**Understanding Fatigue in Persons with Type 2 Diabetes: A Mixed Methods Study**

**Rupali Singh**

**BPT, Punjabi University, India, 2006**

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Patricia Kluding, PT. PhD (Chair)

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Yvonne Colgrove, PT. PhD

_____

Carla Sabus, PT. PhD

_____

Cynthia Teel, RN. FAAN. PhD

_____

Patricia McGinnis, PT. MS. PhD

**August 1, 2013**

Date of Dissertation Defense

**The dissertation committee for Rupali Singh certifies that this is the approved version of the following dissertation:**

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**Chair:**

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Patricia Kluding, PT. PhD

Date approved:

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**Abstract**

Characterized by difficulty in initiating and sustaining mental and physical tasks, fatigue is a common complaint among individuals with diabetes. Unfortunately, fatigue is mostly neglected in those with diabetes because it is often overshadowed by more pronounced complications like neuropathy, retinopathy, and nephropathy. However, fatigue may undermine these patients' essential efforts to self-manage their disease. Fatigue-related difficulties may lead to decreased physical activity levels that often result in reduced cardiovascular fitness. Those with type 2 diabetes often experience the additional challenges of obesity, depression, and impaired glycemic control, each of which may be associated with fatigue. Although complaints of fatigue are common in people with type 2 diabetes, no research has been done investigating its presence or severity of this problem in people with diabetes. Moreover, little research has attempted to examine its causative factors or impact on function or quality of life in this population. Qualitative research has been a primary means of investigating fatigue in other medical conditions. To develop a more complete picture of fatigue and its related factors, there is a need to incorporate both quantitative and qualitative research methods. The overall purpose of this dissertation was to investigate fatigue in people with type 2 diabetes. The specific aims were to: 1) test the presence and severity of fatigue, 2) investigate contributing factors leading to fatigue, and 3) investigate the influence of fatigue on function and quality of life in people with type 2 diabetes.

Although fatigue is a common complaint among individuals with type 2 diabetes, no studies have attempted to quantify it. To begin *Chapter 2* aimed to test the presence and severity of fatigue in people with type 2 diabetes as compared to a non-diabetic group. Three fatigue surveys were completed by 37 individuals with and 33 individuals without diabetes. Results indicated that people with type 2 diabetes scored higher on all three fatigue assessment scales.

Higher levels of fatigue were noted in people with type 2 diabetes as compared to healthy age matched controls; however the cause and impact of these changes were not known.

Fatigue can result from various physiological and psychological factors occurring from diabetes. Additionally, since fatigue is such a complex phenomenon it becomes very challenging to study. *Chapter 3* intended to investigate the contributing factors of fatigue in individuals with type 2 diabetes by using a mixed methods design using both quantitative and qualitative research methods. Forty eight individuals with type 2 diabetes participated in the study. A subsample of 10 participants participated in the qualitative section of the study. Results of the quantitative section revealed that poor sleep quality, pain and high BMI are the independent predictors of fatigue. Interview findings further supported the quantitative results by identifying fatigue as multidimensional in nature. Participants expressed sleep problems, extra body weight, pain, high/low blood glucose levels and depression as chief contributing factors to fatigue.

Since diabetes is associated with high degree of complexity related with the medical management of the disease, this can be a great burden to many patients and can affect quality of life (QoL) of these individuals. Moreover, people with type 2 diabetes are always encouraged to engage in physical activities which could affect their functional status. Fatigue can however, further complicate this burden by compromising the QoL and functional status in individuals with type 2 diabetes. *Chapter 4* investigated the relationship of fatigue with QoL and functional status in individuals with type 2 diabetes by using a mixed method design. Forty eight individuals with type 2 diabetes participated in the study. A subsample of 10 participants participated in the qualitative section of the study. Results indicated a negative relationship of fatigue with QoL and functional status. The qualitative data provided further insight into the compromised QoL and functional status and supported the findings of quantitative analysis.

In summary, this body of work indicates the presence of and contributing factors to fatigue and also emphasizes the negative impact of fatigue on QoL and functional status in people with type 2 diabetes. The present study provides the first evidence uncovering the contributing factors to fatigue via a mixed method approach. Since fatigue is a very subjective experience, the use of qualitative research methods helped us in understanding what the numbers from the quantitative research methods actually mean. Similarly, the impact of fatigue on QoL and function was tested via mixed method approach. We were able to get a better understanding of the negative impact of fatigue since we were able to directly hear the voices of the participants. The results of the present work suggest that clinicians should educate their patients regarding fatigue, and interventions should focus on the contributing factors identified in the present study.

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# Chapter 1

# Introduction

*1.1 Overview*

Patients with type 2 diabetes often experience tiredness with low energy, which is a common symptom of fatigue. Although fatigue is a common complaint in patients with diabetes, no studies have been done so far to determine its prevalence and severity in patients with type 2 diabetes. The presence of fatigue can cause a significant addition to the suffering of these patients. It can affect their functional capability which reduces the amount of physical performance. This decline in physical performance affects quality of life and causes additional burden to their lives.

The proposed study is the first to determine the prevalence of fatigue in patients with type 2 diabetes by means of mixed method design incorporating both quantitative and qualitative methods. The use of a mixed method design provides more comprehensive evidence for examining fatigue in patients with diabetes than either quantitative or qualitative analysis alone. Qualitative research methods help us understand the context of the experience of fatigue, as the voices of the participants will be directly heard. However, the qualitative method relies on personal interpretations made by the researchers. Therefore, the combination of both quantitative and qualitative research offsets the weakness of either approach. The use of a mixed method design gives us an inclusive picture of the presence of fatigue in people with type 2 diabetes.

*1.2. Diabetes* Diabetes is a leading cause of adult disability and is a significant global health problem. Its prevalence is increasing worldwide, and so the economic cost of diabetes management continues to rise. In 2011, 18.8 million people were estimated with diabetes in the United States and this figure is expected to rise to more than 40 million by 2050 (Draznin, 2008) More specifically, type 2 diabetes contributes to 90-95% of the different types of diabetes. Type 2 diabetes occurs when the body does not produce insulin or the cells ignore the insulin (Siegel

et al., 2012). Insulin is required for the body to be able to utilize glucose for energy. When glucose is not utilized by the body, it builds up in the blood and leads to diabetic complications (Siegel et al., 2012).

Without having an energy source, fatigue is a common complaint in people with diabetes. The various complications associated with diabetes frequently overshadow the presence of fatigue; therefore fatigue mostly becomes a neglected issue. However the presence of different complications itself results in fatigue. The presence of fatigue can undermine the individual's efforts to self-manage diabetes. It is very important to recognize the issue of fatigue in people with diabetes.

*1.3 Factors Contributing to Fatigue in Diabetes:* Fatigue can result from various factors which are commonly seen in people with type 2 diabetes. It can result from the long term complications associated with diabetes or from other common comorbidities which are often seen in people with type 2 diabetes like sleep problems, pain, depression, and obesity.

*1.3. a. Complications Arising From Diabetes*: Controlling blood glucose levels is a key component of managing type 2 diabetes. High blood glucose levels can result in a number of complications which can be disabling and even life threatening. Complications from diabetes have the potential to greatly impact the health related quality of life (QoL) in individuals living with diabetes. The presence and number of diabetic complications have been shown to have a significant impact on quality of life (R. M. Anderson et al., 1997; G. C. Brown et al., 2000; Glasgow et al., 1997; Wandell et al., 1997). One measure of blood glucose is the level of glycosylated hemoglobin (HbA1c), which indicates the average blood glucose levels over the last three months. High levels of blood glucose can damage the small blood vessels leading to

complications like retinopathy, nephropathy and neuropathy. The resulting poor circulation can also result in cardiovascular diseases such as heart attack, hypertension and stroke. Acute or short term complications are mainly due to hypoglycemia, hyperglycemia or diabetes ketoacidosis. The main symptoms are sweating, confusion, anxiety and tremors. Some of the common chronic or *long term complications* are listed below.

*1.3a-(i) Cardiovascular Disease:* People with diabetes are more likely to develop complications like heart disease, stroke and high blood pressure. In 2004, heart disease was noted as the cause of death on 68% of diabetes-related death certificates among those 65 years or older, while stroke was listed on 16% of diabetes-related death certificates in this age group (*Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates in general information on diabetes and pre-diabetes in the United States, 2011.*, 2011). The risk factors behind developing cardiovascular disease include dyslipidemias including high triglycerides, high low density lipids (LDL), and low high density lipids (HDL); as well as smoking, obesity, lack of physical activity and poorly controlled blood sugars (Demssie et al., 2009).

As a consequence of diabetes, diabetes-related complications and low physical activity levels, people with diabetes often have low cardio-respiratory fitness. Low physical activity and poor cardiorespiratory fitness are independent predictors of mortality and are related to type 2 diabetes (Telford, 2007). Due to inability to engage in physical activities, people with diabetes have elevated levels of blood glucose, which can cause fatigue and even decrease the desire for participation in physical activities.

*1.3a-(ii) Neuropathy**:*** Diabetic neuropathy (DN) is defined as signs and symptoms of nerve dysfunction in a patient with diabetes mellitus. DN is one the most common forms of peripheral neuropathy and is the most frequent cause of non-traumatic amputation (N. Singh et al., 2005). DN results from hyperglycemia that induces changes in endothelial vascular resistance and reduces nerve blood flow. DN can be classified as peripheral, autonomic, proximal, or focal. Peripheral neuropathy is the most common type of DN, and causes pain or loss of sensation in toes, feet, legs, hands, and arms (Kles et al., 2006). Autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, pupillary impairments and sweating and metabolic disturbances. It causes changes in digestion, bowel and bladder function, and sexual response. It can also affect the nerves that serve the heart and control blood pressure, as well as nerves in the lungs and eyes (Vinik et al., 2003) (Bansal et al., 2006; Tracy et al., 2008) .

People with DN limit involvement in physical activities, which further results in elevated blood glucose. This elevated blood glucose can cause fatigue and can further limit the desire for participation in exercise programs.

*1.3a-(iii) Retinopathy:* Diabetic retinopathy refers to damage to the retina of the eye, and can eventually lead to blindness. Diabetic retinopathy involves microvascular changes in the retinal wall and in the rheological properties of the blood. High amounts of glucose damage the blood vessels of the retina and this damage can lead to leakage of lipids onto the macula, a part of the retina. This leakage of fluids may cause macular swelling, which causes blurring of vision and can directly impact QoL of a person (Cheung et al., 2010; Shah, 2008).

*1.3a-(iv) Nephropathy:* Diabetic nephropathy is a progressive kidney disease caused by damage of glomerular capillaries in the kidneys. It is characterized by proteinuria (leaking of large amounts of protein from blood to urine) and glomerulosclerosis (hardening of glomerulus). Thickening in the glomerulus is the earliest detectable change associated with diabetic nephropathy. At this stage an elevated quantity of serum albumin is excreted by kidneys. This stage is called microalbuminuria. As the disease progresses, nodular glomerulosclerosis destroys more glomeruli, and there is increased excretion of albumin. Symptoms of edema, anorexia, and headaches develop during later stages of the disease.(Fong et al., 2004; Mohamed et al., 2007). Diabetic nephropathy is a primary indication for dialysis. Fatigue is also a common and troublesome symptom associated with diabetic nephropathy (Bonner et al., 2008). Several factors which can be associated with fatigue include prescribed medications and their side effects, nutritional deficiencies, physiological alterations such as abnormal urea and hemoglobin levels (McCann et al., 2000).

*1.3a-(v) Dental Problems:* Dental care is particularly important for people with diabetes because these individuals have higher risk of developing oral problems due to high blood glucose levels (Bjelland et al., 2002). Hyperglycemia results in dehydration and reduced salivary flow, which causes dry mouth and predisposes the patients to periodontal diseases like ulcers, soreness, infections or tooth decay (Mealey, 1999). Hyperglycemia also affects the immune system and the inflammatory responses by producing advanced glycation end products (AGEs) which further progresses periodontal destruction(Salvi et al., 1997). Hyperglycemia can affect healing after oral surgery or cause ulcers because of the impaired blood flow.

*1.3a-(vi) Sexual Dysfunction:* Sexual problems are frequent in individuals with diabetes (Enzlin et al., 2009). Men have been shown to have significantly increased risk of erectile dysfunction (J. S. Brown et al., 2005) (Rosen et al., 2005). The vascular and neurological complications of diabetes can cause abnormalities in the endothelium of the corpora cavernosa, which is linked with the development of sexual dysfunction in men (Rhoden et al., 2005). In addition, women also experience similar rates of sexual dysfunction (Rutherford et al., 2005) (Newman et al., 1986). Autonomic impairments and reduced blood flow can contribute to sexual dysfunction. Such complications may substantially affect interpersonal relationships and the quality of life of an individual with diabetes.

The number of complications associated with diabetes can be a substantial factor in the level of fatigue experienced by this population. Our preliminary study indicates that the number of complications was related to fatigue scores as measured by the Fatigue Severity scale, and/or Fatigue Assessment Scale). The present study will further explore the common complications. A number of complications surveys will be used which contain a list of common complications occurring from diabetes.

*1.3.b. Other common comorbidities:* Comorbidities commonly seen in people with type 2 diabetes can also contribute to fatigue levels. Some of the common comorbidities like sleep apnea, pain, depression, and obesity can cause additional burden to fatigue levels in individuals with type 2 diabetes.

*1.3.b-(i) Sleep Quality:*

Poor sleep quality adversely affects glucose control in people with diabetes. Poor sleep quality is a significant predictor of HbA1c in African Americans with type 2 diabetes (n=161)

(Knutson et al., 2006). There is a strong relationship between sleep quality and Diabetes Care Profile scales, depicting the negative impact of poor sleep quality on diabetes self-management in people with type 2 diabetes (Chasens et al., 2013). Poor sleep quality can result in fatigue in people with diabetes which can further affect their motivation to effectively manage their chronic condition.

Sleep apnea is clinically recognized as a group of disorders characterized by frequent cessation of breathing (apnea) and/or decreased airflow (hypopnea) (Bopparaju et al., 2010). Sleep apnea may disrupt a person's sleep multiple times throughout the night, which results in poor sleep quality causing tiredness and fatigue during the day. Tiredness and fatigue may ultimately lead to excessive day time sleepiness. Sleep problems like insomnia, sleepiness, snoring and sleep apnea are associated with depression, cognitive decline and diabetes (Bonanni et al., 2010). The Sleep Heart Health Study (Resnick et al., 2003) found that subjects with diabetes had increased sleep disordered breathing. Obesity, age, and race are the main factors influencing and increasing the risk of sleep apnea. Obesity is commonly regarded as a risk factor for obstructive sleep apnea (OSA) and insulin resistance. Central obesity in particular is the strongest risk factor for OSA (Kyzer et al., 1998). Obesity, microangiopathy, hypertension, and dyslipidemia often coexist in OSA and type 2 diabetes (Tasali et al., 2008). It has also been observed that people with OSA have increased levels of leptin and C-reactive protein (CRP), indicating a possible contribution to cardiovascular morbidity (Kokturk et al., 2005; Schafer et al., 2002). Furthermore, frequent snoring has also been associated with reduced glucose tolerance and higher levels of HbA1c (Joo et al., 2006).

*1.3.b-(ii) Pain:* Sensory symptoms resulting from neuropathy includes weakness, loss of sensation and pain. Fatigue is often clinically observed in patients with chronic pain (Covington, 1991; Fishbain et al., 2003). For example, Rijken et. al attempted to identify the clinical and functional variables associated with foot pain in 29 individuals with type 1 and type 2 diabetes (Rijken et al., 1998). Fatigue was assessed by the Multidimensional Fatigue Inventory (MFI), with five dimensions (explained below under section 1.4.c.): general fatigue, physical sensations, reduction in motivation, and mental tiredness. They found that foot pain was positively correlated with symptoms of general fatigue ($r=0.63$, $P<.001$), physical fatigue ($r=0.48$, $P<.01$), and reduced activity ($r=0.48$, $P<.01$). This study provides evidence that fatigue can be a significant problem faced by individuals with diabetes.

Due to pain, weakness, and loss of sensation in the extremities, there can be a decline in the amount of physical activities performed by those with diabetes (Kanade et al., 2006). People with DN may avoid exercise programs that require treadmill running or walking, or may avoid physical activity altogether due to the apprehension of getting foot ulcers or wounds. People with DN can limit themselves from being involved in any kind of exercise program (Lemaster et al., 2008). This can again result in high blood glucose and can cause even more damage to the already damaged nerves from DN. Lack of physical activity, pain and weakness issues, and high blood glucose can further worsen fatigue (Ribu et al., 2004). Fatigue and tiredness can further contribute to weakness and decreased muscle strength in individuals with DN.

*1.3.b-(ii) Depression:* There is a strong relationship between depression and diabetes (R. J. Anderson et al., 2001). Depression has been associated with hyperglycemia and complications from diabetes (de Groot et al., 2001; Lustman et al., 2000). Furthermore, depression in people with diabetes has been associated with socio-demographic lifestyle and clinical factors such as

obesity and physical limitations (Egede et al., 2003; Katon et al., 2004; Ryerson et al., 2003). The prevalence of depression is significantly higher in people with diabetes as compared to those without diabetes (Egede et al., 2002). Both diabetes and depression share a common factor: stress. Depression increases cortisol levels, which can increase insulin resistance and ultimately add to the burden of diabetes (Cameron et al., 1984). Diabetes is often accompanied by stress resulting from the management of diabetes and treatment for complications, which can further lead to depression (Talbot et al., 2000). Resulting depression may lead to poor diet and low physical activity, which can further lead to weight gain. Depression along with diabetes can also aggravate fatigue levels in this population, since fatigue is one of the symptoms of depression.

*1.3.b-(iii) Obesity:* Body mass index (BMI) is a reliable indicator of body fatness and is used to screen for weight categories that may lead to health problems (Bjorntorp, 1988; Hodge et al., 1994). High BMI and type 2 diabetes are major risk factors for coronary heart disease. High BMI has been directly linked to the occurrence of type 2 diabetes and has also been positively associated with MFI-20 fatigue scores in type 2 diabetic patients (Lasselin et al., 2012a). Abdominal fat is composed of adipose tissue that acts as an endocrine organ regulating appetite and metabolism. Leptin is a hormone produced by adipose tissue that contributes to this metabolic regulation. Low levels of this hormone have been associated with both obesity and insulin resistance (Unger et al., 2010) . The changes in body composition and accumulation of abdominal fat that occur with aging may thus contribute to increasing insulin resistance.

*1.3.b-(iv) Medications:* People who are diabetic often take multiple medications. Polypharmacy itself can result in a number of complications and side effects, including fatigue. Metformin is the most widely used insulin sensitizer in the therapeutic management of type 2 diabetes. Metformin helps lower blood glucose by reducing hepatic gluconeogenesis, by limiting

the amount of glucose absorbed into the body from diet, and by making insulin receptors more sensitive. Some of the side effects of metformin are GI disturbances and elevated homocysteine levels (an amino acid) (Hermann, 1979). Elevated levels of homocysteine are associated with coronary artery disease, heart attack, chronic fatigue, fibromyalgia, cognitive impairment, and cervical cancer (Khurana et al., 2010). Most of the medications used in the management of diabetes result in fatigue and tiredness. People with diabetes are at least partially dependent on their medications for blood glucose control. However, long term use of these medications itself can result in various side effects including fatigue.

All the contributing factors mentioned above can play a substantial role in the burden of fatigue experienced by those with diabetes. The present study will further explore the role of the following factors in diabetes-related fatigue: 1) depression, 2) obesity, 3) pain, 4) number of complications, 5) hyperglycemia, 6) sleep problems, and 7) duration of diabetes. The role of each contributing factor will be investigated by quantitative and qualitative analysis using regression modeling and semi-structured interviews respectively.

### *1.4. Fatigue*

***1.4.a. Historic View:*** Fatigue is a common health complaint and is an essential component of many physical ailments and psychiatric disorders (David et al., 1990) . Fatigue is a subjective feeling and can be represented as either a single phenomenon or a continuous event. Scientific discussions were held in the early 1920's to expel the terminology of "fatigue" and its related investigations, due to the ambiguous and subjective nature of fatigue. After the late 1980's, more attempts were made to investigate fatigue objectively and subjectively, and theories

started to emerge (Chalder et al., 1993; David et al., 1990; Krupp et al., 1989; Piper et al., 1987; Smets et al., 1995).

Current literature suggests that fatigue is a complex and multidimensional phenomenon that can be defined from different perspectives (Aaronson et al., 1999; Piper et al., 1987; Smets et al., 1995; Tiesinga et al., 1996). Perception of fatigue is subjective in nature (Chalder et al., 1993) , therefore the synonyms used to describe fatigue may be interpreted differently among individuals. This ambiguity makes the study of fatigue challenging. Many definitions of fatigue have emerged from different perspectives and disciplines. In 1999, Aaronson and colleagues wanted to recognize the contributions of physiological and psychological functioning as well as social and cultural factors on the experience of fatigue. The group defined fatigue as the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity (Aaronson et al., 1999).

In 2004, the North American Nursing Diagnosis Association (NANDA) defined fatigue as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work (*Nursing Diagnosis: Definitions & Classifications*, 2004). Following a concept analysis of fatigue, Ream and Richardson (1997) conducted a qualitative research study using phenomenology research design(Ream et al., 1997). Nine themes emerged from the data from individuals with cancer and chronic obstructive airways disease: the physical sensations embodied in fatigue, the mental sensations embodied in fatigue, the impact of fatigue on everyday functioning, the emotional feelings evoked by fatigue, the impact of fatigue on perceived control, the impact of emotions on the management of fatigue, the importance of recognizing and understanding fatigue, the significance of setting and reaching goals, and the

effectiveness of self-care in the alleviation of fatigue. Based on the results of the study, fatigue was defined as "A subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity" (Ream & Richardson, 1997).

All these definitions suggest that fatigue is determined by a person's feeling about the state of one's internal resources and the nature of the activity being performed. Piper and colleagues described fatigue as a multicausal, multidimensional sensation that affects sensory, affective, behavioral, and physiological realms (Piper et al., 1987). Using Piper's multidimensional view of fatigue as a conceptual framework, fatigue will be partially defined as a sensation of depletion of internal resources. The nature of the depleted resource employed for this dissertation project will be blood glucose.

***1.4.b. Fatigue Models:*** The cause of fatigue is still debatable. Nevertheless, several fatigue models have emerged since the 1980's. Early models attempted to explain fatigue in terms of central and peripheral nervous system components (Funk et al., 1989; Gibson et al., 1985). Later models incorporated the physiology of multiple body systems (Becker et al., 1978; Bruno et al., 1993; St Pierre et al., 1992; Walker et al., 1991). The multidimensional nature of fatigue was addressed by Piper, Lindsay, and Dodd in 1987. They suggested that the contributing factors of fatigue can be perceptual, physiological, biomechanical and behavioral (Piper et al., 1987). Likewise, the subjective (perceptual) and the objective (physiological, biochemical, and behavioral) dimensions of fatigue can also be differentiated. In 1989, further dimensions of subjective fatigue were defined as temporal, intensity, affective, sensory, evaluative, associated symptoms, and relief. This model was developed based on cancer patients and it was believed that these subjective dimensions provide insight into how patients experience fatigue.

Piper's fatigue model represented a theoretical framework for other researchers to further investigate the nature of fatigue. In 1999, Portenoy and colleagues proposed an integrated fatigue model consisting of several contributing factors, and physiological and psychosocial dimensions (Portenoy et al., 1999). Physiological components mainly cover the underlying disease and the complications which come with the treatment and the disease. Psychosocial components include depression and anxiety. Consistent with Piper's ideas and recent studies, Portenoy's integrated model (Figure 1.4.b – (i)) considered the multifactorial and multidimensional nature of fatigue (Aaronson et al., 1999; Tiesinga et al., 1996).

Portenoy's fatigue model was based on cancer patients. However, this model can also be applied to patients with diabetes. The various complications and comorbidities associated with diabetes can be integrated into Portenoy's fatigue model. The proposed diabetes adaptation of Portenoy's fatigue model can also have two distinct dimensions: physiological and psychological as illustrated in figure 1.4.b – (ii). Physiological factors include the underlying disease (diabetes), duration of diabetes, disease treatment, sleep disorders, immobility/inactivity, chronic pain, glucose fluctuations, and number of complications. Psychological factors include depression. We believe that it is very important to identify both the physiological and psychological factors in predicting fatigue *(Aim 2)* so that treatment strategies can be developed targeting the specific contributing factors of fatigue. The following figure depicts the proposed diabetes adaptation of Portenoy's fatigue model.

Although all the components mentioned in the diabetes version of Portenoy's fatigue model can play a significant role in contributing to fatigue, this study will focus on the following domains: duration of diabetes, hyperglycemia, number of complications, pain, obesity (BMI),

sleep disorders, and depression. Regression modeling and semi-structured interviews will be conducted to identify the role of each of factors mentioned above in contributing to fatigue.

***1.4.c. Measurement of Fatigue:***

Many attempts have been made to transform fatigue into a quantifiable measure. To date, the most accurate or appropriate fatigue scales remain controversial. It has been suggested that the appropriateness of fatigue scale should be determined by aspects of fatigue that are being measured (Dittner et al., 2004).

Among all existing scales, one particular scale appears to adequately identify and measure fatigue in individuals with diabetes. In 1995, Smets and colleagues developed the Multidimensional Fatigue Inventory (MFI-20), which consists of five subscales: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity (Smets et al., 7636775 1995). The current version of the MFI-20 contains 20 statements, which cover different aspects of fatigue. Each of the 5 scales contains 4 items. The scales are intended to reduce the influence of response tendencies as much as possible, as each scale contains two items indicative for fatigue (e.g. "I tire easily") and two items contra-indicative for fatigue (e.g. "I feel fit"). The respondent has to compare each of the 20 statements with how he or she felt lately. Each item is scored from 1-5, from agreement with the accompanying statement "yes, that is true" to disagreement "no, that is not true". A higher score indicates more fatigue. For each scale, a total score is calculated by summation of the scores of the individual items. Total scores can range from the minimum of 4 to the maximum of 20.

*The MFI*-20 has been tested for its psychometric properties in cancer patients receiving radiotherapy (n=111), patients with chronic fatigue syndrome (n=357), psychology students

(n=481), medical students (n=158), army recruits (n=160) and junior physicians (n=46) (Smets et al., 1995). The MFI-20 appears to have good reliability and validity, with Cronbach's Alpha scores in range of 0.8 - 0.91 in patients with liver dysfunction (n=369) (Unal et al., 2001). The MFI-20 also has strong concurrent validity, as it has shown to have significant correlations with the Sickness Impact Profile, Short form Health Survey (SF-36), and Liver Disease Symptom Index (LDSI) (range of r from 0.74 to 0.87).

The multidimensional nature of MFI-20 supports the several physiological and psychological domains of the proposed diabetes model of fatigue. For the purpose of this dissertation project, the MFI-20 will be used as the primary measure to assess fatigue in people with type 2 diabetes. MFI-20 has also verified its ability to relate fatigue with some of the diabetic variables like pain and BMI, which are important contributing factors in the diabetes version of Portenoy's fatigue model (Lasselin et al., 2012a; Rijken et al., 1998).

### *1.5. Prevalence, Severity, and Effects of Fatigue in People with Diabetes*

***1.5. a. Prevalence and Severity:*** Fatigue is a complaint in people with diabetes, but it is often neglected due to other confounding factors resulting from diabetes. In one recent study conducted in 1137 subjects with type 2 diabetes, the prevalence of fatigue was found to reach 61% (Drivsholm et al., 2005). Despite this high frequency and the potential impact of fatigue on the persons' treatment efficacy, few studies have explored this symptom in diabetic patients, with most of these studies limited to only nonspecific symptoms of fatigue (Fritschi et al., 2010). To our knowledge only a few studies have directly examined the presence and severity of fatigue in persons with diabetes. A recent study explored fatigue and its relationships with some diabetic factors in women with type 2 diabetes (n=83) (Fritschi et al., 2012). These factors included glucose control, diabetes symptoms, diabetes emotional distress, depressive symptoms, BMI and

physical activity. Regression analysis revealed that the strongest explanatory variables for fatigue were diabetes symptoms, depressive symptoms, and BMI which accounted for 48% of variance in fatigue scores. The results further support the proposed diabetes adapted fatigue model (figure 1.4.b.-ii) suggesting that fatigue has physiological (diabetes symptoms, BMI) and psychological (depressive symptoms) components. This study only included women with type 2 diabetes, therefore to generalize the results; future studies should be conducted to include both men and women.

Cuellar et.al. (Cuellar et al., 2008) evaluated fatigue in subjects who had Restless Leg Syndrome (RLS) in addition to type 2 diabetes using the Fatigue Severity Scale (FSS). FSS scores were significantly higher in persons with type 2 diabetes and RLS as compared to persons with diabetes without RLS (3.8 vs. 2.6, $p = 0.028$). The results of this study suggest that fatigue is an issue in persons with diabetes and further research is necessary to explore this issue in more detail.

***1.5. b. Effect of Fatigue on Vocation:*** Since fatigue is a common complaint among patients with diabetes, it is seems likely that this symptom would adversely impact vocational abilities and performance. Weijman et al. (Weijman et al., 2003) evaluated fatigue in employees with insulin dependent diabetes (type 1 and type 2) in order to explore the relation of fatigue with work characteristics (job demands, decision latitude, and social support) and diabetes-related variables (symptoms, seriousness of disease, self-care activities, and disease duration).

A total of 292 individuals (30-60 years) with insulin treated diabetes took part in the study. A self-administered questionnaire assessing work characteristics, diabetes related burden and fatigue was sent to the subjects. Fatigue was assessed using the Check List Individual Strength, which consists of four components (motivation, subjective fatigue, lack of concentration and

physical activity). Both work and diabetes related factors were related to fatigue in employees with diabetes. Stepwise multiple regression revealed that diabetes related variables explain 29.0% of the variance in fatigue ($\beta$= 0.86; p=0.00), mostly because of diabetes related symptoms and the burden of adjusting insulin dosage. Conversely, work characteristics explained 19.1% of the variance in fatigue. Based on the results of this study, it seems clear that fatigue is a major problem for employees with diabetes. However, the employment intensity (full time, part time) and the type of work were not mentioned in the study. The study nevertheless offered additional support that diabetes-related fatigue may have deleterious effects on job or work roles.

***1.5. c. Effect of Fatigue on Muscular Strength:*** Vigorous exercise can also affect a person's muscular strength resulting in from fatigue. The elevated blood glucose levels associated with diabetes affects muscular strength contributing to the burden of fatigue. Anderson et al. (Andersen et al., 2005) found decreased maximal isometric muscle strength after 200 minutes of hyperglycemia in seven subjects with type 1 diabetes. Muscle strength (isokinetic and isometric) was tested using a dynamometer at two different phases; phase of normal glycemia and hyperglycemia. There was a significant decrease in maximum isometric muscle strength during the phase of hyperglycemia. This decrease in muscle strength was thought to be due to the presence of fatigue. However, neither subjective nor objective measures were used to assess fatigue during the testing of muscle strength. In addition, the study had a very small sample size with no control group. Therefore, it is unclear whether the decreased muscle strength was indeed related to presence of fatigue. This study, however, does indicate that hyperglycemia can induce acute fatigue.

***1.5. d. Effect of Fatigue on Cognition and Mood:*** Sommerfield et al. conducted a study to examine the effects of acute hyperglycemia on cognition and mood in individuals with type 2 diabetes (Sommerfield et al., 2004). Twenty subjects with type 2 diabetes were included in the study. Hyperglycemia was induced by hyperinsulinemic glucose clamp. Blood glucose was maintained at either 4.5 (euglycemia) or 16.5 mmol/l (hyperglycemia) on two occasions in a randomized fashion. Cognitive tests of information processing, immediate and delayed memory, working memory, and attention were administered during the two conditions. In addition, a mood questionnaire consisting of a check list documenting changes in mood experienced by the subjects was also administered. The three main mood states were: energetic arousal (feeling lively), tense arousal (feeling anxious), and hedonic tone (feeling happy). Cognitive test results showed impairments in speed of processing, working memory, and some aspects of attention. The mood questionnaires showed significantly low scores in hedonic tone and energetic arousal during the hyperglycemia state, as well as increased scores of tense arousal. These results suggest that subjects experienced greater fatigue during the hyperglycemic state, as evidenced by low scores on energetic arousal (20 vs. 25, $p=0.001$, hyperglycemic vs. euglycemic).

Along the same lines, a recent study compared the fatigue levels and cognitive performance of individuals with diabetes and healthy controls (Lasselin et al., 2012a). The study included 21 subjects with type 1 diabetes, 24 subjects with type 2 diabetes and 15 healthy controls. Fatigue was tested using the Multiple-Fatigue-Inventory (MFI). Cognitive tests of reaction time, pattern recognition memory, and spatial planning were also administered. BMI and HbA1C concentrations were collected, as was information on diabetes complications and disease duration. The study revealed higher levels of fatigue in the type 2 diabetes group, specifically within the dimensions of general and physical fatigue and reduced activity.

Cognitive test results showed alterations in the form of longer reaction times and impaired spatial planning in type 2 diabetic patients treated with insulin. Co-relationship analysis showed that BMI was positively associated with MFI dimensions of general fatigue, physical fatigue and reduced motivation, and mental fatigue. The results of the study support our hypothesis that BMI can be a causative factor behind fatigue. The study further supports the use of the MFI-20 as a tool to measure fatigue in individuals with diabetes, as it has demonstrated its ability to differentiate the relationships between fatigue and diabetic variables. Because fatigue is such a complex phenomenon, a single subjective questionnaire such as the MFI may not capture the whole picture. In order to more fully understand fatigue, there is a need to incorporate more vigorous methods. The addition of qualitative research methods can help in understanding the context of the experience of fatigue. The mixed method approach utilized in our study will allow us to quantitatively assess fatigue levels among our participants, while also allowing the voices of the participants to be heard directly.

***1.5. e. Effect of Fatigue on Function and Quality of Life:*** Fatigue can undermine the daily functional activities of a person. Decline in functional capacity has been seen in patients with chronic disorders like cancer and Parkinson's, as evidenced by significant decreases in distance covered during 6 minute walk tests (Coleman et al., 2011; Garber et al., 2003; van Weert et al., 2006). It appears that fatigue may have a similar impact on the functional capacity of individuals with diabetes. In addition, the high degree of complexity associated with the medical management of the disease is a great burden to many patients. This burden may be further complicated by the acute physical distress of hypoglycemia and/or hyperglycemia and other diabetes related complications. Inadequate or improper diabetes management may worsen glycemic control, and increase the risk for such complications (Lerdal et al., 2011). Therefore,

referring back to the proposed diabetes fatigue model, the causative factors mentioned under the physiological and psychological domains can overall result in decreased functional status and quality of life.

*1.6. Qualitative Studies -- Exploring Fatigue in Persons with Diabetes*

Qualitative research methods can provide in-depth understanding of fatigue in people with diabetes and help to gain insight into people's attitudes, behaviors, concerns, cultures or lifestyle. Unfortunately, the qualitative research method has not been used to explore the issues of fatigue in people with diabetes. The studies mentioned above used quantitative research methods. Only two studies have used qualitative methods to explore the lived experience of diabetes, specifically in relation to diabetic foot ulcers resulting from neuropathy (Ribu & Wahl, 2004; Watson-Miller, 2006). In-depth interviews (subjects n=6 type1, and n=7 type2) revealed that patients experienced pain, insomnia, fatigue, limited mobility, fear of amputation, social isolation, and loneliness along with changes in feet and pain. Participants who hoped to participate in physical activity mentioned the effects of fatigue: "I sort of feel that everything moves slowly, I think that bothers me a little not to have any kind of energy or drive". Fatigue emerged as a prominent concern besides pain and fear of amputation. There is a need to further explore this critical and important issue in people with diabetes.

To obtain a comprehensive understanding of fatigue in people with diabetes both quantitative and qualitative research methods are necessary. Mixed method research will help us answer questions that cannot be answered by qualitative or quantitative analysis alone. What explains the quantitative results of the study? To answer these questions, quantitative or qualitative approaches alone would not provide a satisfactory answer. The combination of these two approaches will provide a more detailed understanding of the phenomenon of fatigue.

A similar mixed method approach has been used to test a dance intervention and to explore the role of peer support in improving diabetes outcomes (HbA1C, weight, body fat, and BP) in African American women with type 2 diabetes. Forty-six women (26-83 years) were randomized to either a 12-week dance group or usual care group. The dance intervention consisted of two 60-minute classes a week taught by an experienced female dance instructor. Focus group interviews were conducted at the end of the dance intervention to explore the role of peer support through semi structured discussions. Thematic analysis was used to assess the participant's experiences participating in the dance intervention. A pretest-post design was used to measure between and within group differences in diabetes outcomes (A1C, weight, body fat, and BP). Results showed significant differences in systolic BP and body fat, significant reductions in all the diabetes outcomes for the dance group and significant increases in HbA1C and systolic BP for the usual care group. Participants expressed peer support as camaraderie, enjoyment, and laughter, which promoted attendance. Some of the quotes from the interviews are: "Just being here laughing and just enjoying yourself. We all had the same thing so you don't really think about it".

The study was limited by the small sample size for quantitative methods, self-limiting progression of dance intensity, and larger size of focus groups. The study also provided a full picture of a person with diabetes participating in a dance intervention along with others who have diabetes. Hence, using both qualitative and quantitative methods together provides a more comprehensive picture of a participant's condition. Adequate use of measures and techniques can provide us a rich source of data and give us a better understanding of the condition.

*1.6. a. Qualitative Studies of Fatigue in Other Populations*

Although, qualitative research methods have not been used to a great extent in understanding fatigue in the diabetic population, it has been extensively used in populations such as cancer and multiple sclerosis. A phenomenological study (Wu et al., 2010) was done with 14 children (age =7-18 years old) suffering from leukemia to understand the lived experience of fatigue from the children's own perspective. Focus groups were conducted (n=4) with a semi-structured interview guideline, including open-ended questions. After analyzing the data via content analysis, trustworthiness was established by the researchers. Three themes emerged:

1. Fatigue is open to interpretation: Two categories supported this theme.

1.a. Description of physical state of being fatigued

1.b. Description of mental state of being fatigued

2. Fatigue is not uni-dimensional, three categories supported this theme.

*2.a. Physiological factors:* Physiologic factors included a set of symptoms, feelings or reactions to treatment that may influence individuals' experiences of fatigue. Nausea, pain, and fever were some of the symptoms categorized under physiological factors.

*2.b. Psychological factors:* Psychological factors included one's mental state, mood, and an individual's concept to illness: Parents being worried about their children being hurt or infected by others, caused the feeling of being obliged or suppressed.

*2.c. Situational factors:* Situational factors referred to physical environment, lifestyle or behavior, and social factors that may influence individuals' experiences of fatigue. For example, change in dietary habits due to the side effects of chemotherapy was a common issue.

3. Children struggle with fatigue. Three categories support this theme.

*3.a. Impact on physical activity:* Most children became less active when receiving treatment.

*3.b. Impact on mental health:* This was defined as easily provoked or easily irritated.

*3.c. Impact on cognitive aspects:* Regarding cognitive function, participants felt their thinking ability had gotten worse and that they had difficulty in remembering things.

The results of the study show that fatigue is a multidimensional and multifactorial symptom which further supports our diabetes version of Portenoy's fatigue model.

*1.7. Relevance of Proposed Research*

The proposed research is the first to identify the contributing factors of fatigue and to understand the impact of fatigue on function and quality of life in individuals with type 2 diabetes. Because fatigue is not well addressed in people with diabetes, we hypothesize that fatigue is present and can be the result of various factors which are associated with diabetes including hyperglycemia, depression, sleep, BMI, pain, duration of diabetes and complications. We also hypothesize that fatigue can affect function and quality of life in individuals with type 2 diabetes. The proposed study will also analyze direct participants perspectives of fatigue via qualitative interviews to understand the subjective nature of fatigue. The results of this study will enable health care providers to incorporate the assessment and treatment of fatigue and will allow more successful self-management strategies like exercise participation, management of hyper or hypoglycemia that are likely to be affected by fatigue.

**1.8. Specific aims and Hypothesis**

The *objectives* of this study are to investigate contributing factors leading to fatigue, and to investigate the influence of fatigue on function and quality of life in people with type 2 diabetes. Our *central hypothesis* is that diabetes and fatigue have a significant impact on the everyday life of those with type 2 diabetes. Qualitative and quantitative methods will be used in

this study to fully explore the issue of fatigue in this population. We plan to accomplish our objective by pursuing the following *specific aims:*

**Aim 1:** To determine the presence and severity of fatigue in people with type 2 diabetes. The Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS) and Visual Analog Fatigue Scale (VAFS) will be used to assess fatigue. *Hypothesis 1:* We predict that FSS, FAS and VAFS scores will be higher in people with diabetes as compared to healthy age matched controls.

**Aim 2**: Identify contributing factors that lead to fatigue in people with type 2 diabetes using both qualitative and quantitative methods. This will be an exploratory aim, in which we will identify the contributing factors to fatigue through a quantitative research method and through a qualitative research method.

**Aim 2b:** We propose to build a multivariable linear regression model to identify contributing factors that lead to fatigue. Data will be collected on some common complications and factors which can contribute to fatigue, which includes: 1) depression 2) obesity 3) pain 4) number of complications 5) hyperglycemia 6) sleep problems and 7) duration of diabetes. First, a correlational analysis will be conducted to determine which of 7 different factors are associated with fatigue based on scores of the Multiple Fatigue Inventory, MFI-20). Correlational analysis results can determine which factors will be used as possible explanatory variables for the regression model. Furthermore, the results of the qualitative interviews will supplement the correlational analysis results. The factors identified by the correlation analysis and by interviews will be used as explanatory variables to build a multivariable linear regression model. The number of explanatory variables will also be decided by the results of the correlational analysis and by qualitative interviews. *We predict that sleep problems, hyperglycemia, depression, high*

*BMI and pain will be the contributing factors to fatigue from multivariable regression model and from the results qualitative interviews (Hypothesis 2)*

**Aim 2b:** We will ask people with type 2 diabetes to describe the impression of fatigue on them. From the qualitative data we will identify the prominent issues or factors which can contribute to their fatigue. *Semi-structured interviews will be used to explore the contributing factors of fatigue.*

**Aim 3:** Determine the impact of fatigue on function and quality of life in people with type 2 diabetes, using both quantitative and qualitative methods. Fatigue can undermine the daily functional activities of a person. The self-management required for diabetes can result in additional burden and therefore may affect the quality of life. Moreover, it is very important to know how fatigue is affecting quality of life and function directly from the participant's perspectives.

**Aim 3a:** The relationship between fatigue (MFI-20 scores), function (6 minute walk test), and quality of life (ADDQoL) will be investigated in individuals with type 2 diabetes. *We predict that fatigue will be inversely related to function and quality of life (Hypothesis 3).*

**Aim 3b:** We will ask people with type 2 diabetes to describe impact of fatigue on function and quality of life. *Semi-structured interviews will be used to explore how fatigue is related to function and quality of life.*

This study will be the first to determine the potential contributors of fatigue and the impact of fatigue in individuals with type 2 diabetes. The proposed study will also directly analyze participants' perspectives of fatigue (via qualitative interviews) which is required to understand the subjective nature of fatigue. Current management strategies for diabetes can then consider assessment of fatigue in patients with type 2 diabetes.

Three manuscripts based on the work presented in this dissertation have been or will be submitted for publication. The first manuscript was based on data collected in this dissertation study with the aim of testing the presences and severity of fatigue in people with type 2 diabetes (Chapter 2; published in *The Diabetes Educator*). The second manuscript utilized the whole dataset of this dissertation research and examined the contributing factors to fatigue in people with type 2 diabetes through a mixed methods approach (Chapter 3; to be submitted to *Diabetes Care*). The third manuscript assessed the impact of fatigue on quality of life and functional status through a mixed methods approach (Chapter 4; to be submitted to *Physical Therapy*).

## 1.9. Figures

Figure 1.4.b –(i). Illustration of Portenoy's fatigue model

Figure 1.4.b – (ii) Illustration of Portenoy's fatigue model applicable to patients with diabetes. The contributing factors highlighted in red are the factors applicable to patients with diabetes

Figure 1.4.b –(i). Illustration of Portenoy's fatigue model:

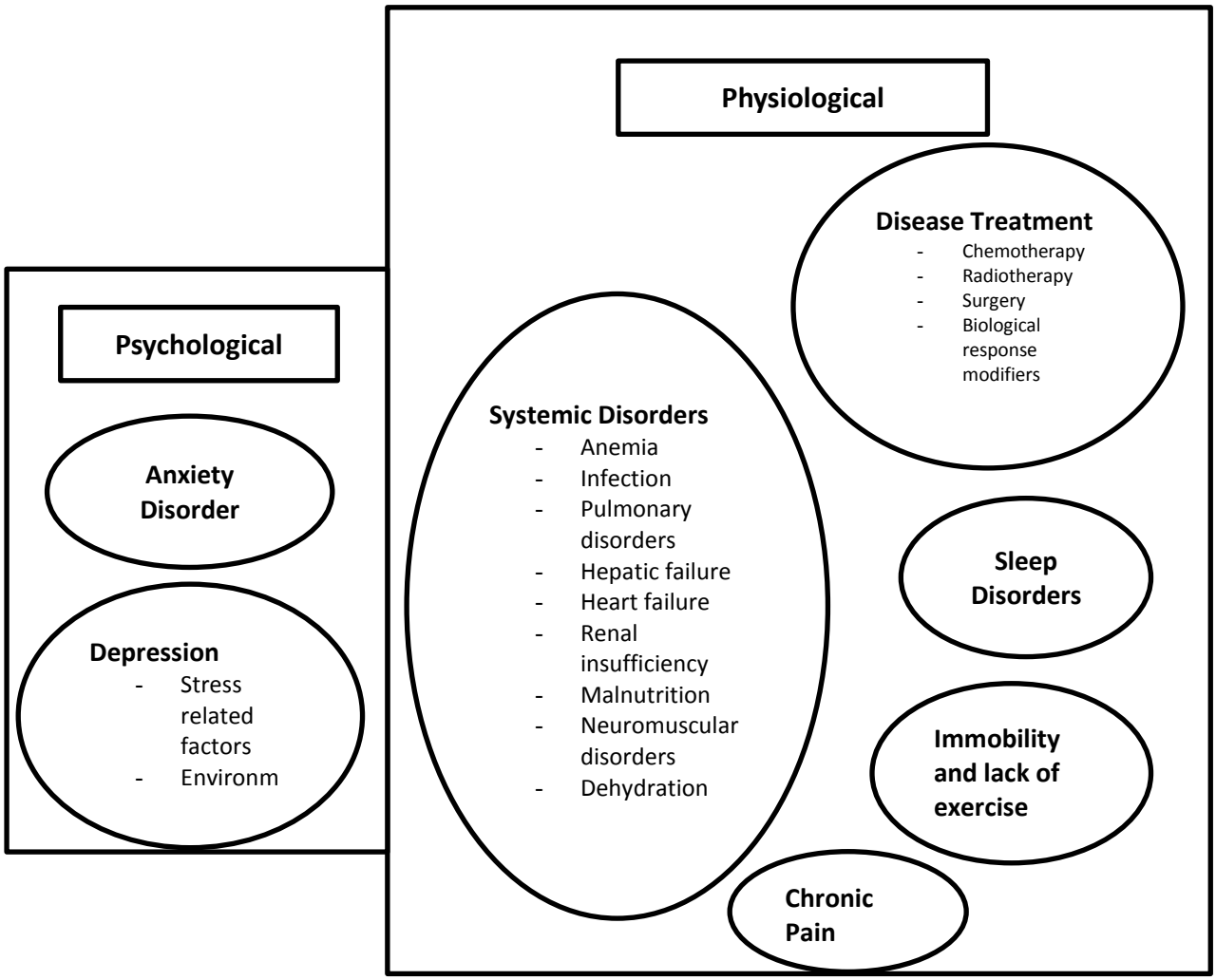
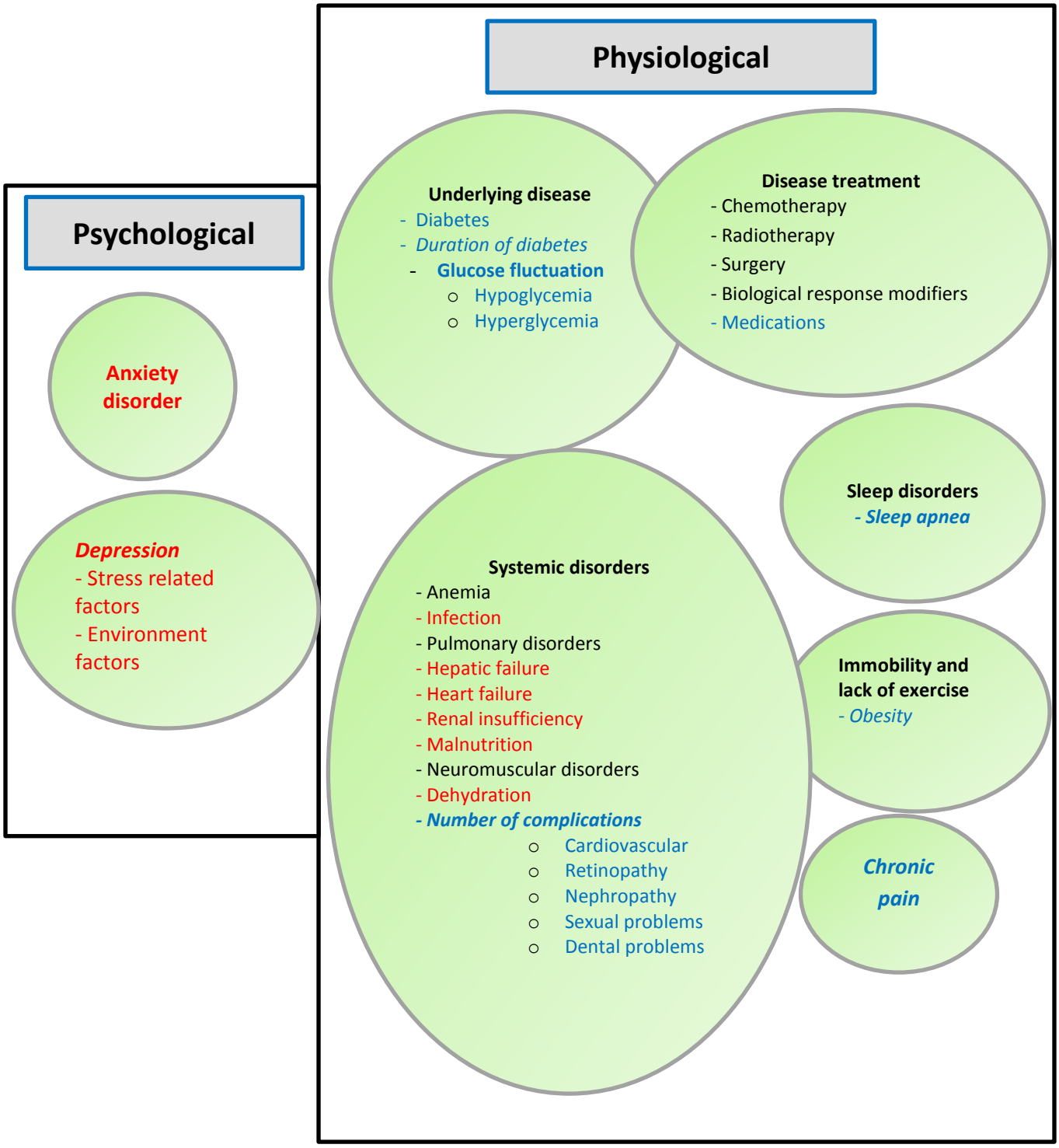


Figure 1.4.b – (ii) Illustration of adaptation of Portenoy's fatigue model applicable to patients with diabetes. The contributing factors highlighted in red are the factors applicable to patients with diabetes



# Chapter 2

## Preface

Chapter 1 provided an overview of what is currently known about fatigue in individuals with type 2 diabetes. One of the questions that remain unanswered is the presence and severity of fatigue in people with type 2 diabetes. Chapter 2 sought to test the presence and severity of fatigue and provides insight into various fatigue testing scales available in literature.

# Chapter 2

## Fatigue and related factors in people with type 2 diabetes

This work was published in *The Diabetes Educator*: Singh R, Kluding PM. Fatigue and related factors in people with type 2 diabetes. *The Diabetes educator.* May-Jun 2013;39(3):320-326.

## 2.1. Abstract

**Purpose:** The purpose of this study was to examine the presence and severity of fatigue in people with type 2 diabetes. **Methods:** The Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), and Visual Analog Fatigue Scale (VAFS) were administered by anonymous survey of 37 individuals with and 33 individuals without diabetes to assess the presence of fatigue. Data on age, gender, weight, height, year of diagnosis, and number/type of complications were also collected. Non-parametric tests tested for differences in fatigue measures between the groups, and distribution characteristics of the FAS, FSS and VAFS scores were examined. Spearman Rank Correlation Coefficients examined the relationships between the variables. **Results:** People with diabetes scored higher on all 3 fatigue assessment scales as compared to controls (FAS: 25.11 vs.19.94; $p = 0.001$, FSS: 4.30 vs. 2.59; $p = 0.000$, VAFS: 4.64 vs. 1.75; $p = 0.000$). Data were normally distributed for FSS in the diabetes and non-diabetes group, and scores of FAS, FSS and VAFS showed no ceiling effects. A positive correlation was noted between fatigue measures and number of complications ($r=0.482$; $p = 0.003$). **Conclusions:** Higher levels of fatigue were noted in people with type 2 diabetes as compared to healthy age matched control; however the cause and impact of these changes remain unclear. FSS is a recommended tool for measuring fatigue in this population. Further studies are needed to explore the contributing factors to fatigue in those with diabetes.

## 2.2. Introduction

Type 2 diabetes is a leading cause of adult disability and is a significant global health problem. In 2011, 25.8 million people were estimated to have diabetes in the United States and this figure is expected to rise to more than 40 million by 2050 (Wu et al., 2010). More specifically, type 2 diabetes contributes to 90-95% of this number. Fatigue is a persistent and distressing complaint among people with type 2 diabetes. While fatigue also occurs in other medical disorders the importance of fatigue may be greater in individuals with type 2 diabetes due to the complex management strategies that must be maintained continuously. Fatigue can take a considerable toll on individuals with diabetes, yet there is little empirical research describing the severity of the problem. Defining fatigue is a challenge because there is a great discrepancy among causes and indicators. In general, fatigue is recognized as a complex phenomenon including physiological, psychological, and situational components(Aaronson et al., 1999; Aistars, 1987; Magnusson et al., 1999; Ream et al., 1996; Rose et al., 1998; Trendall, 2000). Since fatigue itself is difficult to define and is such a complex phenomenon it becomes very challenging to transform fatigue into a quantifiable measure. To date, the most accurate or appropriate fatigue scales remain controversial. However, there are a few scales which appear to adequately identify and measure fatigue in individuals with diabetes, these scales include Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), and Visual Analog Fatigue Scale (VAFS).

Fatigue can result from various physiological factors associated with diabetes, such as hypoglycemia, hyperglycemia, and the wide swings between the two (Morsch et al., 2006; Weijman et al., 2004). Polypharmacy, referring to the numerous medications which this population has to take, can result in a number of complications and side effects including

fatigue(Khurana & Malik, 2010; McCormick et al., 2002) (DeFronzo, 1999) . Numerous complications such as sleep disorders(Resnick et al., 2003) or chronic neuropathic pain (Rijken et al., 1998) can add to the burden of fatigue. The presence and number of diabetic complications have been shown to have a significant impact on quality of life in a number of studies (R. M. Anderson et al., 1997; G. C. Brown et al., 2000; Glasgow et al., 1997; Wandell et al., 1997). Fatigue can also result from various life style issues, such as lack of physical activity or high body mass index (BMI), which is commonly seen in people with type 2 diabetes(Telford, 2007). Certain psychological factors like depression (R. J. Anderson et al., 2001)or stress resulting from the diagnosis of diabetes or from the management of diabetes can also result in fatigue(Egede & Zheng, 2003; Katon et al., 2004; Ryerson et al., 2003). Therefore, it is very important to further explore this issue and identify the potential contributors of fatigue.

In an epidemiological study, of 1137 subjects with type 2 diabetes, the prevalence of fatigue was found to reach 61% (Drivsholm et al., 2005). Despite this high frequency and the impact of fatigue on the persons' treatment efficacy, few studies have explored this symptom dimension in patients with diabetes, and most have been limited to nonspecific symptoms of fatigue (Fritschi & Quinn, 2010). Fatigue studies done in the past were either tested in subjects with additional comorbidities(Cuellar & Ratcliffe, 2008) or with additional challenges of maintaining employment status(Weijman et al., 2003). Therefore future studies need to be done to find out how diabetes itself plays a role in fatigue levels of these individuals.

The primary purpose of this study was to investigate the presence and severity of fatigue in people with type 2 diabetes as compared to a non-diabetic group, and to identify the relationship between fatigue and certain variables of diabetes. An additional purpose was to

compare three standardized measures of fatigue, the Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), and Visual Analog Fatigue Scale (VAFS), to determine which would be the most appropriate tool to measure fatigue in this population.

## 2.3 Research Design and Methods

*Research Design*

This cross sectional study utilized community based surveys.

*Data Collection Procedures*

An invitation letter, fatigue surveys and a brief medical history form were distributed by the researchers among the community, at health fairs, local clinics, and through a diabetes database which has a list of individuals with diabetes willing to be contacted for research purposes. The diabetes database is maintained at the Georgia Holland Research Lab where the study was conducted. The study was approved by University of Kansas Medical Center's Human Subjects Committee. The study utilized self-administered, anonymous surveys, indicating that personal information, regarding the participants' name or date of birth was not stated on the surveys.

*Participants*

Participants with and without type 2 diabetes were included if they were between the ages of 40 and 70 years.

*Methods*

*Measures of Fatigue*

The Fatigue Assessment Scale (FAS) is a reliable scale for detecting the presence and severity of fatigue in terms of both physical and mental domains (Michielsen et al., 2003). It focuses on the physical and mental domains of fatigue. FAS is a 10 item questionnaire that requires a subject to choose one out of five answer categories varying from never to always (1 = never, 2 = sometimes; 3 = regularly; 4 = often; and 5 = always). Responses for each question are summed to generate a score ranging from 10-50. Higher scores indicate more fatigue.

The FAS has previously been shown to have good reliability, with a Cronbach's alpha of 0.90 for employed subjects (n=351). The measure also demonstrates good validity, with factor analysis demonstrating strong construct validity(Michielsen et al., 2003) and concurrent validity with other fatigue scales, such as the Check List Individual Strength – subjective experience of fatigue (r=0.76, $p < 0.001$)(Michielsen et al., 2003) .

The Fatigue Severity Scale (FSS) emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects, which appears suitable for detecting the presence and the severity of fatigue(Krupp et al., 1989; Winstead-Fry, 1998). FSS is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. The FSS tests different domains, including motivation, exercise, and interference with work, family or social life. It emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects, which appears to be suitable for detecting the presence of chronic fatigue. It has 9 item questionnaires and scoring is done by adding up the responses (numbers) and dividing by 9. A score of less than 4 is considered as having no fatigue, scores of 4-4.9 are considered as having moderate fatigue, and scores of 5 or more are considered as having severe fatigue(Krupp et al., 1989).

The FSS has previously shown to have good reliability measures with a Cronbach's Alpha = 0.89 for subjects with systemic lupus erythematosus (n = 28), 0.81 for subjects with multiple sclerosis (n =25), 0.88 for normal healthy adults (n = 20), and 0.88 for total sample of 74 subjects(Krupp et al., 1989). The measure also demonstrates good validity. Results of factor analysis shows strong construct validity when tested in cancer patients(Winstead-Fry, 1998), demonstrating strong construct validity. Additionally, FSS has strong concurrent validity with other scales, such as visual analog scale (n =74) was r =0.68; $p < 0.001$ (Krupp et al., 1989).

The Visual Analog Fatigue Scale (VAFS) is a modified form of a visual analog scale that was designed to assess acute or transient fatigue in patients with stroke (Tseng, Billinger, et al., 2010; Tseng, Gajewski, et al., 2010). It consists of a 10cm unmarked vertical line with written descriptions of "No fatigue", and "Very severe fatigue" at each end. Subjects are asked to mark on the line the point where they feel their perception of fatigue is. Scores range from 0 to 100 and are measured in millimeters on the 10cm vertical line. Scoring is done by measuring the line from "No fatigue" to the point which will be indicated by the subjects. The higher the VAFS score, the higher the fatigue. VAFS has major advantage among the other fatigue tests, in that it avoids recollection among subjects. Rather, it requires subjects to base their answers on intuitive response at the moment, which helps avoid recollections of previous references.

The VAFS has been shown to have good reliability, with Intra-class coefficient values for the VAFS =0.851 (CI = 95%, 0.673∼0.936, $p < .001$), for subjects post stroke(Tseng, Gajewski, et al., 2010). The measure also demonstrates good validity, demonstrating strong concurrent validity, with significant co-relationships with heart rate and systolic blood pressure (r= 0.632; $p = 0.02$)(Tseng, Gajewski, et al., 2010).

*Medical History Form*

Participants completed a medical history form, consisting of questions about age, gender, height, weight, year of diagnosis of diabetes, and a list of possible complications from diabetes which included: nerve problems, kidney disease, blindness or eye problems, heart attack or heart disease, stroke, amputation, high blood pressure, dental problems, problems with pregnancy, and problems with sexual function.

*Data Analysis*

Mann Whitney U test and Wilcoxon signed-rank test were used to test for differences in fatigue measures between diabetic and non-diabetic participants. The Kolmogorov-Smirnov test (K-S test) was used to compare the distribution of FSS, FAS, and VAFS scores in diabetic and non-diabetic participants to a standard normal distribution curve. Potential floor and ceiling effects of the three measures were also analyzed. Spearman Rank Correlation Coefficients were also calculated to explore the relationships between fatigue scores with age, gender, weight, height, year of diagnosis, and number of complications in diabetic participants. Number of complications was calculated by adding up the number of "yes" answers in the list of complications. A significance level of 0.05 was utilized for all testing.

## 2.4 Results

*Survey Responses*

Surveys were received from 82 adult subjects (49 diabetic subjects, 33 controls). Of the 49 surveys from people with diabetes, 42 had type 2 diabetes, 6 had type 1 diabetes, and 1 was unknown. In addition to excluding data from the 7 surveys without type 2 diabetes, surveys were

also excluded from 5 people who did not fall between 40-70 years of age range. A total of 70 surveys (37 with diabetes and 33 controls) were included in the study.

Participant characteristics are provided in Table 2.1. Participants in the group with diabetes had higher BMI (mean BMI 34.24± 8.21 kg/m²) as compared to participants in the control group (mean BMI 34.24± 8.21 vs. 30.45± 8.02 kg/m²; $p < 0.001$). In the survey participants with diabetes, the mean number of years since diagnosis of diabetes was 14.62 ± 11.2 years.

*Measures of Fatigue*

Results of the FAS, FSS, and VAFS fatigue questionnaires are presented in Table 2.2. Subjects with diabetes scored significantly higher on all three fatigue assessment scales as compared to controls.

*Distribution characteristics analysis:* Results of the K-S test indicated that the FSS scores for the participants with diabetes and the FSS scores for participants without diabetes were normally distributed. The other scores were not normally distributed. None of the tests in either group (FSS, FAS and VAFS) showed clustering of scores at the higher end or lower end, which indicated the absence of ceiling or floor effects.

*Relationships between Variables*

Fatigue, as measured by both FAS and FSS, was significantly associated with number of complications ($\rho$=0.483; $p$ = 0.003 and 0.326; $p$ = 0.049 respectively) in participants with diabetes. We also found that VAFS was negatively associated with age ($\rho$ = -0.420; $p$ = 0.011) in

the participants with diabetes. No significant relationships were observed between fatigue scores and years since diagnosis, age, BMI or gender in this small sample of individuals with diabetes.

Also of note, increasing years since diagnosis was significantly associated with number of complications (0.331; $p = 0.045$), while increasing age was associated with lower BMI (-0.380; $p = 0.020$), and increasing BMI was negatively associated with number of complications (-0.361; $p = 0.028$).

**2.5 Discussion and Conclusions**

Participants with diabetes in this study appeared to have higher fatigue levels when compared to non-diabetic controls at a comparable age. Although fatigue is a common complaint among patients with type 2 diabetes, few studies have directly tested the presence and severity of fatigue in people with type 2 diabetes. Our results are in agreement with previous studies that have used FSS as a primary measure to assess fatigue.

For example, Ceullar et al. (Cuellar & Ratcliffe, 2008) conducted a study evaluating fatigue, sleep, glycemic control and depression in subjects with type 2 diabetes; both with and without restless leg syndrome (RLS). FSS was used to test fatigue and it was found that the mean FSS score for subjects with RLS and diabetes was 3.8. These results are in accordance with our pilot study, in which the mean FSS score in the diabetes group was 4.28 ±1.49, representing a moderate level of fatigue (Krupp et al., 1989). This compared to a mean FSS score of 2.60 in the control group, which represents a low level of fatigue (Krupp et al., 1989) . In another study examining subjects with immune mediated polyneuropathies, FSS was used as the primary tool to determine the prevalence and severity of fatigue(Merkies et al., 1999). Mean FSS score was

5.6 ±1.4 in the patient group, which represents severe fatigue. These results may be relevant to our study, because patients with diabetes often have similar symptoms resulting from neuropathy.

Merkies et al defined severe fatigue as an FSS score above the 95th percentile of FSS in healthy controls, or a score of 5.0 or more (Merkies et al., 1999). Following this criteria, severe fatigue was demonstrated in 13 of 37 (35%) individuals in our survey. Additionally, over 45% of the diabetic survey participants scored 5 or more on the 7-point scale for question 8 ("Fatigue is among my three most disabling symptoms") compared with only 12% (4/33) of the healthy controls.

Of the three fatigue measures that were used in this study, all 3 indicated that individuals with diabetes exhibited significantly greater levels of fatigue than control subjects. Since fatigue is such a complex phenomenon and is difficult to measure, three different tools were used to assess fatigue. All these tools have different conceptual definitions; FAS tests the presence and severity of fatigue in terms of both physical and mental domains; FSS emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects; and VAFS assesses acute or transient fatigue at the moment. Thus, although these tools have different conceptual definitions, all tools appear to be valid in measuring fatigue in people with diabetes.

Further analysis of distribution curves revealed that FSS was normally distributed, even in this small sample, which may indicate that FSS is the most appropriate test to use in this population. None of the fatigue measures showed ceiling or floor effects, as the scores were widely spread over a broad range and not clustered at either end of the scoring range.

Surprisingly, we were not able to identify any relationships between fatigue and the diabetic variables, such as BMI or years since diagnosis. Fatigue was only found to be significantly associated with number of complications. This finding supports previous studies that the number of complications can affect quality of life of individuals with diabetes (R. M. Anderson et al., 1997; Glasgow et al., 1997; Wandell et al., 1997). The relationship between fatigue and the number of complications is understandable, as more complications can logically result in more tiredness or fatigue. Our survey participants reported high blood pressure and neuropathy as the most common comorbidities and/or complications resulting from diabetes. Both high blood pressure and neuropathy can cause general tiredness and fatigue. Neuropathy was the most common complication reported by our survey participants, and foot pain (resulting from neuropathy) has been previously found to be positively correlated with symptoms of general fatigue ($r=0.63$, $p < 0.001$) (Rijken et al., 1998) in adults with type 1 and type 2 diabetes.

Our study also showed a surprising negative direction in the relationship of fatigue (VAFS) with age. In contrast, we would expect a positive relationship between fatigue and age. This could be due to the small sample size of the study; and the complexity of fatigue with potential causative factors.

Although this survey successfully identified the presence of fatigue in people with type 2 diabetes, there are several limitations associated with this study. The first and most obvious limitation is the small sample size, which may have influenced the lack of significant relationships between fatigue and variables such as duration of diabetes. This relationship may also be complicated by the fact that there is often a period of unawareness prior to a diagnosis of diabetes being established.(Sacks et al., 2011; Troisi et al., 2000). Future studies should

incorporate other variables, such as fasting blood glucose and glycosylated hemoglobin measures and inclusion of other common comorbidities like depression, pain and sleep problems. This may substantially clarify the relationships and contributing factors to fatigue in diabetes.

Another limitation of the study was the use of anonymous surveys, as we were unable to verify the data or follow up with the subjects. Further, fatigue is such a complex phenomenon that questionnaires alone will not capture the whole picture of fatigue. Therefore, there is a need to incorporate more rigorous methods to capture the whole phenomenon of fatigue in diabetic patients.

As a part of diabetes management, individuals with diabetes are highly encouraged to engage in physical activities. However, due to the presence of fatigue people with diabetes may have difficulty starting or continuing exercise programs. Exercise may actually reduce fatigue (Fulcher et al., 1997; Gowans et al., 1999) as aerobic fitness improves, and this is an important area for future study.

In conclusion, people with type 2 diabetes appear to have greater levels of fatigue, and the number of the complications resulting from diabetes may be a related to this tiredness. FSS is recommended for measuring fatigue in people with diabetes. Overall, these results appear to support previous research suggesting that individuals with diabetes suffer from general tiredness and fatigue, which may be linked to complications from diabetes. As this may be an important area for patient education and diabetes management, further investigation is warranted to examine fatigue and its contributing factors in people with type 2 diabetes.

Acknowledgements

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## 2.6 Tables

Table 2.1: Participant characteristics

| | Diabetes | Controls |
|---|---|---|
| n | 37 | 33 |
| Age (Y) | 57 ± 7 | 53 ± 9.11 |
| Gender (female/male) | 23/14 (62%) | 26/7 (78%) |
| BMI | 34.2 ± 8.21 | 26.20 ± 5.26 |
| Years since diagnosis (Y) | 14.62 ± 11.12 | N/A |
| Neuropathy | 26 (70.27%) | N/A |
| Nephropathy | 0 | N/A |
| Retinopathy | 8 | N/A |
| Cardio-vascular disease | 14 (37.83%) | N/A |
| Stroke | 11 | N/A |
| Amputation | 0 | N/A |
| High B.P | 34 (91.8%) | N/A |
| Dental problems | 11 (29.72%) | N/A |
| Problems with pregnancy | 0 | N/A |
| Problems with sexual function | 8 | N/A |

Abbreviations: BMI: Body mass Index, B.P: Blood Pressure, N/A: not applicable

Table 2.2: Fatigue Scores

| Fatigue Surveys | Diabetes | Control | *p*- value |
|---|---|---|---|
| FAS | 25.10±7.62 | 19.87±4.3 | 0.001** |
| FSS | 4.28±1.49 | 2.60±1.13 | 0.000** |
| VAFS | 4.61±3.17 | 1.60±1.70 | 0.000** |

** Significant at $p \leq 0.01$ level

# Chapter 3

## Preface

Chapter 2 provided the evidence that fatigue is present in people with type 2 diabetes and could be occurring from various complications these people have. Chapter 2 also discussed various fatigue measuring scales. Although we concluded that FSS is recommended to measure fatigue in people with type diabetes, we decided to use the Multidimensional Fatigue Inventory -20 (MFI-20) to measure fatigue for chapter 3 and 4. The reason for this change in our fatigue measuring scale was that MFI-20 supports the several physiological and psychological domains of the diabetes version of Portenoy's fatigue model. MFI-20 has also verified its ability to relate fatigue with some of the diabetic variables like pain and BMI, which are important contributing factors in the diabetes version of Portenoy's fatigue model (Lasselin et al., 2012a; Rijken et al., 1998).

Since chapter 2 provided the evidence of presence of fatigue in people with type 2 diabetes, one of the questions that remain unanswered is what causes fatigue in this population. Chapter 3 aims to investigate the contributing factors to fatigue via a mixed methods approach.

# Chapter 3

## Predicting fatigue in people with type 2 diabetes: A mixed methods study

This work will be submitted for publication to *Diabetes Care*.

## 3.1. Abstract

**Purpose:** Fatigue is a persistent and distressing complaint in people with type 2 diabetes. While fatigue also occurs in other medical disorders, the importance of fatigue is greater in diabetes because it affects self-management strategies. The purpose of this study was to explore the relationship between fatigue and specific diabetes-related factors that may be associated with fatigue via a mixed methods approach. These factors included body mass index (BMI), HbA1C, sleep quality, pain, number of complications from diabetes, years since diagnosis and depression.

**Subjects:** Forty-eight individuals with type 2 diabetes (22 females, 26 males; 59.66±7.24 years of age; 10.45 ±7.38 years since diagnosis) participated in the study.

**Methods**: Fatigue was assessed by using Multidimensional Fatigue Inventory (MFI-20). Other outcomes included diabetes related factors: BMI, HbA1c, sleep (Pittsburg sleep quality index, PSQI), pain (Visual Analog Scale), number of complications, years since diagnosis, and depression (Beck's depression Inventory-2). Pearson correlation analysis was used to determine the relationship between fatigue and potential contributing factors. The significant factors were used as explanatory variables to build the multivariable linear regression model. Interviews were conducted with a sub-sample of 10 participants. A purposeful sampling technique was used. Participants were included who answered "YES" to the following question - Are you tired or fatigued all the time, tiredness which is not relieved by rest? Content analysis technique was used to analyze the interview data to explore the contributing factors to fatigue.

**Results**: Fatigue was significantly correlated with BMI (r =.350, $p$ = .01), pain (r =.437, $p$ =.002), sleep quality (PSQI) (r =.613, $p$ =.003) and depression (r =.442, $p$ = 003). Multivariable

linear regression analysis revealed sleep, pain and BMI as the independent predictors of fatigue (all $p < 0.01$). Interview findings further supported the results of regression analysis by identifying fatigue as multidimensional in nature. Participants expressed that sleep problems, extra body weight, pain, high/low blood glucose levels and depression were main contributing factors to fatigue.

**Conclusion:** Results suggest that although fatigue is a common clinical complaint among individuals with type 2 diabetes, it may signal the presence of physiological (sleep, pain, BMI, high/low blood glucose levels) and psychological (depression) phenomenon that could undermine diabetes health outcomes.

**Clinical Relevance:** Although individuals with type 2 diabetes are encouraged to engage in physical activities, the presence of underlying fatigue can result in apprehension towards exercise programs. Therefore, there is a need to further investigate the complex phenomenon of fatigue so that intervention strategies can be developed to reduce the burden of fatigue. Results from the present study suggest that interventions should focus on addressing healthy sleep habits, weight management, and self-management education on blood glucose levels, depression screening, and pain management.

## 3.2. Introduction

Fatigue is a common clinical complaint among individuals with type 2 diabetes (R. Singh et al., 2013; Weijman et al., 2003) and can interfere in successful self-management of diabetes (Wenzel et al., 2005). Despite this, very little research has been done investigating the cause or severity of diabetes related fatigue. While fatigue also persists in other medical conditions, the importance of fatigue is greater in individuals with type 2 diabetes because of the complex disease management strategies which need to be followed.

Since fatigue is such a complex phenomenon it becomes very difficult to define. There is also a great discrepancy among causes and indictors of fatigue. Nevertheless, several models explaining the cause of fatigue have emerged since the 1980's. Early models attempted to explain fatigue in terms of central and peripheral nervous system components (Funk & Project, 1989; Gibson & Edwards, 1985). Later models incorporated the physiology of multiple body systems (Bruno et al., 1993; St Pierre et al., 1992; Walker et al., 1991). In 1999, Portenoy and colleagues proposed an integrated fatigue model consisting of several contributing factors and physiological and psychosocial dimensions (Portenoy & Itri, 1999) as illustrated in figure 3.1. Physiological components mainly cover the underlying disease and the complications which come with the treatment and the disease. Psychosocial components include depression and anxiety. Consistent with recent studies and earlier models, Portenoy's integrated model considered the multifactorial and multidimensional nature of fatigue (Aaronson et al., 1999; Tiesinga et al., 1996).

Portenoy's fatigue model was based on cancer patients; however this model can also be applied to patients with diabetes. The various complications and comorbidities associated with

diabetes can be integrated into Portenoy's fatigue model. The proposed diabetes adaptation of Portenoy's fatigue model can also have two distinct dimensions: physiological and psychological as illustrated in figure 3.2. Physiological factors include the underlying disease (diabetes), duration of diabetes, disease treatment, sleep disorders, immobility/inactivity, chronic pain, glucose fluctuations, and number of complications. Psychological factors include depression and anxiety.

For the purposes of the study, fatigue was defined as a subjective perception of a decreased capacity to perform physical and/or mental tasks due to one or a combination of physiological or psychological phenomena, including altered glucose control, duration of diabetes, and number of complications, sleep problems, pain, BMI and depression.

Physiological factors and psychological factors explored for the study are: hyperglycemia, sleep apnea, obesity, pain, number of complications, duration of diabetes and depression. It was not within the scope of the study to cover all different factors. *Physiological factors:* Episodes of hyperglycemia or hypoglycemia or the fluctuations between those extremes (Morsch et al., 2006; Weijman et al., 2004) can result in fatigue. Numerous complications and the comorbidities associated with these complications such as sleep problems (Resnick et al., 2003) or chronic pain (Rijken et al., 1998) can also add to the burden of fatigue. Most people with type 2 diabetes are overweight (Rayburn, 1997), and obesity has been associated with higher fatigue levels (Resnick et al., 2006). *Psychological factors*: Several psychological factors like depression (R. J. Anderson et al., 2001) or stress resulting from the diagnosis or from the vigorous management of diabetes can also result in fatigue (Egede & Zheng, 2003; Katon et al., 2004; Ryerson et al., 2003)

Since fatigue is such a complex phenomenon, the contributing factors should be investigated by a mixed method design, using both quantitative and qualitative methods. Quantitative methods will help us understand the relationship of fatigue with the potential contributing factors. Qualitative methods on the other hand can help us in understanding the context of how individuals experience fatigue, as voices of the participants will be directly heard. Therefore, the purpose of this study was to investigate the contributing factors of fatigue in individuals with type 2 diabetes by using a mixed methods design.

## 3.3. Methods

*Design*

A convergent (parallel or concurrent) (Creswell, 2011; Gedaly-Duff et al., 2006; Morse, 2009; Ostlund et al., 2011) mixed methods design was used. A convergent design is intended to merge concurrent quantitative and qualitative data to address the aims of the study, so that the data can be merged and compared. Quantitative data was collected first followed by qualitative interviews (on the same testing day). Quantitative methods are described first, followed by description of qualitative methods.

Participants were recruited from a research participant registry at the University of Kansas Medical Center where the study was conducted. The study was approved by the University of Kansas Medical Center's Human Subjects Committee. Participants who were eligible for the study signed an institutionally-approved informed consent form, which explained the optional interviews for qualified participants.

*Participants*

Individuals between 40-70 years, with a confirmed diagnosis of type 2 diabetes were included. Individuals were excluded if they 1) had a known history of stroke, cancer or other central nervous system pathology which may cause additional burden of fatigue besides diabetes, 2) inability to ambulate, or 3) amputation.

*Quantitative data collection procedures*

Fatigue: Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20). It consists of five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity (Smets et al., 1995). For the purpose of this study “general fatigue” was used as a composite measure of overall subjective fatigue experience, and it also fits with the definition of fatigue used to guide the study. Each of the 5 scales contains 4 items. The respondent has to compare each of the 20 statements with how he or she felt lately. Each item is scored from 1-5, from agreement with the accompanying statement "yes, that is true" to disagreement "no, that is not true". A higher score indicates more fatigue. For each scale a total score is calculated by summation of the scores of the individual items. Total scores can range from the minimum of 4 to the maximum of 20. MFI-20 appears to have good reliability and validity measures, with Cronbach’s Alpha of 0.890 in women with type 2 diabetes (n=83) (Fritschi et al., 2012) . The MFI-20 also has strong concurrent validity, as the general fatigue dimension of MFI-20 has shown to have significant correlations with Fatigue Inertia subscale of the Profile of Mood States (r = 0.774) (Fritschi et al., 2012).

Physiological factors:

1. Hyperglycemia was evaluated by taking the glycosylated hemoglobin (A1C) with a finger stick blood test using a disposable A1C analyzer (A1CNow+, Bayer Medical Care; Tarrytown, New York). This test gives an indication of the level of glycemic control over a 3-month period. The accuracy of this test is 99% as reported by the manufacturer.
2. Sleep quality was assessed by using Pittsburg Sleep Quality Index (PSQI). PSQI is a self-report questionnaire assessing sleep quality over a 1 month interval. PSQI generates a global score ranging from 0 to 21. Higher global score indicates worse sleep quality. PSQI has been demonstrated to have good reliability and validity (Buysse et al., 1989) and has been used in individuals with diabetes (Vigg et al., 2003).
3. Pain was assessed by using unmarked 10cm Visual analog scale to indicate the pain level at the moment of testing.
4. Diabetes duration was evaluated by calculating the number of years since diabetes was diagnosed.
5. BMI was calculated by dividing weight in kilograms by height (mtrs) $^2$ (kg/m$^2$).
6. Number of complications (NOC) was calculated by counting "Yes" to a list of complications. List of complications include: Heart problems, kidney problems, eye problems, tingling in toes/feet, decreased sexual interest, oral infection, depression, gastroparesis, sleep problems. The details are provided in appendix -1.

Psychological factors:

Depression was evaluated by Beck's depression inventory-2 (BDI-2). The BDI-2 is a 21-item survey, with each item consisting of a list of four statements arranged in increasing

severity about a particular symptom of depression. Scores range 0 from 13 (normal), 14 to 19 (mild depression), 20 to 28 (moderate depression), and 29 to 63 (severe depression).

*Data Analysis*

Descriptive statistics (mean, standard deviation, median, and range) of the measures (MFI-20, HbA1c, PSQI, VAS, years since diagnosis, BMI, NOC) were calculated.

Assumptions of normality and equality of variances were met. We had to exclude data from two participants because of two outliers in BMI, which were skewing the data. SPSS version 20 was used to perform Pearson product-moment correlation coefficient to determine the relationship of fatigue (general fatigue – MFI-20) with HbA1c, PSQI, VAS, years since diagnosis, BMI, NOC.

The results of the Pearson product-moment correlation guided the next step of the study. The significant variables were used to build the multivariable linear regression model. Assumptions of normality, linear relationship, equal variance and multi-collinearity were tested. Decisions on assumptions were made on the residuals of the main outcome variable (MFI-20). Residuals are the differences between the observed value and estimated function value. No transformations were done since the residuals of all outcome variables were following the assumptions of normal distribution. It is more important for the residuals to follow normal distribution as compared to the independent variables (predictors) (Field, 2005).

Once the regression model was built, an assessment of multi-collinearity using variance inflation factors (VIF) was conducted to determine whether or not this issue has resulted in a

biased model (Field, 2005) Forward stepwise entry was used to enter the 4 variables that were ultimately selected as possible explanatory variables into the regression model.

*Qualitative data collection procedure*

Qualitative interviews immediately followed the quantitative testing, for those participants who qualified and who agreed to participate in the interviews.

*Participants*

A subset of participants from the quantitative study was selected for qualitative interviews, using a purposeful sampling approach. We included those participants who answered "YES" to the following question: "Are you tired or fatigued all the time, tiredness which is not relieved by rest?" In addition, to rule out impaired cognition, MMSE was performed to ensure that the participants would be suitable for the interview process and will have no difficulty in answering questions for the interview process. Participants were excluded if they answered "NO", to the above question, or if their score was below 23 on MMSE. Out of 48 participants, 38 met the inclusion criteria. However, based on the participant's and the researcher's availability to spend another hour for the interview, 10 participants were interviewed. Data was collected until data saturation was achieved. Data saturation refers to the point at which no additional data are being found whereby the researcher can develop properties of the category (Glaser, 1967).

*Interviews*

The interview guide was based on issues identified in the literature and expert opinion (Wu et al., 2010). The interview guide was then tested with role play (with an expert in qualitative methods) and field tested with one individual who fitted some criteria for the study.

Modifications to the interview guide were done after the role play and field testing. The interviews were held in a private room and were audio-taped. Interviews lasted for 30 - 45 minutes. We used the semi-structured interview guide (Table 3.1) and a descriptive qualitative approach was followed to describe the impact of fatigue in everyday language (Sandelowski, 2000). In-depth interviews were conducted and additional questions were posed as needed. Data was collected until data saturation was achieved.

*Data Analysis*

Data was analyzed by using comprehensive content analysis techniques. For this process, the audiotape recordings from each of the interview sessions were transcribed, and transcripts were compared to the original tapes for accuracy of language and notations. The analysis of the interview text was conducted in a stepwise method. First, the interviews were read through several times to get a sense of the whole picture. Meaning units were then identified from the interviews, and meaning units were then condensed and coded manually and by using qualitative data management software (NVivo 9). Some examples of codes were, 'less energetic' and 'get sleepy and get the head nodding'. Preliminary subcategories were identified based on similarities and differences in the codes. Examples of preliminary subcategories were, 'effects of fatigue' and 'sleep problems'. The analysis was continued by going back and forth between the interview text and preliminary categories to refine and validate the content, which resulted in five categories. This classification refers to the manifest analysis on a descriptive level (Downe-Wamboldt, 1992). To understand the underlying meaning of the content, a latent analysis was conducted and two themes were formed. Themes are threads of underlying meaning which are gained from condensed meaning units, codes and categories (Graneheim et al., 2004).

*Trustworthiness (mechanism to establish scientific rigor)*

Our study verified the issues of trustworthiness by following Lincoln and Guba's guidelines to establish credibility, transferability, dependability, and confirmability (Lincoln, 1985).

*Credibility* (internal validity): To enhance credibility for our study, member check strategy was used. Member checking refers to revealing the research materials to the participants to ensure that the researcher has accurately translated the participants' viewpoints into data (Lincoln, 1985). As a part of member check strategy, summary of evolving description of impact of fatigue was send to all interview participants asking for the areas of disagreement. All participants agreed to description of impact of fatigue and no suggestions for change were made. Triangulation was achieved by collecting data from the interviews as well as data from quantitative analysis. Transcribed interviews were also sent to other researchers having qualitative research background. Discussions were held regarding the emerging codes and categories until an agreement was reached. To test the validity of our findings we established referential adequacy. Referential adequacy refers to identifying a portion of data to be stored, but not analyzed. The researcher then analyzes the remaining data and develops preliminary findings. The researcher then returns to the stored data and analyzes it as a way to test validity of his/her findings (Lincoln, 1985). To achieve referential adequacy, codes and themes were developed first, and to further justify the themes, observations were added later. This helped in enhancing the validity of the themes.

*Transferability* (external validity): Transferability was established by including a wide range of participants (Table 3.6) who answered "YES" to the following question: "Are you tired or fatigued all the time, tiredness which is not relieved by rest?" The results of the study can be applied to the general population by including a wide range of participants experiencing different levels of fatigue.

*Dependability* (reliability): To support dependability we composed our audit trail which included our transcripts and demographic data for the participants. External auditing was done by sending the transcribed interviews to other researchers with qualitative research background.

*Confirmability* (objectivity): Audit trail and theme formation through discussion served this concept. Confirmability was further enhanced by reducing the researcher's bias towards certain beliefs. For example, the researcher had strong beliefs that participants having high BMI will identify BMI as their contributing factor to fatigue. Therefore, no direct questions (such as – do you think you are tired because of your extra weight?) were asked.

## 3.4. Results

*Quantitative Results*

*Demographics*

Fifty participants participated in the study. Data from 48 participants is presented. We had to exclude data from two participants because of two outliers in BMI, as previously described. Participant characteristics are provided in Table 3.2. The mean age of the sample was 59.66 years, with 22 females and 26 males.

Table 3.2 also presents the mean and standard deviation (SD) of outcome variables and results of Pearson correlation analysis of general fatigue (MFI-20) with other outcome variables which includes: BMI, HbA1c, sleep quality (PSQI), pain (VAS), NOC, years since diagnosis, and depression (BDI-2).

The significant variables were then used as explanatory variables to build the multivariable linear regression model which includes: BMI, PSQI, VAS and BDI-2. Forward step wise multiple regression analysis was performed (Table 3.3), using fatigue as the dependent variable. Sleep quality, BMI and VAS remained the significant predictors of fatigue in individuals with type 2 diabetes. The model accounted for 57.3 % of variance in fatigue scores. Sleep (PSQI) explained 37% of variance in fatigue. Sleep and BMI explained 50% of variance in fatigue. The model was further improved by adding pain (VAS). There was no issue of multi-collinearity as VIF was close to 1 for all the outcome variables. Depression was not a significant predictor in this model.

Since sleep quality itself explained 37% of variance in fatigue we decided to run another multivariable linear regression analysis to find out the predictors of sleep. BMI, BDI-2, VAS were used as independent variables, since these were significantly related to MFI-20 (table 3.3). Table 3.4 presents the results of forward step wise multiple regression analysis using PSQI as the dependent variable. Depression was the single predictor of sleep explaining 48% of variance of sleep in individuals with type 2 diabetes.

Result of regression analysis suggests that poor sleep quality contributes significantly in explaining fatigue variance in individuals with type 2 diabetes, and depression is a significant contributing factor to poor sleep quality (fig 3.3).

*Qualitative results*

*Demographics*

Six females and 4 males (aged 44-66 years) consented and participated in the qualitative section of the study. Participant characteristics are provided in table 3.5.

Comparison of two samples: quantitative and qualitative sample

Table 3.6 describes and compares some of the descriptives of the outcome variables in two samples. The fatigue scores (general fatigue), PSQI scores and BDI-2 scores were significantly high in the qualitative sample as compared to the quantitative sample. BMI, VAS scores and NOC were also high in the qualitative sample but did not reach a significant level.

The participants described what fatigue means to them and what the causative factors of fatigue are. Two broad themes were generated: Description of fatigue and Multidimensional nature of fatigue. Three categories supported the first theme (Description of fatigue): Description of physical fatigue, description of mental fatigue and alleviating factors to fatigue. Two categories supported the second theme (Multidimensional nature of fatigue): Physiological factors and Psychological factors.

*Qualitative themes and categories*

***Theme 1: Description of fatigue***

Fatigue was described as overall tiredness that includes both physical and mental components (e.g. worn out, listless, problems with concentration). Some common characteristics

of fatigue sensation, such as tiredness, sleepiness and lack of energy, were experienced by all participants.

*Category: Description of physical fatigue*

Participants described the physical fatigue sensation occurring in their bodies resulting in inability to do physical tasks, for example participants described quality of fatigue as being "heavy, the need to sit". Some quotes from the interviews:

> "When I'm fatigued I find myself completely worn out, where I need to just sit" (participant No. 1Q).

> "Just like I am out of everything. I can't do anything. I don't feel like doing anything" (participant No. 7Q).

*Category: Description of mental fatigue*

Besides describing the physical state of being fatigued, participants also described the mental state of being fatigued. The description of mental fatigue included: lack of concentration, sleepy state and loss of motivation. Most participants (n=8) felt "I do not want to do anything", "feel like lying in the bed all day", "feeling sleepy". Some participants (n=5) emphasized their fatigue was mainly derived from mental burden, as evidenced by some quotes from the interviews:

> "I think responsibility, mental list of things I want to do, my goals for the day, and then my ability to complete them are my causes of my fatigue" (participant No. 3Q).

> "I think a lot of times mine is more of a mental fatigue, being overwhelmed here at work. There is a lot that you have to know in my position" (participant No. 1Q).

*Category: Alleviating factors to fatigue*

While describing the state of being fatigued most of the participants (n=8) also discussed the alleviating methods to tackle fatigue. Participants emphasized that improving sleep quality can help them in alleviating some of their issues with fatigue. Some participants (n=3) even suggested using a Constant Positive Airway Pressure (CPAP) machine or sleep medications. Some other methods like meditation, exercise, and head massage, taking a break from work and a snack or coffee during work hours were also described. Some participants gave a rich description of alleviating factors as quotes from one interview show:

> "I went through the process of getting used to the CPAP machine…..I knew from the night that I tried it, I mean I slept so well that night….so consequently I am not as fatigued, but the other thing is the exercise and activities....I am that refreshed and energized because of having had good sleep the night before and also exercise" (participant No. 2Q).

***Theme 2: Multidimensional nature of fatigue***

The causative factors were grouped into two subcategories: Physiological factors and Psychological factors.

*Category: Physiological factors*

Physiological factors included a set of symptoms and extra amount of weight and medications. The set of symptoms included: sleep problems, pain, and high/low blood glucose. When discussed, other contributing factors like years since diagnosis and number of complications, limited information was provided.

*Sleep problems*: Poor sleep quality was discussed commonly among all participants. Participants described that because they have poor sleep quality during the night they usually end up taking frequent naps, which also does not help. Most of the participants (n=8) mentioned that after their work hours or during the day also they would prefer to stay in their bed all day. Taking frequent restroom breaks also disturbs sleep quality. Participants who were employed (n=6) had to take frequent breaks from their work because they 'get sleepy 'during their work as described by one participant:

> "I get sleepy sometimes. I get the nodding and everything. And then…if I'm real, real sleepy then I'll go ahead and take my lunch so I can go to my car and go to sleep. If I can wait until 1:00 I'll be okay" (participant No. 4Q).

*Pain*: All participants emphasized the relationship of fatigue with pain. Participants described pain in form of muscle cramps, sore feet, cold feet, or an ache that may be a result of neuropathy, which limits their ability to walk and causes them to be more fatigued. Some quotes from interviews:

> "I had significant pain and I had…I was very tired" (participant No. 4Q).

> "My feet get sore, especially, you know and I just get tired and I'll be sleeping in my chair for no reason" (participant No. 6Q).

*High/low glucose levels:* Participants described that after eating a high sugar diet, they get 'very sleepy', 'weak' and 'less energetic'. An event of high blood glucose is described by one participant in this quote from an interview:

> "having your feet stuck in tar because you just feel like everything is in slow motion, because you're afraid to move, you're afraid to…I mean it just pretty much just zaps all energy you have" (participant No. 5Q).

Some participants (n=4) also described glucose fluctuations, as this quote from an interview:

> "because seriously the effect of eating the sugar and then going through the low afterwards really and truthfully isn't all that fun (participant No. 5Q).

Low blood glucose also came up in the discussion regarding the contributing factors to fatigue. Participants described the event of low blood glucose as 'shaky', leaving them with no energy.

*Extra amount of weight:* Participants described the effect of extra weight on their tiredness and daily activities (especially walking). Diabetes is associated with extra body weight which was mentioned by all participants. Participants emphasized that extra weight would hinder their ability to walk which makes the participants more fatigued. Some quotes from interviews:

> " You're carrying around a small person, so if you get rid of that you've absolutely got more energy and you're not going to be as fatigued and tired" (participant no. 2Q); "it's effected  my ability to walk and to get it all" (participant no. 3Q).

*Medications:* Two participants described medications as their cause of fatigue. Taking medications 'on time' was perceived as a burden because this could lead to a high blood glucose episode, so there was fear to be on the schedule with the medications. One participant described medications as 'chemicals' which can cause tiredness, as described by this quote from an interview:

> "I really do think even the medications are helping, I think they also hinder, because I think they…the chemicals and all that junks going on in your system and it's like your body's going okay, what am I supposed to do with this" (participant No. 5Q).

*Category: Psychological factors*

Psychological aspect played an important role in triggering and adjusting to fatigue. Psychological factors included depression and stress (from work, from diabetes). Although only 5 participants were diagnosed with depression, 16 out of 48 had high scores on BDI-2, suggesting that depression goes undiagnosed in diabetes. Out of 16 participants with scores on BDI-2, 7 had scores under 'mild depression' category, 6 participants scored under 'moderate depression' category and 3 participants scored under 'severe depression' category. Some participants emphasized that because of being depressed, they were not being socially active. Medications for depression helped some participants. Most of the participants (n=7) described a strong relationship of fatigue with depression. Some quotes from interviews:

> "I've gotten irritated and not want to be around people and not be social" (participant No. 6Q).

> "I think because it's like I want to shut out the whole world and so I'll just go in my room and turn on the TV and just lay in the bed" (participant No. 7Q).

Overall, sleep problems, pain, extra weight, blood glucose and depression were the most commonly discussed issues among the participants.

### 3.5. Discussion

The purpose of this study was to investigate the predictors of fatigue in people with type 2 diabetes. Our primary findings from the quantitative data revealed that sleep quality, BMI and pain were the strongest explanatory factors for fatigue. Overall fatigue among individuals with type 2 diabetes in this study as measured with MFI-20 was similar to previously reported fatigue scores in women with type 2 diabetes (13.29 ±7.35 vs. 12.4 ±7.9) (Fritschi et al., 2012).

Findings from the present study support the previous studies exploring the relationship of fatigue with sleep quality, pain and BMI in people with diabetes. The significant relationship of fatigue with pain was similar to previously reported findings. Reijkan et. al reported similar pain scores in people with diabetes (2.87±2.48 vs.2.64±2.37) and also supported the relationship of fatigue with pain (with a spearman rank relationship of .63; general fatigue with pain, $p = 0.000$) (Rijken et al., 1998). High BMI was also identified as a contributing factor to fatigue in two other studies investigating the relationship of fatigue and cognition with other diabetes related variables in people with type 2 diabetes (Lasselin et al., 2012b) cog). Furthermore, diabetes is considered as one of the strongest risk factor of Excessive day time sleepiness (EDS), besides depression (Bixler et al., 2005) . EDS often results from poor sleep quality. Poor sleep quality has also been previously related to fatigue in people with diabetes, n=39 (r=.58; $p$ <.01) (Cuellar

& Ratcliffe, 2008), which further supports the findings of the present study. The present study also reported a strong relation of fatigue with poor sleep quality (r=.613; $p$ = 0.00).

The primary findings of the qualitative analysis revealed poor sleep quality, extra weight, pain, high/low blood glucose and depression as the contributing factors to fatigue. There has not yet been enough evidence exploring fatigue by using qualitative research methods in diabetes population. The present study is the first one, exploring fatigue by using qualitative research methods. Findings like poor sleep quality, pain, depression and extra weight as contributing factors to fatigue are in agreement with other studies exploring fatigue in cancer patients (Borneman et al., 2012; Siegel et al., 2012; Wilmoth et al., 2004; Wu et al., 2010).

The factors supported by approaches i.e. quantitative and qualitative analysis included poor sleep quality, pain and BMI as the contributing factors to fatigue. In addition to these factors qualitative analysis also supported other factors which included depression and high/low blood glucose concentrations. Poor sleep quality, pain and BMI were the only factors supported by quantitative analysis.

Poor sleep quality can adversely affect the glucose control in people with diabetes (Knutson et al., 2006). There also has been a strong relationship between poor sleep quality and Diabetes Care Profile scales, depicting the negative impact of poor sleep quality on diabetes self-management in people with type 2 diabetes (Chasens et al., 2013). Poor sleep quality can result in fatigue in people with diabetes which can further affect their motivation to effectively manage their chronic condition. Poor sleep quality has been identified as a contributing factor to fatigue by our quantitative and qualitative analysis. Qualitative analysis further revealed issues of ‘excessive napping during day’, ‘insomnia’ and ‘sleep apnea’. There is still an uncertainty as to

what causes poor sleep quality. Therefore future studies should be done incorporating more vigorous methods to test sleep quality which can include testing sleep quality in a sleep lab or sleep clinic.

Pain was also identified as a contributing factor to fatigue by both quantitative and qualitative analysis. Resulting from pain, there can be a decline in the amount of physical activities performed by those with diabetes (Kanade et al., 2006). People may avoid exercise programs which require treadmill running or walking, or may avoid physical activity altogether due to the apprehension of getting foot ulcers or wounds (Lemaster et al., 2008). This can result in high blood glucose and can cause fatigue (Ribu & Wahl, 2004). Fatigue and tiredness can further contribute to weakness and decreased muscle strength in individuals with DN. Our qualitative analysis further supports the findings of quantitative analysis identifying pain as a contributing factor to fatigue. Interview participants strongly expressed the pain resulting from 'neuropathy' and how pain has affected the 'ability to walk' and 'sleep'. Pain was assessed quantitatively by a generic scale (VAS), which does not provide information on areas of pain, duration of pain, type of pain or reasons for pain. Therefore, other measures of assessing pain levels, like, Brief Pain Inventory (BPI), BPI for patients with painful diabetic peripheral neuropathy (BPI-DPN), should be used which can provide more information about the areas of pain, duration and type of pain.

High BMI has been directly linked to the occurrence of type 2 diabetes and has also been positively associated with fatigue scores of MFI-20 in type 2 diabetic patients(Lasselin et al., 2012a). Our quantitative and qualitative analysis further supports this by identifying high BMI as a contributing factor to fatigue. Interview participants further emphasize the extra weight as a

contributing factor to fatigue by describing extra weight as ‘carrying around another person’. Participants described how weight has affected their ‘ability to walk’. Obesity is a major risk factor for developing type 2 diabetes; however, BMI does not provide exact body composition. Abdominal fat plays a very crucial role in diabetes, as accumulation of abdominal fat may contribute to insulin resistance (Unger et al., 2010).Therefore other measures of assessing body composition like dual energy x-ray absorptiometry (DEXA) or bod pod can be used to examine the role of body fat percentage in contributing to fatigue.

Differences were observed when the qualitative and quantitative samples were compared. Overall, fatigue was a significant problem in the sample; however, when explored further by using qualitative interviews, it was found that the fatigue scores were significantly higher in the qualitative sample as compared to quantitative sample (table 3.6). Scores of other outcome variables were also significantly higher in the qualitative sample as compared to quantitative sample which included sleep quality and depression. Furthermore, BMI, pain and NOC were also relatively high in the qualitative sample but did not reach a significant level. The other surprising difference was noted while comparing the depression scores of quantitative and qualitative samples. The regression analysis did not reveal depression as a predictor of fatigue, however, when the scores of BDI-2 were compared between the qualitative and quant sample, it was noted that the qualitative sample’s scores were significantly high as compared to the quant sample (9.71 vs 18.50) with a *p* value of .004. A score of 18.50 falls in the ‘mild depression’ category. Since we used a purposeful sampling approach for our subsample for qualitative research, we were able to capture these differences in the outcome variables between two samples (quantitative and qualitative), which would not have been otherwise noticed if we had followed

quantitative method or qualitative method alone. If only quantitative method was used it would have shown that there are no issues of depression in this population. However, after using the mixed method approach we can now say that depression can be a concern in this population. Furthermore, comparison was performed between the sample (n=28) who answered “yes” to the question of fatigue, but were not interviewed and the sample who was interviewed (n=10) (table 3.7). There was no significant difference observed between the two samples, suggesting that the qualitative findings can be generalized to all who would say “yes” to the specific question of fatigue.

Depression was identified as a contributing factor to fatigue by the interview participants. A second regression analysis model testing the predictors of poor sleep quality in people with type 2 diabetes revealed depression as the strongest explanatory factor for sleep, accounting for 48% of variance in sleep quality. Moreover, epidemiological studies have confirmed poor sleep quality in 50-90% of patients diagnosed with depression (Casper et al., 1985; Riemann et al., 2001). Depression is also considered to be one of the most frequent and prominent causes of insomnia (Vollrath et al., 1989). Therefore, our results also support the contribution of depression to poor sleep quality among individuals with type 2 diabetes.

Although an association was expected between fatigue and blood glucose (as measured by HbA1c), none was found. These findings are consistent with other studies in which only minor (Warren et al., 2003),(Van der Does et al., 1996) or no (Bulpitt et al., 1998) relationships were found. HbA1c tests the average blood glucose for the last 3 month period. Since the test gives an average of blood glucose, the fluctuations between high and low blood glucose are not captured by the HbA1c test. Fatigue can result from these blood glucose fluctuations or from

high/low blood glucose events (Bonora, Calcaterra, et al., 2001; Bonora & Muggeo, 2001). However, HbA1c cannot capture blood glucose fluctuations (Chen et al., 1990). Moreover, HbA1c gives the average of glycemic control for the last 3 months, as this is the average life span of a red blood cell (RBC). This delay of detecting blood glucose 3 months later and the lack of capturing blood glucose fluctuations would have resulted in lack of relationship of fatigue with HbA1c. However, when the participants were interviewed most of them (n=8) emphasized on blood glucose levels. They expressed the feeling of fatigue when they have high and also low blood sugars (n=4). Therefore, future studies should be done using other measures of blood glucose like fasting blood glucose (FBG) or continuous glucose monitoring (CGM) (Sachedina et al., 2003) to further explore the relationship of fatigue with blood glucose concentrations. FBG will provide the blood glucose concentration right away. CGM captures blood glucose fluctuations which can result in fatigue. Wearing CGM's for three days can help in capturing glucose variability, which may occur rapidly or over longer periods of time and cannot be detected by clinical tests, such as HbA1c. Accuracy of the CGM system has already been established (Gross et al., 2000) and can help in exploring the relationship of fatigue with glucose fluctuations.

Diabetes duration or years since diagnosis were also not related to fatigue scores. There was a limitation to exploring this variable during qualitative interviews. None of the participants mentioned anything about years since diagnosis. When questions were asked about this factor, most of the participants expressed uncertainty regarding the relationship of fatigue with years since diagnosis. Participants emphasized that it's difficult to tell if fatigue is due to this time period since diagnosis or if it's just a matter of increasing age.

NOC was also not related to fatigue scores. There was a limitation to exploring this variable during qualitative interviews. NOC was also not expressed in the interviews. When further probes were asked about NOC, participants started discussing about the complications they have or do not have. No information was gathered about NOC itself however, this implies that the type or severity of complications is more relevant to the participants than the number of complications. Therefore, type or severity of complications should be considered for future studies, exploring the relationship of fatigue with diabetes related complications.

The results of the regression analysis are based on an exploratory regression model. We used 48 research participants to perform the regression analysis, which gives not enough power to test the large number of variables. A sample size of 80 research participants could have given us a sufficient power to test seven dependent variables used in the study. Future studies can use a large sample size to conduct confirmatory regression analysis

The results of our mixed method study support some aspects of the Portenoy's fatigue model. Physiological factors supported by our analysis include hyper/hypoglycemia (from qualitative interview) sleep disorders, obesity, chronic pain (from qualitative and quantitative), medications (from qualitative). Psychological factors supported by our analysis include depression (from quantitative and qualitative). Since, the results of the study support several aspects of Portenoy's fatigue model; the model is renamed as "diabetes fatigue model". Figure 3.4 shows the results of the present study, supporting components of the diabetes fatigue model. Numbers of complications and duration of diabetes were not supported by the results of the present study. Based on the results of the study it is hard to identify if the physiological

dimension is more significant than the psychological dimension. Quantitative results suggest that physiological factors are the only ones which contribute to fatigue. On the other hand, qualitative results suggest that both physiological and psychological dimensions are important contributors to fatigue. Therefore future studies need to be done incorporating all different factors under physiological and psychological dimensions.

### 3.6. Limitations

There were some limitations to this study. One limitation was the nature of data being collected, which is fatigue. The participants could be biased towards their fatigue levels and could be saying what they think the researcher wants to hear and because of the Hawthorne effect (Homan, 1965 ) an raise questions on validity of the findings. We tried to minimize this matter by clearly explaining the purpose of the study to the participants. The other limitations of the study are the different domains of fatigue which were not tested. Since we only focused on general fatigue, we have not analyzed other domains of fatigue like mental fatigue or physical fatigue. Future analysis should be done exploring the contributing factors to other domains of fatigue (physical fatigue, mental fatigue, reduced activity, and reduced motivation). Rich qualitative data was not obtained when questions were asked regarding years since diagnosis or number of complications, because participants showed uncertainty regarding age and fatigue. Similarly, participants were not sure if increase in fatigue is because of the age factor or because of complications from diabetes.

The other limitation of the study was lack of control group. The use of a control group using age/sex/BMI matched people without diabetes could have helped us in identifying the diabetes measures which can influence fatigue in people with diabetes. Future studies should

include a control group to help provide a better understanding of diabetes measures influencing fatigue in this population.

We were not able to test all different factors of physiological dimension of the fatigue model (figure 3.2). We were also not able to test 'medications' quantitatively. However interview participants expressed medications as a contributing factor to fatigue. People who are diabetic often take multiple medications and polypharmacy can also result in a number of complications and side effects, including fatigue. Metformin, which is the most widely used insulin sensitizer, can result in side effects including GI disturbances and elevated homocysteine levels (an amino acid) (Hermann, 1979). Elevated levels of homocysteine levels can result in chronic fatigue (Khurana & Malik, 2010). We were also not able to test other dimensions of adapted diabetes fatigue model which included immobility and lack of exercise. Low levels of physical activity have been strongly associated with fatigue in people with type 2 diabetes (Thomas et al., 2004). Common barriers to physical activity include obesity (Stewart et al., 1994) and fatigue complaints (Hume et al., 2010). Therefore future studies should be done addressing the medications, immobility and lack of exercise dimension of Portenoy's fatigue model. It was not in the scope of the study to test 'Systemic disorders' and 'Anxiety disorder' from the fatigue model.

### 3.7. Conclusion and Implications of the study

Fatigue is common in individuals with type 2 diabetes and is likely affected by a combination of physiological and psychological phenomena, especially the presence of poor sleep quality, pain, and high BMI and depressive symptoms. Fatigue in this population is similar in magnitude to chronically ill populations (Lin et al., 2009). Poor sleep quality, high BMI, pain, depression and high/low blood glucose were all significant predictors of fatigue, quantitatively

and qualitatively. Even so, a large portion of the variance in diabetes related to fatigue remains unexplained. Future studies could use a large sample size testing all the factors in the modified Portenoy's fatigue model.

The results of the present study support the need for inclusion of symptom assessment in diabetes education. Clinicians should use complaints of fatigue as a starting point for further evaluation of comorbid conditions, including sleep problems and psychological illness like depression. In conclusion, results from the present study suggest that interventions strategies should be developed to reduce the burden of fatigue in individuals with type 2 diabetes. Intervention should focus on addressing healthy sleep habits, weight management, depression screening, and self-management education in regards to high/low blood glucose and pain management. As this may be an important area for diabetes management, further research is warranted to examine fatigue.

### 3.8. Tables

Table 3.1. Interview guide

| |
|---|
| • What does it feels like to be fatigued? |
| • Some people describe fatigue as being “knocked out”, how will you describe it? |
| • What do you think are the causes of your fatigue? |
| • What makes it better/worse? |
| • Can you give me some of your worst experiences you have dealt with your tiredness? |
| • I am going to list problems that affect some individuals with diabetes. Based on your experience you can describe the impact of |
| ○ Extra weight - on your tiredness |
| ○ Depression - on your tiredness |
| ○ Sleep problems - on your tiredness |
| ○ High blood sugar - on your tiredness |
| ○ Pain – on your tiredness |
| • As you know there are so many other problems or complications associated with diabetes like problems with kidneys, eyes, pain in feet, do you think this number of complications can contribute to your fatigue |
| • It’s been ….years since you were diagnosed with your diabetes, do you think this period of time that since your diabetes was diagnosed and till now. This period has some relationship with severity of your fatigue |
| **Probes:** |
| • What it feels like to be fatigued? |

| |
|---|
| ○ Probe : Describe the feeling, how does it feels to you |
| • Some people describe fatigue as being “knocked out”, how will you describe it |
| ○ Probe : if you have to describe it in one word – how will you describe it |
| • What do you think are the causes of your fatigue |
| ○ Probe : why does it happens |

Table3.2: Demographics, mean and standard deviation (SD) of outcome variables and results of Pearson correlation analysis of general fatigue (MFI-20) with other outcome variables which include: BMI, HbA1c, sleep quality (PSQI), pain (VAS), NOC, and years since diagnosis, and depression (BDI-2).

| | Mean (SD)<br>n = 48 | Pearson-correlation (r) | *p*-value |
|---|---|---|---|
| Age | 59.66 (7.24) | ---------- | ---------- |
| Sex | 22 females, 26 males | ---------- | ---------- |
| General Fatigue (MFI-20) | 13.29 (7.35) | ---------- | ---------- |
| HbA1C | 7.38 (1.85) | -.218 | .140 |
| BMI | 35.28 (7.35) | .350 | .015* |
| Sleep quality (PSQI) | 8.12 (3.64) | .613 | .000** |
| Pain (VAS) | 2.64 (2.37) | .437 | .002** |
| NOC | 3.91 (2.11) | .199 | .176 |
| Years since diagnosis | 10.45 (7.38) | -.125 | .399 |
| Depression (BDI-2) | 11.54 (8.75) | .422 | .003** |

*significance at $p \leq .05$, ** significance at $p \leq .01$

Table 3.3 Results of forward stepwise multiple regression analysis using General fatigue as dependent variable.

| Predictors | Unstandardized Coefficients B | Standardized Coefficients β | *p*-value of t-test | $R^2$ | Correlations | | VIF |
|---|---|---|---|---|---|---|---|
| | | | | | Partial | Part | |
| PSQI | .563 | .552 | .000 | .375 | .632 | .534 | 1.070 |
| PSQI, BMI | .170 | .337 | .001 | .507 | .456 | .335 | 1.011 |
| PSQI,BMI, VAS | .416 | .266 | .013 | .573 | .365 | .256 | 1.079 |
| BDI-2 | -.017 | -.039 | .753 | | -.048 | -.032 | 1.567 |

Estimated standardized regression coefficients (β) and variance explained ($R^2$) are presented.

Table 3.4 Results of forward stepwise multiple regression analysis using poor sleep quality (PSQI) as dependent variable.

| Predictors | Unstandardized Coefficients B | Standardized Coefficients β | *p*- value of t test | $R^2$ | Correlations | | VIF |
|---|---|---|---|---|---|---|---|
| | | | | | Part | Partial | |
| BDI-2 | .201 | .483 | .001 | .483 | .445 | .431 | 1.256 |
| BMI | -.061 | -.124 | .357 | | -.139 | -.121 | 1.043 |
| VAS | .094 | .061 | .673 | | .064 | .055 | 1.215 |

Table 3.5 Demographics of the subsample of participants participated in the interviews.

| | Mean (SD) (n=10) |
|---|---|
| Age | 57.1 (7.59) |
| Sex | 6 females, 4 males |
| Years with Diabetes | 9.50 (6.04) |
| HbA1c | 7.20 (1.85) |
| BMI | 36.86 (7.34) |
| Employment status | 6 employed; 4 unemployed |

Table 3.6 Comparison of descriptive statistics of the outcome variables from two samples.

| | Quantitative sample (n = 38) Mean (SD) | Qualitative Sample (n = 10) Mean (SD) | Independent sample t-test *p* - value |
|---|---|---|---|
| General Fatigue (MFI-20) | 12.60 (3.69) | 15.90 (2.51) | .011* |
| BMI | 34.87 (7.39) | 36.86 (7.34) | .451 |
| HbA1C | 7.43 (1.87) | 7.20 (1.85) | .723 |
| VAS | 2.49 (2.40) | 3.23 (2.27) | .391 |
| PSQI | 7.15 (3.24) | 11.80 (2.65) | .000* |
| NOC | 3.73 (2.28) | 4.60 (1.07) | .254 |
| Years since diagnosis | 10.71(7.74) | 9.50 (6.04) | .649 |
| BDI-2 | 9.71(7.66) | 18.50 (9.51) | .004* |

* Significant at $p \leq 0.05$ level

Table 3.7 Comparison of descriptives of the outcome variables in two samples: qualitative sample (n=10) and sample who said "yes" to the question of fatigue (n=28).

| | Sample (n=28) Mean (SD) | Qualitative Sample (n=10) Mean (SD) | Independent sample t test *p*- value |
|---|---|---|---|
| Age | 60.67(7.28) | 57.10 (7.59) | .208 |
| General Fatigue (MFI-20) | 13.92 (3.01) | 15.90(2.51) | .118 |
| BMI | 35.59 (7.34) | 36.86 (7.34) | .986 |
| HbA1C | 7.33 (1.76) | 7.20 (1.85) | .910 |
| VAS | 2.79 (2.37) | 3.23 (2.27) | .390 |
| PSQI | 7.75(3.18) | 11.80(2.65) | .065 |
| NOC | 3.67(2.12) | 4.60(1.07) | .215 |
| Years since diagnosis | 11.60(7.97) | 9.50 (6.04) | .733 |
| BDI-2 | 9.89 (7.80) | 18.50(9.51) | .065 |

* Significant at $p \leq 0.05$ level

### 3.9. Figures

Figure 3.1: Illustration of Portenoy's fatigue model

Figure 3.2: Illustration of Portenoy's fatigue model applicable to patients with diabetes.

Figure 3.3: Depicting contributing factors to fatigue and poor sleep quality

Figure 3.4: Illustration of results supporting Diabetes fatigue model applicable to patients with diabetes – reflecting the results. The factors highlighted in green are the factors supported by our analysis. Factors highlighted in green and bolded are supported by both quantitative and qualitative analysis. Factors like: medications, nutritional status, sleep apnea, immobility/lack of exercise, anxiety disorders, should be investigated for future study.

Figure 3.1: Illustration of Portenoy's fatigue model:

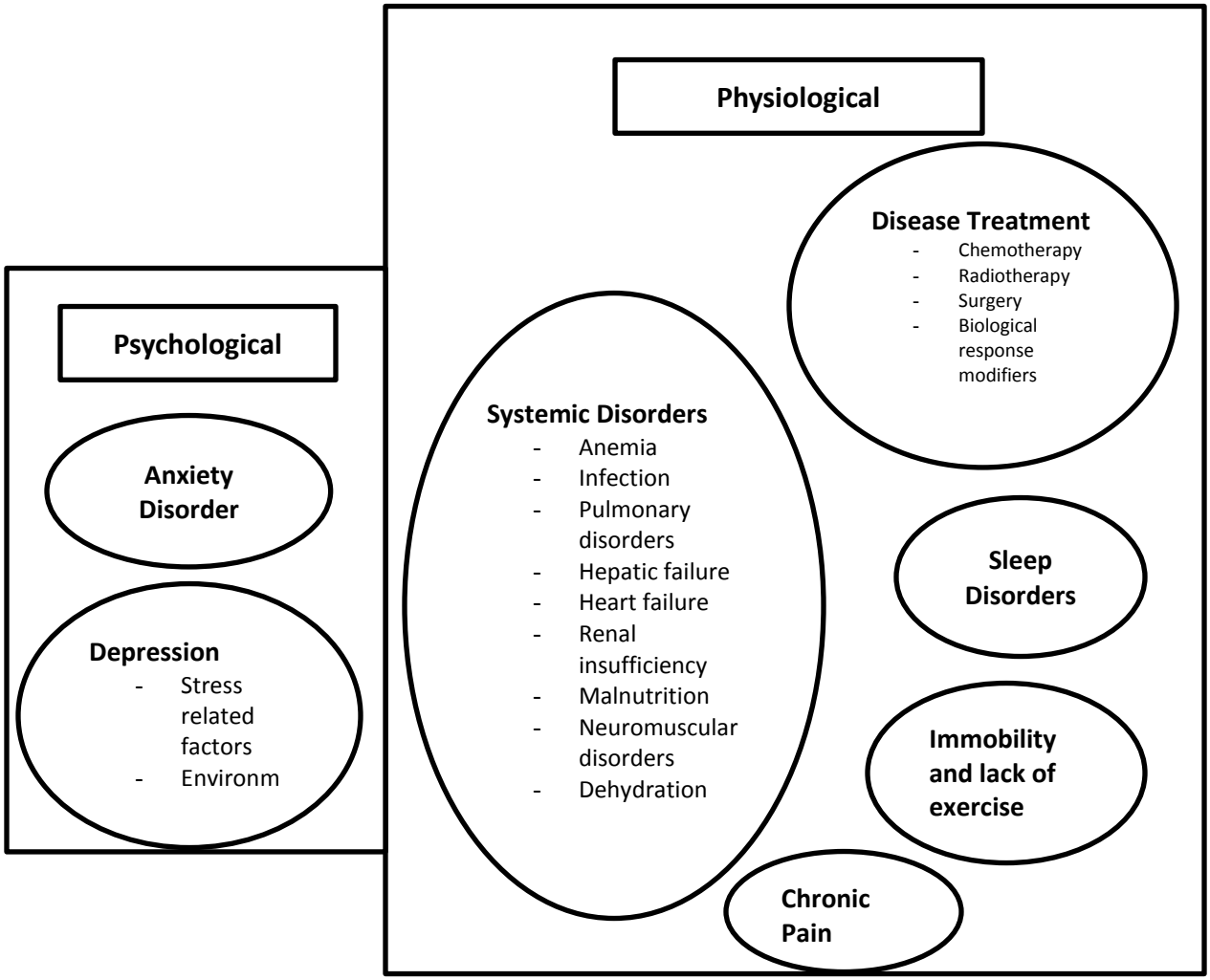
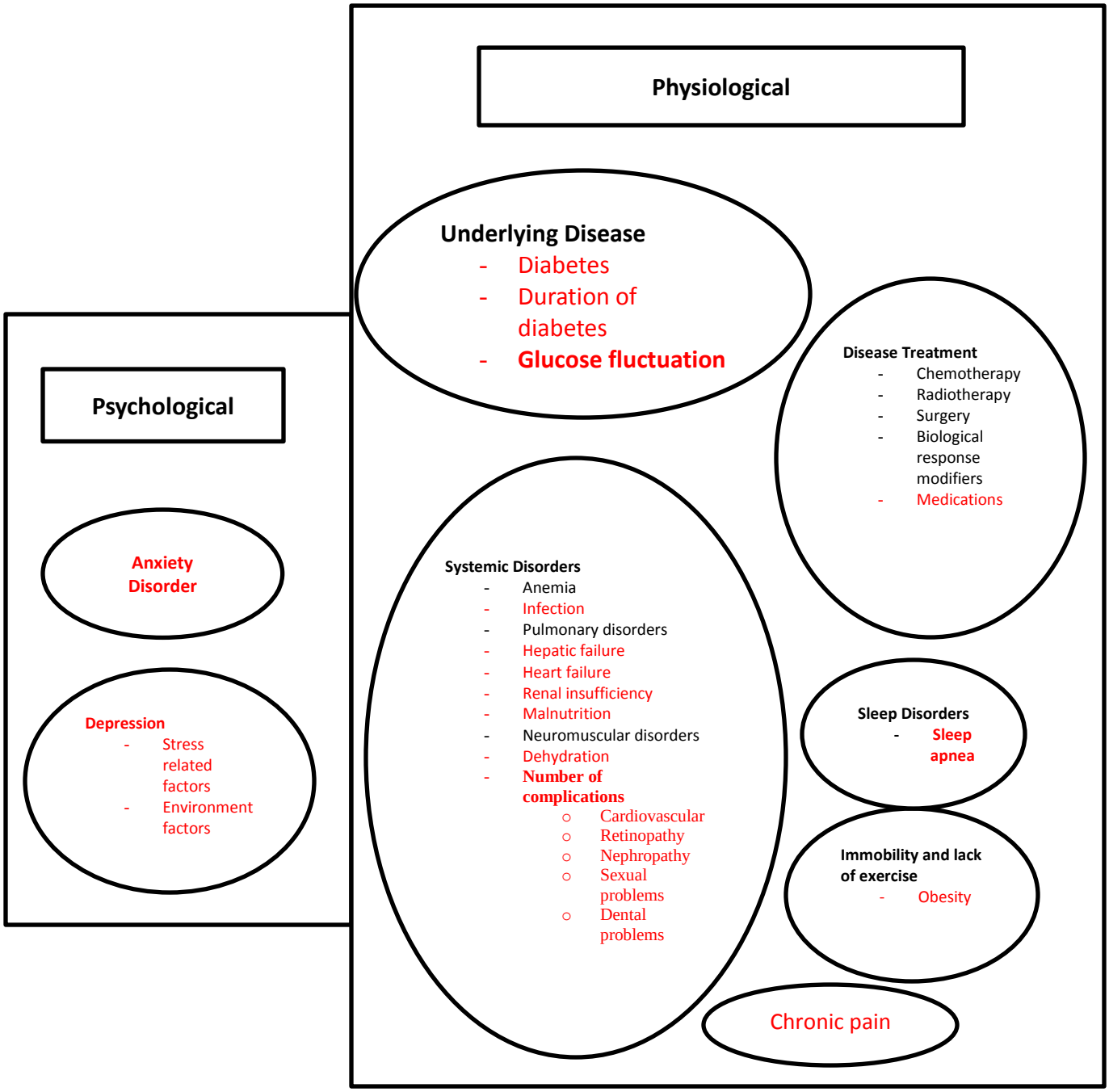


Figure 3.2: Illustration of Portenoy's fatigue model applicable to patients with diabetes:




The contributing factors highlighted in red are the factors applicable to patients with diabetes.

Figure 3.3: Depicting contributing factors to fatigue and poor sleep quality

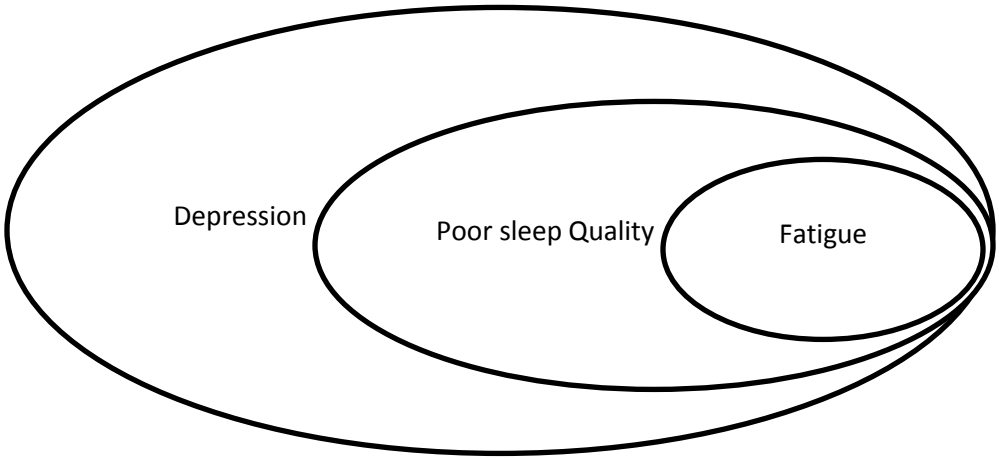
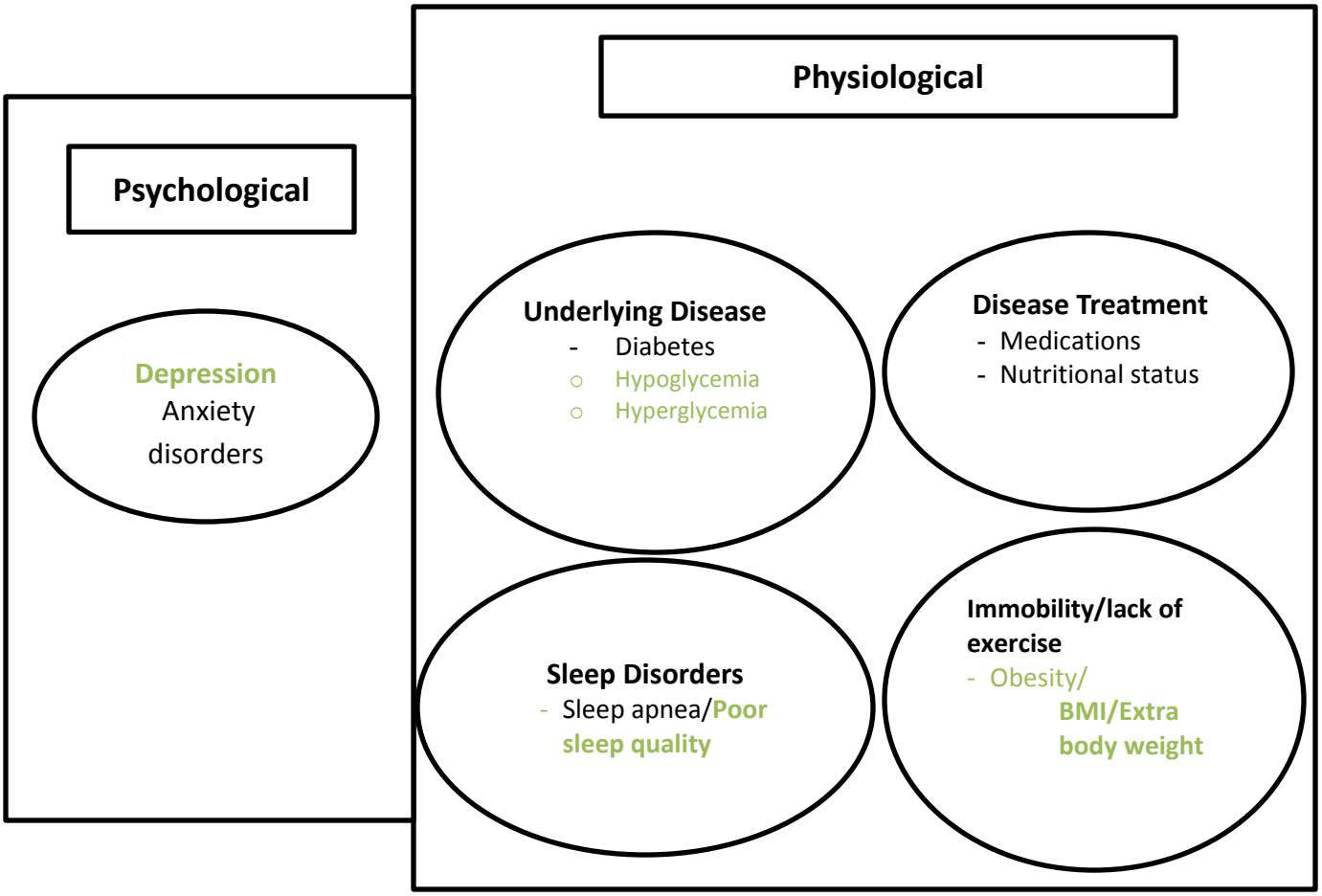


Figure 3.4: Illustration of results supporting Diabetes fatigue model applicable to patients with diabetes:




The factors highlighted in green are the factors supported by our analysis. Factors like: medications, nutritional status, sleep apnea, immobility/lack of exercise, and anxiety disorders should be investigated for future study.

# Chapter 4

## Preface

Chapter 2 and chapter 3 described the presence and contributing factors to fatigue. Since fatigue is a common complaint among these individuals, Chapter 4 sought to address the negative impact of fatigue. Aim of chapter 4 is to describe the negative impact of fatigue on quality of life and functional status of these individuals through a mixed methods approach.

# Chapter 4

## Impact of fatigue on quality of life and functional status in people with type 2 diabetes: A mixed methods study

This work will be submitted for publication to *Physical Therapy*.

## 4.1. Abstract:

Background and Objectives: Fatigue is a common complaint in people with type 2 diabetes. Fatigue can also severely affect quality of life (QoL) and function of these individuals. The purpose of this study was to use a mixed method approach to evaluate the impact of fatigue on QoL and functional status in individuals with type 2 diabetes.

Participants: Forty eight individuals with type 2 diabetes (22 females, 26 males), with a mean age of 59 years (SD=7.24) participated in the study.

Methods: Fatigue was assessed by using the Multidimensional fatigue inventory (MFI-20). QoL was assessed by using Audit of Diabetes Dependent QoL (ADDQoL) survey. Functional status was evaluated by measuring the distance covered during a 6 minute walk test (6MWT). Pearson correlation coefficient was performed to assess the relationship of fatigue (MFI-20), QoL (ADDQoL), and functional status (6MWT). Our qualitative research was based on a sub sample of 10 participants who were interviewed to understand the impact of fatigue on QoL and functional status. We used qualitative content analysis to analyze the interviews.

Results: Fatigue was negatively related to ADDQoL ($r = -.445$; $p = 0.002$) and functional status ($r = -.386$; $p = 0.007$). The qualitative data provided further insight into the compromised QoL and functional status. One theme (struggles with fatigue) was identified with five categories: impact of fatigue on normal day, impact of fatigue on housework, impact of fatigue on relationships, and impact of fatigue on employment.

Conclusion: Fatigue can affect QoL and functional status in individuals with type 2 diabetes. Therefore, there is a need to further investigate the complex phenomenon of fatigue so that intervention strategies can be developed to reduce the burden of fatigue.

## 4.2. Introduction

Fatigue is a continuous and distressing complaint among people with type 2 diabetes. Since fatigue is such a complex phenomenon it is very difficult to define. In general, fatigue can be defined as a complex phenomenon involving physiological, psychological and situational components (Aaronson et al., 1999; Aistars, 1987; Magnusson et al., 1999; Ream & Richardson, 1996; Rose et al., 1998; Trendall, 2000). Fatigue can result from various episodes of hyperglycemia or hypoglycemia or the fluctuations between those extremes (Morsch et al., 2006; Weijman et al., 2004). Numerous complications of diabetes and the comorbidities associated with these complications such as sleep problems (Resnick et al., 2003) or chronic pain(Rijken et al., 1998) can also add to the burden of fatigue. Moreover, depression (R. J. Anderson et al., 2001) or stress resulting from the diagnosis or from the vigorous management of diabetes can also result in fatigue (Egede & Zheng, 2003; Katon et al., 2004; Ryerson et al., 2003). All these factors can then eventually contribute to compromised QoL. There is ample evidence in the literature stating the negative impact of hyper/hypoglycemia(Testa et al., 1998), number of complications (R. M. Anderson et al., 1997; G. C. Brown et al., 2000; Glasgow et al., 1997; Wandell et al., 1997) and depression (Goldney et al., 2004) on QoL of individuals with type 2 diabetes.

The presence of fatigue can also undermine the daily functional activities of a person. Decline in functional capacity due to fatigue has been seen in patients with other chronic disorders like cancer and Parkinson's Disease, as evidenced by significant decreases in distance covered during 6 minute walk test (6MWT) (Coleman et al., 2011; Garber & Friedman, 2003; van Weert et al., 2006). Fatigue related to cancer or Parkinson's disease may result in

physiological deconditioning which further leads to decreased functional status. It appears that fatigue may have a similar impact on the functional capacity of individuals with diabetes. This decline in functional capacity can be explained by several factors like low cardiorespiratory fitness (Wei et al., 2000), low physical activity levels (Morrato et al., 2007) and high body mass index (BMI) in people with type 2 diabetes. Individuals with diabetes covered less distance during a 6MWT as compared to age and sex matched controls (Ingle et al., 2006). This decline in functional status can be due to the presence of fatigue, which has not yet been investigated.

Additionally, individuals with type 2 diabetes are encouraged to engage in physical activities for self-management of their disease(Mensing et al., 2006). However, these individuals have a tendency to avoid physical activities (Morrato et al., 2007). This apprehension towards exercise may be due to the presence of fatigue. Thus, fatigue can take a toll on the self-management procedures which should be continuously maintained in diabetes. Lack of participation in exercise programs may result in a decline in functional status. This decline in functional status can result in low cardio-respiratory fitness which itself is an independent predictor of mortality (Telford, 2007).

Since fatigue is such a complex phenomenon, the impact of fatigue on QoL and functional status is well suited for investigation by a mixed method design using quantitative and qualitative methods. Quantitative methods helped us examine the relationship of fatigue with measures of QoL and functional status. Qualitative methods on the other hand helped us in understanding the context of the fatigue experience, as voices of the participants were directly heard through interviews. Therefore, the purpose of this study was to investigate the relationship of fatigue with QoL and functional status in individuals with type 2 diabetes by using a mixed

method design. Our hypothesis was that fatigue will be negatively related to QoL and functional status in individuals with type 2 diabetes.

## 4.3. Methods

*Design*

A convergent (parallel or concurrent) design (Clark, 2011; Morse, 2009; Ostlund et al., 2011) was used. A convergent design is intended to merge concurrent quantitative and qualitative data to address the aims of the study, so that the data can be merged and compared. Quantitative data was collected first, immediately followed by qualitative interviews (on the same testing day). Quantitative and qualitative data were analyzed separately, and then converged during interpretation. Quantitative methods are described first followed by description of qualitative methods.

Participants were recruited from a research participant registry at the University of Kansas Medical Center where the study was conducted. The study was approved by the University of Kansas Medical Center's Human Subjects Committee. Participants who were eligible for the study signed an institutionally-approved informed consent form.

*Participants*

Individuals between 40-70 years with a confirmed diagnosis of type 2 diabetes were included. Individuals were excluded if they 1) had a known history of stroke, cancer or other central nervous system pathology which may cause additional burden of fatigue besides diabetes, 2) inability to ambulate, or 3) amputation.

*Quantitative data collection procedure*

Qualitative interviews immediately followed the quantitative testing, for those participants who qualified and who agreed to participate in the interviews.

*Outcome variables*

Fatigue: Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20). It consists of five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity (Smets et al., 1995). For the purpose of this study "general fatigue" was used as a composite measure of overall subjective fatigue experience, and it also fits with the definition of fatigue used to guide the study. Each of the 5 scales contains 4 items. The respondent has to compare each of the 20 statements with how he or she felt lately. Each item is scored from 1-5, from agreement with the accompanying statement "yes, that is true" to disagreement "no, that is not true". A higher score indicates more fatigue. For each scale a total score is calculated by summation of the scores of the individual items. Total scores can range from the minimum of 4 to the maximum of 20. MFI-20 appears to have good reliability and validity measures, with Cronbach's Alpha=of 0.890 in women with type 2 diabetes (n=83) (Fritschi et al., 2012) . The MFI-20 also has strong concurrent validity, as the general fatigue dimension of MFI-20 has shown to have significant correlations with Fatigue Inertia subscale of the Profile of Mood States (r =0.774) (Fritschi et al., 2012).

Quality of Life (QoL): QoL was assessed using audit of diabetes-dependent quality of life (ADDQoL). The ADDQoL is a widely used health status questionnaire comprised of 19 items. The ADDQoL aims to measure individual's feelings about the impact of diabetes such as work,

family, food and sex. It also tests whether the impact of diabetes on different life domains is positive or negative and what is the perceived importance of each of these domains on their QoL. Participants could provide both impact (range -3 to +3) and importance (range 0-3) scores. These two scores were multiplied to get a weighted impact score for each applicable domain (range -9to +9). An average weighted impact (AWI) score was then taken by adding the weighted impact scores for each domain and dividing by the number of applicable domains. The lower scores indicate a greater negative impact of diabetes and positive scores indicate positive impact of diabetes on QoL. The ADDQoL has been shown to have good reliability with a Cronbach's Alpha = 0.85-0.94 and results of factor analysis has shown strong validity(Bradley et al., 2002; Bradley et al., 1999; Kong et al., 2011; Soon et al., 2010; Watkins et al., 2004).

Functional Status: Functional status was evaluated by the 6 minute walk test (6MWT). 6MWT is a well-known instrument for assessing functional capacity of a variety of groups, and is a predictor for morbidity and mortality. It evaluates the global and combined responses of all the systems involved during walking (Laboratories, 2002). 6MWT has high reliability and validity scores (Hamilton et al., 2000). 6MWT is a safe and inexpensive tool that uses an exercise mode to everyday activities. Since it is self-paced and submaximal in nature, it is a good measure of functional status. The test was conducted along a straight corridor (18 cm long) with a hard surface and standardized instructions were followed.

*Data Analysis*

Descriptive statistics (mean, standard deviation, median, and range) of the measures (MFI-20, AAQoL, 6MWT) were calculated. Assumptions of normality and equality of variances were met. SPSS version 20 was used to perform Pearson product-moment correlation coefficient

to determine the relationship of fatigue (general fatigue –MFI-20) with QoL (ADDQoL) and functional status (6MWT).

*Qualitative data collection procedure*

*Participants*

A subset of participants from the quantitative study was selected for qualitative interviews, using a purposeful sampling approach. We included those participants who answered "YES" to the following question - Are you tired or fatigued all the time, tiredness which is not relieved by rest? In addition, to rule out impaired cognition, MMSE was performed to ensure that the participants would be suitable for the interview process and would have no difficulty in answering questions for the interview process. Participants were excluded if they answered "NO", to the above question, or if their score was below 23 on MMSE. Out of 48 participants, 38 met the inclusion criteria. However, based on the participant's and the researcher's availability to spend another hour for the interview, 10 participants were interviewed. Data was collected until data saturation was achieved. Data saturation refers to the point at which no additional data is being found whereby the researcher can develop properties of the category (Glaser, 1967).

*Interviews*

The interviews were held in a private room and were audio-taped. Interviews lasted for 30-45 minutes. We used the semi-structured interview guide (Table 4.1) and a descriptive qualitative approach was followed to describe the impact of fatigue in everyday language (Sandelowski, 2000). In-depth interviews were conducted and additional questions were posed as needed. The interview guide was based on issues identified in the literature and by expert

opinion (Wu et al., 2010). The interview guide was then tested with role play (with an expert in qualitative methods) and field tested with one individual who fit some criteria for the study. Modifications to the interview guide were done after the role play and field testing.

*Data Analysis*

Data was analyzed by using comprehensive content analysis techniques. For this process, the audiotape recordings from each of the interview sessions were transcribed, and transcripts were compared to the original tapes for accuracy of language and notations. The analysis of the interview text was conducted in a stepwise method. First, the interviews were read through several times to get a sense of the whole picture. Meaning units were then identified from the interviews, and meaning units were then condensed and coded manually and by using qualitative data management software (NVivo 9). Some examples of codes were, 'less energetic' and 'affects verbal communication'. Preliminary subcategories were identified based on similarities and differences in the codes. Examples of preliminary subcategories were, 'effects of fatigue' and 'work'. The analysis was continued by going back and forth between the interview text and preliminary categories to refine and validate the content, resulting in four categories. This classification refers to the manifest analysis on a descriptive level (Downe-Wamboldt, 1992). To understand the underlying meaning of the content, a latent analysis was conducted and a theme was formed. Themes are threads of underlying meaning which are gained from condensed meaning units, codes and categories (Graneheim & Lundman, 2004).

*Trustworthiness (mechanism to establish scientific rigor)*

Our study verified the issues of trustworthiness by following Lincoln and Guba's guidelines to establish credibility, transferability, dependability, and confirmability (Lincoln, 1985).

*Credibility* (internal validity): To enhance credibility for our study, member check strategy was used. Member checking refers to revealing the research materials to the participants to ensure that the researcher has accurately translated the participants' viewpoints into data (Lincoln, 1985). As a part of member check strategy, summary of evolving description of impact of fatigue was send to all interview participants asking for the areas of disagreement. All participants agreed to description of impact of fatigue and no suggestions were made. Triangulation was achieved by collecting data from the interviews as well as data from quantitative analysis. Transcribed interviews were also sent to other researchers having qualitative research background. Discussions were held regarding the emerging codes and categories until an agreement was reached. To test the validity of our findings we established referential adequacy. Referential adequacy refers to identifying a portion of data to be stored, but not analyzed. The researcher then analyzes the remaining data and develops preliminary findings. The researcher then returns to the stored data and analyzes it as a way to test validity of his/her findings (Lincoln, 1985) . To achieve referential adequacy, codes and themes were developed first, and to further justify the themes, observations were added later. This helped in enhancing the validity of the themes.

*Transferability* (external validity):

Transferability was established by including a wide range of participants (Table 4.3) who answered "YES" to the following question – Are you tired or fatigued all the time, tiredness which is not relieved by rest? The results of the study can be applied to the general population by including a wide range of participants experiencing different levels of fatigue. The detailed description of the subset is provided in table 4.3.

*Dependability* (reliability): To support dependability we composed our audit trail which included our transcripts and demographic data of the participants. External auditing was done by sending the transcribed interviews to other researchers with qualitative research background.

*Confirmability* (objectivity): Audit trail and theme formation through discussion served this concept. Confirmability was further enhanced by reducing the researcher's bias toward certain beliefs, using open-ended questions with neutral wordings for the interview guide. For example, the researcher had strong beliefs that participants having high BMI will identify more challenges towards completing their housework. Therefore, no direct questions related to their BMI and housework was asked.

## 4.4. Results

*Quantitative Results*

*Demographics*

Fifty participants participated in the study. Data from 48 participants is presented. We had to exclude data from two participants because of two outliers in BMI, which were skewing

the data. Participant characteristics are provided in Table 4.2. The mean age of the sample was 59.66 years, with 22 females and 26 males.

Fatigue: Overall, the participant's (n=48) mean fatigue score in "general fatigue" dimension was 13.26 (SD = 3.71).

QoL: The participants (n=48) mean average weighted impact score (AWI) was -2.19 (SD 1.65). Fig 4.1 shows the impact of diabetes on different life domains as measured by ADDQoL. The negative impact of diabetes was greater on the following domains: Dependence, Motivation and Financial situation.

6 MWT: The mean distance walked by the participants (n=48) during the 6MWT was 361.06 m (SD 73.43).

Relationship: There was a significant inverse relationship between general fatigue (MFI-20) and QoL (AWI scores of ADDQoL) (r=-.445; $p$=0.002) and general fatigue (MFI-20) and functional status on 6MWT (r=-.386; $p$=0.007).

Secondary analysis: Independent t test was performed to test for a difference between sexes and there was no difference in fatigue scores between males and females.

*Qualitative Results*

*Demographics*

Six females and 4 males (aged 44 - 66 years) consented and participated in the qualitative section of the study. Participant characteristics are provided in table 4.3.

Comparison of two samples: quantitative and qualitative sample

Differences were observed when quantitative and qualitative sample was further compared (table 4.4.). The scores on all outcome variables (MFI-20, ADDQoL, and 6 min walk test) were significantly lower in the qualitative sample as compared to the quantitative sample. Low scores on 6MWT and ADDQoL suggest a greater negative impact of fatigue on QoL and functional status in the qualitative sample. Figure 4.2 shows the comparison of ADDQoL scores of the quantitative and qualitative sample. The negative impact of diabetes was greater on the following domains: Dependence (in qualitative sample) and Freedom to eat (in quantitative sample).

*Qualitative theme and categories*

Fatigue was described as overall tiredness that includes both physical and mental components (e.g. worn out, listless, problems with concentration). Some common characteristics of fatigue sensation, such as tiredness, sleepiness and lack of energy, were experienced by all participants. The detailed description of fatigue described by participants is provided in *Chapter 3*.

***Theme: Struggles with fatigue.***

Fatigue seems to be an always-present feeling that involves the whole human being, and fatigue made it more difficult for the participants to cope with day-to-day activities which involved housework and employment duties. Participants seemed to be aware of fatigue, and they seemed to reconcile with the symptom because they thought it was a consequence of diabetes resulting from hypo/hyperglycemia. Thus, it can be interpreted that fatigue remains unexpressed. However, when explored further, fatigue was found to have negative affect on all participants on

their normal day, housework, relationships, and the participants who were employed had a negative impact of fatigue on employment.

*Category: Impact of fatigue on normal day*

With regard to their activities on a normal day, all participants were less active. They described that they don't do a lot of activity during a normal day due to fatigue. This lack of physical functioning was also supported in fig 4.2, explaining the negative impact of diabetes on QoL. 'Physical functioning' domain is the second most negatively impacted domain of ADDQoL. Participants had difficulty in undertaking everyday activities, causing them to avoid things such as taking a shower or washing their hair, walking and cooking as described by a comment from a participant:

> " I don't walk down the stairs…sometimes it's just having the energy to go take a shower and wash my hair because I haven't washed my hair in two and half weeks, cause I'm just too tired" (Participant No. 3Q).

*Category: Impact of fatigue on housework*

Some participants (n=5) described that because of fatigue they are not able to do their daily house work activities. Some quotes from interviews:

> "I haven't done any housework in over a month" (Participant No. 7Q).

Some participants (n=7) living with their partners/family mentioned that because of their persistent fatigue, most of the housework is done by the partner or other family member. This

dependency on the partners/family members is further supported in fig 1 as the negative impact of diabetes is greatest on 'Dependency' domain of ADDQoL. Some comments from interviews:

> "Well I never do that much anyway. She (daughter) and my wife do everything" (Participant No. 9Q).

Other participants (n=2) described that they keep on delaying their household chores. A comment from one participant:

> "You would always find an excuse not to do it (sweep the garage)" (participant No. 4Q).

For others it takes a tremendous amount (n=5) of effort to do housework activities, like running a dishwasher or doing the laundry. Some quotes from interviews:

> "I have a dishwasher and it's such an effort to run it once a week. I will do it, but if I don't feel like it, I won't" (Participant No. 1Q).

*Category: Impact of fatigue on relationships*

Participants described the negative impact of fatigue on their relationships. Participants perceived fatigue as a limiting factor to spending quality time with their partners/kids, as a comment from an interview:

> "She (daughter) has to literally drag me out. I really don't do anything. She will come in and I will be asleep and then she may come in a little bit later I'll be up and she is like okay, let's go. I say well give me couple hours and within that couple of hours I am back to sleep" (Participant No. 7Q).

One participant emphasized the impact of fatigue on relationships by not being able to take her dog out for a walk. As a comment from interview:

> "I don't walk my dog, because I'm tired" (Participant No. 5Q).

Participants (n=7) described that partners play a very significant role in their lives. Participants living with their partners explained how partners have to always watch out for symptoms of hyper/hypoglycemia. Partners have to be prepared for such episodes, which indicate the issues of 'dependency towards partners'. A comment from one participant:

> "I have got a very diabetic friendly wife. If my blood sugar is low I get really shaky and my wife is aware of it. She would always keep a candy or orange juice or something to give me a shot of sugar to make that go away" (participant No. 2Q).

The negative impact of fatigue on relationships was further explained by two participants whose partners think that he/she (participant) makes excuses for not spending time with them. Some quotes from interview:

> "It kind of upsets my wife…she's going to through her own physical problems, but sometimes she thinks some of it is my convenience" (Participant No. 9Q).

> "Because I'm tired, sometimes I just don't want to deal with people" (Participant No. 7Q).

*Category: Impact of fatigue on employment*

Participants described the negative impact of persistent fatigue on their employment such as needing to take frequent breaks or sometimes having to take a day off from their work to recover from fatigue. Some quotes from interviews:

> "I always have to go to the car during lunch so that I can at least get a little rest" (Participant No. 4Q).

> "A Sunday or a day off makes me feel better where I stay in the bed all day and that gives me energy to make it through the rest of the week" (Participant No. 1Q).

**4.5. Discussion**

The purpose of this study was to investigate the impact of fatigue on QoL and functional status in individuals with type 2 diabetes. Although fatigue is a common complaint in people with type 2 diabetes, the impact of fatigue on these individuals has never been investigated. This study identified the negative impact of fatigue on QoL and functional status through a mixed method approach. Our primary findings from the quantitative data revealed that fatigue has a significant negative relationship with QoL and functional status in people with type 2 diabetes.

The impact of fatigue on QoL and functional status (Goldman et al., 2008) has been investigated in other populations such as cancer (Visser et al., 1998) and multiple sclerosis (Nortvedt et al., 1999). The results of the present study depicting the negative relationship of fatigue with QoL and functional status are in agreement with previous studies. The negative relationship of QoL and fatigue has been previously related to QoL in people with cancer, n=263 (r=.63; $p < .001$) (Redeker et al., 2000). Bowser et. al further reported similar QoL scores in people with depression and diabetes (-2.19 ± 1.65 vs.-2.35 ± 1.69) (Bowser et al., 2009).

Similarly, the impact of fatigue on functional status in individuals with type 2 diabetes also follows the evidence which already exists in literature, in other populations like multiple sclerosis. Goldman et al. reported similar 6MWT scores in people with severe multiple sclerosis (316 ± 73.43 vs. 389 ± 77.7) and also supported the negative association of fatigue with 6MWT (with a spearman rank relationship of .59; $p = 0.001$) (Goldman et al., 2008).

The primary findings of the qualitative analysis revealed struggles with fatigue, impacting normal day to day activities, housework, relationships and employment. There has not yet been enough evidence exploring fatigue by using qualitative research methods in a diabetes population. The present study is the first one, exploring fatigue by using qualitative research methods. Findings like 'struggles with fatigue' are in agreement with other studies exploring fatigue in cancer patients (Gedaly-Duff et al., 2006; Langeveld et al., 2000; Wu et al., 2010).

The result of the qualitative interviews complements and enhances the data gained by the QoL questionnaire and functional status test. The interview participants revealed their struggles with fatigue during their house work and their normal day. These struggles were reflected by the significant inverse relationship of fatigue with 6MWT, suggesting that decline in functional status can result in struggles with housework or normal day activities. Therefore, future studies should be done exploring these relationships between decline in functional status and struggles with housework or normal day activities. Similarly, interview participants also revealed their struggles with fatigue on their employment and on their relationships. These struggles were also reflected by the negative relationship of fatigue with ADDQoL questionnaire. ADDQoL questionnaire also includes domains of 'Working life' and 'close personal relationship'. Future studies should be done exploring these domains further to get a better understanding of negative relationship of fatigue with employment and relationships (identified by interview participants).

The issue of ‘dependence’ was brought up by 7 interview participants while discussing the impact of fatigue on their relationships. Participants described that they are so dependent on their partners when they have a hypoglycemic event or when it comes to housework. Participants further emphasized that because of fatigue they are not able to help their partners with housework which affects their relationships. This issue of dependence is further supported by our quantitative analysis. The negative impact of diabetes was greater on ‘Dependence’ domain in the overall sample (figure 4.1) and also in the qualitative sample (figure 4.2), which further complements and supports the data gained by qualitative interviews. Similarly, ‘physical function’ was the second most affected domain of ADDQoL which was also supported by our qualitative data. Five of our participants mentioned that they do not do any household chores or it takes a tremendous effort for them to do household chores. Participants also described their difficulty in undertaking everyday activities, causing them to avoid things such as taking a shower or washing their hair, walking and cooking. The other domains of ADDQoL were also negatively impacted by diabetes in the qualitative sample (figure 4.2), but were not deeply discussed in the interviews. The reason behind this disconnection can be the participants’ focus of the interviews. ADDQoL captures the impact of diabetes on quality of life and the interviews were focused on the impact of fatigue on quality of life. Interview participants were focused on describing their issues with fatigue on quality of life, therefore more discussions were held on issues of housework, normal day to day activities, relationships and employment.

Diabetes requires extensive management and care, which can result in increased burden from the demands of this disease. The burden may be more complicated by the acute physical distress of hypoglycemia or hyperglycemia and by the distress of diabetes related complications.

The tremendous burdens required from management can sometimes result in inaccurate behavior towards managing diabetes which can affect quality of life of people with diabetes. The results of the present study show a negative relationship of fatigue with QoL; however, the cause behind this negative relationship is unknown. Therefore, future studies need to be done investigating the cause and the predictors of compromised QoL in relation to fatigue.

Worsening of glycemic control can increase the risks for complications and can lead to compromised QoL (Lombardo et al., 2003), which can further affect the functional status of individuals with type 2 diabetes. The present study provides support for the negative relationship of fatigue with functional status. High BMI, physical inactivity (Lakka et al., 2003) and pain (Hulens et al., 2003) have been identified in the literature as the predictors of poor functional capacity in individuals with diabetes. Since poor sleep quality can also cause fatigue (results from chapter 3), it can be said that poor sleep quality can also lead to decrease functional status. Therefore future studies need to be done exploring the contributing factors to decrease functional status in relation to fatigue, high BMI, physical inactivity, pain and poor sleep quality. Additionally, 6 MWT scores are themselves significant predictors of QoL, general health and mortality (Bittner et al., 1993; Enright, 2003; Enright et al., 2003). In order to obtain more information regarding relationship of fatigue with cardiovascular fitness measures, future studies could use more specific methods for testing functional capacity, like maximal oxygen consumption (VO2 max) test (Noakes, 1998).

Since a subsample was used for the qualitative research, we were able to capture the differences between the outcome measures of the two samples (qualitative and quantitative sample), which would not have been otherwise noticed. Since a subsample was further explored through qualitative interviews, we were able to investigate more details about functional

activities and QoL issues. The subsample was more fatigued and QoL and functional status was more compromised in this subsample (Table 4.4). This is also demonstrated in figure 4.2 which shows the impact of diabetes on different domains of QoL in quantitative and qualitative sample. Overall, there was a significant impact of diabetes on QoL on the whole sample (n=48) (figure 4.1), but when the quantitative (n=38) and qualitative (n=10) samples were compared (figure 4.2), the impact of diabetes was much greater in the qualitative sample. This difference was only observed because of the use of both methods; quant and qualitative, which could have otherwise been overlooked. This further supports the use of mixed methods design depicting the capability to detect the differences between quantitative and qualitative sample. Furthermore, comparison was performed between the sample (n=28) who answered "yes" to the question of fatigue, but were not interviewed and the sample who was interviewed (n=10) (table 3.7). There was no significant difference observed between the two samples, suggesting that the qualitative findings can be generalized to all who would say "yes" to the specific question of fatigue.

Since fatigue is such a complex phenomenon, using quantitative method or qualitative method alone does not provide the complete picture. Quantitative method provides us with certain numbers but does not show us how these numbers relate to a participant's responses. This is where qualitative methods come into play and help us to get a better understanding of the issue from a participant perspective. Qualitative research methods can provide in-depth understanding of fatigue in people with diabetes and help to gain insight into people's attitudes, behaviors, concerns, cultures or lifestyle. Therefore, to obtain a comprehensive understanding of fatigue in people with diabetes both quantitative and qualitative research methods are necessary. Mixed method research helps to answer questions that cannot be answered by qualitative or quantitative

methods alone. The combination of these two approaches provided the content validity of the quantitative aspect of the QoL and functional status assessment.

### 4.6. Limitations

There were some limitations to this study. One limitation was the nature of data being collected (fatigue.) The participants could be biased toward their fatigue levels and could be saying what they think the researcher wants to hear. The Hawthorne effect (Homan, 1965 ) can cause question to the validity of the findings. We attempted to minimize this issue by clearly explaining the purpose of the study to the participants. The other limitations of the study are the different domains of fatigue which were not analyzed. Since we only focused on general fatigue, we have not analyzed the data on other domains of fatigue like mental fatigue or physical fatigue, which could also affect the QoL and functional status. Future analysis should be done to explore other domains of fatigue and investigate the relationship of all different domains of fatigue on QoL and functional status.

### 4.7. Conclusion and Implications of the study

We identified the negative impact of fatigue on QoL and functional status. People with type 2 diabetes are encouraged to engage in physical activities as part of a self-management program. However, clinicians should also consider the presence and effect of fatigue in these individuals, which may lead to difficulty starting or continuing exercise programs. There is also a possibility that the decline in functional status in these individuals with type 2 diabetes is due to the presence of fatigue. Therefore clinicians should also screen their patients for the presence of fatigue.

Exercise can actually reduce fatigue (Fulcher & White, 1997) by improving aerobic fitness. Therefore, it can be said that there is sufficient support to study exercise intervention strategies to address function, fatigue and QoL in people with type 2 diabetes. The pathology and mechanisms behind diabetes related fatigue are unknown. It will be beneficial to investigate the pathogenesis of diabetes related fatigue with the intent of developing treatment options in this area.

In conclusion, people with type 2 diabetes have decreased QoL and functional status, which may be due to the presence of fatigue. The negative impact of fatigue on QoL and functional status is also supported by qualitative interviews. Overall, the results appear to support previous research suggesting that fatigue could be the cause behind decreased QoL and functional status in individuals with type 2 diabetes. As this may be an important area for diabetes management, further research is warranted to examine fatigue.

### 4.8. Tables

Table 4.1: Interview Guide

| |
|---|
| • Describe how fatigue can affect your normal day |
| • How does tiredness/fatigue impact upon your daily life? |
| ○ Employment |
| ○ Relationships |
| ○ Social life |
| ○ Housework |
| • In your opinion, what limits you in performing your activities of daily living? |
| • Could you describe how your everyday life has been affected by fatigue? |
| • What stops you from following your daily management/treatment strategies for your diabetes? |
| ○ Why this does happens? |
| ○ What causes it? |

Table 4.2: Demographics

| | Mean (SD) (n=48) |
|---|---|
| Age | 59.66 (7.24) |
| Sex | 22 females, 26 males |
| Years with Diabetes | 10.45 (7.38) |
| HbA1c | 7.38 (1.85) |
| BMI | 35.28 (7.35) |

Table 4.3 Demographics of the subsample of participants participated in the interviews.

| | Mean (SD) ( n=10 ) |
|---|---|
| Age | 57.1 (7.59) |
| Sex | 6 females, 4 males |
| Years with Diabetes | 9.50 (6.04) |
| HbA1c | 7.20 (1.85) |
| BMI | 36.86 (7.34) |
| Employment status | 6 employed; 4 unemployed |

Table 4.4 Comparison of descriptive of the outcome variables in two samples.

| | Quantitative sample ( n=38 ) Mean (SD) | Qualitative Sample ( n=10 ) Mean (SD) | Independent sample t test *p* - value |
|---|---|---|---|
| General Fatigue (MFI-20) | 12.60 (3.69) | 15.90 (2.51) | .011* |
| ADDQoL | -1.94 (1.67) | -3.13 (1.24) | .043* |
| 6 Min walk test | 373.88 (70.34) mts | 322.32 (77.11) mts | .049* |

* Significant at $p \leq 0.05$ level

Table 4.5 Comparison of descriptives of the outcome variables in two samples: qualitative sample (n=10) and sample who said "yes" to the question of fatigue (n=28).

| | Sample<br>(n = 28)<br>Mean (SD) | Qualitative Sample<br>(n = 10)<br>Mean (SD) | Independent sample t test<br>*p* - value |
|---|---|---|---|
| Age | 60.67 (7.28) | 57.10 (7.59) | .208 |
| General Fatigue (MFI-20) | 13.92 (3.01) | 15.90(2.51) | .118 |
| ADDQoL | -2.13 (1.80) | -3.13(1.24) | .088 |
| 6 Min walk test | 364.66 (66.06) meters | 322.32(77.11)meters | .114 |

* Significant at $p \leq 0.05$ level

## 4.9. Figures

Fig. 4.1: Impact of diabetes on individual life domains.

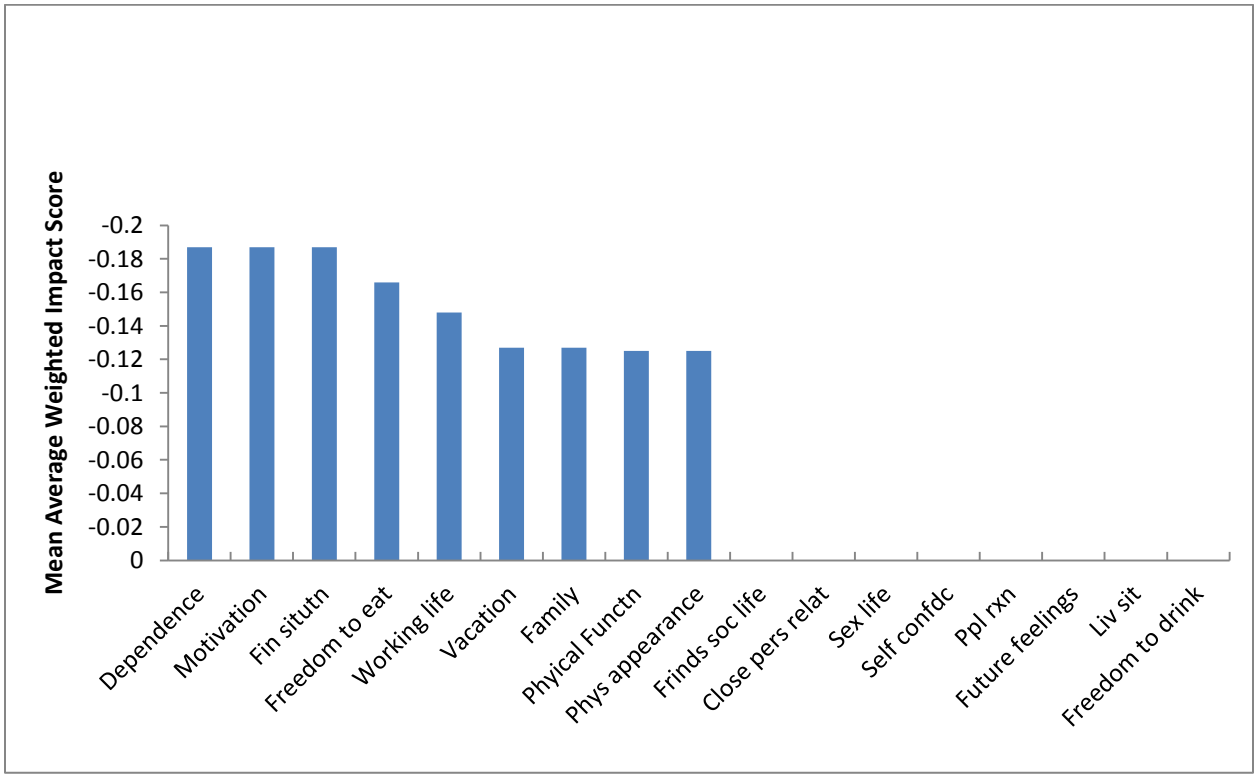
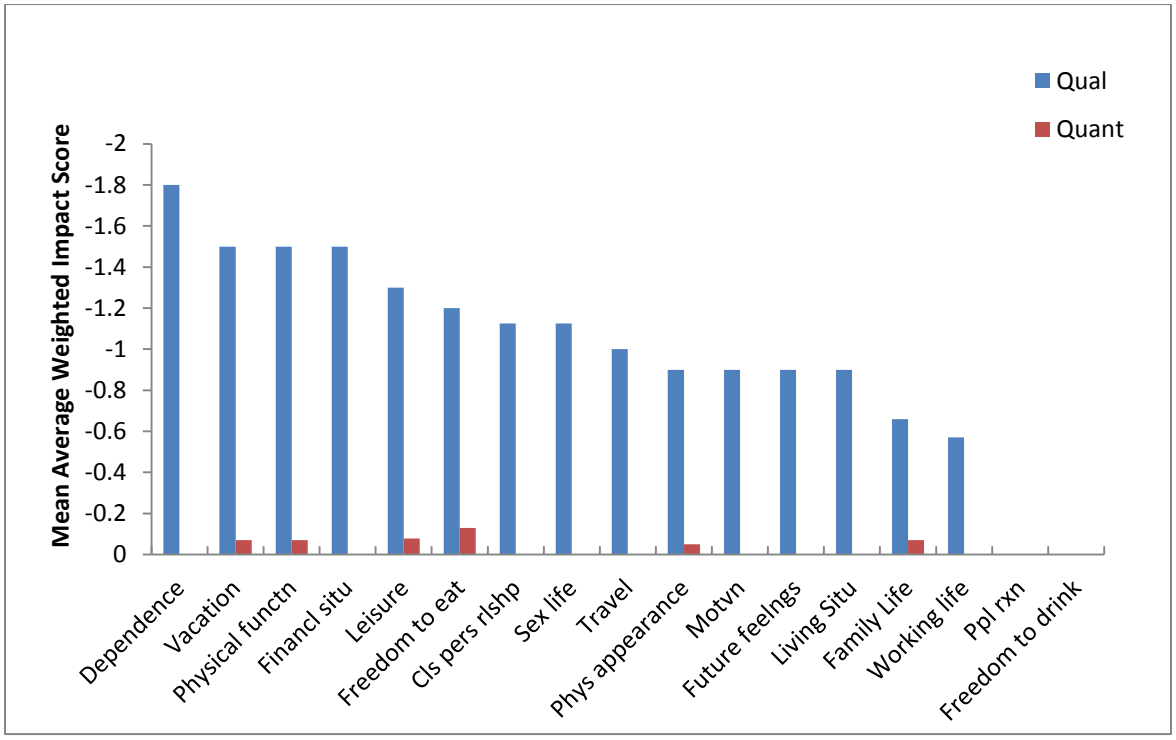


Fig. 4.2: Impact of diabetes on individual life domains, comparing quantitative and qualitative sample.



# Chapter 5

# Discussion and Conclusion

## 5.1. Summary of findings

The body of work presented here was conducted in order to gain a better understanding of the phenomenon of fatigue in people with type 2 diabetes. This research extends the literature, examining the presence and severity of fatigue, its contributing factors and its impact on QoL and functional status in people with type 2 diabetes. Our aims of the study were:

**Aim 1:** To determine the presence and severity of fatigue in people with type 2 diabetes.

**Aim 2**: Identify contributing factors that lead to fatigue in people with type 2 diabetes, using both qualitative and quantitative methods.

**Aim 3:** Determine the impact of fatigue on function and quality of life in people with type 2 diabetes, using both quantitative and qualitative methods.

This research is the first to explore the issue of fatigue by using a mixed methods approach. Overall, findings of this work demonstrate that fatigue is a significant problem in people with type 2 diabetes. Through this work and follow-up studies beyond, it is hoped that a better understanding will be gained of the challenges faced by those who suffer from diabetes related fatigue.

*Chapter 2 Fatigue and related factors in people with type 2 diabetes*

Fatigue can directly affect self-management strategies among individuals with type 2 diabetes. Despite the effect of fatigue on treatment efficacy, very few studies have explored this symptom dimension in patients with diabetes, and most have been limited to nonspecific symptoms of fatigue. Therefore, the purpose of Chapter 2 was to investigate the presence and severity of fatigue in people with type 2 diabetes as compared to a non-diabetic group, and to

identify the relationship between fatigue and certain variables of diabetes. Chapter 2 provides the first evidence that fatigue is a significant problem in people with type 2 diabetes when compared to people without diabetes. The number of complications resulting from diabetes may be related to this tiredness.

*Chapter 3 Predicting fatigue in people with type 2 diabetes: A mixed methods study*

Fatigue can result from various physiological and psychological factors which can be related to diabetes. Only 1 study has examined the role of these factors, and this study was limited to female gender only. Other studies exploring fatigue have been conducted with subjects having comorbidities or with subjects having the additional burden of maintaining their employment status. Since fatigue is such a complex phenomenon, using a single subjective questionnaire cannot capture the whole picture. The mixed methods approach can allow quantitative assessment of contributing factors to fatigue, and can also allow participant opinions toward the factors that contribute to fatigue by qualitative assessment of fatigue. The purpose of Chapter 3, therefore, was to investigate the contributing factors of fatigue in individuals with type 2 diabetes by using a mixed methods design. Poor sleep quality, high BMI and pain were identified as contributing factors to fatigue by both quantitative and qualitative approach. Additionally, high/low glucose concentration and depression were identified as contributing factors to fatigue by qualitative analysis. Based on the results of the study Portenoy's fatigue model is renamed as "diabetes fatigue model".

*Chapter 4 Impact of fatigue on quality of life and functional status in people with type 2 diabetes: A mixed methods study*

Since fatigue is a common complaint among people with type 2 diabetes it can also affect QoL in these individuals. Additionally, involvement in physical activities is an important component of a self-management strategy. Individuals with type 2 diabetes have a tendency to avoid exercise participation. This apprehension toward exercise may be due to the presence of fatigue. Lack of participation in exercise programs may result in decline in functional status. To date, no studies have attempted to examine the impact of fatigue on QoL and functional status in individuals with type 2 diabetes. Therefore, the purpose of the Chapter 4 study was to investigate the relationship of fatigue with QoL and functional status in individuals with type 2 diabetes by using a mixed methods design. In Chapters 2 and 3 we found that fatigue is present in people with type 2 diabetes and can result from poor sleep quality, high BMI, pain, depression and high/low blood glucose concentrations. In Chapter 4 we assessed whether fatigue can impact QoL and functional status in people with type 2 diabetes, by a mixed methods approach. Quantitative analysis revealed that fatigue was negatively related to QoL and functional status. Qualitative analysis supported the quantitative analysis by emphasizing the struggles with fatigue, impacting normal day housework, relationships and employment.

**5.2 Integration of findings:**

Overall results: Results of the qualitative analysis generated three themes: Description of fatigue, Multidimensional nature of fatigue and Struggles with fatigue. Themes with their supporting categories are further explained in the layout below:

1. Description of fatigue
    - Description of physical fatigue
    - Description of mental fatigue

- Alleviating factors

2. Multidimensional nature of fatigue
    - Physiological factors
        - Sleep
        - Pain
        - High/low glucose
        - Extra amount of body weight
        - Medications
    - Psychological factors
        - Depression
3. Struggles with fatigue
    - Impact on normal day
    - Impact on housework
    - Impact on relationships
    - Impact on employment

Interviews regarding contributing factors to fatigue and impact of fatigue were conducted in one session. There seemed to be a relationship between three themes. Overall theme # 3 (struggles with fatigue) was a consequence of theme # 1 (Description of fatigue) and theme # 2 (Multidimensional nature of fatigue). While describing fatigue, participants mentioned both the physical and mental state of being fatigued. Participants described physical fatigue sensation as their inability to do physical tasks. Mental fatigue was described as ‘loss of concentration’, ‘sleep

state'. Physical and mental fatigue can eventually impact the housework, employment, relationships, and normal day which further explain the consequence of theme #1 (description of fatigue) on theme # 3 (struggles with fatigue). Furthermore, while describing the contributing factors to fatigue, participants were focused on discussing issues with sleep, pain, high/low glucose levels, extra weight and depression. Participants described that because of frequent naps during the day, pain and frequent restroom breaks during night, they end up having poor sleep quality. All participants emphasized the relationship of fatigue with pain. Resulting from neuropathy, participants described pain in form of muscle cramps, sore feet, cold feet, or an ache, which limits their ability to walk and causes them to be more fatigued. Participants discussed the events of high and low glucose levels causing them to feel 'weak' and 'shaky'. Extra weight was discussed as 'a limiting factor to ability to walk'. Depression was considered as a reason for not being socially active and played an important role in triggering and adjusting to fatigue. All these issues; sleep, pain, extra weight, high/low glucose levels and depression, directly point towards the consequences of these issues which are explained in theme 3 (struggles with fatigue). For example, poor sleep quality can consequently result in impacting housework (may result from frequent naps), impacting employment (may result from need to nap), impacting normal day (may result from the need to stay in bed all day, as explained in Chapter 3), impacting relationships (may result from need to take frequent naps and need to stay in bed all day, as explained in chapter 4), which further explains the relationship of theme 2 (multidimensional nature of fatigue) and theme 3 (struggles with fatigue).

Overall both quantitative and qualitative results complement each other. Because a mixed methods approach was used, we were further able to identify some significant differences in

some of the factors like fatigue, sleep, depression, QoL and functional status between the quantitative and qualitative sample, which would not have been otherwise noticed.

Interpretation of contributing factors to fatigue: Interview questions were asked regarding 'contributing factors to fatigue'. It is still not clear if the issues identified by our qualitative and quantitative analysis (poor sleep quality, pain, BMI, depression, high/low glucose level) causes fatigue or if fatigue causes the issues (poor sleep quality, pain, BMI, depression, high/low glucose level). For example, it is not clear if poor sleep quality causes fatigue or if fatigue causes poor sleep quality. Regression analysis confirmed the causative factors of fatigue. Interview participants also revealed that these issues; poor sleep quality, pain, BMI, depression, and high/low glucose level causes them fatigue. It can be explained as cause and consequence issue. The cause of fatigue is poor sleep quality, pain, high BMI, depression, and high/low glucose level. The consequence of having pain, poor sleep quality, high BMI, depression and high/low blood glucose is fatigue.

Based on the results of the regression analysis and qualitative interviews, Portenoy's fatigue model is renamed the diabetes fatigue model. Portenoy's fatigue model was based on cancer patients. Several factors related to diabetes were incorporated to the original model. The model was then tested by a combination of quantitative and qualitative analysis. The theoretical model based on the factors incorporated (diabetes related factors) to the original model (Portenoy's fatigue model) was tested and confirmed. Based on the results of model testing Portenoy's fatigue model can be renamed as diabetes fatigue model. We tested various components of Portenoy's fatigue model but we were not able to capture all of them. The diabetes fatigue model will be further validated by testing all different potential contributing factors for future study.

### 5.3. Clinical Implications

With approximately 18.8 million people diagnosed with diabetes (Draznin, 2008), it is the responsibility of health professionals of all disciplines to help and share the burden and consequences of diabetes. The findings of the current research project may help clinicians treat people with fatigue and diabetes.

The results of the present work provided the evidence of presence of fatigue (chapter 2) in individuals with type 2 diabetes.

The next step was to identify potential contributing factors. Poor sleep quality, pain, high BMI, depression and high/low blood glucose were identified in this body of work as the contributing factors for fatigue. Clinicians should also consider other potential contributing factors such as medication side effects, aerobic fitness and physical activity.

Health care professionals should consider asking the question of fatigue (i.e. are you tired or fatigued all the time, which is not relieved by rest) to their patients. Based on the results of the study we can say that if someone answers "yes" to this question, then it signifies other potential underlying issues which patients might be dealing with, like sleep/weight problems or issues with pain, depression or hyperglycemia, which need to be addressed.

The other concern noted while comparing the depression scores was that a lot of participants (16 out of 48) scored high on the depression scale. Considering the high scores of depression in this sample, it is suggested that there is a need for depression screening or depression assessment in this population. Future studies can use more specific depression

diagnosis assessment tools like the patient health questionnaire (PHQ-9) to further test the role of fatigue in people with diabetes.

Based on the results of the study, it can be said that clinicians should assess and educate their patients on fatigue management. Since fatigue is neglected in diabetes, in addition to management of different complications, clinicians should also consider that diabetes outcomes can be affected because of presence of fatigue. To elaborate it further, it can be said that in addition to maintaining the glycemic index in a normal range, clinicians should also address fatigue management which could actually be the cause of hyperglycemia, as addressed by the results of the study. Fatigue management should focus on promoting healthy sleep habits, weight management, depression screening, and self-management education in regards to high/low blood glucose and pain management. Clinicians should use complaints of fatigue as a starting point for further evaluation of comorbid conditions, including diabetes complications and psychological illnesses like depression. Therefore, there is a need for inclusion of symptom assessment of fatigue in diabetes education.

Strategies to address fatigue were also discussed by our participants, which can be used or recommended for reducing fatigue. Participants suggested improving sleep quality by using Constant Positive Airway Pressure (CPAP) machine or sleep drugs which could help in alleviating fatigue. Some other methods like meditation, exercise, massage, taking a break from work and a snack or coffee during work hours were also described.

*Recommendation for assessment of fatigue:* Since fatigue is a complex phenomenon it becomes very difficult to assess fatigue. FSS was recommended as the assessment tool for measuring fatigue in people with type 2 diabetes in Chapter 2. FSS conceptually is defined as a

measuring tool emphasizing the impact of fatigue on daily life in terms of accumulation of functional fatigue effects. Analysis of distribution curves of another measure of fatigue, i.e. MFI-20 revealed that scores obtained on MFI-20 was normally distributed, which indicates that MFI-20 is another appropriate measure to use in this population. MFI-20 scores showed no ceiling or floor effects, the scores were widely spread over a broad range. Moreover, MFI-20 has been used in the past for testing fatigue in people with diabetes. Conceptually, MFI-20 covers a broad range of different domains of fatigue, i.e., general fatigue, physical fatigue, mental fatigue and also tests the impact of fatigue on person's motivation and activities. On the other hand FSS gives a cumulative fatigue scores based on impact of fatigue on daily life. Considering the different dimensions of fatigue which can be captured by MFI-20, it is recommended that MFI-20 should be used for assessing fatigue in people with type 2 diabetes.

### 5.4 Possible mechanisms for diabetes related fatigue

In agreement with previous studies that suggest a relationship between poor sleep quality and fatigue (Cuellar & Ratcliffe, 2008; Lopes et al., 2005), we found that poor sleep quality explained 37% of variance in fatigue (Chapter 3). Although underlying pathology of poor sleep and fatigue is still debated, Feinberg and colleagues have suggested that excessive day time sleepiness (EDS) is associated with undiagnosed diabetes, suggesting that individuals with EDS may have underlying pathology of diabetes leading to EDS (Feinberg, 1993).

The neuroendocrine system, specifically the hypothalamic - pituitary – adrenal (HPA) axis, may influence level of fatigue (J. Payne et al., 2006). The HPA axis is a complex set of interactions among the hypothalamus, the pituitary gland, and the adrenal gland, which constitutes a major part of the neuroendocrine system that controls reactions to stress and

regulates body processes such as mood, emotions, sexuality, digestion, immune system and energy storage. The underlying mechanism of fatigue may attribute to dysregulation of HPA (Redwine et al., 2000), which can influence the production levels of serotonin and melatonin.

It is important to address that serotonin and melatonin are important regulators of the 24-hour sleep and wake cycles also called circadian cycle (Cupp, 1997). Melatonin production is sensitive to light, more specifically; melatonin is inhibited by light and promoted by darkness (Cupp, 1997). Therefore, individual's wake cycle and sleep cycle parallels with melatonin production. In a study done by Payne and colleagues, observing the day time melatonin levels over three months during chemotherapy suggested elevated fatigue intensity experienced by subjects (J. K. Payne, 2002). Therefore, it is important to consider the link among fatigue, serotonin and melatonin, because serotonin may be an indicator of fatigue.

**5.5. Limitations:**

*Fatigue*

One limitation of the present work was the type of data being collected (fatigue.) Fatigue is very complex in nature, and it becomes difficult to transfer fatigue into a quantifiable measure. MFI-20 was used to assess fatigue, but MFI-20 can't also capture the whole dimension of fatigue. Fatigue is a subjective experience and participants can be biased towards their own fatigue levels, and could exaggerate their fatigue issues thinking that this is what the researchers want to hear. We tried to minimize this issue by clearly explaining the purpose of the study to the participants.

*Small sample size*

Although we established the presence and severity of fatigue in people with type 2 diabetes (*Chapter 2*), there were some limitations to it. Small sample size was a limitation to the study. The results were based on anonymous surveys, so we were not able to verify the data or follow up with the subjects, which was another limitation to the study.

*Other diabetes related factors*

The limitation of *Chapter 3 and Chapter 4* was not being able to test all other diabetes related factors which could contribute to fatigue. Though we tested several diabetes related factors, we were not able to test all of them. Several factors in Portenoy's fatigue model were not tested. The results of our study supported several aspects of the Portenoy's fatigue model. Figure 3.4 explains the results of the present study, supporting components of Porteney's fatigue model. Numbers of complications and duration of diabetes were not supported by the results of the present study. However, testing all different factors in the fatigue model was not under the scope of our study. For instance, 'medications' was not tested in the study. However, interview participants expressed medications as a contributing factor to fatigue. People with diabetes often take multiple medications and polypharmacy can also result in a number of complications and side effects, including fatigue. We were also not able to test other dimensions of Portenoy's model which included immobility and lack of exercise. Low levels of physical activity have been strongly associated with fatigue in people with type 2 diabetes. Common barriers to physical activity include obesity and fatigue complaints. Therefore, future studies should be done addressing the medications, immobility and lack of exercise dimensions of Portenoy's fatigue model. In regards to the psychological dimension of fatigue model, we did not test anxiety or

stress in our study. Future studies can use specific measures like Diabetes Distress Scale to address stress from the aspect of psychological dimension. Nutritional status (not included in the fatigue model) of these individuals was not evaluated. Nutrition can also play an important role in contributing to fatigue in people with diabetes, especially in relation to carbohydrate content. Therefore, future studies should be done considering all these factors that can also influence fatigue in people with type 2 diabetes.

*Other dimensions of fatigue*

We were focused on testing 'general fatigue' and did not analyze other dimensions of fatigue like mental fatigue or physical fatigue, which is another limitation of the present work. Blood glucose concentrations were tested by using HbA1c measures which did not result in significant quantitative associations with fatigue. Using other measures of blood glucose such as fasting blood glucose and continuous glucose monitoring (CGM) might have resulted in significant association. Blood glucose concentrations were strongly identified qualitatively as a significant contributing factor to fatigue by the participants, therefore using another blood glucose measure in the future would be informative.

### 5.6. Future Directions

The primary purpose of the present work was to obtain a better understanding of fatigue. The short term goal of this research is to continue characterizing the nature of diabetes related fatigue by expanding investigation with a use of control group in order to capture additional potential contributing factors; while the long term goal is to develop therapeutic countermeasures and evaluate its efficacy via intervention studies in people with type 2 diabetes.

*Control group*

A mixed method comparison of group with diabetes and without diabetes can help us in determining the differences between two groups. The use of a control group using age/sex/BMI matched people without diabetes can help in identifying the diabetes measures which can influence fatigue in people with diabetes. Since poor sleep quality was also identified as a contributing factor to fatigue, a control group should use age/sex/BMI/sleep quality matched people without diabetes. Matching people with poor sleep quality is very challenging. Therefore, future studies should include a control group using age/sex/BMI/poor sleep quality matched people without diabetes. This can help provide a better understanding of diabetes measures influencing fatigue in this population. Additionally, depression and glucose concentration were not picked up by our quantitative analysis. However, depression and glucose concentration were strongly expressed as contributing factors by our interview participants. Therefore other measures of testing depression (like PHQ-9) or glucose concentration should be used to explore these variables. We used only BDI-2 for assessing depression which is just a depression screening instrument. Other measures of testing depression like PHQ-9 can specifically help in depression diagnosis. Additionally, glucose concentration can be assessed by fasting blood glucose or continuous glucose monitoring, which gives glucose concentration right away. Complications resulting from diabetes can play a significant role in contributing to fatigue. Therefore, future studies should test specific type or severity of complications, which can be included in the qualitative interviews also.

*Exercise intervention*

To the author's best knowledge, no studies have yet to develop a sound therapeutic exercise intervention program and evaluate its efficacy in people with type 2 diabetes with fatigue complaints. Previous research has shown that people with diabetes can benefit from aerobic exercise training to achieve healthier lifestyle (Boule et al., 2001; Short et al., 2003). In addition, it has been seen that exercise can reduce fatigue in patients with chronic fatigue syndrome, using graded aerobic exercise for 12 weeks (Fulcher & White, 1997) . The same exercise regimen may be considered in training people with fatigue and diabetes. Qualitative interviews can be followed after the intervention, to determine if the intervention helped the participants in reducing the burden of fatigue.

*Exploration of other potential variables*

Biomarkers – Any electrolyte or fluid imbalance can potentially effect neurotransmission and muscle force and result in fatigue (Piper et al., 1987). Payne and colleagues identified melatonin as a biomarker to support fatigue mechanisms in women with breast cancer (J. K. Payne, 2002). Cortisol also has been identified as relieving factor for fatigue and stress, considering its role in HPA axis (J. K. Payne, 2004). Although these studies were directed towards cancer patients, we suggest the implication of a conceptual framework in other clinical populations with fatigue issues. These biomarkers may offer physiological evidence and may explain the underlying mechanisms of fatigue in diabetes. Future studies may consider the effect of exercise intervention on biomarkers such as serotonin and melatonin.

## 5.7. Conclusion

The work presented in this dissertation provides the evidence of presence and severity of fatigue in people with type 2 diabetes. Furthermore, the presented work provides the contributing factors to fatigue via a mixed method approach. The negative impact of fatigue on QoL and functional status was also emphasized by the present work. Clinically, these findings suggest that health care providers should educate their patients regarding fatigue, importance of healthy sleeping, weight and pain management strategies and self-management of glucose control.

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**Appendix -1**

**Number of complications – Number of complications survey**

Subject I.D: Date of visit:

Have you ever been told by your doctor that:

1. You had a heart attack? YES , NO
2. You had something wrong with your kidneys because of diabetes? YES , NO
3. Diabetes has affected your eyes? YES , NO
4. Diabetes has affected your toes or feet? YES , NO
5. Diabetes has affected the nerves in your legs or arms? YES , NO
6. You had decreased sexual interest because of diabetes? YES , NO
7. You had frequent oral infection because of diabetes? YES , NO
8. You had depression? YES , NO
9. You had gastroparesis/delayed gastric emptying? YES , NO
10. You had sleep problems because of diabetes? YES , NO

**Scoring: Number of "yes":……..**