOL-DN scores (total pain, $p=0.001$; SAFE fear of falling, $p=0.009$; PASE, $p=0.028$; MNSI, $p=0.173$) (Table 4.2). Assumptions of linearity, homoscedasticity and normality were met. Collinearity diagnostics indicated that collinearity did not influence the results of the analysis. MNSI total score was removed from the final model because it was not significantly associated with Norfolk QOL-DN scores. Total variance in Norfolk QOL-DN scores explained by the final model was 64.3% (R Square = 0.643). Contributions to the explanation of variance for total pain, SAFE fear of falling and PASE scores were 43.1%, 15.1%, and 6.1%, respectively. The scatter plots and associated R^2 values for each of the 4 variables entered into the regression analysis are depicted in Figure 4.1. Total pain and SAFE fear of falling scores were directly related to Norfolk QOL-DN scores. PASE physical activity scores were inversely related to Norfolk QOL-DN scores. The SAFE fear of falling scores demonstrated the strongest relationship ($R^2 = 0.4225$) with Norfolk QOL-DN scores, followed by total pain scores ($R^2 = 0.4075$), PASE physical activity scores ($R^2 = 0.2355$), and MNSI total score ($R^2 = 0.2154$).

4.4 Discussion

The aim of this study was to investigate the relationships between 4 different variables and HRQOL in people with DPN. The results from this study confirm previous findings that

neuropathic pain is a significant predictor of HRQOL but do not support previous findings relating neuropathy severity to HRQOL. In addition, this research extends previous findings in other populations to our sample of people with DPN, namely, that fear of falling and physical activity levels are significant predictors of HRQOL.

It was not surprising that pain scores were significant predictors of HRQOL as this is consistent with current pain-related literature. A study by Davies and colleagues (Davies, et al., 2006) found that people with DPN with neuropathic pain had significantly poorer quality of life than people that had non-painful DPN or pain of non-neuropathic origin. This finding was supported by another study in which patients with painful DPN demonstrated significantly worse quality of life in the physical and mental domains of the 12-item Short-Form Health Survey, than patients that had non-painful DPN. (Van Acker, et al., 2009) A unique aspect of the current study is that we did not group participants into painful and non-painful neuropathy but rather assessed the pain and HRQOL of all participants, and still, pain significantly predicted quality of life in people that have DPN. This would suggest that effective treatment of the painful symptoms of DPN may improve HRQOL for these individuals.

Even though it was hypothesized that the MNSI, our measure of neuropathy severity, would be a significant predictor of HRQOL, it was the only variable that did not contribute significantly to the prediction of HRQOL scores. Even when this measure was forced into the simple linear regression analysis, it did not demonstrate significance while the other 3 measures continued to do so. A study that likewise assessed neuropathy severity with a tool that assessed both symptoms and signs of neuropathy found a significant relationship between neuropathy severity and HRQOL. (Vinik, et al., 2005) One major distinction, however, between their assessment of neuropathy and ours was the extensive nature of their assessment. Their

assessment included a 37-item Neurologic Impairment Score that reflected motor and sensory function of the whole body and a 38-item Neurologic Symptom Score.(Vinik, et al., 2005) The relatively less extensive nature of the MNSI assessment may have precluded it from being predictive of HRQOL. In addition, evidence suggests that specific measures of physiologic function, like the physical exam portion of the MNSI, are not related to quality of life(Vickrey, et al., 2000) and that patient reported symptoms of neuropathy are more relevant. Other studies that have found a relationship between neuropathy severity and HRQOL assessed neuropathy severity based solely on patient symptoms rather than a combination of signs and symptoms(Currie, et al., 2006; Happich, et al., 2008). It appears then that if there is a relationship between neuropathy severity and HRQOL, the methods that are used to assign neuropathy severity may influence the ability to detect that relationship. A patient's symptomatic experience of DPN may be more relevant to quality of life than signs associated with DPN.

Fear of falling, as measured by the SAFE, made a significant contribution to the explanation of HRQOL scores in this study. As fear of falling increased, reported quality of life decreased. This is consistent with current literature that indicates that fear of falling is inversely related to quality of life in older adults.(Ozcan, et al., 2005) While this relationship is clear, how fear of falling impacts HRQOL is not fully understood. Recent findings indicate that fear of falling leads to activity avoidance(Bertera & Bertera, 2008), which can lead to negative physical consequences and disability. This was confirmed by a large scale prospective study by Deshpande and colleagues(Deshpande, et al., 2008) that reported that activity restriction secondary to a fear of falling resulted in increased ADL disability and worsening of lower extremity performance as it relates to mobility. Although there is a significant relationship between fear of falling and quality of life we cannot infer from our study that an increase in fear

of falling causes a reduction in quality of life; perhaps there are other factors, such as ADL disability or activity avoidance, that mediate the relationship between fear of falling and HRQOL. Additional research is needed to better understand how fear of falling influences HRQOL, more specifically, to substantiate whether or not a change in fear of falling would result in a change in perceived quality of life in people with DPN.

We also found that physical activity levels, as measured by the PASE, significantly contributed to explaining the variance in HRQOL scores. A challenge encountered when reviewing the literature related to physical activity levels and quality of life was the different types of physical activities assessed; some have specifically investigated exercise while others investigated employment and disability. Glasgow et al.(Glasgow, et al., 1997) found that the level of self-reported exercise was the only self-management behavior to predict quality of life in a sample of over 2000 diabetic patients. A study by Vickrey and colleagues(Vickrey, et al., 2000) found that no employment and increased disability days were both associated with decreased quality of life. Although these two studies used methods other than the PASE to assess physical activity, the PASE is unique in that it assesses many different types of physical activity including exercise and physical activity associated with employment or volunteerism. While the PASE provides a comprehensive assessment of physical activity levels associated with many different types of activities, no specific recommendations can be made as to which types of physical activity are most beneficial for or most related to HRQOL. Additional research that investigates the various types of physical activities addressed by the PASE would be helpful towards making specific physical activity recommendations. The results of this study suggest that lower physical activity levels, in general, are associated with lesser perceived quality of life in our sample of participants with DPN.

Inferences made from this study need to be made in context of its limitations and the limitations of the outcome measures used. The sample of participants tested was rather small and homogenous when compared to participant samples in other HRQOL-related literature; therefore, additional research needs to be conducted with a larger number of participants who are more diverse in their DPN severity to improve generalizability of the results. The PASE only assesses physical activity levels over the past 7 days and therefore may not be an accurate representation of physical activity levels over a longer period of time. Similarly, although the cross-sectional nature of this study afforded useful information with regards to factors that influence quality of life in our sample of participants with DPN, non-intervention longitudinal studies would allow for a more robust understanding of the nature of the relationships identified in this study. In addition, before studies are conducted to determine the effect of treatments on HRQOL assessed by the Norfolk QOL-DN, studies need to be conducted to determine the Norfolk QOL-DNs sensitivity to changes in HRQOL. Once established as a tool that is sensitive to change, longitudinal intervention studies investigating changes in HRQOL associated with interventions that target pain, fear of falling and physical activity levels would be useful to guide clinicians towards treatment interventions that improve patient HRQOL. As mentioned previously, quality of life needs to be a "priority outcome" because it is meaningful to patients.(Magwood, et al., 2008)

4.5 Conclusion

HRQOL is an important outcome that needs more attention in today's research and clinical care environments because it is important to patients. This study confirms and expands on the limited research findings related to HRQOL in people with DPN. Self-reported measures

of pain, fear of falling and physical activity levels are significant predictors of HRQOL in people with DPN. Additional research needs to be conducted with larger, more heterogeneous samples of people with DPN to confirm these findings as a preparatory step to longitudinal intervention studies that target improving HRQOL in these individuals.

Tables and Figures

Table 4.1 Descriptive Statistics

Means, standard deviations and ranges for selected factors. (n=35)

Outcome Measure	Mean	St. Dev.	Range (max possible)
Age (years)	57.2	6.1	42-65
Body Mass Index (kg/m ²)	34.7	7.6	22-55
Years with DPN	4.4	3.2	0.25-10
Norfolk QOL-DN score	28.5	23.0	1-79 (115)
Pain, Total score (cm)	11.0	6.9	0.10-24.15 (30)
MNSI, Total score	9.2	4.1	3-18 (23)
SAFE, Fear of Falling score	0.6	0.6	0-2 (3)
PASE score	127.1	73.9	2-321

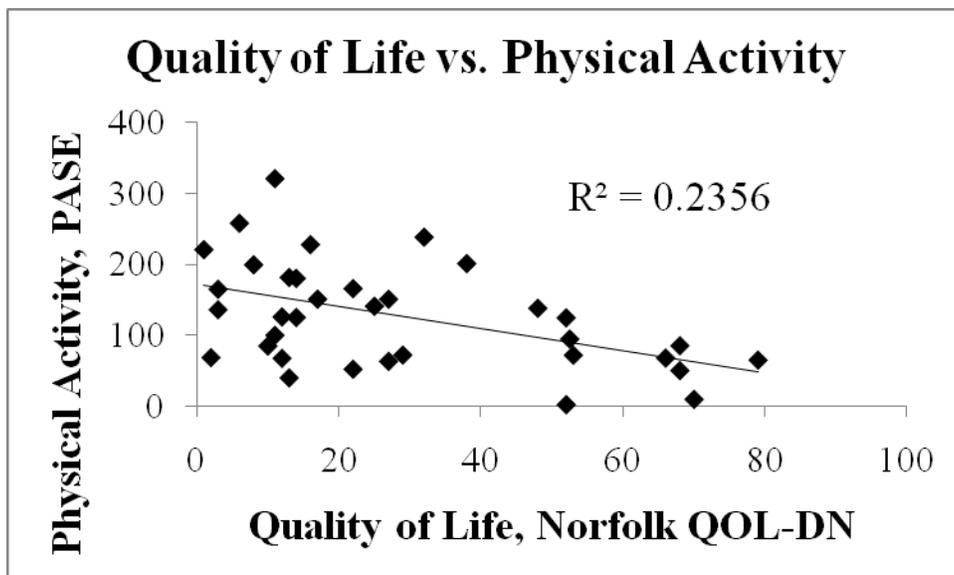
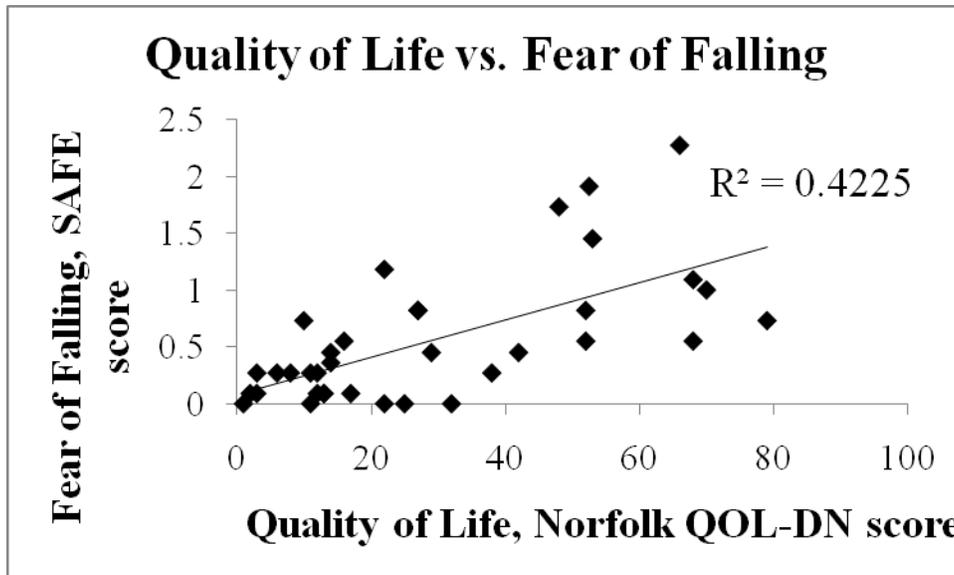
Table 4.2 Multivariable Linear Regression Analysis

This table contains the models built for the linear regression analysis. A backward elimination method was used to build the model. Model 2 was the final model associated with this study. Significant variables were determined using an α -level of 0.05. Dependent variable: Norfolk QOL-DN scores.

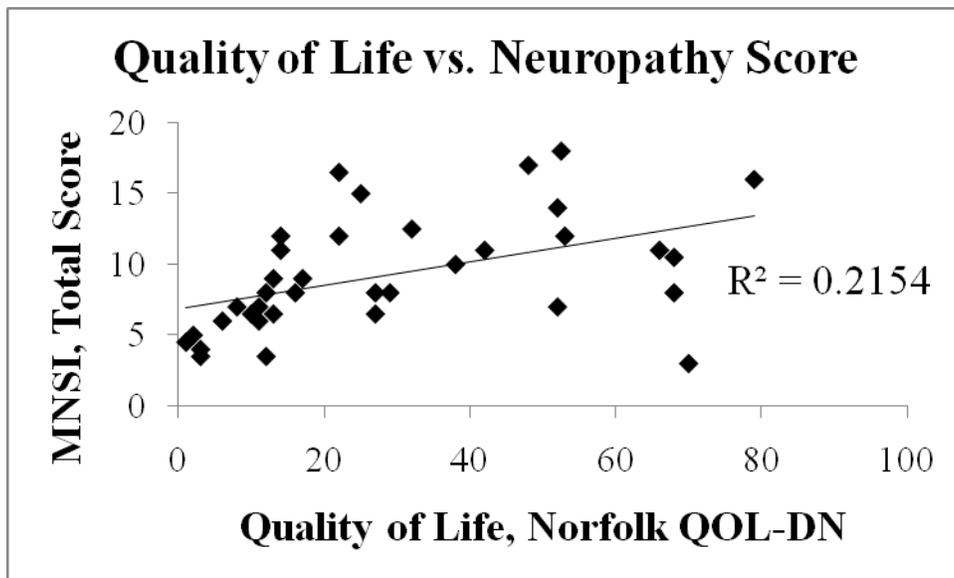
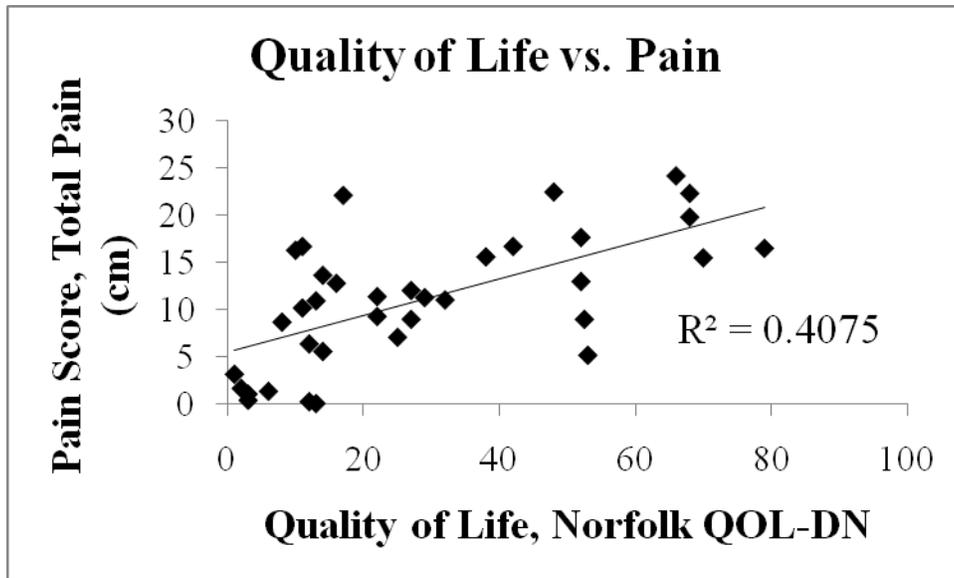
Model	Unstand. Coefficients		Stand. Coefficients	<i>t</i>	<i>Sig.</i>	95% Conf. Int. for B	
	<i>B</i>	<i>Std. Error</i>	<i>Beta</i>			<i>Lower</i>	<i>Upper</i>
1 (Constant)	9.768	8.247		1.185	0.246	-7.074	26.610
Pain Total	1.322	0.402	0.397	3.287	0.003	0.501	2.144
MNSI Total	0.930	0.666	0.166	1.396	0.173	-0.430	2.291
SAFE	12.099	5.242	0.305	2.308	0.028	1.393	22.806
PASE	-0.088	0.036	-0.281	-2.421	0.022	-0.161	-0.014
2 (Constant)	15.300	7.342		2.084	0.046	0.325	30.275
Pain Total	1.453	0.397	0.436	3.658	0.001	0.643	2.263
SAFE	14.189	5.101	0.358	2.782	0.009	3.786	24.592
PASE	-0.084	0.037	-0.271	-2.302	0.028	-0.159	-0.010

Figure 4.1 Scatter Plots

This figure depicts the scatter plots associated with each of the 4 variables entered into the linear regression analysis. The independent variables are on the y-axis and the dependent variable (quality of life) is on the x-axis. Corresponding R^2 values are listed on each scatter plot.



(Figure 4.1 continued)



Chapter 5

Conclusion

5.1 Summary

The overarching goal of this body of work was to establish knowledge and extend previous findings that could ultimately improve care for patients that have DPN; specifically, care that relates to falls and health-related quality of life (HRQOL).

Chapter 2

The work associated with Chapter 2 established knowledge that was previously, to our knowledge, unstudied and is relevant to improving fall-related care in people with DPN. Fall risk assessment tools are often used as relatively objective means of identifying patients that have fall risk, in hopes that fall prevention interventions can be commenced before these individuals experience a fall. The ability of many of these tools to accurately identify persons that have fall risk has been studied in older adults(K. Berg, et al., 1995; Bogle Thorbahn & Newton, 1996; Duncan, et al., 1992; O'Sullivan & Schmitz, 2005; Podsiadlo & Richardson, 1991; Weiner, et al., 1992), people who have experienced a stroke(Blum & Korner-Bitensky, 2008), people with Parkinson's disease(Dibble, et al., 2008; Dibble & Lange, 2006) and those with vestibular dysfunction(Marchetti, et al., 2008); yet, it appears that no studies have been conducted to determine the ability of these tools to accurately identify possible fall risk in people with DPN. In order to fill this void in the literature, we set forth using a cross-sectional design to establish whether or not 4 common fall risk assessment tools were able to accurately discriminate between persons with and without a self-reported history of falls. In doing so, we were able to provide new information about the fall risk assessment tools assessed and their potential utility for accurately identifying fall risk in people with DPN.

Chapter 3

The work associated with Chapter 3 extends knowledge of factors related to falls, which has been extensively studied in older adults, to people with DPN. While many studies have established that DPN results in physical dysfunction (Boucher, et al., 1995; Courtemanche, et al., 1996; Mueller, et al., 1994; Richardson, et al., 1992; Simoneau, et al., 1994), very few studies (Richardson, et al., 1992; Schwartz, et al., 2008) have specifically tried to determine if these physical deficits, or other factors, relate to falls in these individuals. In order to add to this small body of knowledge, we set forth to conduct a more comprehensive investigation into factors that relate to self-reported fall history in a sample of participants with DPN. This investigation has provided new information about a few factors that relate to fall history, which may influence fall risk.

Chapter 4

The work associated with Chapter 4 expands a small but growing body of knowledge and is relevant to improving HRQOL in people with DPN. HRQOL was selected as a target for research because it is meaningful to individuals but also because it is thought to measure function at the "participation" level, which is one of the 3 major categories of human function in the World Health Organization's International Classification of Functioning, Disability and Health (ICF) model. (WHO, 2002) It seems clear that HRQOL is negatively influenced by DPN (Benbow, et al., 1998; Currie, et al., 2006; Happich, et al., 2008; Vinik, et al., 2005) but due to limited research in this area, it is not entirely clear what exactly contributes to this reduction in HRQOL for people that have DPN. In order to have increased clarity around factors that are associated with HRQOL in people with DPN, this cross-sectional study was conducted. The

results of this study confirm previous findings and extend those findings to include additional, previously unidentified factors that relate to HRQOL in people with DPN. The identification of these factors may aid clinicians in their efforts to improve quality of life in patients with DPN.

5.2 Limitations

This body of work has limitations, most of which have been addressed in each chapter. Two of the most substantial limitations were the small sample size and external validity.

Small Sample Size

The small sample size directly influenced our ability to conduct more substantial and definitive statistical analyses. Had the sample size been larger, it would have been interesting to conduct sub-analyses based on the number of falls (0, 1, and 2) for Chapters 2 and 3, rather than having only a dichotomous fall status designation. The proportion of fallers (27.8%, 10/36) in our small sample of participants limited the ability to include more than one variable at a time into the simple logistic regression analysis associated with Chapter 3. This limited our ability to assess the relative contribution of the independent variables to fall status; this seemed to be the analysis most limited by the small sample size. Lastly, only 4 factors could be included in the multivariable regression model associated with the work in Chapter 4. A larger sample size would have enabled a multivariable logistic regression analysis (Chapter 3) and allowed for the inclusion of more factors in the multivariable linear regression analysis (Chapter 4), both of which would have allowed for more comprehensive results and greater additions to the small body of knowledge related to falls and quality of life in people with DPN. In spite of the statistical limitations of this body of work, appropriate inferences have been made that are

important to and achieve the aims of the study, although less robust than they might have been had a larger sample size been used.

Although the sample size was small, recruitment efforts for this study were substantial. Some relatively successful recruitment strategies included collaboration with the principal investigator's mentor's diabetes project and a committee member's neurology clinic (and research assistants), collaboration with diabetes educators at the principal investigator's institution, another large hospital in the metro area and independent health service organizations, engaging patients through the principal investigator's and collaborators' clinical practice in the areas of physical therapy, neurology and internal medicine, presenting at neuropathy and diabetes related support groups, participating in a trial use of a hospital database program created to assist researchers in their recruitment efforts at the investigators' institution, selection of participants from a diabetes database created by and for the principal investigator's mentor's laboratory, and advertising through broadcast emails within the institution, fliers throughout the institution and in the community (grocery stores, community centers, etc.), local mailings, radio advertisement, marketing opportunities through the Neuropathy Association newsletter and registration with Clinical Trials.gov. Attempts at establishing recruitment opportunities that were not fruitful or strategies that were established but less successful included attending city-wide American Diabetes Association marketing events, collaboration with colleagues in internal medicine, endocrinology, ophthalmology and nephrology, collaboration with multiple safety net clinics in the metro area, and collaboration with a local chiropractic clinic that treats DPN using phototherapy. By a wide margin, the most successful recruitment strategies, from numbers recruited and time efficiency perspectives, included strategies in which face-to-face meetings were conducted (collaboration with mentor's diabetes project and diabetes education classes)

with potential participants. Although very time-intensive, another rather successful strategy included the trial use of a hospital database program by which searches could be conducted and contact information obtained for patients that had DPN diagnostic codes associated with their previous hospital visits. Future recruitment strategies should entail more collaboration with health care practitioners through which in-person recruitment efforts could be made on a regular basis. The most successful strategies were those where a relationship was established with a health care provider through which regularly scheduled face-to-face interactions with potential participants were accomplished.

External Validity

The small sample size may have also indirectly influenced the external validity of the study results. As with any sample, a larger sample of people with DPN will likely be more representative of the population of people with DPN. For example, only 4 (11.1%) of the participants used assistive devices of any kind; we had expected a larger number of individuals in our sample to use an assistive device, as is evidenced by the hypothesis associated with Chapter 3. Had a larger sample of persons with DPN participated, it is likely that the percentage of participants using an assistive device would more closely approximate that of the population of people with DPN.

External validity was also likely influenced substantially by the recruitment methods. Our sample of participants was fairly homogeneous in that all participants were community ambulators and the majority had mild DPN (sural nerve response still present). As mentioned previously, some of the more successful recruitment strategies were those where face-to-face interactions took place, like the diabetes education classes. The persons who attended the

diabetes education classes were often individuals who were newly diagnosed with diabetes and required to attend classes to learn about management of their diabetes or had diabetes for a few years and were having difficulty with managing their disease. Sometimes these individuals had diabetes for long time and had severe DPN but that was not often the case, unless their ability to access these services was limited earlier in the course of their disease. In addition, many of the individuals that attended these education classes from which I recruited participants were able to ambulate independently in the community. Persons that participated in the study and that were recruited through the diabetes education classes had relatively mild DPN and community ambulatory for the reasons stated above.

The exclusion criteria for the study may have also limited the participation of people that had more severe DPN. One of the primary and possibly most limiting exclusion criterion associated with our study was the exclusion of people that had any non-diabetes related musculoskeletal problems that limited their balance and/or gait. Of the 126 people that were screened through conversation over the phone, 14 (11.1%) that would have otherwise qualified for the study were excluded based on the aforementioned exclusion criterion. This criterion resulted in the exclusion of any persons that had surgery on lower extremity joints, notable arthritic changes that are common in obese individuals, or any foot deformities often associated with more severe DPN. This criterion, although useful for filtering out potential confounding variables, resulted in the recruitment of individuals that functioned physically at relatively high levels. Other persons that were excluded that would have otherwise qualified included 13 (10.3%) that were either older (11/13) or younger (2/13) than 40 to 65 years of age, 7 (5.6%) that had a history of stroke or non-diabetes related neuropathy, 3 (2.4%) that had wounds on the weight-bearing surfaces of the feet, 3 (2.4%) that had significant visual problems, 2 (1.6%) that

used prosthetic lower extremities and 1 (0.7%) that reported major medical depression. An additional 16 (12.7%) persons did not report a diagnosis of or any signs or symptoms of DPN, 7 (5.6%) either canceled or did not show for the scheduled informed consent and testing session, 9 (7.1%) were not interested in participating, and 15 (11.9%) gave other reasons for not wanting to participate, including wanting payment, being too busy, having personal issues, or not able to travel to the testing location. Of the 126 people that were screened, 110 people had DPN and 43 (39.1%) of these individuals were excluded from participating in the study based on the study's inclusion and exclusion criteria. These criteria were established primarily to allow for a focused investigation into fall risk and quality of life as they relate, specifically, to DPN. While these criteria helped to control for possible confounding variables, they also clearly limited the generalizability of the results of the study; more participants were excluded than participated because of these criteria. Future studies, if sample sizes are large enough to support statistical analyses that could account for greater heterogeneity, should include people that are older and those that have musculoskeletal limitations.

The rather homogeneous nature of our sample is likely not representative of the entire population of people with DPN, which needs to be considered when inferring from the results of this study. It is important, when applying research results in patient care, to be sure that the sample of participants tested in the research is representative of the patients before specific results can be appropriately applied. For example, the modified cut-off scores associated with Chapter 2 should not be applied to all patients with DPN. In fact, additional validation studies need to be conducted to validate the modified cut-off scores that were determined on our small sample of participants with DPN.

Other Limitations

Other study limitations included the use of fall history in Chapter 2 as the "gold standard" for comparing fall risk assessment tool utility (this is addressed below), insufficient research supporting the reliability and validity of some of the measures used (i.e. ankle proprioceptive testing), and limitations inherent to some of the tools used (i.e. PASE only assessing physical activity over the past 7 days).

5.3 Clinical Significance and Future Directions

While there are limitations associated with this study, the results are meaningful and should be considered when engaging patients with DPN around the issues of falls and HRQOL.

Chapter 2

It is important, when assessing fall risk in a specific patient population, to ensure that the tool being used has been validated for use with that patient population. One of the most important results from Chapter 2 is that none of the 4 fall risk assessment tools, when using traditional cut-off scores, identified more than 3 of the 10 fallers with DPN. The false negative rate was high and proved to be worse than chance for discriminating between fallers and nonfallers. In addition, it appears that when assessing people that are similar to our sample, modified cut-off scores can substantially improve the usefulness of these tools for discriminating between those that have a history of falls and those that do not. It appears that fall risk assessment tools that involve more dynamic lower extremity mobility challenges and have either continuous (i.e. TUG) or rather detailed interval category outcome measures for multiple items (i.e. DGI) are most useful for discriminating between fallers and nonfallers that have mild DPN.

It is also important to infer appropriately from the results of this study, in particular, as it relates to the concept of fall risk. Because an assessment of self-reported fall history was used to assess fall status, as opposed to gathering data about falls prospectively, our assessment of the fall risk tools discriminative accuracy lends only to an inference about their ability to identify those that have a recent history of recurrent falls. Fall risk assessment tools are not needed to identify those that have fallen in the past but rather, they are most useful in their ability to identify current fall risk and predict future falls. Although a “history of falls” was listed as the second most common risk factor for falls("Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention," 2001) and some suggest that a history of recent falls has been associated with an increased risk of falling again(Brians, et al., 1991; Dibble, et al., 2008; Rubenstein & Josephson, 2002; Russell, et al., 2006; Schmid, 1990; Shumway-Cook, et al., 1997), inferences from this study to fall risk per se need to be made judiciously.

Future studies related to Chapter 2 need to use prospective approaches to allow for inference about fall risk, rather than fall history. Not only would this approach allow for appropriate inference about fall risk, it could also be used to validate the findings associated with the traditional and modified cut-off scores. This could be achieved by assessing fall risk at the start of a study and recording fall incidence longitudinally, while also assessing fall risk at different time points. Also, if generalizability is to be improved for future studies, larger and more heterogeneous samples of people with DPN need to be recruited.

If these future studies find that the modified cut-off scores are not valid for a more heterogeneous sample of people with DPN, if the sample is large enough, the pool of participants could be grouped in a number of different ways and validity reassessed for different groups of

participants. This would require significant time and effort but other options, such as developing a new fall risk assessment tool that is specific to people with DPN, would be equally if not more time intensive. Future assessments of the use of multiple fall risk assessment tools, as opposed to just a single tool, to maximize discriminative accuracy could also be conducted. As stated in Chapter 2, the use of a comprehensive fall risk assessment program, as opposed to solely using a single tool, is important if wanting to more fully understand a patient's risk of falling. However, a single reliable and valid fall risk assessment tool can serve a very important purpose if part of a comprehensive fall risk assessment program and, ultimately, lead to improved fall-related care in people with DPN.

Chapter 3

Fall-related research clearly indicates that there are a myriad of risk factors for falls.(Rubenstein & Josephson, 2002) The results of Chapter 3 indicate that physical activity levels, fear of falling, and balance and gait (as measured by fall risk assessment tools) are related to fall history in our sample of participants with DPN. While we cannot definitively assert that these factors caused the falls or have resulted because of the falls, we do know that there is a clear relationship between these factors and our participants' fall history. The results are useful clinically in the sense that practitioners, after learning of these results, will have increased awareness of these factors as playing some role in fall-related outcomes for patients with DPN. More importantly perhaps is the forward steps that can be taken, from a research perspective, now that a relationship has been established between these factors and fall history.

Future studies that are prospective and longitudinal in design could provide a more definitive understanding of the nature of the relationships between these factors and falls. For

example, if physical activity levels are assessed at the beginning of a study and then at different time points throughout the study, and fall incidence is recorded during the same time period, it could be determined how certain levels of physical activity influence fall incidence.(Portney & Watkins, 2009) The same approach could be applied to fear of falling as well. These examples were chosen specifically because we are interested learning more about the relationship of these two factors to one another and how their interaction influences fall incidence. It is possible that after a person falls, s/he develops a fear of falling and begins to restrict activity, which then results in deconditioning that leads to additional falls. Similarly, a fear of falling could develop before a person falls, for various reasons, which can then lead to decreased physical activity and ultimately, a fall. If a more definitive understanding of the relationships between these factors and fall incidence is achieved, accurate inference about whether or not these factors are risk factors for falls could be made. Specific strategies to reduce falls in people with DPN could also then be substantiated and guide clinicians towards the use of more targeted fall prevention programs.

Much of the fall-related literature categorizes risk factors for falls as either intrinsic (i.e. decreased muscle strength, arthritis, visual deficits, balance deficits, etc.) or extrinsic (i.e. environmental hazards, use of a walking aid, etc.). After reviewing substantial amounts of fall-related research, an interesting and relevant point has been made only a couple times that could be addressed in future fall-related research. Laessoe and colleagues(Laessoe, Hoeck, Simonsen, Sinkjaer, & Voigt, 2007) found that a 9-test battery used to assess physiologic balance performance in a sample of healthy and active older adults was not predictive of falls. Similar results were found by Boulgarides and colleagues.(Boulgarides, McGinty, Willett, & Barnes, 2003) They proposed that while physiological performance may play a role in fall risk, this

needs to be evaluated in relation to the person's activity profile. They suggest that a person's choice to engage in fall-risky behaviors may also be an important component to the multifactorial nature of fall risk. This idea can be illustrated by an observation made while testing participants for the current study. Two participants used the same assistive device and yet one participant was identified as a faller and the other identified as a nonfaller. The nonfaller presented as a very cautious and careful individual who was very deliberate in most mobility choices. However, the faller appeared to approach mobility with much less caution and very little deliberation. While many other differences could explain the difference in their fall status, thought was directed towards the issue that Laessoe and colleagues pointed out, namely, that the activity profile or mobility choices made by each individual may also play a significant role in fall risk, not just the typical intrinsic or extrinsic fall risk factors. While this may broach a more cognitive or behavioral approach to factors that influence fall risk, we think it is a unique perspective that warrants further investigation. It seems reasonable that even a couple factors that were identified by this body of work (fear of falling and physical activity levels), may influence or be influenced by each person's activity profile and/or willingness to engage in fall-risky behaviors.

Chapter 4

Magwood and colleagues (Magwood, et al., 2008) wrote a review of intervention outcome studies in diabetes and stated that quality of life continues to be insufficiently addressed and that health care providers should consider using HRQOL as a "priority outcome". The results from this body of work and previous research by other groups (Davies, et al., 2006; Van Acker, et al., 2009) suggest that current efforts directed towards relieving neuropathic pain in patients with

DPN should be continued as it appears that pain is an important predictor of quality of life. The results associated with Chapter 4 also confirm that fear of falling and physical activity levels are also significantly linked to HRQOL in our sample of participants with DPN. However, as with factors related to fall history in Chapter 3, it is important that the nature of the relationships between HRQOL and fear of falling and physical activity levels is more fully understood, which could be accomplished through prospective, longitudinal studies. In particular, it would be beneficial to conduct larger scale studies that allow for a more comprehensive assessment of other possible factors that may directly impact HRQOL or serve as mediators of the relationships identified and presented in Chapter 4. Engaging in physical activity, especially exercise, has often been encouraged by health care professionals as an important part of managing diabetes; the results from Chapter 4 suggest that exercise, in addition to other types of physical activity (i.e. activity during household chores, work, or volunteer experience, etc.) may influence HRQOL. While it is not possible to suggest one type of physical activity over another based on the nature of the PASE and the results of this study, the results do beg this exact question. Future research that aims to understand the relative impact of different types of physical activity, including but not limited to exercise-related activity, on HRQOL in people with DPN is warranted.

Now that relationships have been established between HRQOL and pain, fear of falling and physical activity levels in people with DPN, research that assesses change in HRQOL due to interventions that target these 3 factors would help guide clinicians in their efforts to meaningfully influence their patients' perceptions of their HRQOL. However, as mentioned in Chapter 4, it would first be important to determine if the measure used to assess HRQOL is sensitive to changes that might take place. There is a great deal of research that could be

conducted in the area of HRQOL in people with DPN; the current body of work is a step in the right direction and will help to inform future studies.

5.4 Conclusion

This research established new and important information about fall risk assessment and factors related to falls and quality of life in people with DPN. Prior to this research, these areas were understudied and not well understood specifically as they relate to the growing population of people that experience DPN, an unfortunate complication of diabetes. Although this body of work has increased our understanding of falls and quality of life in people with DPN, it seems clear that there is a substantial need for additional related research. This additional research would build on the foundation that has been established by the current body of work and may ultimately lead to improved care for people with DPN.

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