The Impact of Type 2 Diabetes and Associated Diabetic Peripheral Neuropathy on Grip Force Control and Hand Function

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Submitted to the graduate degree program in Rehabilitation Science and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Abstract

There is cumulative evidence that fine motor skills and hand function are deficient in individuals with type 2 diabetes (T2D) and associated diabetic peripheral neuropathy (DPN). This might impact their ability to perform essential tasks such as buttoning a shirt, picking up pills, and monitoring blood sugar. Understanding the nature of such deficits is of utmost importance. This dissertation explores the sensorimotor involvement to deficits in hand dexterity: Sensory such as proprioception and motor such as grip force control. Several questions were addressed. First, does T2D and DPN cause finger proprioception deficits? Second, does T2D and DPN affect grip force control? Third, what is the role of sensation, specifically proprioception, in motor performance?

Because little is known about testing proprioception in a manner relevant to dexterity tasks, data presented in Chapter 2 tested the reliability and feasibility of a novel device and methods of pinch proprioception. Twenty-one healthy subjects attempted to actively reproduce a target position between the index finger and thumb without visual feedback over two consecutive days. Nineteen subjects performed the same procedure, but in a one-day setting and under two conditions: With and without vibration applied to the dorsal part of their dominant hand. Two additional subjects with T2D and DPN were tested as well. Similar results of pinch proprioception were achieved between the two consecutive days indicating that the device and methods were reliable in tracking proprioception between the index finger and thumb. Also, disruption of pinch proprioception sense was achieved as subjects were less accurate in matching the target position under the influence of vibration. The two subjects with T2D and DPN showed less accuracy in matching the target position indicating that their sense of proprioception is affected by their disease.

While the pinch proprioception device and methods showed promise in detecting proprioception deficits in subjects with T2D and DPN as shown in Chapter 2, we did not know whether DPN is the leading cause of such deficits. It is known that DPN causes sensory deficits hindering proprioception in the lower extremities, but the evidence is limited on the hands. To address this limitation, Chapter 3 describes an experiment with 13 subjects with T2D and DPN, 11 subjects with T2D *without* DPN, and 12 healthy subjects; all groups were age-matched. All subjects were tested for pinch proprioception utilizing the same device and methods described in Chapter 2. It was found that the accuracy and precision of the pinch proprioception were particularly affected in subjects with T2D and DPN. The T2D *without* DPN subjects showed similar findings to the healthy subjects indicating that DPN is a contributing factor to these deficits. Therefore, building on the findings from Chapter 2, it was concluded that damage to muscle spindles associated with DPN is very likely what caused pinch proprioceptive deficits.

In Chapter 4, the focus shifted to grip force control. Several recent studies have shown deficits in controlling grip force in people with diabetes (type 1 and T2D). For instance, some studies showed an increase in grip force magnitude while others demonstrated that this variable was decreased in diabetic subjects with and without DPN. The same subjects described in the previous chapter were asked to grip and lift an object and then hold it at a specific height to address the inconsistent findings. Grip force magnitude, as well as temporal parameters of grip force control, were analyzed. It was found that the grip force magnitude was higher in subjects with T2D and DPN, and they took longer to perform the lifting task as compared to those with T2D *without* DPN and healthy subjects. These data provide evidence that T2D by itself does not present with any deficits in grip force control, and DPN might be responsible for deficits in grip force magnitude and temporal parameters.

Finally, Chapter 5 is focused on the study of dexterous motor activities that involve object manipulation and require sensory feedback that plays a major role in adjusting grip forces when holding an object. Deficits in hand dexterity in people with T2D have been shown via Jebsen-Taylor Hand Function Test (JTHFT) and Moberg Pickup Test (MPUT); i.e., subjects spent more prolonged time to perform functional tasks. In addition to the finding of impairments in pinch proprioception, grip force control, and hand dexterity in people with T2D and DPN, decrements in pinch proprioception were positively correlated with longer time to perform dexterity tasks. Other aspects of sensory deficits (tactile sensation) were more associated with higher grip force magnitude. It was concluded that while tactile sensation was more associated with higher grip forces, pinch proprioception deficits appear to contribute to increasing the time needed to perform a lifting task.

Overall, the results suggest that DPN is a major concern that causes proprioceptive, grip force control, and hand dexterity problems. The integrity of proprioceptive signals, as well as tactile sensation, affect different profiles of grip force control to different degrees. Proprioception is more related to timing while tactile sensation appears to affect the grip force production. Therefore, intact sensory information (tactile and proprioceptive) is necessary to perform dexterity tasks which seem to be problematic for subjects who suffer from T2D and DPN. Clinicians should be aware of the nature of hand dexterity deficits in the presence of DPN when screening and developing rehabilitation programs.

Acknowledgments

"The first level of knowledge is intention, then listening to it, then understanding it, then memorizing it, then acting upon it, then spreading it"-Ibn Almubarak

First and for most, I would like to thank the Creator for all the bounties and blessings He bestowed upon me throughout my life, but especially during this time. I thought I was coming to KUMC for education, but I got so much more than that; friendship, support, independence, guidance, and a push when I needed it the most. Thank you all for being a part of my epic journey.

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List of Abbreviations

2PD: Two-point discrimination

9HPT: Nine-Hole Pegboard Test

AGEs: Advanced Glycation End products

ANOVA: Analysis of Variance

CI: Confidence Interval

CNS: Central Nervous System

CTS: Carpal Tunnel Syndrome

DAG: Diacylglycerol

DPN: Diabetic Peripheral Neuropathy

GFC: Grip Force Control

GFR: Grip Force Ratio

GFP: Grip Force Peak

HbA1c: Glycosylated hemoglobin

ICC: Intraclass Coefficient

IGFA: Index of Grip Force Adjustments

IR: Insulin Resistance

JTHFT: Jebsen-Taylor Hand Function Test

LF: Load Force

LFP: Load Force Peak

MPUT: Moberg Pickup Test

Ms: Millisecond

OS: Oxidative Stress

PNS: Peripheral Nervous System

SF: Static Force

SWME: Semmes-Weinstein monofilament Exam

T1D: Type 1 Diabetes

T2D: Type 2 Diabetes

T2D-only: Type 2 Diabetes without Diabetic Peripheral Neuropathy

T2D+DPN: Type 2 Diabetes and Diabetic Peripheral Neuropathy

TAG: Triacylglycerol

T-Lag: Time Lag

Chapter 1: Introduction

1.1. Overview of Diabetes

The prevalence of diabetes is continuously and rapidly growing in all nations, estimated at 366 million and more than 371 million individuals worldwide in 2011 and 2012, respectively [1]. Of these cases, 90% are diagnosed with T2D while 50% go undiagnosed.

The etiology of T2D is poorly understood in the presence of a variety of genetic and environmental risk factors. Perhaps, one of the major risk factors associated with T2D is obesity marked with high levels of triacylglyceride (TAG), diacyl glyceride (DAG), and cholesterol [2]. Several studies showed that higher fat levels can be linked to improper use of insulin and increased body resistance to its action leading to the occurrence of T2D [2-6]. In addition, it is widely known that reduced insulin secretion from beta cells in the pancreas and poor utilization of insulin by muscle tissues are the main characteristics of T2D [7]. Both reduced insulin secretion and inadequate use of insulin by muscle tissues increase glucose levels in the blood; this is known as hyperglycemia [2]. Nevertheless, diabetes is known for the relative fluctuations of glucose levels leading to hypo or hyperglycemia episodes [8]. Such fluctuations may put patients at higher risk of complications such as diabetic neuropathy—simply defined as a nerve defect solely due to diabetes [3, 6, 9].

Diabetic nerve damage presents mainly in the peripheral nervous system (PNS), but growing evidence is showing the involvement of the central nervous system (CNS) as well [8, 10-16]. There are many theories postulated to explain how diabetes causes neuropathy, and perhaps the most common cause is chronic hyperglycemia. Hyperglycemia consequently will cause oxidative stress, inflammation, accumulation of advanced glycation end products (AGEs), and gene expression changes [17-21]. In addition to the direct impact of diabetes on nerve tissues, other mechanisms can also be responsible. It has been postulated that micro- and

macrovascular complications associated with diabetes might be the driving cause of nerve damage as a result of ischemic infarcts [15, 22]. For instance, T2D increases the relative risk of developing ischemic strokes by 2-5 folds, which indirectly highlights the impact of diabetes on the central nervous system [22, 23]. In fact, higher rates of infarcts have been documented in people with T2D affecting the cerebellum, basal ganglia, thalamus, and other brain structures [24]. As presented in the next few sections, all these secondary complications of T2D will ultimately lead to neural damage and consequently upper extremity dysfunction (Figure 1).

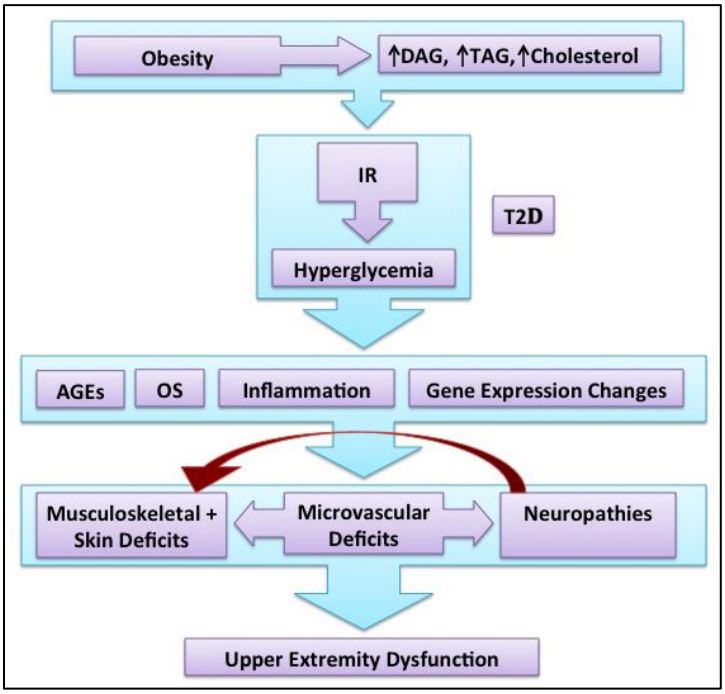

Figure 1.1. Schematic diagram showing the main events leading to upper extremity dysfunction in the presence of T2D. Obesity, elevated fat levels such as diacylglycerol (DAG), triacylglycerol (TAG), and cholesterol are the main causes of insulin resistance (IR). Consequently, the main symptoms of T2D, like hyperglycemia, start to manifest. Hyperglycemia in return causes the accumulation of advanced glycation end products (AGEs), oxidative stress (OS), inflammation, and gene expression changes. Ultimately, microvascular deficits, musculoskeletal and skin deficits, and neuropathies start to develop over the process of T2D. Subsequent to all of those complications, upper extremity function gets worse over time.

1.2. Neuropathy

1.2.1. Definitions and classifications

Neuropathy, in general, is a defect in a nerve that can affect any part of the human body. This broad description highlights the severity and complexity of this illness. In most cases, neuropathy is considered to be a side effect or a subsequent event of other diseases like a tumor, amyloidosis, and diabetes [25, 26]. The term "DPN" is derived from the fact that it occurs in people with diabetes and commonly starts distally, affecting the lower extremity first. Therefore, DPN can be defined as any damage to the peripheral nerves solely due to diabetes after excluding other causes of neuropathy such as vitamin B12 deficiency, a tumor, cervical radiculopathy, carpal tunnel syndrome, and radial nerve compression [27]. DPN can be further divided into typical DPN (diabetic sensorimotor polyneuropathy) and atypical DPN [27]. The former has been defined as symmetric length-dependent sensorimotor polyneuropathy mostly asymptomatic and it can be associated with prolonged hyperglycemia and microvascular alterations. Atypical DPN can be defined as a monophasic or fluctuating disorder that affects small sensory and autonomic nerve fibers. However, atypical DPN does not seem to be associated with chronic hyperglycemia nor with microvascular abnormalities found in the typical form of DPN and it can occur anytime [27].

Symmetric sensory polyneuropathy, typical, especially in the lower extremities, is more common than mono-neuropathy among people diagnosed with DPN. However, DPN could also affect motor nerves and the autonomic nervous system as well [28, 29]. It is widely known that DPN advances from distal to proximal parts of the upper and lower extremities [30]. DPN mainly affects the small sensory fibers first and it correlates with the severity of the disease itself [31-33]. However, the loss of fine motor movements might not appear until the neuropathy severely affects large motor fibers [32]. In other words, even before the presence of small fiber

neuropathy, changes in motor function might still exist without noticing (asymptomatic manifestations) [34, 35]. Nevertheless, the majority of the available evidence in the literature supports the involvement of motor and sensory nerves (77% and 90%, respectively) of the lower and upper extremities in the presence of T2D [36, 37]. It should be noted that we will recruit patients with the typical form of neuropathy. Therefore, the term DPN refers to distal symmetric diabetic sensorimotor polyneuropathy, and it will be used throughout the manuscript.

1.2.2. Clinical presentation

DPN is one of the major complications of T2D. Research has shown that it affects approximately 26% of T2D populations, and the prevalence might reach 80% with larger sample sizes [38]. In the upper extremities, the median nerve diabetic neuropathy accounts for almost 17% of people diagnosed with T2D [39]. This can be due to the direct impact of diabetes on the nerve structures or due to structural changes in the surrounding tissues. For instance, changes in the transverse carpal ligament are what causes median nerve compression as it passes through the wrist. Such changes have been attributed to the effect of chronic hyperglycemia on collagen cross-linkage due to the direct effect of AGE products on collagen fibers in diabetic patients [40]. The nerve entrapment that causes median nerve compression is commonly known as carpal tunnel syndrome (CTS) [41, 42]. The main symptoms associated with CTS are pain and paresthesia over the thumb, index and middle finger, and thenar muscle atrophy, but usually in severe cases. The most common symptom that accompanies DPN is pain, which can be described as allodynia (higher sensitivity to any stimulus that generally does not cause any pain), and hyperalgesia (increased sensitivity to a stimulus that usually causes pain). Other symptoms are, for example, burning sensation, coldness, or hotness of the extremities, tingling, numbness, and hypoalgesia (reduced perceived pain by a normally painful stimulus) [17].

1.3. Tactile sensation

The majority of the symptoms mentioned above have been linked to the decreased density and morphological changes of the tactile sensory receptors at the fingertips due to the impact of prolonged hyperglycemia and DPN associated with T2D [43]. This explains the reduced discriminatory tactile sensation, which is a major concern in people with T2D [43]. Discriminative touch is the ability to perceive pressure (light touch), vibration, and texture sensations. Specialized receptors at the tips of the fingers provide afferent sensory information about the object in hand [44]. Meissner corpuscles and Pacinian corpuscles at the tips of the fingers are the mechanoreceptors responsible for initiating the sensory signals carried through rapidly adapting type I and II afferent fibers (respectively) [44]. Such receptors will start firing at the moment when the fingers make contact with an object and when we let go of it [44]. Those receptors are also capable of detecting micro-slips which might happen when holding an object steady or during perturbation [44]. Merkel cells and Ruffini endings at the tips of the fingers will continue firing while holding an object giving continuous feedback carried through the slowly adapting type I and II afferent fibers (respectively) [44]. Recognizing different textures can be detected through slowly adapting type I afferent nerve fibers (Merkel cells) [44]. T2D impacts the normal function of all of these different receptors and hence presenting with different kinds of symptoms [43].

1.4. Proprioception

Proprioception is the awareness of limb position and movement in space. Specialized mechanoreceptors located in the skin, joints, ligaments, tendons, and muscles generate signals that collectively contribute to the sense of proprioception [45-48]. Optimal proprioceptive performance is achieved when all signals from the skin, joints, and muscles are intact. Proprioceptive signals travel through the afferent nerves into the spinal cord to be processed in

the CNS, which produce the sense of one's body position and movements [49]. Within the spinal cord, the signals are transmitted back through alpha nerve fibers to the same muscle or towards the cerebellum (lateral spinocerebellar tracts). The ventroposterior lateral thalamic (VPL) nucleus receives input from dorsal columns (discriminatory sensations and proprioception) and projects to the primary somatosensory area [50].

Different methodologies used to test for proprioception in the hands. Proprioception is commonly tested by asking subjects to determine the direction of the finger when the assessor points it towards the ceiling or the floor [51, 52]. This method is commonly used during neurological exams, but growing research showing that it lacks reliability and sensitivity [52-55]. Experimental approaches have been developed to measure finger proprioception more objectively; for instance, using goniometry to measure proprioception in the index finger at the metacarpophalangeal joint [56]. Other methods adopted more functional approaches, i.e., utilizing more than one finger to test for proprioception [57]. While each method has advantages and disadvantages, measuring proprioception between two fingers (index finger and thumb) has an ecological advantage where it relates to many activities such as using pair of scissors, picking up pills, and writing.

1.4.1. Proprioception mechanoreceptors

1.4.1.1. Skin

Skin mechanoreceptors located over the joints convey proprioceptive information, likely to some degree, about changes in the kinematics and the contact surface between the body parts and the object in hand [58]. There is a difference between mechanoreceptors located in skin areas covered with hair compared to glabrous palmar skin in that their response to vibration is 5-10 times greater [44, 59]. It is possible that applying vibration to skin mechanoreceptors can change the cutaneous contribution to the sense of proprioception [60]. Pacinian and Meissner's

corpuscles fire in response to vibration with a similar frequency when first applied, and their response attenuates over time [60]. Pacinian corpuscles are located mostly in the glabrous skin of the hands, but they also exist in joints and in muscle tissues [44]. Merkel corpuscles respond to skin indentations while Ruffini endings respond to skin stretch and vibration [61]. They both continue firing and sending nerve impulses through the slowly adapting type I and II afferent nerve fibers as long as the object is still in contact [60].

1.4.1.2.Joints

Growing evidence shows that mechanoreceptors located within joint surfaces and capsules contribute less to the sense of proprioception as compared to the skin. This is obvious from total joint replacements (knee and hip) that the contribution of Pacinian corpuscles and Ruffini endings located in the joint capsule exert lesser importance to the sense of proprioception [62, 63]. In addition, the ability to perceive finger position after applying digital and joint anesthesia of the fingers is indicative of the involvement of other structures [64]. There is limited evidence on the direct effect of vibration on the joint capsule as compared to skin or muscles. However, proprioceptive impairments are more pronounced at the extreme ranges of motion [63, 65, 66]. Perhaps this highlights the importance of joint mechanoreceptors as limit detectors.

1.4.1.3.Muscle spindles

The principle muscle receptor involved in proprioception is the muscle spindle, which has been studied with the use of vibration [48, 67-69]. Muscle spindles, located within the skeletal muscle belly, fire in response to static and dynamic changes in position [70]. Therefore, they stretch when the muscle lengthens and shorten when muscle contracts [70]. Primarily, when the muscle spindles are stretched they generate action potentials [70]. Each muscle spindle is enclosed with a capsule and contains at least four nuclear chain intrafusal muscle fibers and two nuclear bags [70]. The action potentials are carried via fast adapting type Ia (annulospiral

terminals) and slower adapting type II (flower-spray endings) afferent nerve fibers towards the spinal cord [71]. Type Ia fast afferent fibers respond to dynamic changes in muscle length while type II slow afferent fibers respond to static position or the actual length of the muscle [71]. In addition, signals generated from muscle spindles travel to the cerebellum via spinocerebellar tracts to trigger coordinated movements and automatic adjustments and to the cerebral cortex via dorsal columns for conscious position sense [71]. Muscle spindles receive supraspinal inputs through rubrospinal and reticulospinal tracts to activate gamma motor fibers [71]. Gamma motor fibers can trigger an independent contraction of the intrafusal muscle spindle fibers, which help with the muscle tone and the rate of contraction [71].

1.4.2. Proprioception and Diabetes

Most of the studies investigating proprioception in people with T2D and DPN have been done on the lower extremities [67, 72, 73]. There is a scarcity of research on the effect of T2D and DPN on the sense of proprioception in the hands. Preliminary evidence showed possible proprioceptive deficits in people with T2D [74]. Ochoa [74] and his colleagues applied wrist and forearm median nerve anesthesia to 9 subjects with T2D and 9 healthy matched subjects and passively moved the thumb into abduction/adduction, and opposition with the index and little finger [74]. Although the differences between groups were not significant, subjects with T2D had more errors [74]. The significant differences were between the locations of the anesthesia and surprisingly more pronounced at the wrist [74]. The results can be attributed to mismatch from afferent signals (possibly muscle spindles) from the forearm muscles or central nerve damage. However, using anesthesia to test for proprioceptive deficits is not feasible for clinical purposes, and the testing procedure does not relate to functional tasks. In addition, no study has investigated pinch (between thumb and index finger) proprioception in patient populations or in people with diabetes. The pinch maneuver is essential to perform a variety of tasks such as

holding an insulin injection or an insulin cartridge, picking up small items, writing, and lifting objects with different weights.

1.5. Type 2 diabetes and central nervous system

Contrary to the common belief that diabetes mainly disrupts the PNS, the CNS has also been shown to be affected [8, 10-16]. Spinal cord atrophy exists in people with clinical (25.6%) and subclinical (8.7%) DPN as an early complication of diabetes [16]. Furthermore, diabetes might cause deficits in the thalamic sensory neurons, VPL nucleus, in particular [50]. The output from the VPL projects to the primary somatosensory cortex. With the use of MRI studies, the primary somatosensory cortex has been shown to be decreased in size in the presence of DPN when compared to healthy subjects [75]. This direct nerve damage affecting structures within the CNS is mostly the result of metabolic byproducts of acute and chronic hyperglycemia. Accumulating evidence is showing the risk of developing cognitive deficits is high in people with T2D, especially when it coincides with the presence of DPN [12]. Subjects with T2D showed cognitive impairments affecting their working memory and their speed of information processing [12]. This evidence strengthens the association between diabetes and the risk of dementia and perhaps supports the epidemiological studies to consider diabetes as an independent risk factor for causing cognitive deficits [12].

1.6. Concepts in Grip Force Control

In the presence of sensory and proprioceptive deficits, the ability to safely manipulate objects may also be impaired. The grip forces we apply through our fingers can be precisely adjusted when manipulating a variety of objects [76]. This unique skill ensures that we do not apply excessive force that might damage the object or cause unnecessary fatigue, but at the same time not too small for an object to slip [77]. Johansson and Flanagan [44] mentioned that in order to pick up an object, a sequence of actions should take place. The first phase is the planning

phase, where the required action is processed based on the task on hand. The second, processing phase is where the brain starts collecting necessary information about the task; for example, lifting a cup of water requires visual feedback about the physical properties of the cup such as the amount of water that is still in the cup, the material and probably even the smoothness of the cup to anticipate the friction forces [78]. At this point, a forward model will be established, anticipating how much force is needed to lift the cup [79] and the hand trajectory [80]. Once contact between the fingers and the cup is established and based on the task, haptic feedback starts feeding into the brain [81]. This feedback will be used to correct any miscalculations primarily fed from the brain through the anticipatory and forward model [76, 80, 82-85]. This whole process of processing the information, sending the nerve signals to the desired muscles, and receiving the sensory feedback from the periphery back to the brain is what constructs the sensorimotor loop [76]. Figure 2 summarizes the main events of grip force control during a commonly used lifting task. Initial contact between fingers and object (A) corresponds with a rise in grip force trace. Grip force will continue developing until the object leaves the table (B), which corresponds to the grip force at liftoff on the grip force trace. The static force corresponds to the stage where the object is held at a specific height (C) until the object returned back to the starting position.

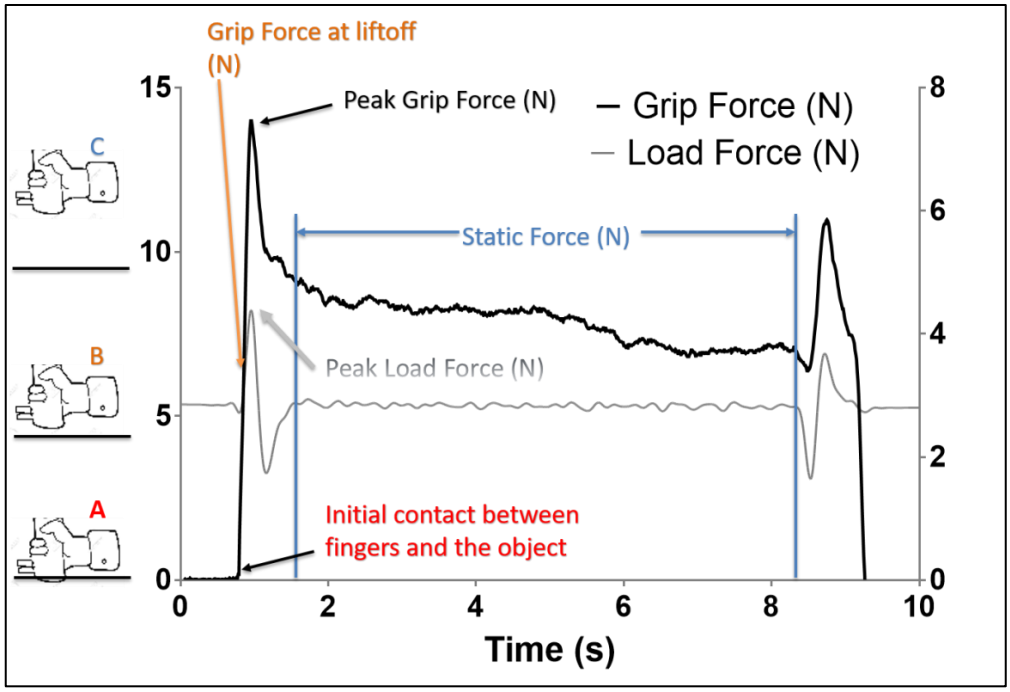

Figure 1.2. Main time points during the lifting task of a novel object. Data of grip force traces are represented on the left vertical axis. The right vertical axis represents data for the load force traces. Time in seconds are represented on the x-axis. (A) time of initial contact; (B) time when the object leaves the table matching the moment of grip force at liftoff; (C) time when the object is held steady (static force). This graph was developed from a healthy control subject.

Any deficits in the sensorimotor loop will cause a delay in the nerve signal, which could contribute to what we think is a centrally or peripherally mediated impairment [10, 84]. The grip force needed to hold an object stationary has to be higher than the minimum force needed to prevent it from slipping; this is known as the safety margin [86]. The task of holding and lifting an object vertically generates two distinct forces; horizontal grip force, the applied force from fingers against the contact surface of the object, and vertical load force, the weight of the object times the acceleration. Grip force must be adjusted efficiently and simultaneously in parallel to load force changes generated from moving an object in space during lifting. As such, an increase in load force will be associated with an increase in grip force to secure the object in hand during

the vertical movement; this is known as the grip force scaling. The higher the ratio of peak grip force to the peak of load force, the less efficient the grip force scaling. This can be a result of pathological problems affecting either the peripheral or central nervous system or both. The temporal coupling between the peak of grip force and the peak of load force is known as the time lag, which usually ranges between -10 to +15 milliseconds on average [87]. Such a short time indicates that the temporal coupling must be centrally driven through anticipatory/predictive and automatic actions. In fact, a longer time lag between the peak of grip force and the peak of load force has been shown to be associated with pathological conditions involving the CNS [77, 88-91].

The richness of the data derived from a simple lifting task suggests that grip force control can be a good model to study peripherally and centrally mediated pathological conditions as evidenced by studies on patients with stroke [83, 89-92], Parkinson [89], cerebellar lesion [88], multiple sclerosis [77], osteoarthritis of the hand [93], and CTS [79]. Continuous cutaneous sensory information from the finger pads are used to control for the optimal grip force required to hold an object. This afferent information can be driven from concurrent online feedback and/or previous experiences. Therefore, the role of sensory feedback is not only crucial for reactive grip force control adjustments, but also for predictive measures established from previous experiences with the object, which can be used as a reference point for future encounters [44, 82, 94]. Due to the importance of tactile sensory and possible proprioceptive information as a source of feedback when manipulating an object, the focus of this dissertation will be about the impact of T2D and DPN on grip force control measures.

1.7. Diabetes and Grip Force Control

Because of the apparent deficits associated with T2D and DPN, grip force control might be majorly affected. Recently, only a few studies have investigated the impact of diabetes on grip force control [35, 74, 86, 95-97]. One study investigated the impact of diabetes on safety margin [86]. This study included 24 subjects: 12 diabetics without DPN diagnosis and 12 age- and gender-matched healthy controls. All subjects were right-handed and between the ages of 31 and 60 years. The only significant finding of this study was that the diabetic group exhibited a lower safety margin compared to the healthy controls. The authors referred to the lower safety margin as a subclinical sign of sensory or proprioception deficit and indicated that this would put subjects at risk of dropping an object during its manipulation. In a follow-up study, the same group investigated the safety margin in 10 subjects with T2D and DPN as compared to healthy ag-and-gender matched subjects [97]. Interestingly, subjects with T2D and DPN showed similar results (lower safety margin). Another study by Gorniak, Khan [35] used a different approach to study grip force control. They utilized the submaximal testing (5 levels; 15%, 20%, 30%, 40%, and 50% of maximal voluntary pinch). Subjects were recruited into two groups; control and T2D group. This study included 10 T2D (five males and five females) half of whom diagnosed with DPN, age- and gender-matched subjects with 10 healthy controls. The results of this study showed that the grip force control was disrupted in subjects with T2D, and neuropathy does not seem to drive such deficits. A follow-up study by the same group utilized median nerve blocks at the forearm and hand in 9 subjects with T2D and healthy age-and-gender matched subjects [74]. In the presence of hand and forearm median nerve blocks, grip force control was more impaired as compared to the healthy control group. This significant difference was magnified when neuropathy was controlled for suggesting other mechanisms responsible for grip force deficits other than tactile sensory deficits [74].

Chiu, Hsu [95] recruited 159 (83 males and 76 females) subjects with type 1 diabetes (T1D) with associated DPN and 95 (48 males and 47 females) healthy age, gender, and handedness matched subjects. It should be noted that neuropathy was established on 138 of the subjects based on nerve conduction studies from the lower extremities. Interestingly, the authors aimed to identify any sensorimotor disabilities in the presence of DPN, but without any neurological and clinical manifestations in the hands using pinch hold up activity. Subjects were asked to lift an object for 5cm and hold it for few seconds and then lift it to 30cm and return it to the starting position. GF/LF ratio was significantly higher in the diabetic group indicating a less efficient grip force control. Part of the same study, the authors investigated the impact of chronicity (longer duration of the disease) and severity (worse glycemic control based on higher HbA1c values) on the same group of subjects with T1D [96]. As hypothesized, GF/LF ratio was more affected for T1D subjects with more severe and chronic DPN [96].

Therefore, based on these studies, it is difficult to determine the impact of T2D, specifically, with and without DPN, on grip force control. For instance, the study by de Freitas and Lima [86] systematically used the term “diabetes” without proper clarification, whether it was meant T1D or T2D or both. In either case, the authors recruited subjects with diabetes and without DPN. The results of the follow-up study [74] were controversial and different from what has been reported in the literature [98, 99]. Gorniak, Khan [35], on the other hand, recruited a mixed sample of subjects with T2D, with and without DPN. Finally, the other 2 studies [95, 96] included subjects with T1D and with DPN. In this dissertation work, we will divide groups of subjects based on their diagnosis into 3 groups; subjects with T2D without DPN, subjects with T2D with DPN, and healthy controls.

1.8. Hand Dexterity

Dexterity is the ability to use hands skillfully in performing challenging tasks [100]. In diseases such as T2D, hand dexterity might be affected. The most common assessment tools used in measuring dexterity in subjects with T2D are the Purdue Pegboard Test, 9-Hole Pegboard Test (9HPT), Jebsen-Taylor Hand Function Test (JTHFT), and Moberg pick-up test (MPUT). The Purdue Pegboard Test requires using each hand separately and both hands together in placing pegs into holes and attaching washers into them. The 9HPT is a short version of the former, and time is the primary response variable for both versions. Studies that investigated hand dexterity in subjects with T2D have shown inconsistent results [35, 101, 102]. One study showed that hand dexterity, as measured by the 9HPT, got worse over a period of two years [102]. In another study, only the assembly task of the Purdue Pegboard Test was significantly impacted by the presence of T2D, while the single-handed task did not show any significant differences [35]. Based on the 9HPT findings, two studies showed no differences in hand dexterity in subjects with diabetes from healthy controls [86, 101]. Although the Shah, Clark [101] study showed no significant difference in hand dexterity, subjects with T2D spent longer time to complete the task (p-value = 0.056). In addition, de Freitas and Lima [86] recruited 12 subjects with diabetes (it is not mentioned whether T1D or T2D or both) and another 12 healthy control subjects, age-and-gender matched. The study findings showed no difference in hand dexterity based on 9HPT and JTHFT [86]. In a follow-up study by the same group, 10 subjects with T2D and DPN were age-and-gender matched with a healthy control group [97]. Time performance on both 9HPT and JTHFT was deteriorated (i.e., took longer) as compared to the healthy control group [97]. Another study investigated hand dexterity using JTHFT [103]. A hundred subjects were recruited, 25 in each of the four groups: healthy, T1D, T2D (40-70 years), and T2D over 70 years of age. Contrary to the studies by Shah, Clark [101] and de Freitas and Lima [86], subjects

with T2D spent a longer time to perform JTHFT compared to healthy and T1D subjects. This difference in findings was noted with factors of lifting light and heavy objects, lifting small objects, simulated page turning, and writing. This study was heterogeneous in terms of neuropathy: 28% (T1D), 44% (T2D, 40-70 years of age), and 52% (T2D, older than 70 years of age).

1.9. Rationale and Significance

The findings of the proposed study may lead to a better understanding of the impact of T2D and DPN on hand function. Activities such as self-monitoring of blood glucose, grooming, and dressing can be significantly impacted by complications from diabetes, thereby compromising the quality of life in people diagnosed with T2D [38, 103, 104]. Although less studied in comparison to lower extremities, the impact of T2D on the upper extremity function (grip force control, proprioception, and dexterity) is becoming a subject of greater interest [9, 35, 86, 95, 96, 101-103, 105-109]. More importantly, reactive grip force control has been investigated utilizing the average of static grip force while holding an object stationary in space [88, 92, 110]. Central tendency measures fail to capture change over time [111-113]; i.e., the average of static grip force does not represent the change in static force when holding an object stationary. We believe that change in reactive grip force control is better measured by regression analysis of the grip force trace. This can provide a better understanding of the general pattern of reactive grip force adjustments based on actual sensory feedback of the manipulated object. One study has reported the percentage change of grip force overtime [110]. The authors in this study used the maximum pinch strength to calculate for the grip force percentage change [110]. However, it has been documented elsewhere that there is no correlation between grip force control and maximum pinch strength [93], and for the majority of the items we manipulate

throughout the day only 14% of the maximum strength is required [114]. Hence the percentage change of grip force might not have been well represented.

In addition, proprioception might be affected in people with neurological disorders [67, 72, 73]. However, the only available clinical test for finger proprioception is the "up or down" test given during the peripheral neurological examination at the distal interphalangeal joint [51, 52, 56]. This clinical maneuver, however, does not take into account the complexity of the natural grip function, which involves multiple fingers acting simultaneously during daily manual tasks. Therefore, there is a need for a reliable portable apparatus to measure pinch proprioception in people with T2D and DPN. Because of the lack of such a device to measure hand proprioception, we purpose to use a novel apparatus made at our laboratory to measure proprioception in a functional manner (Chapter 2).

The dissertation work is highly significant for two main reasons. Firstly, this work will provide data to establish the basis for proper interventions and prevention strategies for hand function deficits in T2D individuals with and without DPN. Detection of specific hand function deficits will allow for early intervention strategies to prevent further complications and to improve hand function. Secondly, improving the current rehabilitation programs dealing with hand function requires a better understanding of the actual deficits. The majority of the available clinical tests used to examine hand dexterity focus only on time as a measure of efficiency. Increasing the speed as a strategy to improve performance will not fix the underlying problems. Therefore, treatment plans should focus on why subjects take a longer time to perform a specific task rather than focusing on increasing speed without sufficient understanding of the underlying problems. This is critical for physical therapists when following up with a treatment strategy that focuses on proprioceptive and grip force control deficits.

1.10. Specific Aims

This dissertation will potentially clarify the nature and magnitude of the upper extremity dysfunction related to T2D and DPN. Three central aims directed this research.

1. Examine pinch proprioception sense in people with T2D with and without DPN (Chapters 2 & 3). If it is commonly known that DPN causes sensorimotor deficits, then the proprioception sense of the fingers might be affected. It was hypothesized that people with T2D+DPN would exhibit larger pinch error differences compared to people with T2D only and controls. Before we could test these hypotheses, we had to test whether our device and methods were reliable in measuring proprioception sense as well as capable of detecting proprioceptive deficits in the presence of vibration. Indeed, healthy subjects were able to reproduce the same results on different days of testing, and we were able to detect proprioceptive deficits under the influence of vibration. Furthermore, in Chapter 3, pinch proprioception (accuracy and precision) was deteriorated only in the DPN group. In order to understand the role of muscle spindles in pinch proprioception, the contribution of tactile sensory deficits to pinch proprioceptive deficits were explored. The results showed weak to moderate correlations indicating a bigger role of possible muscle spindle damage to pinch proprioceptive deficits.

2. Determine the anticipatory and reactive grip force control in people with T2D with and without DPN (Chapter 4). If it is commonly known that DPN causes sensorimotor deficits, then grip force control might be affected. It was hypothesized that people with T2D+DPN would exhibit a higher grip force magnitude than people with T2D only and healthy controls. Other parameters of grip force control were explored. Results showed that subjects with T2D+DPN showed higher grip force magnitude as well as longer latencies when lifting an object while T2D alone showed no differences from the healthy group.

3. Determine the associations between grip force control, sensory, and hand dexterity measures in people with T2D and DPN (Chapter 5). In the presence of T2D and DPN, pinch proprioception, grip force control, and hand dexterity are affected. Understanding the interplay among these measures is key to achieving accurate diagnoses and best treatment plans for hand function deficits in this population. It was hypothesized that the sensory measures (tactile and proprioceptive) would be positively correlated with higher grip force magnitude and longer time to perform dexterity tasks. It was found that deficits in pinch proprioception were more positively correlated with time parameters as compared to tactile sensation, where it was found to be more correlated with grip force magnitude. The results showed possible mechanisms responsible for hand dexterity deficits and highlighted mechanisms responsible for such deficits.

In summary, the presented work in this dissertation has or will lead to the submission of 4 unique manuscripts: 1) pinch aperture proprioception: reliability and feasibility study (published in the Journal of Physical Therapy Science) [115], 2) the impact of diabetic peripheral neuropathy on pinch proprioception (published in the Journal of Experimental Brain Research) [116], 3) the impact of type 2 diabetes and diabetic peripheral neuropathy on reactive and predictive grip force control (to be submitted to the Journal of Clinical Neurophysiology), 4) The associations between grip force control, sensory, and hand dexterity measures in people with type 2 diabetes and diabetic peripheral neuropathy (to be submitted to the journal of hand therapy).

Chapter 2 Preface

In Chapter 1, previous work on proprioception was presented. This included the theoretical basis of how proprioceptive signals are generated, transmitted, and processed. Different methods exist on how proprioception is measured, yet there is still a limitation. Specifically, the current methods are not relevant to the majority of tasks performed in everyday life, such as using a pair of scissors. Having established this foundation of existing knowledge, Chapter 2 explores a new method to measure proprioception between the index finger and thumb. The reliability and feasibility of the novel device and methods were established.

Chapter 2: Pinch Aperture Proprioception: Reliability and Feasibility Study

This Chapter has previously been published as an open access article and is reprinted here with adaptations. Yahya A, von Behren T, Levine S, Dos Santos M. Pinch aperture proprioception: reliability and feasibility study. Journal of physical therapy science. 2018;30:734-40 doi: 10.1589/jpts.30.734.

2.1. Abstract

To establish the reliability and feasibility of a novel pinch aperture device to measure proprioceptive joint position sense. The reliability of the pinch aperture device was assessed in 21 healthy subjects. Following familiarization with a 15° target position of the index finger and thumb, subjects performed 5 trials in which they attempted to actively reproduce the target position without visual feedback. This procedure was repeated at a testing session on a separate date. In addition, extensor tendon vibration was applied to 19 healthy subjects, and we investigated the performance under vibration and no-vibration conditions. Pinch aperture proprioception was also assessed in two individuals with known diabetic neuropathy. The results showed that the pinch aperture device demonstrated excellent reliability in healthy subjects, and the tendon vibration disrupted pinch aperture proprioception, causing subjects to undershoot the target position "15°". This tendency to undershoot the target position was also noted in individuals with diabetic neuropathy. This study describes a reliable, feasible, and functional means of measuring finger proprioception. Further research should investigate the assessment and implications of pinch aperture proprioception in neurological and orthopedic populations.

2.2. Introduction

The awareness of position and movement of the body and its segments without visual cues is known as proprioception [58, 117]. Proprioceptive feedback signals are collectively derived from mechanoreceptors -- or "proprioceptors" as coined by Charles Sherrington more than 100 years ago [118]-- located in the skin, joints, ligaments, tendons, and muscle [45-48]. The stresses or strains signaled by the mechanoreceptors travel through the peripheral nerves into the spinal cord to be processed in the central nervous system (CNS), which produces the sense of one's body position and movements [49]. For instance, during an everyday task of object manipulation between the fingers, the proprioceptive feedback has a crucial role in the position of the arm, hand, and fingers as well as guiding the movement from the starting to the ending points [119-121]. In addition, grip force control studies suggest that proprioception is important for updating anticipatory or online commands to control for the magnitude of grip forces and the stability of joints [122]. Hence, in the presence of proprioceptive deficits, manual activities that require fine finger movements and force are impaired. Such deficits can be the result of musculoskeletal injuries and neurological diseases affecting peripheral and central nerve structures like peripheral neuropathy, spinal cord injuries, multiple sclerosis, stroke, and others [67, 72, 73, 83, 84, 123-126].

A common clinical method used to measure finger proprioception, as part of peripheral neurological examination, is the "up or down" test applied at the distal interphalangeal joint while the patient keeps his/her eyes closed [51]. Experimentally, proprioception in the index finger was investigated via a novel apparatus, which isolates the index finger, allowing full flexion and extension of the metacarpophalangeal joint while preventing the movements at the distal and proximal interphalangeal joints [56]. The ability to reproduce the desired position was measured by the difference between the finger positions with and without visual feedback [56].

The device used by these authors provides a quantitative measure of proprioception as compared to the traditional/clinical method, but still lacks the relevance to many functional tasks. For instance, these clinical or experimental methods for testing proprioception do not consider the complexity of natural grip function, which involves multiple fingers acting simultaneously during daily manual tasks, especially the pinch between index finger and thumb that are responsible for several fine motor skills. Recently, only one study has investigated proprioception between index finger and thumb using the finger active movement extent discrimination assessment (FAMEDA), which involved the subjects pinching a device with their index finger and thumb in the presence of a "stopping point" on five different predetermined aperture sizes [57]. Proprioception assessed through this method (i.e., using predetermined endpoints for the position of the joint based on signal detection theory) takes into account that the majority of decisions subjects make about the target endpoint are clouded with uncertainty [127-130]. Nonetheless, joint position reproduction, which requires the subjects to replicate a previously given position in space, is the most commonly test used in clinical sites[131]. In addition, it is still unknown whether the pinch movement proprioception (even the method aforementioned) is able to detect proprioceptive deficits. While hand proprioception deficits are common among people with musculoskeletal and neurological disorders [67, 72, 73], to our knowledge, no study has investigated pinch aperture proprioception using joint position reproduction sense. In this study, we defined pinch aperture as the distance between the thumb and index finger during the performance of movement towards one another as when executing a pinching grasp.

The pinch aperture proprioception is important to perform a variety of tasks such as buttoning a shirt, picking up small items, writing, and lifting objects with different weights. In

fact, many studies have proposed the importance of proprioception in many manual tasks and its relevance in grip force control abilities [132, 133]. Therefore, there is a need for a reliable portable apparatus to measure pinch aperture proprioception. The purpose of this study is to test the reliability of a novel and simple device designed to measure pinch aperture proprioception. In addition, this device will be tested to detect potential proprioceptive deficits generated by vibration and neurological diseases. Our hypothesis is that the tested device will be reliable and able to detect proprioceptive impairments during vibration and in patients with neurological diseases.

2.3. Subjects and methods

A total of 21 healthy subjects (11 females and 10 males between 21 and 51 years) were recruited to test for the reliability of the new device, and 19 subjects of those (11 females and 8 males between 21 and 51 years) were enrolled in the vibration study. We also tested 2 subjects (AJY and MJS) with diabetic peripheral neuropathy (DPN) as a result of type 2 diabetes (T2D), and two healthy matched for age, gender, and handedness (SRF and SJM). The demographic and clinical data for the DPN subjects and the healthy matched subjects are summarized in table 1. The two subjects with DPN were screened for diabetes by using glycosylated hemoglobin (HbA1c) following the American diabetic association guidelines. The presence of neuropathy was confirmed using a battery of tests performed on the lower extremities that include the use of pinprick (tested using a safety pin), light touch (10g monofilament), vibration using the on-off method (128hz tuning fork applied on the bony prominence of the big toe proximal to the nail bed), position sense of the big toe (up or down), bilateral knee and ankle reflexes (Taylor Percussion Reflex-Hammer), and temperature sensation (Darco Temp Touch) [134, 135]. In addition, subjects were asked about symptoms of pain, loss of balance, numbness, tingling, upper limb sensation, and general weakness. They were also tested for index finger and thumb

sensation via Semmes-Weinstein monofilament examination (SWME) and 2-point discrimination (2PD) test, which confirmed decreased sensation in the upper limb as well. In addition, hand dexterity was assessed for the DPN subjects, and the healthy control matched subjects using the Moberg pickup test. All subjects were right handed (confirmed by the Edinburgh Inventory) with no history of hand injuries and showed no other pathological conditions, except for the two diabetic patients with DPN. All subjects were volunteers, and the informed consent was signed before data collection following the guidelines of the Human Subjects Committee at the University of Kansas Medical Center (STUDY00003358).

Table 1- Clinical Features

Groups	Age	BMI	HbA1c	2PD	SWME (g)	MPUT	Pinch Aperture
Control							
SRF (female)	50	24.24	5.3	4	0.4	25.06	15±0.6[a]
SJM (male)	51	24.11	5.1	5	0.16	24.89	15±0[a]
Neuropathy							
AJY (female)	53	37.46	7.7	6	0.16	34.13	20.3±1.5[a]
MJS (male)	55	23.62	6.5	6	0.6	45.8	20±2.65[a]

BMI: body mass index; HbA1c: glycated hemoglobin A1c; 2PD: 2-point discrimination; SWME: Semmes-Weinstein monofilament examination; MPUT: Moberg pickup test.
[a] Average and standard deviation from three trials

2.3.1. Pinch Proprioception

The device that we used to measure pinch aperture proprioception in this study was a lab-made device that includes a modified goniometer affixed on a cardboard box (4×17×10 centimeters; height, length, and width respectively). Two rounded pads were attached to both ends of the goniometer arms, which served as the subjects' index finger and thumb placement. The attachment between the box and the goniometer allows the fulcrum of the goniometer (along

with his body) to move within a 1-inch distance to compensate for any angular movement of the moving fingers (Figure 2.1).

A lab-made vibrator was used to disturb the proprioception of the thumb and index finger through the vibration of their extensor tendons (see details below). The vibrator consisted of 5 phone vibrators (DC3V/0.1A 1.5V/0.05A 10×2.7 mm Coin Mobile Vibration Motor) connected to universal AC plug-in Adapter (3-volt output, 30W power). This power allowed the vibrators to operate at a frequency of 100 hertz.

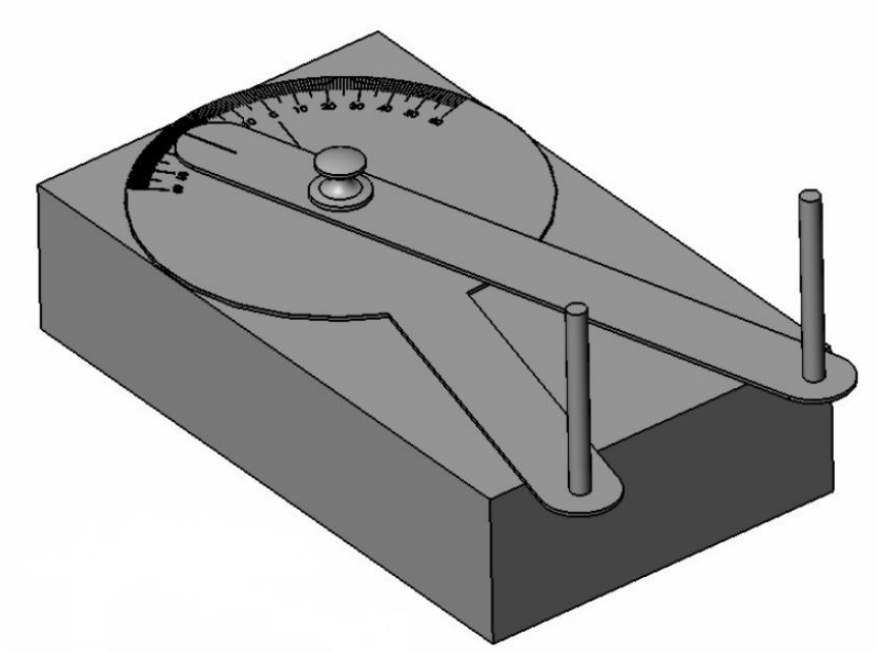

Figure 2.1. Schematic representation of the pinch aperture proprioception device.

2.3.2. Procedure

Subjects were asked to place the tips of their index finger and thumb along the perpendicular pads attached to the modified goniometer. Subjects placed their tested hand on the table and were asked to keep the wrist in a neutral position allowing their index and thumb fingers to move freely. First, subjects were familiarized with the device by letting them squeeze both arms of the modified goniometer throughout the full range using their index finger and thumb (pinch aperture) once. The full range of the device corresponded to 30^{o} of maximal pinch opening (a distance of 6.99 cm between the tip of index finger and thumb) to the complete closure (i.e., when one of the goniometer arms touched the opposing round pad). The test began with the examiner asking the subjects to close their eyes and positioned the device along with the subjects' fingers to the starting point, which was 30° of pinch aperture; subsequently, the examiner adjusted the arms of the goniometer to a 15° of pinch aperture (target point), which corresponded to a distance of approximately 3.5 cm between the index finger and thumb. The pinch apertures of 30^{o} and 15^{o} correspond with aperture sizes for holding a regular cup and a large medicine container, respectively. We have used just one testing target point in this study because past studies have shown this approach produces better validity and reliability of the measures[136, 137]. At the target position with eyes closed, the subjects were required to concentrate in this position and memorize the exact aperture size they were in. Thereafter, the examiner passively moved the goniometer arms along with the subject's fingers to the starting position of the test at 30°. During this maneuver, the subjects were instructed to follow the goniometer movement without resisting the pinch aperture. The subjects performed 2 memorization tasks to the target point (15^{o}). Finally, the subjects were instructed to actively move the goniometer arms from the starting point back to the target point that was previously memorized (i.e., from 30° to 15°). Once they reached the memorized target, they were instructed

to inform the experimenter by saying the word “here.” Subjects were instructed to keep their fingers in contact with the perpendicular pads at all times during the testing session to allow for consistency of finger placements throughout the experiments.

For reliability assessment **(experiment 1)**, the subjects performed 5 trials on the first day of testing and repeated 5 additional trials on a consecutive day under the same conditions. For the disturbed proprioception via vibration **(experiment 2)**, the identical experimental procedure described above was performed, including the hand placement and starting (30°) to target point (15°) positions. The subjects were asked to perform 3 testing trials of matching the target under two experimental conditions: with and without vibration. Five vibrators were positioned as follows: 2 vibrators were attached over the extensor tendon of the index finger (approximately ¾ of an inch and 1 ¼ inch proximal to the first knuckle, respectively). In addition, 2 vibrators were positioned over the extensor pollicis longus tendon, one directly over the wrist joint and the other over the extensor pollicis longus tendon just below the metacarbo-phalangeal joint. The fifth vibrator was positioned over the extensor pollicis brevis and the abductor pollicis longus tendons, approximately over the wrist joint. The position of the vibrators was based on previous studies [138, 139]. An adhesive tape was used to fix the vibrators to the subjects’ skin. Subjects were asked each time before the experiment if they felt any restrictions on the movement of their fingers, and if so, the tape was adjusted accordingly.

After the practice trial for familiarization and two practice trials for memorization as described above, vibration was turned on, and subjects were asked to move the goniometer arms to the target endpoint. Vibration was applied for thirty seconds prior to moving the goniometer arms to allow for the vibration to take effect. The subjects were then asked to confirm whether they could feel the vibration effect. The order of vibration and no vibration was randomly

assigned between subjects. At least one minute of rest between the conditions (with and without vibration) was provided. A single examiner performed all experiments to eliminate potential variability between different testers.

The experiment with the two neurological patients **(experiment 3)** was used to determine whether our device has the potential to detect changes in pinch aperture proprioception in neurologic patients. Subjects performed 2 practice trials with eyes closed and an additional 3 trials of testing using the same target point (15°). The examiner used the same procedures described above for familiarization, memorization, and assessment trials.

2.3.3. Statistical analysis

The examiner wrote down, on an assessment sheet, all actual target angles reached by the subjects during all experiments and conditions. The principal outcome variable was the measured angles from the subjects' trials compared to the actual target position. All data were entered in an Excel spreadsheet for posterior analysis. For experiment 1, the average of all 5 trials performed each day was used to test for the reproducibility between day 1 and day 2 using the intra-class correlation coefficient (ICC) with a 95% confidence interval. A Bland-Altman plot was developed to represent the agreement of the measurements from day 1 and day 2. The differences between percentages of day 1 and day 2 were plotted against the mean target reached by the subjects during the two consecutive days. This shows how far the subjects were from the target across the two days. All assumptions were met to construct a Bland-Altman plot, which include no significant differences between the measurements on either day, and the trend of the data above and below the mean difference line are not significantly different, indicating no proportional bias [140]. For experiment 2, the average of the 3 trials was used for each subject to compare the differences between vibration and no vibration. Paired sample t-test was used to test for the difference between these two conditions. Alpha was set at 0.05 significance level, and

SPSS 16.0 for windows (SPSS Inc., Chicago, IL, USA) was used for data analysis. For experiment 3, we provided the mean values of 3 trials for each of the subjects with DPN and the healthy matched subjects.

2.4. Results

2.4.1. Experiment 1 (reliability)

We used a two-way random effect model. The average measure intra-class correlation coefficient (95% confidence interval) between day 1 and day 2 was 0.88 degrees (0.70-0.95). This shows a very good to excellent reproducibility over a two-day period ($p < 0.001$). Bland-Altman plot showed a small percentage of error between day 1 and day 2 (Figure 2.2). The average percentage of error is less than 2 percent between day 1 and day 2.

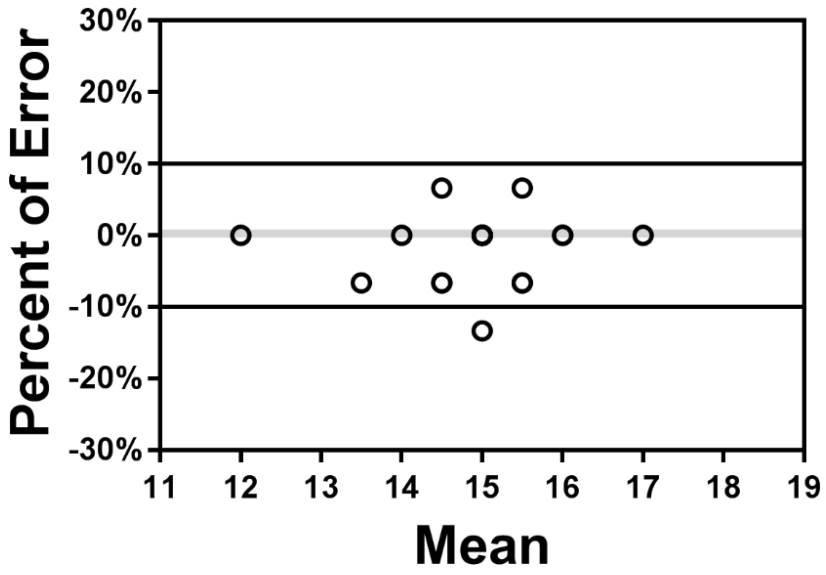

Figure 2.2. Bland-Altman graph of pinch aperture proprioception (n=21). The grey line represents the target value with no error. The black lines represent the percentage error (±10%) from the target value. The values on the x-axis represent the average reproduced pinch aperture proprioception measurements between day 1 and day2

2.4.2. Experiment 2 (vibration)

Applying vibration over the extensor tendons of the index and thumb fingers elicited changes in the pinch aperture proprioception. The majority of the subjects undershot the target during the vibration conditions. Figure 2.3 shows the mean values reached by the subjects during vibration (18.1°±2.59) and no vibration (14.8°±0.76) conditions, which were statistically significantly different between both conditions ($p < 0.001$).

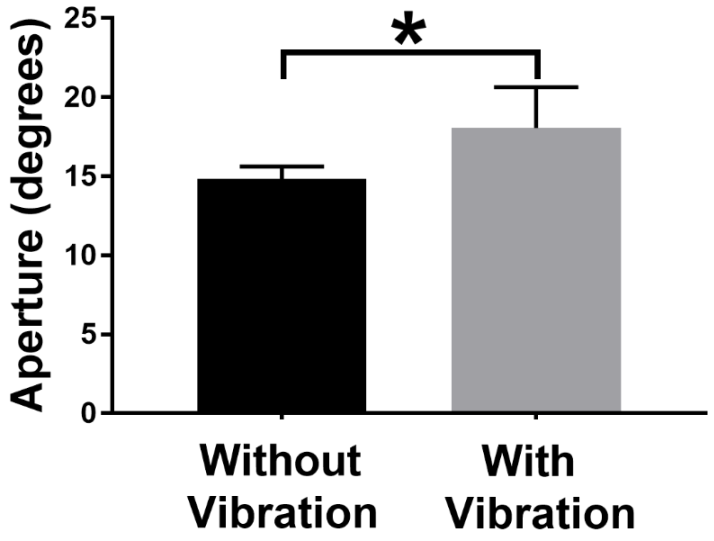

Figure 2.3. Means and standard deviations for the pinch aperture proprioception during the pinch tasks with and without vibration (n=19). * denotes significant differences ($p < 0.001$) between the conditions.

2.4.3. Experiment 3 (neurological subjects).

Table 1 shows the clinical evaluation results for the two subjects with DPN (AJY and MJS) and the two healthy controls (SRF and SJM). Both subjects with DPN undershot to the target with an average of 20.17° while the two healthy control subjects matched the target with an average of

15°. In comparison, the entire healthy control group who participated in the second experiment had an average of 14.8° without vibration.

2.5. Discussion

This study is the first to examine pinch aperture proprioception between the index finger and the thumb in a functional and clinically accessible way using the joint position reproduction. Our findings confirmed our hypothesis that our novel and simple device would show high reliability and has the potential to capture changes in pinch aperture due to proprioceptive disruption (vibration) and in patients with neurological diseases. In addition, our methods for this specific test are easy to follow, practical, and quick to apply, taking approximately 5 minutes to perform under normal conditions.

2.5.1. Experiment 1

The reliability study we conducted to test our device showed moderate to excellent reproducibility for the pinch aperture proprioception over two consecutive days. Similar reliability was observed in other studies investigating proprioception in the index finger only or between the index finger and thumb. For instance, Wycherley and his colleagues [56] measured proprioception of the index finger, specifically the metacarpophalangeal joint position sense over three consecutive days in a control group of 12 healthy subjects. The ICC (95% CI) was 0.96 (0.90-0.98) between days 1 and 2, 0.86 (0.67-0.94) between days 2 and 3, and 0.92 (0.85-0.96) between all days. In the present study, we had a larger sample size (21 subjects), and the ICC between days 1 and 2 was 0.88 (0.70-0.95). In Addition, the Bland-Altman plot (Figure. 4) shows that the healthy subjects had a low percentage of error (less than +/-10%), and the mean values cluster around 15^{o}. These are reasonable numbers that allow our device and methods to be used clinically [141].

Most of the previous studies have investigated the proprioception of the proximal interphalangeal joint of the index finger [56, 142-145]. Although such investigations are important, they do not represent the complex nature of the grasping maneuvers involved in the majority of the manipulative tasks we perform during ADLs, such as buttoning a shirt, holding a key, using a scissor, administering a medicine using an injection, and picking up pills. There is one study, however, that tested proprioception between the index finger and thumb, which was termed as FAMEDA [57]. This study tested index finger and thumb "pinch movement discrimination" in 8 healthy subjects using a similar experimental setup. They asked the subjects to actively pinch with the index finger and thumb bringing the device arms together at 5 different stopping points. Subjects were provided with 15 practice trials with visual feedback, while vision was occluded for the 50 testing trials. Although both studies by Han and his colleagues [57] and ours used different methods to test pinch aperture proprioception, the reliability values were higher in our study (i.e., the ICC was 0.85 between days 1 and 8 in their study while in our study the ICC was 0.88 between days 1 and 2). The principal difference between the methods of the study by Han et al. [57] and our study is that we used the joint position reproduction to test for proprioception, which is a common approach in clinical sites and only requires 3 to 5 repetitions to detect the position sense [131]. The method used by Han and his colleagues[57] was based on signal detection theory, which states that the majority of decisions we make are taken in the presence of some uncertainty, i.e., larger amount of trials is needed to establish certainty in the decision-making process about the aperture sizes being tested [129, 146]. In addition, they used the receiver operating characteristic (ROC) curve analysis to account for the probability of correct and wrong responses made by the subjects recalling the 5 different positions. In our study, we calculated the average of 3 to 5 testing trials [147]. Furthermore, in our study, the

practice trials were performed without visual feedback, while in the study by Han et al. [57], it was performed in the presence of vision. It is known that vision contributes to the sense of proprioception, and it can be argued that subjects might not have focused on the peripheral sense generated from muscle spindles and rather focused more on the central effort and the visual feedback fed into the internal model [148]. Finally, regardless of the two different techniques used, the results of both studies show that index finger-thumb aperture proprioception is reliable, and both methods have the potential to test the pinch aperture proprioception.

2.5.2. Experiment 2

The purpose of the second experiment was to determine the feasibility of our device in detecting disruptions in pinch aperture proprioception via tendons' vibration. Goodwin and colleagues [48] were the pioneers in applying vibration to a muscle tendon to excite muscle spindles. As such, the signal carried through the Ia afferent nerve fibers will be interpreted in the CNS as an elongation in the muscle fibers [68, 69]. In the study by Goodwin et al. [48], the subjects experienced more elbow flexion movement due to the biceps vibration, and the tracking forearm undershot the target when trying to keep both forearms parallel to each other. In addition, vibration to the tibialis anterior/soleus muscles produced a lengthening of the stimulated muscles perceived as plantarflexion/dorsiflexion, respectively [149]. Our findings agree with this previous research in which most of our subjects undershot relative to the target point when applying vibration to the tendons of thumb and index finger extensor muscles. Most importantly, our device and methods were able to detect such a disruption on the pinch aperture proprioception, which might facilitate the assessment of proprioception between the thumb and index finger. In addition, our apparatus and methods have greater potential to correlate its outcomes with outcomes of functional manual activities, which is our plan for future studies.

2.5.3. Experiment 3

In addition to disrupted proprioception provoked by tendon vibration, our device and methods were able to detect proprioceptive deficits in two patients with DPN due to T2D. AJY and MJS exhibit profound deficits on the big toe during vibration and temperature testing. As compared to the healthy controls, both subjects also showed worse sensation on the hands (via SWME and 2PD tests), which was consistent with DPN. Furthermore, MJS showed deficits in the toe-up and down maneuver, indicating proprioceptive deficits. Both subjects also performed the Moberg Pickup Test with eyes closed, which is known to test for proprioceptive deficits [132, 133]. In this test, subjects were asked to use the thumb and index finger when picking up the small items. Both subjects with DPN took a longer time to pick up small items as compared to the healthy matched subjects. This could possibly be related to pinch aperture proprioception deficits. However, no study has investigated the relationship between Moberg Pickup Test and pinch aperture proprioception deficits. Future studies should further investigate this premise.

2.6. Conclusion

This study provides a simple, novel, and clinical approach to test for pinch aperture proprioception. The device used by the present study has the potential to quantitatively and reliably measure pinch aperture proprioception deficits. This will help improve the diagnosis of hand and finger proprioception and current rehabilitation programs dealing with hand function that requires a better understanding of the actual deficits. This may be critical for occupational and physical therapists when following up with a treatment strategy that focuses on improving the proprioception of the hand and fingers. Future studies should investigate the reliability of the device between different therapists and in the neurological and orthopedic populations who have the potential to exhibit pinch aperture proprioception deficits such as patients with Parkinson's, stroke, carpal tunnel syndrome, and hand osteoarthritis. Thus, our present device and methods

can be used as another tool to measure proprioception in these subjects in the future. Finally, decrements in hand dexterity can be correlated with proprioceptive deficits affecting the pinch aperture, which must be the topic for future studies.

Chapter 3 Preface

Chapter 2 established the foundation for testing finger proprioception in a functional way. We established the reliability and feasibility of the device and methods. It is known that T2D and DPN affect the upper and lower extremities. Although many studies have shown proprioceptive deficits affecting the lower extremities, it is as important to understand the contribution of T2D and DPN to finger proprioception of the upper extremities. However, the evidence is very limited on the impact of T2D and DPN on the proprioception sense of the fingers. Chapter 3 explores the impact of T2D and DPN on pinch proprioception utilizing the device and methods described in Chapter 2. Specifically, we established the contribution of T2D and DPN as compared to T2D alone and healthy controls.

Chapter 3: The Impact of Diabetic Peripheral Neuropathy on Pinch Proprioception

This Chapter has previously been published in whole and is reprinted here with adaptations. Yahya A, Kluding P, Pasnoor M, Wick J, Liu W, Dos Santos M. The impact of diabetic peripheral neuropathy on pinch proprioception. Experimental brain research. 2019 doi: 10.1007/s00221-019-05663-3.

3.1. Abstract

This study aims to investigate the impact of type 2 diabetes (T2D) and diabetic peripheral neuropathy (DPN) on pinch proprioception and to establish the correlations with sensory impairments. We collected data from a total of 36 participants (healthy, n=12; T2D without DPN, n=11, and T2D+DPN, n=13), all matched for age, 60±6 years. Pinch proprioception was determined through 3 trials of attempts to actively reproduce 15° of pinch position without visual feedback. Sensation was tested through the two-point discrimination and Semmes-Weinstein Monofilaments applied on the fingers. Sensory measures were correlated to pinch proprioception measures via Spearman's rank test. The T2D+DPN group showed significant decrements in accuracy and precision as compared to the T2D-only and the healthy groups; no significant differences were found between T2D-only and healthy. Moderate correlations between pinch proprioception and sensory measures. Our results showed pinch proprioception disruption in people with T2D+DPN, but not in people with T2D-only. The awareness of pinch proprioceptive deficits is paramount for the safety of individuals with T2D and DPN. Moderate correlations between sensory impairments and pinch proprioceptive deficits suggest that not only superficial/discriminative sensation is implicated in proprioceptive decrements. Other mechanisms, such as damage to muscle spindles or central nervous system associated with T2D+DPN, warrant further investigations.

3.2. Introduction

Sensory nerves carry important proprioceptive information about the position of our body parts in relation to each other and to the surrounding environment [46, 58, 63]. Proprioceptive signals are derived from mechanoreceptors located in the skin, joints, tendons, ligaments, and muscles [58, 118]. In particular, muscle spindles play a major role in the sense of proprioception throughout the range of joint motion [45, 63]. Collectively, the action potentials generated from the mechanoreceptors are carried through afferent nerve fibers and processed in the central nervous system (CNS) to provide the sense of proprioception [118].

The sense of proprioception will be disrupted by any interference with the generation, transmission, and processing of the proprioceptive signals [150, 151]. The presence of proprioceptive deficits in the upper extremities with sensory deafferentation has been shown in a multitude of studies [152, 153]. For instance, both accuracy and precision of the thumb, while performing flexion movements, at the interphalangeal joint, were severely disrupted in a subject suffering from peripheral sensory neuropathy of unknown cause [152]. Likewise, proprioception movements at the index finger were also impaired in a subject with right upper limb deafferentation due to post-surgical removal of a tumor located at the level of medulla oblongata [153]. In addition, severe cases of nerve damage to the CNS, such as multiple sclerosis and stroke, are associated with significant finger proprioceptive deficits. This is mainly due to impairments in the processing of the proprioceptive signals received from, otherwise, intact mechanoreceptors and afferent nerve fibers [53, 54, 154, 155].

In a disease such as type 2 diabetes (T2D), peripheral nerves are susceptible to damage [156-158], and hence, that might lead to finger proprioceptive deficits. Specifically, the most common form of nerve damage in subjects with T2D is diabetic peripheral neuropathy (DPN), with distal symmetric sensorimotor polyneuropathy as the most common form that can affect

upper and lower extremities [27, 159]. Research has mostly shown proprioceptive deficits to occur in the lower extremities in individuals with T2D+DPN [36, 72, 73]. On the other hand, proprioceptive deficits in the upper extremities in subjects with T2D+DPN has not been as commonly studied. One study by Ochoa, Gogola [160] explored the effect of median nerve blocks on finger proprioception in healthy subjects and in subjects with T2D. This type of anesthesia blocks sensory nerve signals from areas innervated by the median nerve. Finger proprioceptive disruptions were shown to be more pronounced in subjects with T2D as compared to healthy subjects under the influence of median nerve blocks. This preliminary evidence on the impact of anesthesia on sensation is not specific to either mechanoreceptors from the skin or muscle spindles. In addition, it was not investigated whether DPN might be the main contributing factor for such proprioceptive deficits. Using anesthesia to unveil any concealed proprioceptive deficits is not feasible for clinical purposes. Nevertheless, there is strong evidence showing that DPN severely impacts the sense of proprioception [36, 72, 73]. However, the damage from T2D+DPN, specifically, to finger proprioception generated by muscle spindles is still unclear. Furthermore, the difficulty of observing finger proprioceptive deficits under normal circumstances can be attributed to the limitations of the current testing methods used to screen for proprioceptive deficits [147].

The most common proprioceptive test used during a clinical neurological examination is the finger up or down test performed at the distal interphalangeal joint and at the metacarpophalangeal joint of the index finger [51, 52]. In this test, the examiner would passively move the subject's finger in up and down movements. Subjects would be asked to keep their eyes closed and determine what direction their finger moved. However, this traditional approach has been suggested to be subjective, insensitive, and unreliable [52-55]. In addition, this

approach lacks the functional relevance to most of the dexterous tasks, which require the use of more than just one finger. Contrary to passive movements, active joint position reproduction has an advantage to test proprioception during an actual voluntary movement requiring more activity of the muscle spindles (two bags and chain fibers, static and dynamic) [47, 63]. Multiple studies have used active joint position reproduction to test for the sense of proprioception at different joints such as metacarpophalangeal joint of the index finger [56], wrist joint [161], and elbow joint [162]. In addition, the precision pinch between the index finger and thumb is responsible for the majority of tasks that require dexterous manipulation during daily living such as administering an insulin injection, picking up pills, using pair of scissors, writing, and buttoning a shirt. In previous work, we tested a novel device designed to assess the pinch proprioception quantitatively in healthy participants under the effect of extensor tendon vibration and in two subjects with T2D+DPN [115]. Contrary to median nerve blocks, vibration has been shown to influence muscle spindles and hence provide more evidence on the contribution of muscle spindles to the sense of proprioception [45, 48, 63, 67]. Hence testing for pinch proprioception can be used as part of the comprehensive screening for DPN and potentially help improve rehabilitation programs focused on hand function. For instance, rehabilitation programs should focus on raising the awareness of possible proprioceptive deficits that might be responsible for missing a target, bumping into objects, and dropping them off the hand.

Therefore, the main objective of this study is to investigate the impact of T2D and DPN on the accuracy and precision of pinch proprioception. We hypothesize that subjects with T2D+DPN will exhibit impairments in pinch proprioception as compared to age-matched T2D-only and healthy participants. A secondary objective is to establish the level of relationship between tactile sensory and pinch proprioceptive deficits. We hypothesize that sensibility

measures will be positively correlated with the decrements in accuracy and precision of the pinch proprioception. This will help us understand the role of muscle spindles by investigating the contribution of tactile sensory aspects to the sense of proprioception.

3.3. Methods

This is a cross-sectional study, and all measurements were collected in a one day setting for each subject. Three distinct groups were matched for age, and all testing was performed on the dominant hand. Hand dominance was confirmed using the Edinburgh Handedness Inventory [163]. The local ethics committee at the University of Kansas Medical Center approved this study, and all subjects signed an approved informed consent document before participating (STUDY00003358).

3.3.1. Participants

Subjects were included if they were healthy or if they had a diagnosis of T2D with and without DPN. We included subjects with ages between thirty to seventy years. Participants were excluded if they reported a history of type 1 diabetes, prediabetes, any injuries to the hands that might interfere with any of the testing procedures, history of neurological conditions (stroke, Parkinson's disease, multiple sclerosis, and neuropathy symptoms due to chemotherapy) or musculoskeletal conditions such as myasthenia gravis.

In addition, we screened for acute symptoms of carpal tunnel syndrome, as confirmed by Phalen's test and Tenile's sign. In the Phalen's test, subjects were asked to push the dorsal surface of both hands with complete and forced flexion of their wrists for 30 to 60 seconds. In the Tenile's sign, the examiner lightly tapped over the course of the median nerve at wrist joint Subjects were excluded if they had a positive sign that provoked symptoms of tingling or pins and needles from both tests [164]. We also screened for severe limited range of motion, as confirmed by the prayer sign. Subjects were asked to approximate fingers and palms while

pressing hands together. The prayer sign is classified into stage 0; normal findings on both hands, stage 1; inability to approximate one or two interphalangeal joints (IPJ) involved, stage 2; inability to approximate 3 or more IPJ, stage 3; hand deformity at rest [165]. Subjects were excluded if they had severe deformity at rest (stage 3).

3.3.2. T2D and DPN screening

We differentiated between the three groups based on the presence or absence of T2D and DPN. T2D was defined by a positive confirmation to a question asking whether any healthcare provider has told them that they have T2D. In addition, following the American Diabetes Association guidelines [166, 167], Glycated Hemoglobin A1c (HbA1c) testing was conducted (PTS Diagnostics Polymer Technology Systems A1CNow+™ Systems [168]). This is to confirm the presence or absence of T2D diagnosis across the groups. Blood was drawn by a fingerstick at the tips of the fingers. The diagnosis of T2D is based on a value of 6.5% (48 mmol/mol) or above, prediabetes between 5.7% and 6.4% (39 and 46 mmol/mol), and healthy less than 5.7% (39 mmol/mol) [166, 167].

Our subjects in the T2D+DPN group have a confirmed diagnosis of DPN by a neurologist clinical exam and nerve conduction studies. To confirm the absence of DPN in the T2D-only group, testing was completed using a 10g monofilament (protective sensation), superficial pain sensation, and vibration by the on-off method on the big toe to screen for neuropathy. If subjects had five incorrect responses out of 8 trials for any of these three tests, that would indicate neuropathy with high sensitivity and specificity [134, 135]. In addition, other clinical examinations included position sense of the big toe (up or down test), bilateral knee and ankle reflexes (using Taylor Percussion Reflex-Hammer), and temperature sensation (using Darco Temp Touch). Subjective examination included asking about symptoms of pain, loss of balance, numbness, tingling, upper limb sensation, and general weakness.

In people with T2D+DPN, the severity of neuropathy was determined with a clinical screening measure of subjective and physical exam as described above with a total possible score of 19 points and classified into mild (6-8), moderate (9-11), and severe (12 and above) [134, 135].

3.3.3. Hand sensibility testing

Sensory deficits on the tips of the fingers innervated by the median nerve were assessed using the Semmes Weinstein monofilament examination (SWME) (NC12775, North Coast Medical Inc.) at the tips of the thumb, index and middle fingers 3 times on each site [169]. The monofilaments were pressed until they bowed, making a C-shape against the finger's skin while the participants were asked to keep their eyes closed and verbally respond whenever they felt the touch of the monofilament on their fingers. There are five levels that represent the severity of tactile sensory dysfunction. We recorded the perceived threshold based on the monofilament size that the subjects were able to detect. If the subjects were not able to detect the smallest monofilament, we applied a larger one until they do. Normal function was represented with 4 monofilament sizes ranging from 1.65 to 2.83, diminished light touch with 2 monofilament sizes that included 3.22 and 3.61, diminished protective sensation with4 monofilament sizes ranging from 3.84 to 4.31, loss of protective sensation was represented with 9 monofilament sizes ranging from 4.56 to 6.45, and loss of deep pressure sensation with 1 monofilament size of 6.65 [170, 171]. If the perceived threshold was different between the three fingers, we reported the average score. We collected data from both hands, but we utilized data from the dominant hand only.

The 2 points discrimination (2PD) testing was performed on the same locations indicated above for three times on each location alternating between one and two points randomly (2 Discrim-A-Gon, 12-1492, Baseline 2-point discriminator set). We recorded the smallest distance between

two points that can be perceived by the subjects. A distance of 5mm is considered normal, 6 to 10mm is fair, and 11 to 15mm is poor [172].

3.3.4. Pinch proprioception testing

The device used to test for pinch proprioception is described in detail in our previous study [115]. In short, it included a modified goniometer with its fulcrum fixed on top of a small cardboard, Figure 2.1. The goniometer arms extended out the cardboard's edge and included circular pads on its extremities attached perpendicularly for the fingertip placement. All participants were asked to rest their dominant hand on the table and to hold the perpendicular pads, using their index finger and thumb. Subjects were familiarized with the device and then performed two practice trials starting at 30° and ending at 15° with vision occluded. The pinch of 30^{o} and 15^{o} correspond with aperture sizes for holding a regular cup (6.99 cm) and a large medicine container (3.5 cm), respectively. In these practice trials, the index finger and thumb were moved passively by the examiner to the target position (15°), and the participants were given enough time (30 seconds, on average) to memorize that position. Subsequently, during the testing condition, the examiner moved the goniometer arms to the starting position (30°) and instructed the participant to pinch their fingers actively trying to reproduce the target position (15°) without visual feedback. Three testing trials were performed. Accuracy was defined as the average absolute error difference from the target position and precision as the variability of the three testing trials represented by the standard deviation [123].

3.3.5. Pinch strength testing

Pinch strength was assessed utilizing a pinch gauge (PG-30, B&L Engineering Santa Fe, CA, USA) following the recommendations of the American Society of Hand Therapists [173, 174]. Subjects were seated on an armless chair with shoulder abducted and neutrally rotated while the forearm was held at 90 degrees of elbow flexion. Both the forearm and the wrist were

held at a neutral position (midway). Subjects were asked to use their thumb and index finger to press and hold the pinch gauge for at least 5 seconds using their maximum force. A break of 30 seconds was given upon completion of each trial of maximal pinch force to prevent fatigue. The average of three trials was recorded. Subjects were encouraged to perform the activity as hard as they could. Verbal feedback was provided in the same tone, such as (squeeze the device as hard as possible). Only the dominant hand was tested.

3.3.6. Data analysis

The sample size was based on our preliminary study of pinch proprioception under the effect of extensor tendon vibration (effect size of 1.68) [115] and another study investigating proprioception of the ankle joint in individuals with DPN (effect size of 0.55) [72]. A total of 9 subjects, 3 in each group, and a total of 36 subjects, 12 in each group, was sufficient to show group differences with 80% power, respectively. Therefore, the larger sample size was considered for this current study (36). Dependent variables were tested for normality with the Shapiro-Wilk test. Kruskal-Wallis test or one-way ANOVA were used to compare demographic and clinical data between groups. Post-hoc analyses tested the differences between groups utilizing Bonferroni adjustments, and alpha (0.05) was divided by the number of groups (3) yielding 0.0167. As for the correlations, we divided 0.05 by the number of comparisons (4) yielding 0.0125. All p-values are two-tailed.

Pinch proprioception data was analyzed based on the accuracy (the average of absolute error difference of the three testing trials) and precision (the standard deviation of the actual three testing trials) of reproducing the target position (15°). Correlations between tactile sensory measures (SWME and 2PD) and pinch proprioception variables were drawn using Spearman's rho coefficient. In addition, a secondary analysis was performed where the coefficient of determination (R squared) was used to account for the variability in proprioceptive measures

(accuracy and precision) that can be explained by sensory measures (SWME and 2PD). Alpha was set at 0.05, and all data were processed either in Excel or in SPSS.

3.4. Results

The demographic and clinical data of the three groups are presented below. A total of 36 participants (18 males and 18 females) took part in this study: 12 healthy participants (7 males, 58±6 years), 11 participants with T2D-only (5 males, 61±6 years), and 13 participants with T2D+DPN (6 males, 60±6 years). The majority of subjects were right-handed (one left-handed in the healthy control group and 2 left-handed in the T2D+DPN group). We were successful in matching for age as there were no significant differences between the three groups (ANOVA: $F(2, 33) = 0.84$, $p = 0.4$), Table 3.1. One healthy subject was referred to his primary physician to confirm the presence of T2D based on our HbA1c findings. As the diagnosis of this subject was confirmed, new informed consent was signed, and the data were included in the T2D-only group. Two subjects in the T2D+DPN group were originally not aware that they have neuropathy. The DPN diagnosis of these two subjects was later confirmed by a neurologist using nerve conduction studies and nerve biopsies.

Table 3.1- Participants' Demographics, Clinical Characteristics, and Pinch Proprioception

	HC (12)	T2D-only (11)	DPN+DPN (13)	P value
Gender (female/male)	5/7	6/5	7/6	
Age (years)	58±6	61±6	60±6	0.44
BMI (kg/m^2)	24.5±2.4	31.1±5.4	34.2±4.5	<0.001
Right-hand dominance	11/12	11/11	11/13	
HbA1c (%)	5.3±0.3	7.2±1.04	7±0.7	<0.001
Diabetes duration (years)	N/A	9.4±6.6	13.1±9.1	0.27[a]
Neuropathy duration (years)	N/A	N/A	4.8±3.5	
Neuropathy severity (n)				
Mild	N/A	N/A	4	
Moderate	N/A	N/A	8	
Severe	N/A	N/A	1	
2PD (mm)	4.8±1	5±1	6±1	<0.001[b]
SWME (threshold)	3.6±0.4	3.6±0.1	3.8±0.7	0.058[b]
Trigger finger (n)	0	2*	1*	
History of carpal tunnel syndrome (n)	0	1*	1^	
Prayer sign (n)	4	5	7	
Pinch Proprioception:				
Accuracy (degrees)	0.67±0.67	0.33±1.67	3.67±3.84	0.002[b]
Precision (degrees)	0.58±0.42	0.58±0.57	2±3	0.003[b]
Pinch strength (Newton)	65.3±22.2	59.7±16.7	68.6±17.9	0.53

HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, type 2 diabetes and diabetic peripheral neuropathy; BMI, body mass index; HbA1c, glycated hemoglobin A1c; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination.

Data represented as mean ± standard deviation unless otherwise indicated. P values from one-way ANOVA test.

[a] P-value from an independent t-test.

[b] Data represented as median and interquartile range. P-values from Kruskal-Wallis test.

* Non-dominant hand

^ Dominant hand

HbA1c (ANOVA: $F(2,33) = 22.2$, $p < 0.001$) and BMI (ANOVA: $F(2, 33) = 15.4$, $p < 0.001$) differed significantly by group. Specifically, post-hoc analyses showed significantly lower HbA1c values in the healthy control group (Mean, (95% CI): 5.3, (5.2, 5.5) as compared to T2D+DPN (7, (6.5, 7.5), p < 0.001) and T2D-only (7.2, (6.5, 7.9), p < 0.001). BMI was significantly lower in the healthy control group (24.5, (23.2, 26.5) as compared to T2D+DPN (34.2, (31.5, 36.9), p < 0.001) and T2D-only (31.1, (27.5, 34.7), p < 0.001). No significant differences in HbA1c, diabetes duration, and BMI between the T2D+DPN and T2D-only groups, Table 1. No significant differences between all groups in SWME (Kruskal-Wallis: $H(0.05, 2) = 5.7$, $p = 0.06$), and pinch strength (ANOVA: $F(2,33) = 0.65$, $p = 0.53$). Groups also differed on the 2PD (Kruskal-Wallis test: $H(0.05, 2) = 21.03$, $p < 0.001$), Accuracy (Kruskal-Wallis: $H(0.05, 2) = 12.7$, $p = 0.002$), and Precision (Kruskal-Wallis: $H(0.05, 2) = 11.8$, $p = 0.003$). The 2PD showed significantly higher deficits in the T2D+DPN group (Median, IQR: 6, 1) as compared to T2D-only (5, 1, p = 0.001) and healthy controls (4.8, 1, p < 0.001). Accuracy showed significantly larger errors in the T2D+DPN group (3.67, 3.84) as compared to T2D-only (0.33, 1.67, p = 0.003) and the healthy control groups (0.67, 0.67, p = 0.002). Precision showed significantly larger errors in the T2D+DPN group (2, 3) as compared to T2D-only (0.58, 0.57, p = 0.006) and healthy control groups (0.58, 0.42, p = 0.002). The T2D-only did not show significant differences from the healthy control group in accuracy and precision, Table 3.1, Figure 3.1.

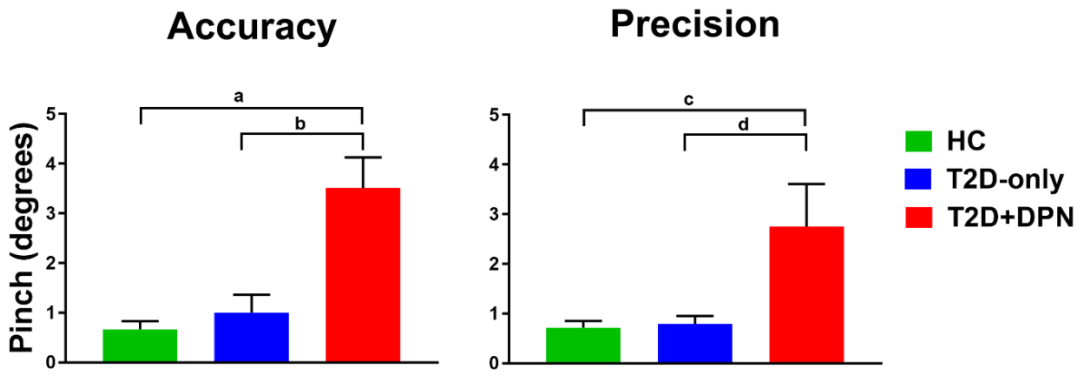

Figure 3.1. Pinch proprioception measures. HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, type 2 diabetes and diabetic peripheral neuropathy. The T2D+DPN group is significantly different from the other two groups for accuracy and precision. [a] (p-value = 0.002), [b] (p-value = 0.003), [c] (p-value = 0.002), [d] (p-value = 0.006). Data for pinch proprioception values are represented as mean ± standard deviation.

Spearman's rho was performed for all correlations presented below. As shown in Table 3.2, the associations between SWME, and precision and accuracy were moderate (r=0.45, p=0.007 and r=0.46, p=0.005, respectively). Likewise, the associations between 2PD and precision and accuracy were moderate (r=0.58 and 0.66, p<0.001, respectively), Table 3.2, Figure 3.2.

Table 3.2- Correlations between Pinch Proprioception and Hand Sensibility Measures

Variables	r value*	P value
Accuracy and SWME	0.46	0.005
Precision and SWME	0.45	0.007
Accuracy and 2PD	0.66	<0.001
Precision and 2PD	0.58	<0.001

SWME, Semmes-Weinstein monofilament examination; 2PD, 2-point discrimination.
* Spearman's Rho test

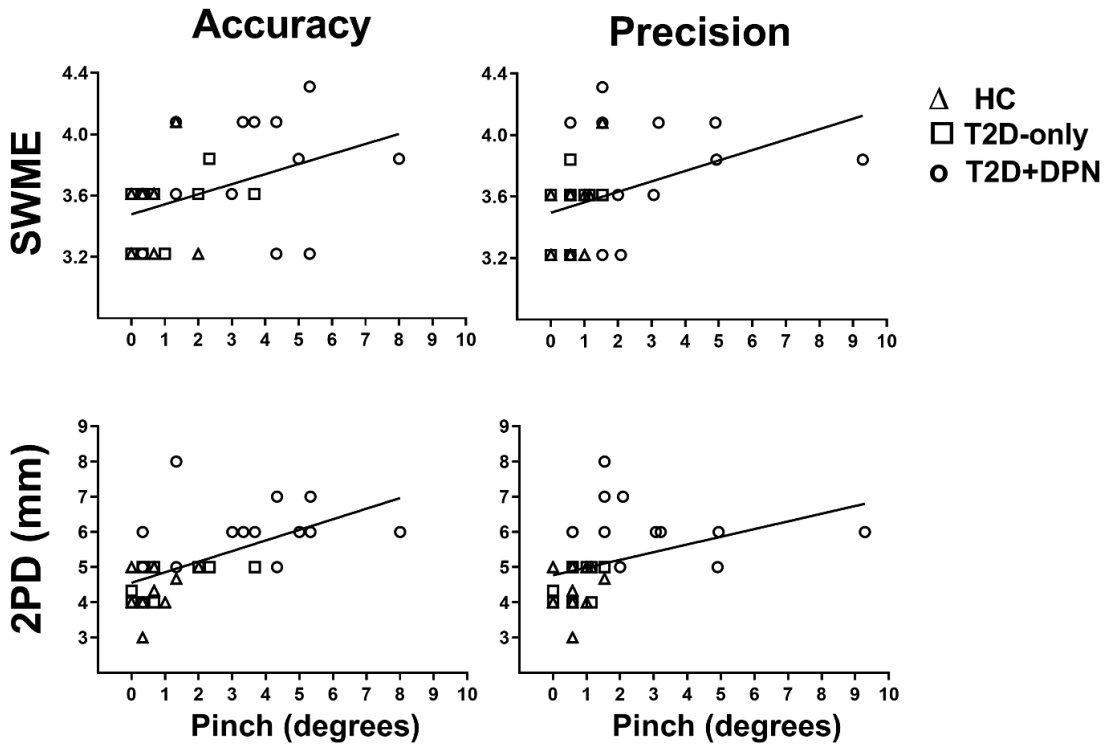

Figure 3.2. Correlations between pinch proprioception (accuracy and precision), and cutaneous measures (SWME and 2PD). SWME, Semmes-Weinstein Monofilament Examination; 2PD, 2-point discrimination. HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, type 2 diabetes and diabetic peripheral neuropathy.

3.5. Discussion

The main objective of the present study was to evaluate pinch proprioceptive changes in individuals with T2D and DPN as compared to age-matched healthy individuals using our novel device and methods. Our results confirmed our hypotheses, and a significant decline of the pinch proprioception (accuracy and precision) was observed in the T2D+DPN group. In addition, we found moderately significant correlations between sensory decline and pinch proprioceptive deficits.

Similar to the present study, past studies have demonstrated finger's proprioceptive impairments in subjects with sensorial deficits and in healthy subjects under the influence of local nerve blocks. For instance, Rothwell, Traub [152] reported severe proprioceptive deficits in terms of accuracy and precision at the interphalangeal joint of the thumb in a deafferented subject with sensory peripheral neuropathy of unknown cause. Interestingly, even with visual feedback, the subject was less accurate and less precise than healthy subjects. When the visual feedback was removed, the precision, especially, worsened even further. In the present study, practice, as well as testing trials, were performed between the index finger and thumb without visual feedback. For instance, the mean accuracy and precision for the T2D+DPN group were significantly worse than those of the healthy and T2D-only groups, Figure 3.1. Similar to our study, Ochoa, Gogola [160] assessed finger proprioception in 9 subjects with T2D as compared to 9 healthy matched control subjects in conditions with and without median nerve anesthesia. The total number of errors was calculated at three conditions: baseline, wrist anesthesia, and forearm anesthesia for both groups. The T2D group, particularly the wrist block condition, showed a larger number of errors under the anesthesia conditions as compared to the healthy control group. This finding is consistent with the results of the present study. However, unlike the present study, which confirmed proprioceptive deficits in subjects from T2D+DPN group, the

study by Ochoa, Gogola [160] showed no difference in proprioceptive performance between patients with T2D and healthy controls. One of the possible explanations for this discrepant result is that the present study used a different approach. For instance, the subjects in our study moved their index finger and thumb actively to replicate a target position while in the study by Ochoa and colleagues, the assessors passively moved the subject's thumb in the non-anesthetized hand to perform opposition movements with the index and little fingers. Finally, the proprioceptive deficits observed in the study by Ochoa and colleagues were possibly due to wrist and forearm anesthesia targeting the median nerve and blocking sensory (muscle spindles and skin mechanoreceptors) signals. By blocking the afferent systems of the upper extremity distally and having the testers moving the fingers, the subjects might have relied more on the cognitive system or on afferences from the forearm (muscle spindles). These were probably "less efficient" in T2D than those of the healthy subjects. In the present study, the subjects depended on afferences of the distal parts of the upper extremity and motor commands from the feedback. Thus, patients with T2D without DPN had no problem in performing the task properly (i.e., similar to healthy individuals).

It is plausible that the pinch proprioceptive deficits we observed in the T2D+DPN group might indicate muscle spindle damage as a result of DPN**.** Consistent with this speculation, morphological and structural changes in the muscle spindles and Ia and II nerve fibers have been shown in post-mortem cases for subjects who had suffered from T2D+DPN. These changes were more prominent with a longer duration of DPN [175]. Our previous experiment [115] corroborates with the studies mentioned above in that muscle spindles may play an important role in proprioceptive deficits observed in patients with T2D+DPN. Using the same device (modified goniometer attached on top of a small cardboard) and methods, we applied vibration

on the hand extensor tendons of the healthy participants [115]. The results showed that in the presence of vibration, the participants significantly missed the target, while without vibration the participants had high precision and accuracy in matching the 15^{o} target. To further understand the role of muscle spindles, we investigated the relationship between sensory deficits associated with DPN and pinch proprioceptive deficits.

Both SWME and 2PD have been shown to be strongly associated with the presence of neuropathy when applied to areas innervated by the median nerve at the fingertips [169]. The associations between SWME and precision and accuracy were moderate (r=0.45 and r=0.46, respectively). Likewise, the associations between 2PD and precision and accuracy were moderate as well (r=0.58 and 0.66, respectively), Table 3.2, Figure 3.2. However, based on the coefficient of determination (R squared), the decline in the fingertip cutaneous sensation (SWME and 2PD) does not explain alone the proprioceptive deficits found in the participants with T2D+DPN. For instance, SWME only explained 21% and 20% of the variability in the accuracy and precision of the pinch proprioception, respectively. Also, the 2PD only explained 43% of the accuracy and 33% of the precision variabilities of the pinch proprioception. This is indicative of other contributing factors to the proprioceptive deficits observed in people with T2D and DPN. Similar findings were observed in the lower extremities [72]. It was found that cutaneous decline, as measured by SWME, explained 45% of the ankle joint proprioception. However, this finding is higher than what we found in our study, suggesting that cutaneous sensation may contribute more to the sense of proprioception in the lower extremities than it is in the upper extremities.

Other possible mechanisms that might lead to proprioceptive deficits could be mechanical in nature. Musculoskeletal conditions associated with T2D are very common such as

carpal tunnel syndrome, trigger finger, and limited joint mobility [165, 176, 177]. The majority of the musculoskeletal changes in T2D are strongly associated with the length of the disease [165, 176, 177]. However, in our study, the duration of diabetes in both groups, T2D-only and T2D+DPN, was not significantly different. In addition, the number of subjects in both groups was almost identical in terms of complications such as trigger finger, the chronic incidence of carpal tunnel syndrome, and the limited range of motion as measured by the prayer sign, Table 3.1. Although this cannot be conclusive, the pronounced pinch proprioceptive deficits in the T2D+DPN group might indicate a larger contribution of neuropathy to the deficit regardless of the presence of other musculoskeletal conditions associated with T2D. Furthermore, the pinch proprioception testing was performed between the index finger and thumb. These two fingers have far less involvement by musculoskeletal conditions than other fingers, as seen from the prayer sign. The aperture of 15° to 30°, resembling the diameter of a large medicine container and a regular cup, respectively, was within the middle range of the pinching position. Proprioceptive signals from the skin and joint mechanoreceptors will work at the extreme joint range of motion [49]. Therefore, any proprioceptive signals received from the skin or joint would be negligible in the range we tested in the present study. Hence, the proprioceptive deficits could indeed be related to damaged muscle spindles.

It is worth mentioning that, while the device and methods of the current study have functional relevance to a variety of dexterous tasks, researchers should be aware that active joint position reproduction can be influenced by additional sensorimotor processes, i.e., fine motor control that is involved in tuning the pinch movement towards the target position. The literature, however, provides controversial findings in terms of the fine motor function of the hand associated with T2D and DPN. Clinically, few studies reported that fine motor function is not

affected [86, 101] as reflected in activities including, but not limited to, placing pegs into holes and attaching washers into them, writing a sentence, picking up small objects, and lifting heavy and light objects while others show the opposite [97, 103]. None of these studies, however, investigated whether proprioceptive deficits did exist. Furthermore, DPN initially affects sensory nerves in a distal to proximal progression that can advance to impact motor nerves [27, 159]. In the current study, pinch strength was assessed to investigate the motor function across the groups. Although pinch strength is not a direct measure of fine motor control, past studies have shown moderate to strong (-0.60 to -0.80) associations between pinch strength and fine motor control [178, 179]. Our findings showed no significant differences in the pinch strength between healthy and diabetic groups, which indicated that motor function is not affected (Table 3.1). The normal pinch strength further supports our view that pinch proprioception deficits are most likely the result of sensory damage primarily affecting the muscle spindles. Hence, differences in active joint position reproduction between the groups can be primarily the result of sensory damage in the T2D+DPN group leading to pinch proprioception deficits. However, we acknowledge the limitation of our method that tested proprioception using active joint position reproduction movement that involved sensory (proprioception) and motor (fine pinch movement) systems. Hence, there is a need for future studies to investigate the interaction between pinch proprioception and fine motor control. Finally, we cannot exclude the involvement of CNS as a possible explanation for our findings. In a systemic disease such as T2D, CNS damage has been documented [13], and it has been suggested as a possible mechanism for impaired sensorimotor control [160]. For instance, diffuse axonal degeneration and demyelination of the sensory nerves in the spinal cord and brain stem have also been observed in people with DPN [16]. This could result in a delay in central sensory processing [54], which might affect the sense of

proprioception. In addition, damage to peripheral sensorimotor nerves may reflect differences in central processing. Future studies may either use neurophysiological and MRI studies or more complex tests that have a motor piece such as trial making B, digit symbol test, and reaction time. Dual-task testing paradigm could also add more demand on the CNS and thereby better differentiate the decrements in pinch proprioception.

3.6. Conclusion

Using our novel device and methods, the results of this study showed that T2D per se does not cause pinch proprioceptive deficits, but DPN does. Sensory deficits alone were limited in explaining the variability in pinch proprioception deficits, indicating a greater role of muscle spindles. Future studies should investigate the correlation between nerve conduction measures of the sensory and motor nerves with pinch proprioceptive deficits in subjects with T2D and DPN. In addition, the contribution of pinch proprioceptive deficits to the dexterity impairments commonly reported in this population should be investigated. This premise will help refine our assessment and rehabilitation approaches for individuals with neurological and orthopedic injuries impacting the hand function.

Chapter 4 Preface

In Chapter 1, we laid down the basic concepts of grip force control and elaborated on anticipatory and reactive mechanisms adopted during a lifting task. In addition, in Chapter 2 and Chapter 3, pinch proprioception was found to be disrupted in subjects with T2D+DPN. Chapter 4 is focused on studying the reactive and anticipatory grip force control in people with T2D and DPN in comparison to people with T2D alone and healthy controls.

Chapter 4: The Impact of Type 2 Diabetes and Diabetic Peripheral Neuropathy on Reactive and Predictive Grip Force Control

4.1. Abstract

This study aims to investigate the impact of type 2 diabetes (T2D) and diabetic peripheral neuropathy (DPN) on grip force control (GFC) during object manipulation. The study included 3 age-matched groups: T2D-alone (n=11), T2D+DPN (n=13), and healthy controls (n=12). GFC variables derived from a task of lifting-and-holding an experimental cup were grip force ratio (GFR), latency, and time lag (T-lag) during the lifting phase, and static force (SF), and index of grip force adjustments (IGFA) during the holding phase. GFR and latency showed significant differences between groups. GFR in the T2D+DPN group showed larger ratios as compared to T2D-alone and healthy controls. Latency in the T2D+DPN group showed a longer time as compared to T2D-alone and healthy controls. No significant differences were found between T2D-alone and healthy controls for GFR and latency. No significant differences between the groups were found for SF, IGFA, and T-lag. Our results showed impaired GFR and latency in participants with T2D+DPN while the T-lag was preserved. People with T2D-alone did not present with significant deficits (magnitude and temporal variables) in GFC compared to healthy controls. These results are significant as higher grip forces might expose people with T2D and DPN to risk of fatigue, damaging objects, and injuring their hands. Future studies should investigate strategies to help adjust grip forces during object manipulation.

4.2. Introduction

Our hands possess an extraordinary ability to efficiently and economically accommodate the demands of any task. For instance, the task of holding and lifting an object vertically generates two distinct forces; horizontal grip force, the applied force from fingers against the contact surface of the object, and vertical load force, the weight of the object times the acceleration [79, 180]. In healthy people, grip force is adjusted efficiently and simultaneously in parallel to load force changes generated from lifting and holding an object in space [89]. As such, an increase in load force will be associated with an increase in grip force and vice versa to secure the object in hand during the vertical movement; this is known as the grip force scaling [76, 89]. The higher the ratio of grip force peak (GFP) to the load force peak (LFP), the less efficient the grip force scaling [89]. This can be a result of pathological problems affecting either the peripheral or central nervous system (CNS) or both [89]. Therefore, not only the sensory feedback is important for concurrent grip force adjustments, but also predictive measures established from previous experiences with the object which can be used as reference values for future manipulation with an identical object [44, 82, 94].

The temporal coupling between the GFP and LFP is known as the time lag (T-lag), which normally ranges between -10 to +15 milliseconds on average [87]. Such a short time indicates that the temporal coupling must be centrally driven through anticipatory/predictive and automatic actions [76, 98]. In fact, the longer time lag between the peak of grip force and the peak of load force has been shown to be associated with pathological conditions involving the CNS [77, 88-91]. Continuous cutaneous sensory information from the finger pads are used to control for the optimal grip force required to hold an object [44]. This afferent information can be driven from concurrent online feedback and/or previous lifting experiences [98]. The richness

of the data derived from a simple lifting task suggests that grip force control (GFC) can be a good model to study peripherally and centrally mediated pathological conditions as evidenced by studies on patients with stroke [83, 89-92], Parkinson [89], cerebellar lesion [88], multiple sclerosis [77], osteoarthritis of the hand [93], carpal tunnel syndrome [181], and sensory deafferentation [85, 98, 182].

Peripheral and perhaps central nerve damage is one of the major complications of type 2 diabetes (T2D) [10, 11, 13, 16, 156-158, 183]. Specifically, diabetic peripheral neuropathy (DPN) is the most common form of nerve damage in subjects with T2D presented as distal symmetric sensorimotor polyneuropathy, which is the most common form that can affect upper and lower extremities [27, 159]. In addition, there are extensive scientific literature showing damage in the CNS of diabetic subjects such as shrinkage in the primary somatosensory cortex and thalamus and diffuse axonal degeneration and demyelination of the sensory nerves in the spinal cord and brain stem[12, 16, 75]. This could result in a delay in central sensory processing [12, 54]. Therefore, peripheral and possible central nerve damage associated with T2D might lead to GFC deficits.

Although there is accumulating evidence pointing to the generalized impact of T2D on the central and peripheral nervous system, little is known whether anticipatory GFC is preserved while manipulating objects. Furthermore, results in the literature have not been consistent about the magnitude of grip force when lifting and holding an object in space, with some studies finding an increase in grip force [95, 96] while others report a decrease in grip force in subjects with T2D regardless the presence or absence of DPN [86, 97]. These inconsistent findings can be the result of different patient characteristics and study designs. For instance, the diabetes status: some studies recruited individuals with type 1 diabetes [95, 96] while other studies either

recruited individuals with a confirmed diagnosis of T2D [97] or no report about the diabetes status whether type 1 or 2 or both [86]. Furthermore, none of these studies investigated anticipatory GFC in age-matched groups of individuals with T2D with and without DPN. This knowledge can help us understand the contribution of DPN to deficits in GFC. In particular, reactive and anticipatory GFC is part of almost every manual task that requires gripping and lifting maneuvers such as drinking from a glass of water or administering insulin injections.

Therefore, the main objective of this study is to investigate the impact of T2D and DPN on reactive and anticipatory GFR during lifting and holding task. To further understand the nature of the GFC deficits, we also investigated the time coordination (latency to reach GFP), temporal coupling (T-lag), static force (SF), and the index of grip force adjustments (IGFA). We hypothesize that subjects with T2D and DPN will exhibit higher: GFR (hypothesis #1), latency (hypothesis #2), T-lag (hypothesis #3), SF (hypothesis #4), and IGFA (hypothesis #5) as compared to age-matched T2D without DPN and healthy participants.

4.3. Methods

4.3.1. Subjects and study procedures

The inclusion criteria for this study were: healthy or a diagnosis of T2D with and without DPN and ages between thirty to seventy years old. The exclusion criteria were: a history of type 1 diabetes, prediabetes, any injuries to the hands that might interfere with any of the testing procedures, history of neurological (e.g., stroke, Parkinson's disease, multiple sclerosis, and neuropathy symptoms due to chemotherapy) or musculoskeletal conditions (e.g., recent hand injuries or fractures, movement limitations, myasthenia gravis). All measurements were collected in a one-day setting for this cross-sectional study. Three distinct groups were matched for age, and all testing was performed on the dominant hand. Hand dominance was confirmed using the

Edinburgh Handedness Inventory [163]. The local ethics committee at the University of Kansas Medical Center approved this study, and all subjects signed an approved informed consent document before participating (STUDY00003358).

4.3.2. T2D and DPN screening

We differentiated between the three groups based on the presence or absence of T2D and DPN. T2D was defined by a positive confirmation to a question asking whether any healthcare provider has told them that they have T2D. In addition, following the American Diabetes Association guidelines [166, 167], Glycated Hemoglobin A1c (HbA1c) testing was conducted (PTS Diagnostics Polymer Technology Systems A1CNow+™ Systems [168]). This test confirmed the presence or absence of T2D diagnosis across the groups. Blood was drawn by a fingerstick at the tips of the fingers. The self-reported diagnosis of T2D was confirmed based on a value of 6.5% or above, and non-diabetics or 'healthy' less than 5.7% [166, 167].

Our subjects in the T2D+DPN group had the diagnosis of DPN confirmed through a clinical exam and nerve conduction studies performed by a neurologist. To confirm the absence of DPN in the T2D-alone group, testing was completed using a 10g monofilament (protective sensation), superficial pain sensation, and vibration by on-off method on the big toe to screen for neuropathy. If subjects had five incorrect responses out of 8 trials for any of these three tests, that would indicate neuropathy with high sensitivity and specificity [134, 135].

4.3.3. Hand sensibility testing

Sensory deficits on the tips of the fingers innervated by the median nerve were assessed using the Semmes Weinstein monofilament examination (SWME) (NC12775, North Coast Medical Inc.) at the tips of the thumb, index and middle fingers 3 times on each site [169]. The monofilaments were pressed until they bowed against the finger's skin while the participants

were asked to keep their eyes closed and verbally respond whenever they felt the touch of the monofilament on their fingers. There are five levels that represent the severity of the tactile sensory dysfunction for a total of 20 different monofilament sizes ranging from 1.65 to 6.65 [170, 171]. If the subjects were not able to detect the smallest monofilament, we applied a larger one until they sensed the monofilament. We recorded the perceived threshold based on the monofilament size that the subjects were able to detect. If the perceived threshold was different between the three fingers, we reported the average score. We collected data from both hands, but we utilized data from the dominant hand only.

The 2 points discrimination (2PD) testing was performed on the same locations indicated above for three times on each location alternating between one and two points randomly (2 Discrim-A-Gon, 12-1492, Baseline 2-point discriminator set). We recorded the smallest distance between two points that can be perceived by the subjects. A distance of 5mm is considered normal, 6 to 10mm is fair, and 11 to 15mm is poor [172].

4.3.4. GFC instrumentation

We performed the GFC test using a similar setting and equipment used in previous experiments by our research group [93, 99, 184, 185] (Figure 4.1.). In short, the object consists of a cylindrical plastic cup (183 g) fitted with a piezoelectric force sensor (model 208CO3; PCB Piezotronics Inc., Depew, NY, USA) placed at the object's center (Figure 4.1., A). Two metallic projections connected the force sensor to two circular plastic pads on the external surface of the object to serve as the grasping surface (Figure 4.1., C). The height and width of the cup are 5.5 inches and 3 inches, respectively. The diameter of the two plastic pads is identical, and they are located 2 inches from the cup's center and 4 inches above the bottom of the cup. A three-axial piezoelectric accelerometer (model 333B32; PCB Piezotronics Inc., Depew, NY, USA) is fixed

to the cup to register acceleration in the X, Y and Z planes (Figure 4.1., B). During data collection, the accelerometer and force sensor signals were passed through two signal conditioners (ICP R Sensor Signal Conditioner, Model Y482A22 and Line-Powered (AC) ICP R Signal Conditioner, Model 484B06, respectively, PCB Piezotronics Inc., Depew, NY, USA) and were connected to the computer via an Analog-to-digital converter board (PCI-62xx, National Instrument BNC 2110).

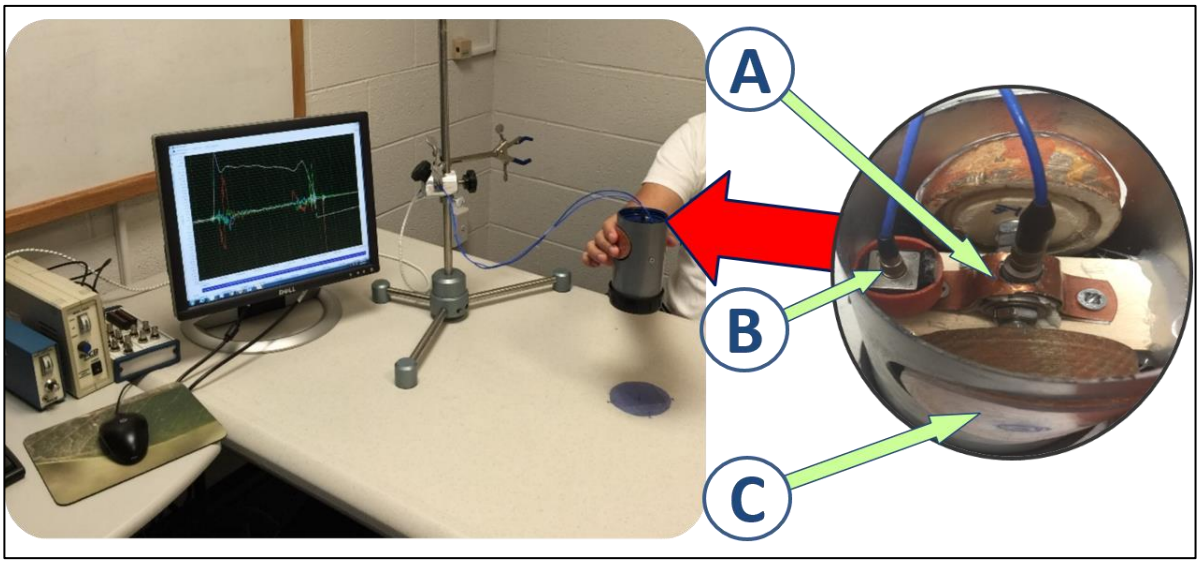

Figure 4.1. Experimental setting and the instrumented object. (A) uniaxial force sensor to register grip forces; (B) three-axial accelerometer to measure kinematic and gravitational accelerations in three dimensions (X, Y, and Z axes; (C) grasping surface (plastic pads).

4.3.4.1. GFC testing procedure

Before data collection, subjects washed their hands with soap and the plastic surfaces of the novel instrument were cleaned using alcohol swaps. Subjects were seated on a comfortable armless chair in front of the testing table feet flat on the floor and keeping their trunk upright. Subjects were asked to keep their shoulders at approximately 30 degrees of flexion, elbows at about 90 degrees of flexion, wrist, and forearm as neutral as possible. Subjects held the

instrument (the experimental cup) using a pinch of three fingers (opposition of the thumb with the index and middle fingers together) and lift it vertically from the table to a height of 20 cm (marked with a ruler), held it for 10 seconds and placed the cup back on the table. Testing was performed on the dominant hand only. In order to familiarize subjects with the procedure, subjects completed 3 practice trials with a lifting task of an empty cup. Subjects then lifted the cup in blocks of 5 trials with 2 different weights: light, 100 grams, and heavy, 500 grams. Subjects were blinded about the specific weight that was introduced in each time. The subjects completed a total of 11 blocks, 5 lifting trials in each block, adding up to a total of 55 trials. The sequence of the heavy and light blocks was the same for all subjects in the following order: light, light, heavy, light, light, heavy, light, heavy, heavy, light, light. The weight replacement in this procedure allowed us to study the subsequent grip force changes adopted by the subjects due to the unexpected weight change. This procedure has been used extensively in the literature by many researchers to challenge the subject's ability to make grip force adjustments in a similar lifting task [44, 76, 79, 91, 94, 186]. Only the data from the heavy blocks were used for data analysis, as described below. This transition was used because past experiments showed that lifting heavier weights will create larger contact surface areas between the tips of the fingers and the object allowing for greater tactile sensory inputs [61].

4.3.4.2. GFC data processing

The GFC data were collected in the software Signal Express (NI Signal Express 2014) and saved in a text file for further processing using a customized MATLAB program (version R2015b, The Math Works Inc) (Figure 4.2.). The following variables were automatically identified and calculated: (1) load force (LF; Newtons), calculated as the product of the object mass, and the vector sum of the acceleration signals (vertical, horizontal, and lateral) taking into

account gravity [187]. The load force trace during the entire task was used to specify the data points on the grip force trace from which the other variables were calculated; (2) grip force peak (GFP; Newtons), the maximum grip force during the lifting phase of the cup; (3) load force peak (LFP; Newtons), the maximum load force during the lifting phase; (4) GFR, the ratio between the maximum grip and load forces during the lifting phase; (5) static force (SF; Newtons), the average of grip force during the holding phase for a time window of 4 seconds; (6) time lag (T-lag, milliseconds), the time difference between the GFP and LFP; (7) latency (milliseconds), the time spent to reach the GFP from the first contact with the cup while gripping it; (8) the index of grip force adjustments (IGFA), the grip force trace during the holding phase fitted in the power regression model ($Y = a \times (X^b)$) for a time window of 4 seconds; the value of the power coefficient, *b*, represented the IGFA score, which will indicate the grip force change during the holding phase. The starting point of the fitted line was identified when the acceleration signals returned to baseline values marking the beginning of the holding phase (or SF) while the subject is holding the cup steady in space.

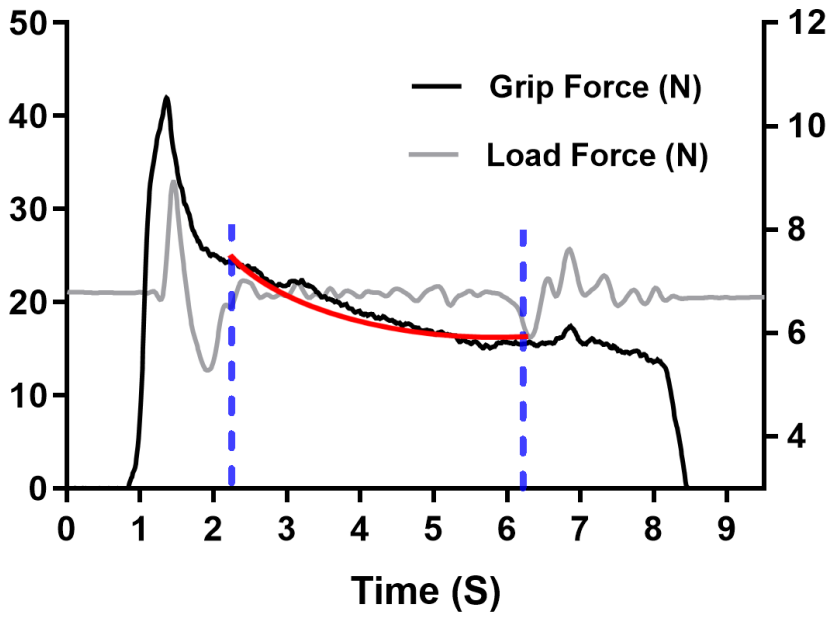

Figure 4.2. Grip and load force traces from a subject with T2D+DPN. The grip force (Newtons) is represented on the left Y-axis. The load force (Newtons) is represented on the right Y-axis. The vertical blue dotted lines in the middle of the graph represent the time window used to calculate for the static force and the index of grip force adjustments as represented by the curved red line.

4.3.5. Statistical analysis

The sample size was based on a previous study [95] (effect size of 0.57) for the primary outcome variable (GFR). A total of 33 subjects, 11 in each group, should be sufficient to show group differences with 80% power. We also performed power analysis for our novel outcome variable (IGFA) based on a pervious study [110] (effect size of 0.71) that resulted in a total sample size of 24 subjects, 8 in each group, with 80% power to show differences between groups. The dependent variables were tested for normality with a Shapiro-Wilk test. For the homogeneity, we used the Levene statistic test, the ratio between the maximum and minimum standard deviation between the groups (>2.5 violated the homogeneity assumption), and visual

inspections of box plots. Kruskal-Wallis test or one-way ANOVA were used for demographic and clinical data and GFC data, accordingly. Post-hoc analyses tested the differences between groups (Mann-Whitney u test for non-parametric data or Fisher's least significant difference (LSD) for parametric data).

For all GFC data, we used the average of the last three trials of each heavy block (500 g). Table 2 summarizes the data by the mean and 95% confidence interval to further understand the variability within the groups for the GFC data. One-way ANOVA and LSD tests were used to analyze the differences between the groups for LF, GFR, and SF. Kruskal-Wallis test and Mann-Whitney u tests were used to analyze the differences between groups for latency, T-lag, and IGFA. Alpha was set at 0.05, and all data were processed in SPSS software (version 25, IBM SPSS; Somers, New York).

4.4. Results

The demographic and clinical data are shown in Table 4.1. A total of 36 participants took part in this study: 12 healthy participants (7 males, 58±6 years), 11 participants with T2D-alone (5 males, 61±6 years), and 13 participants with T2D+DPN (6 males, 60±6 years). The majority of subjects were right-handed (11 in the healthy control group and 11 in the T2D+DPN group). We were successful in matching for age, as there were no significant differences between the three groups ($p=0.44$).

Table 4.1- Participants' Demographics and Clinical Characteristics

	HC	T2D-alone	DPN+DPN	P value
Gender (female/male)	5/7	6/5	7/6	
Age (years)	58±6	61±6	60±6	0.44
BMI (kg/m^2)	24.5±2.4	31.1±5.4	34.2±4.5	<0.001
Left-hand dominance	1/12	0/11	2/13	
HbA1c (%)	5.3±0.3	7.2±1.04	7±0.7	<0.001
Diabetes duration (years)	N/A	9.4±6.6	13.1±9.1	0.27[a]
Neuropathy duration (years)	N/A	N/A	4.8±3.5	
2PD (mm)	4.8±1	5±1	6±1	<0.001[b]
SWME (threshold)	3.6±0.4	3.6±0.1	3.8±0.7	0.058[b]

HC, healthy control; T2D-alone, type 2 diabetes; T2D+DPN, diabetic peripheral neuropathy; BMI, body mass index; HbA1c, glycated hemoglobin A1c; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination.
Data represented as mean ± standard deviation unless otherwise indicated. P values from one-way ANOVA test.
[a] P-value from an independent t-test.
[b] Data represented as median and interquartile range. P-values from Kruskal-Wallis test.

Post-hoc analysis showed no significant differences in the HbA1c, diabetes duration, and BMI between the T2D-alone and T2D+DPN groups. The 2PD was significantly different between the groups ($p<0.001$) with higher deficits in the T2D+DPN group as compared to the other groups. The SWME was approaching significance ($p=0.058$) across the three groups with higher deficits in the T2D+DPN group as compared to the other groups.

For the grip force control variables (Table 4.2), there were no significant differences in the LF (Newtons) between the groups ($p=0.79$), which indicates that all subjects in the 3 groups performed the lifting task in a similar manner. GFR showed significant differences between the groups ($p=0.013$); T2D+DPN group (mean ± SD; 3.67±0.84) showed larger ratios as compared

to T2D-alone (2.87±0.66; p=0.018) and healthy (2.76±0.84; p=0.007) while no significant differences were found between T2D-alone and healthy for GFR (p=0.75). The latency (milliseconds) showed significant differences between the groups (p=0.025); T2D+DPN group (465.64±180.73) showed significantly longer time to reach the GFP as compared to healthy (307.92±42.44; p=0.009) and approaching significance between T2D+DPN and T2D-alone (373.48±168.84; p=0.054). No significant differences between the T2D-alone and healthy groups were found for the latency (p=0.55). There were no significant differences between the groups for T-lag (milliseconds) (p=0.79), and SF (Newtons) (p=0.22). The IGFA was not statistically different between groups as well but approached significance (p=0.058). Figure 4.3. represents GFC variables as mean ± SEM.

Table 4.2- Grip force control variables

	HC (12)	T2D-alone (11)	T2D+DPN (13)	P value
GFR	2.8(2.2, 3.3)	2.9(2.4, 3.3)	3.7(3.2, 4.2)	0.013[a]
Latency(ms)	307.9(281, 334.9)	373.5(260.1, 487)	465.6(356.4, 574.9)	0.025[b]
T-lag(ms)	0.33(-1.2, 1.9)	3.2(-1.9, 8.3)	4.4(-6.8, 15.6)	0.789[b]
SF(N)	15(11.7, 18.3)	16(13.2, 18.8)	18.6(15, 22.1)	0.22[a]
IGFA	-0.13(-0.16, -0.12)	-0.13(-0.19, -0.07)	-0.22(-0.3, -0.14)	0.058[b]

HC, healthy control; T2D-alone, type 2 diabetes; DPN, diabetic peripheral neuropathy; GFR, grip force ratio; SF, static force; T-lag, time lag; IGFA, index of grip force adjustments.
Data represented as mean (95% confidence interval).
[a] P-value from one-way ANOVA test.
[b] P-values from Kruskal-Wallis test.

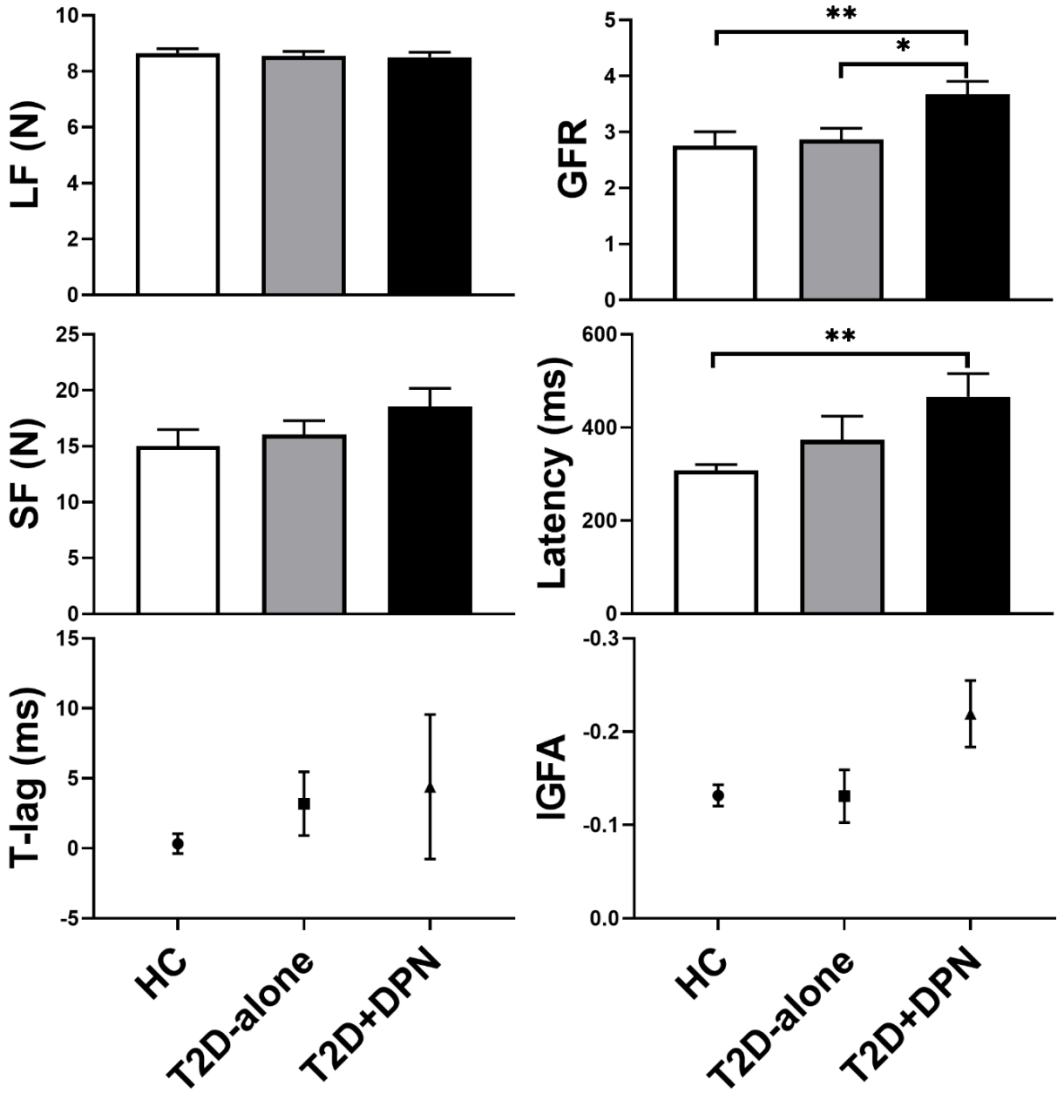

Figure 4.3. Grip force control variables. LF, load force; GFR, grip force ratio; SF, static force; T-lag, time lag; IGFA, index of grip force adjustments; HC, healthy control; T2D-alone, type 2 diabetes without diabetic peripheral neuropathy (DPN); T2D+DPN, type 2 diabetes with DPN. Data represented as (mean ± SEM) and the double asterisks represent significant findings at a p-value <0.001 while the single asterisk represents significant findings at a p-value <0.05.

4.5. Discussion

The main objective of the present study was to evaluate the grip force scaling in individuals with T2D+DPN as compared to age-matched T2D-alone and healthy individuals using a lifting and holding task of an instrumented cup. Our results confirmed our main hypothesis (hypothesis #1) that the GFR was higher in people with T2D+DPN group as compared to the other 2 groups. In addition, our hypothesis regarding to the latency (hypothesis #2) was partially fulfilled since it was higher in people with T2D+DPN as compared to the healthy control group. The rest of the hypotheses (T-lag: hypothesis #3, SF: hypothesis #4, IGFA: hypothesis #5) were not confirmed. The discussion will be tailored based on the lifting phase (GFR, latency, and T-lag) and then the holding phase (SF and IGFA).

4.5.1. Lifting phase

Johansson and Flanagan [44] reported that 1 to 3 trials are sufficient to update the anticipatory grip forces during a lifting and holding task. In our study, we calculated the average of the 3rd, 4th, and 5th trials of each heavy block (4 heavy blocks). Apparently, 3 to 5 trials were still not enough for the subjects with T2D+DPN to scale their grip force in an efficient manner similar to the healthy and T2D-alone subjects. The participants with T2D+DPN performed the task using higher GFR, which might be a result of the higher grip force peak (GFP) applied to the object during the lifting phase since the load force peak (LFP) was not statistically different among the three groups. Similarly, higher GFR has been reported in subjects with neurological diseases such as stroke [188] and peripheral sensory deficits such as carpal tunnel syndrome [98]. Higher grip force was also demonstrated in patients with type 1 diabetes, but the authors did not directly investigate the contribution of DPN to such deficits [95]. Our results confirmed not only the presence of anticipatory grip force deficits in people with T2D like type 1 diabetes but also the major contribution of DPN to such deficits.

Latency reflects the effectiveness of sensorimotor processing [88]. Similar to our findings, subjects with carpal tunnel syndrome reported longer latency while lifting a novel object [99]. It has been suggested that such a time delay might be the result of higher magnitude of GFP to compensate for sensory deficits [91, 99, 189]. This speculation stands to support our findings in the T2D+DPN group. In addition, it takes about 100 milliseconds after the object's lifting for the brain to receive sensory feedback and send motor commands back to the grasping muscles to make the necessary corrective actions [44]. Furthermore, delays of up to 500 milliseconds are necessary for a voluntary response, indicating that subjects are aware of force perturbations [190]. In Table 4.2, subjects with T2D+DPN reached the GFP, on average, in 465.6 milliseconds, which should be enough to trigger corrective grip forces. In table 2, the latency showed a small overlap of the 95% confidence interval between the T2D+DPN and T2D-alone. We further divided the latency into two periods defined by the moment when the object cleared the table: pre-load and load phases. Pre-load phase measures the time from the first contact up to the moment of lifting whereas the load phase measures the time from the moment of lifting up to the GFP. Interestingly, the most significant difference was the result of time delay in the pre-load period. Similar results were documented in subjects with stroke [91] indicating a generalized strategy regardless of the source of the problem; whether central or peripheral nerve damage.

As we initially hypothesized, if central deficits were to exist, the T-lag should be different between groups. As such, the lack of significant differences in the T-lag between the groups might rule out the involvement of nerve damage affecting the CNS. Similar results have been reported in people with type 1 diabetes [95], and perhaps the T-lag can greatly be disrupted only if profound damage to the CNS exists, such as in cerebellar diseases [88] or in cases of complete deafferentation [85]. In fact, the cerebellum is responsible for coordinating the temporal profiles

of GFC [84] and is known to increase its activity to compensate for cognitive decline reported in people with diabetes [75]. The contribution of CNS to deficits in GFC, however, requires further confirmation, especially with the growing evidence that tactile sensory deficits alone do not explain grip force deficits and hand function impairments common in individuals with T2D [74, 102].

4.5.2. Holding phase

During the holding phase, we assessed the average of the grip force (SF) and the change in grip force (IGFA). Although there were no significant differences in the SF between the groups, higher SF was observed in the T2D+DPN group as compared to the other groups (Table 4.2). The lack of significant differences might be the result of similar tactile sensation (SWME) between the groups. Similarly, subjects with carpal tunnel syndrome with well-preserved tactile sensation showed no deficits in static force [181]. Contrary, subjects with carpal tunnel syndrome and digital anesthesia (reduced to complete loss of tactile sensation, respectively) generally showed higher static force as compared to healthy subjects without digital anesthesia [98, 110]. Our findings from the IGFA indicates that the majority of our subjects in the T2D+DPN group cautiously kept adjusting their grip force during the holding phase. This could indicate the ability of our subjects to overcome the conflict between concurrent sensory signals (tactile and proprioceptive) and inaccurate anticipatory grip forces formed in the internal model based on previous encounters with the object [81]. For instance, a similar pattern was observed under the influence of digital anesthesia only with a small difference [110]. Subjects dropped the object during the holding phase in the study by Augurelle and his colleagues [110] while no case of dropping the object in our study. A possible explanation could be the complete block of tactile

sensation at the grasping digits in the study by Augurelle as compared to well-preserved tactile sensation (SWME) reported in our study.

Finally, corroborating the findings from the lifting and holding phases, the lack of significant differences in the SF might explain the ability of the subjects with T2D+DPN to adjust their grip forces. Perhaps, the CNS takes over and filters out the mismatch from the afferent signals fed during the lifting phase. However, this does not explain why subjects with T2D+DPN fail to efficiently adjust their GFR and optimize the latency during the lifting phase. Possible reasons could be the high variability observed in the T2D+DPN and T2D-alone groups (Table 4.2 and Figure 4.3). It is also plausible that the short-living anticipatory grip force memories [82] might have contributed to our current findings.

4.6. Conclusion

Individuals with T2D+DPN present with deficits in GFR as they apply unnecessary high grip force during the lifting task; they apply greater forces more than normally required to prevent the object from slipping. This general strategy might put subjects at risk of damaging their fingers or the object at hand or cause hand fatigue, which might decrease their precision and productivity. Future research should focus on developing rehabilitation programs to target this problem. T2D-alone did not have different GFR than healthy suggesting that neuropathy is the main contributor to GFC deficits. Future research should further investigate the associations between tactile sensory, possible proprioceptive and cognitive decline associated with T2D and DPN, and GFC variables. This study identified that neuropathy can influence GFC in people with diabetes.

Chapter 5 Preface

In chapters 3 and 4, pinch proprioception and grip force control were found to be disrupted in people with T2D and DPN. In addition, there is cumulative evidence showing that hand dexterity is disrupted in people with T2D and DPN. Chapter 5 is focused on studying associations between deficits in grip force control, sensory deficits, and hand dexterity impairments in people with T2D with and without DPN and healthy participants.

Chapter 5: The Associations between Grip Force Control, Sensory, and Hand Dexterity Measures in People with Type 2 Diabetes and Diabetic Peripheral Neuropathy

5.1. Abstract

Type 2 diabetes (T2D) and diabetic peripheral neuropathy (DPN) may result in sensory (tactile and proprioception), hand dexterity, and grip force control (GFC) deficits. This study aims to assess the relationship among these measures. A total of 36 participants (12 healthy, 11 with T2D-only, and 13 with T2D+DPN) completed this study. Correlations were determined between hand dexterity measures (Moberg pickup test, MPUT, and Jebsen-Tailor hand function test, JTHFT) and measures of tactile sensation (2-point discrimination, 2PD, and Semmes-Weinstein monofilament examination, SWME) and pinch proprioception (accuracy and precision). Measures of GFC obtained during lifting (grip force ratio, GFR, and latency) and holding (static force, SF) task of a handheld object were also correlated with 2PD, SWME, pinch proprioception, and hand dexterity measures. Spearman's correlation coefficient of data from all subjects showed significant positive correlations between all sensory and hand dexterity measures (r=0.35-0.73). Significant and positive correlations existed between GFC parameters during the lifting phase and most tactile and proprioception parameters, while only the SF during the holding phase was correlated with SWME (r=0.35-0.51). Significant positive correlations existed between parameters of GFC during the lifting phase and hand dexterity measures, while only SF during the holding phase was correlated with MPUT (r=0.35-0.58). Sensory decrements might be responsible for changes in GFC and hand dexterity. The established correlations between GFC parameters and hand dexterity measures in people with T2D and DPN might help clinicians and researchers to find better targets for screening and rehabilitation of hand function for this population.

5.2. Introduction

Type 2 diabetes (T2D) causes major complications that affect almost every part of the human body. One of the major complications is the nerve damage that commonly involves the peripheral nerves of the upper and lower extremities. The most common form is the diabetic peripheral neuropathy (DPN), which presents as distal symmetric sensorimotor polyneuropathy [27, 159]. This might contribute to impaired hand function in individuals with T2D leading to significant limitations in manual activities, including picking up and handling objects with different weights and sizes.

Limitations in hand dexterity can be assessed using different dexterity tests such as the Jebsen-Tailor hand function test (JTHFT), Moberg pickup test (MPUT), and 9-hole peg test (9HPT) [133, 191, 192]. For instance, significant limitations of hand dexterity in individuals with T2D were confirmed by using JTHFT and 9HPT [35, 97, 103, 193]. These hand dexterity tests utilize common tasks and items such as writing a sentence, simulated feeding, picking up small objects, lifting heavy and light objects, and simulated page turning. However, MPUT has an advantage over the JTHFT and 9HPT in which it can assess the functional performance of the hand based on proprioceptive and tactile sensation inputs in the absence of visual feedback [132, 133]. However, there is limited evidence to identify relationships between hand dexterity and sensory (tactile and proprioceptive) deficits in individuals with T2D and DPN. Understanding the relationship between sensory and dexterity measures might help clinicians develop treatment plans focused on the actual deficits affecting hand function in individuals with T2D.

The commonly used hand dexterity tests described above are timed, and while hand dexterity tests measure time, they fail to capture the actual kinetics of the manipulative tasks. An alternative approach is studying grip force control (GFC) during a manipulative task of lifting and holding an object. Two distinctive forces are generated during manipulation tasks, namely,

grip and load forces [180]. Grip force is the horizontal force applied by the fingers against the object contact surface [180]. Load force is a tangential force between the contact surface of the fingertips and the object, which is dependent on the weight and the acceleration of the object during a manipulative task [180]. During manipulation tasks, an increase or decrease in the load force must be accompanied by almost an instantaneous increase or decrease in the grip force to prevent object slippage, such adjustments in grip force are accomplished via anticipatory mechanisms [76]. In case if the object is held stationary then the load force will be the same as the weight of the object and the grip force will be adjusted based on sensory feedback derived from the object's weight and the friction generated by the contact between the fingertips and the object, such adjustments in grip force are accomplished via reactive mechanisms [76]. Then, the ability to efficiently coordinate changes in load and, subsequently, grip force is governed by feedforward/anticipatory actions intertwined with sensory feedback [44, 76]. Accounting for the interaction between grip and load force changes during a manipulative task, many studies have reported that the higher the ratio between the peak of grip and load forces, the less efficient the GFC would be [95, 98, 188].

While there is growing evidence showing that GFC is disrupted in the presence of diabetes [35, 74, 86, 97, 160], the contribution of sensory (tactile and particularly proprioceptive) feedback to changes in anticipatory and reactive GFC is still lacking. In addition, no study has evaluated the contribution of anticipatory and reactive grip force to the dexterity deficits commonly observed in an individual with T2D and DPN. Investigating the relationships between GFC and hand dexterity measures in these individuals will help to provide a better understanding of how deficits in different mechanisms of grip force control can impact hand function. Thus,

based on this information, more focused hand assessment and rehabilitation strategies, as well as physical therapy interventions, can be developed.

Therefore, three exploratory aims were developed for this study. First, investigate whether relationships exist between hand dexterity and sensory measures. We hypothesized that MPUT and JTHFT would be positively correlated with tactile sensory and proprioceptive deficits associated with T2D and DPN. Second, investigate whether relationships exist between parameters of GFC and sensory measures. We hypothesized that applied force and temporal parameters of GFC would be positively correlated with tactile sensory and proprioceptive deficits associated with T2D and DPN. Third, investigate whether relationships exist between parameters of GFC and hand dexterity tests. We hypothesized that the applied force and temporal parameters of GFC would be positively correlated with MPUT and JTHFT.

5.3. Methods

5.3.1. Participants

A total of 36 participants (18 males and 18 females) took part in this study. Three age-matched groups were included based on the presence or absence of T2D and DPN: 12 healthy participants (7 males, 58±6 years), 11 participants with T2D-only (5 males, 61±6 years), and 13 participants with T2D+DPN (6 males, 60±6 years). Participants were excluded if they reported a history of type I diabetes, prediabetes, and any injuries to the hands that might interfere with any of the testing procedures. In addition, study participants were excluded if they reported a history of neurological conditions (stroke, Parkinson's disease, multiple sclerosis, and neuropathy symptoms due to chemotherapy) or severe musculoskeletal conditions (myasthenia gravis, acute symptoms of carpal tunnel syndrome and profound limitations in the hand/fingers' range of motion confirmed by prayer sign). The prayer sign is classified into stage 0; normal findings on both hands, stage 1; inability to approximate one or two interphalangeal joints (IPJ) involved,

stage 2; inability to approximate 3 or more IPJ, stage 3; hand deformity at rest [165]. As such, subjects in stage 2 or 3 based on the prayer sign were excluded if the limitations significantly involved thumb, index, and middle fingers.

All subjects signed an informed consent document before participating in this study. It was approved by the local ethics committee at the University of Kansas Medical Center (STUDY00003358). All measurements were collected in a one-day setting for each subject. All testing was performed on the dominant hand and hand dominance was confirmed using the Edinburgh Handedness Inventory [163].

5.3.2. T2D and DPN screening

We differentiated between the three groups based on the presence or absence of T2D and DPN. T2D was defined by a positive confirmation to a question asking whether any healthcare provider has told them that they have T2D. In addition, following the American Diabetes Association guidelines [166, 167], Glycated Hemoglobin A1c (HbA1c) testing was conducted (PTS Diagnostics Polymer Technology Systems A1CNow+™ Systems [168]). This was to confirm the presence or absence of T2D diagnosis across the groups. Blood was drawn by a fingerstick at the tips of the fingers. The diagnosis of T2D is based on a value of 6.5% (48 mmol/mol) or above, prediabetes between 5.7% and 6.4% (39 and 46 mmol/mol), and healthy less than 5.7% (39 mmol/mol) [166, 167].

Our subjects in the T2D+DPN group have a confirmed diagnosis of DPN by a neurologist clinical exam and nerve conduction studies. To confirm the absence of DPN in the T2D-only group, testing was completed using a 10g monofilament (protective sensation), superficial pain sensation, and vibration by on-off method on the big toe to screen for neuropathy. If subjects had five incorrect responses out of 8 trials for any of these three tests, that would indicate neuropathy with high sensitivity and specificity [134, 135].

5.3.3. Dexterity testing

The JTHFT has been used extensively to assess daily manual activities including seven timed tasks in this sequence: writing a short sentence, turning cards, lifting small objects, simulated feeding, stacking checkers, and lifting heavy and light objects identical in size [35, 103, 133, 191, 194, 195]. The MPUT involves measuring the time needed to pick up small objects while eyes are closed. The test includes 12 small objects (such as coins and paper clips), a container (5.9 inches in diameter), and a wooden surface (11.5 × 17.5 inches) [132, 133]. Subjects were seated in front of a table and required to perform the tasks assigned for each test. The sequence of tasks for the JTHFT was fixed, and the small items used for the MPUT were randomly arranged on a wooden surface. All tasks were demonstrated to the subjects before the actual testing and the timer started with the beginning of each task with the mark "ready and go." One trial of each task from the JTHFT and three trials of picking up the small items while eyes are closed were allowed for MPUT. Subjects were asked to perform all the tasks as fast as they can while seated properly on a handless chair facing the testing table. Times were recorded in seconds for all tasks. All testing procedures were performed on the dominant hand.

5.3.4. GFC instrumentation

We performed the GFC test using a similar setting and equipment used in previous experiments by our research group [93, 99, 184, 185]. In short, the object consists of a cylindrical plastic cup (183 g) fitted with a piezoelectric force sensor (model 208CO3; PCB Piezotronics Inc., Depew, NY, USA) placed at the object's center. Two metallic projections connected the force sensor to two circular plastic pads on the external surface of the object to serve as the grasping surface. The height and width of the cup are 5.5 inches and 3 inches, respectively. The diameter of the two plastic pads is identical, and they are located 2 inches from the cup's center and 4 inches above the bottom of the cup. A three-axial piezoelectric

accelerometer (model 333B32; PCB Piezotronics Inc., Depew, NY, USA) is fixed to the cup to register acceleration in the X, Y and Z planes (Figure 4.1). During data collection, the accelerometer and force sensor signals were passed through two signal conditioners (ICP R Sensor Signal Conditioner, Model Y482A22 and Line-Powered (AC) ICP R Signal Conditioner, Model 484B06, respectively, PCB Piezotronics Inc., Depew, NY, USA) and were connected to the computer via an Analog-to-digital converter board (PCI-62xx, National Instrument BNC 2110).

5.3.4.1. GFC testing procedure

Before data collection, subjects washed their hands with soap and the plastic surfaces of the novel instrument were cleaned using alcohol swaps. Subjects were seated on a comfortable armless chair in front of the testing table feet flat on the floor and keeping their trunk upright. Subjects were asked to keep their shoulders at approximately 30 degrees of flexion, elbows at about 90 degrees of flexion, wrist, and forearm as neutral as possible. Subjects held the instrument (the experimental cup) using a pinch of three fingers (opposition of the thumb with the index and middle fingers together) and lift it vertically from the table to a height of 20 cm (marked with a ruler), held it for 10 seconds and placed the cup back on the table. Testing was performed on the dominant hand only. In order to familiarize subjects with the procedure, subjects completed 3 practice trials with a lifting task of an empty cup. Subjects then lifted the cup in blocks of 5 trials with 2 different weights: light, 100 grams, and heavy, 500 grams. Subjects were blinded about the specific weight that was introduced in each time. The subjects completed a total of 11 blocks, 5 lifting trials in each block, adding up to a total of 55 trials. The sequence of the heavy and light blocks was the same for all subjects in the following order: light, light, heavy, light, light, heavy, light, heavy, heavy, light, light. The weight replacement in this procedure allowed us to study the subsequent grip force changes adopted by the subjects due to

the surprising weight change. The weight-size illusion has been used extensively in the literature by many researchers to challenge the subject's ability to make grip force adjustments in a similar lifting task [44, 76, 79, 91, 94, 186]. Only the data from the heavy blocks were used for data analysis, as described below. This transition was used because past experiments showed that lifting heavier weights will create larger contact surface areas between the tips of the fingers and the object allowing for greater tactile sensory inputs [61].

5.3.5. Tactile sensation testing

Sensory deficits on the tips of the fingers innervated by the median nerve were assessed using 2-point discrimination (2PD) (2 Discrim-A-Gon, 12-1492, Baseline 2-point discriminator set) and the Semmes Weinstein monofilament examination (SWME) (NC12775, North Coast Medical Inc.) at the tips of the thumb, index and middle fingers 3 times on each site [169]. For the 2PD testing, we alternated between one and two points randomly and recorded the smallest distance between two points that can be perceived by the subjects. Subjects were asked to keep their eyes closed throughout the testing procedure and respond verbally to indicate whether they felt one or two points. A distance of 5mm is considered normal, 6 to 10mm is fair, and 11 to 15mm is poor [172].

The SWME testing was performed on the same locations indicated above for three times on each location. The monofilaments were pressed until they bowed, making a C-shape against the finger's skin while the participants were asked to keep their eyes closed and verbally respond whenever they felt the touch of the monofilament on their fingers. There are five levels that represent the severity of tactile sensory dysfunction. We recorded the perceived threshold based on the monofilament size that the subjects were able to detect. If the subjects were not able to detect the smallest monofilament, we applied a larger one until they did. Tactile sensory function was represented with 20 monofilament sizes ranging from 1.65 to 6.65 [170, 171]. If the

perceived threshold was different between the three fingers, we reported the average score. We collected data from both hands, but we utilized data from the dominant hand only.

5.3.6. Pinch proprioception testing

The device used to test for pinch proprioception is described in detail in our previous studies in Chapter 2 and Chapter 3 [115, 116]. In short, it included a modified goniometer with its fulcrum fixed on top of a small cardboard. The goniometer arms extended out the cardboard's edge and included circular pads on its extremities attached perpendicularly for the fingertip placement (Figure 2.1.). All participants were asked to rest their dominant hand on the table and to hold the perpendicular pads, using their index finger and thumb. Subjects were familiarized with the device and then performed two practice trials starting at 30° and ending at 15° with vision occluded. The pinch of 30^{o} and 15^{o} correspond with aperture sizes for holding a regular cup (2.75 inches) and a large medicine container (1.38 inches), respectively. In these practice trials, the index finger and thumb were moved passively by the examiner to the target position (15°), and the participants were given enough time (30 seconds, on average) to memorize that position. Subsequently, during the testing condition, the examiner moved the goniometer arms to the starting position (30°) and instructed the participant to pinch their fingers actively trying to reproduce the target position (15°) without visual feedback. Three testing trials were performed. Accuracy was defined as the average absolute error difference from the target position and precision as the variability of the three testing trials represented by the standard deviation [123].

5.3.7. Data processing

The outcomes of MPUT (time in seconds), and JTHFT (time in seconds) tests, 2PD (measured in millimeters), SWME (perceived threshold), pinch proprioception (accuracy, the average of absolute error difference of the three testing trials; and precision, the standard deviation of the actual three testing trials of reproducing the target position (15°), were tabulated

in Excel (Microsoft Office Excel, version 365 pro plus). The GFC data were collected in the software Signal Express (NI Signal Express 2014) and saved in a text file for further processing using a customized MATLAB program (version R2015b, The Math Works Inc) (Figure 4.1, part A). The following variables were automatically identified and calculated: (1) load force (LF; Newtons), calculated as the product of the object mass, and the vector sum of the acceleration signals (vertical, horizontal, and lateral) taking into account gravity [187]. The load force trace during the entire task was used to specify the data points on the grip force trace from which the other variables were calculated; (2) grip force peak (GFP; Newtons), the maximum grip force during the lifting phase of the cup; (3) load force peak (LFP; Newtons), the maximum load force during the lifting phase; (4) GFR, the ratio between the maximum grip and load forces during the lifting phase; (5) static force (SF; Newtons), the average of grip force during the holding phase for a time window of 4 seconds; (6) latency (milliseconds), the time spent to reach the GFP from the first contact with the cup while gripping it. All figures were created in the software GraphPad Prism (version 8.2.1).

5.3.8. Statistical analysis

The dependent variables were tested for normality with a Shapiro-Wilk test. Kruskal-Wallis test or one-way ANOVA were used for demographic and clinical data accordingly. Post-hoc analyses tested the differences between groups (Mann-Whitney u test).

Spearman's rho coefficient was used to draw the correlations between sensory (SWME, 2PD, accuracy, and precision), GFC (GFR, latency, and SF), and hand dexterity measures (JTHFT and MPUT). In addition, GFC parameters were correlated with hand dexterity measures utilizing the Spearman's rho coefficient. Alpha was set at 0.05, and all data were processed either in Excel or in SPSS (software version 26.0).

5.4. Results

The demographic and clinical data of the three groups are shown in Table 5.1. Most subjects were right-handed (one left-handed in the healthy control group and 2 left-handed in the T2D+DPN group). We were successful in matching for age, as there were no significant differences between the three groups (p=0.4), Table 5.1. Summary of the results of all variables are presented in Table 5.1 for hand dexterity, GFC, and sensory measures, and more details about the group differences were provided in our previous study [116].

Table 5.1- Participants' Demographics and Clinical Characteristics

	HC (12)	T2D-only (11)	DPN+DPN (13)	P value
Gender (male/female)	7/5	5/6	6/7	
Age (years)	58±6	61±6	60±6	0.44
BMI (kg/m^2)	24.5±2.4	31.1±5.4	34.2±4.5	<0.001
Left-hand dominance	1/12	0/11	2/13	
HbA1c (%)	5.3±0.3	7.2±1.04	7±0.7	<0.001
Diabetes duration (years)	N/A	9.4±6.6	13.1±9.1	0.27[a]
Neuropathy duration (years)	N/A	N/A	4.8±3.5	
Hand dexterity:				
MPUT (seconds)	33.4±10.9	35.4±7.2	47.6±14.4	0.009
JTHFT (seconds)	43.5±9.9	49.4±8.4	54.8±11.5	0.005[b]
Tactile sensation:				
2PD (mm)	4.8±1	5±1	6±1	<0.001[b]
SWME (threshold)	3.6±0.4	3.6±0.1	3.8±0.7	0.058[b]
Pinch Proprioception:				
Accuracy (degrees)	0.67±0.67	0.33±1.67	3.67±3.84	0.002[b]
Precision (degrees)	0.58±0.42	0.58±0.57	2±3	0.003[b]
Grip force control:				
GFR	2.8±0.8	2.9±0.7	3.7±0.8	0.013
Latency (milliseconds)	320±40	306±145	422±194	0.025[b]
SF (Newton)	15±5.2	16±4.1	18.6±5.8	0.22

HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, diabetic peripheral neuropathy; BMI, body mass index; HbA1c, glycated hemoglobin A1c; MPUT, Moberg pickup test; JTHFT, Jebsen-Tailor hand function test; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination; GFR, grip force ratio; SF, static force.
Data represented as mean ± standard deviation unless otherwise indicated. P values from one-way ANOVA test.
[a] P-value from an independent t-test.
[b] Data represented as median and interquartile range. P-values from Kruskal-Wallis test.

5.4.1. Relationships between hand dexterity and sensory measures

Spearman's rho was performed for all correlations presented below. Table 5.2 and Figure 5.1 show the significant correlations found between MPUT and 2PD ($r = 0.47$, $p = 0.004$), SWME ($r = 0.56$, $p < 0.001$), accuracy ($r = 0.63$, $p < 0.001$), and precision ($r = 0.73$, $p < 0.001$). JTHFT showed significant positive correlations with 2PD ($r = 0.59$, $p < 0.001$), SWME ($r = 0.43$, $p = 0.009$), accuracy ($r = 0.35$, $p = 0.037$), and precision ($r = 0.46$, $p = 0.004$).

Table 5.2- Correlations between Hand Dexterity and Sensory Measures

Variables	MPUT	JTHFT
2PD	r = 0.47**	r = 0.43**
SWME	r = 0.56***	r = 0.59***
Accuracy	r = 0.63***	r = 0.35*
Precision	r = 0.73***	r = 0.46**

MPUT, Moberg pickup test; JTHFT, Jebsen-Tailor hand function test; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination.
r values calculated from Spearman's Rho test
* P-values < 0.05
** P-values < 0.01
*** P-values < 0.001

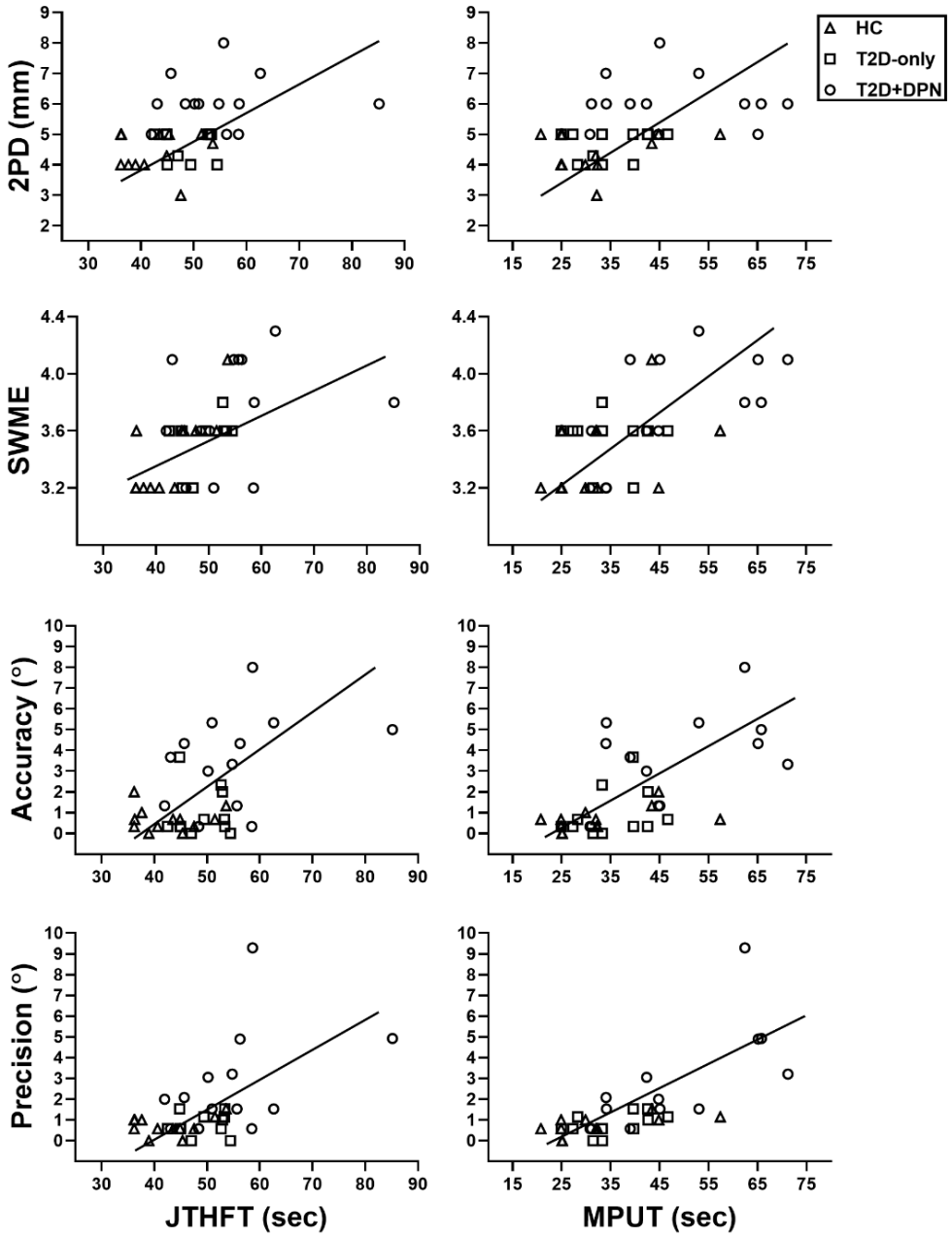

Figure 5.1. Moderate to strong (steeper lines) correlations between hand dexterity and sensory measures. HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, type 2 diabetes and diabetic peripheral neuropathy; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination; JTHFT, Jebsen-Tailor hand function test; MPUT, Moberg pickup test.

5.4.2. Relationships between GFC and sensory measures

As shown in Table 5.3 and Figure 5.2, significant positive correlations were found between grip force ratio and 2PD ($r = 0.40$, $p = 0.015$), SWME ($r = 0.51$, $p = 0.002$), and precision ($r = 0.35$, $p = 0.036$) during the lifting phase. Significant positive correlations exist between latency and 2PD ($r = 0.43$, $p = 0.01$), accuracy ($r = 0.51$, $p = 0.001$), and precision ($r = 0.48$, $p = 0.003$) during the lifting phase. Significant positive correlations exist between static force and SWME ($r = 0.35$, $p = 0.036$) and approached significance with precision ($r = 0.30$, $p = 0.08$) during the holding phase. No significant correlations were found between grip force ratio and accuracy ($r = 0.24$, $p = 0.16$) and between latency and SWME ($r = 0.27$, $p = 0.11$) during the lifting phase. No significant correlations between static force and accuracy ($r = 0.24$, $p = 0.16$) and 2PD ($r = 0.26$, $p = 0.13$) were found during the holding phase. Figure 5.3. Part (A and B) illustrates how sensory drive greatly affects parameters of GFC during the lifting phase while it seems to fade away during the holding phase.

Table 5.3- Correlations between Grip Force Control and Sensory Measures

Variables	GFR	Latency	SF
2PD	r = 0.40*	r = 0.43*	r = 0.26
SWME	r = 0.51**	r = 0.27	r = 0.35*
Accuracy	r = 0.24	r = 0.51**	r = 0.24
Precision	r = 0.35*	r = 0.48**	r = 0.30

GFR, grip force ratio; SF, static force; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination.
r values calculated from Spearman's Rho test
* P-values < 0.05
** P-values < 0.01

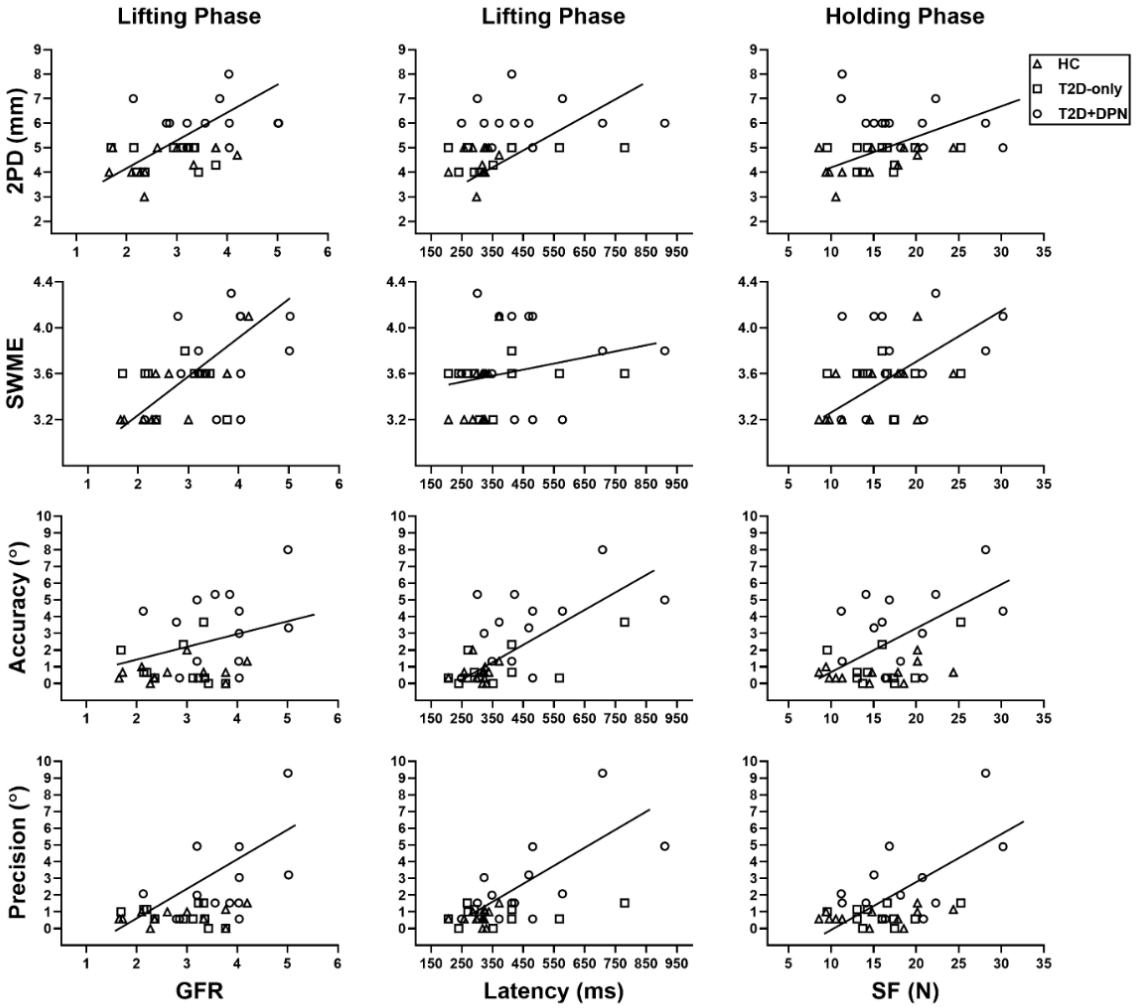

Figure 5.2. Moderate correlations between grip force control and sensory measures. HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, type 2 diabetes and diabetic peripheral neuropathy; 2PD, 2-point discrimination; SWME, Semmes-Weinstein monofilament examination; GFR, grip force ratio; SF, static force.

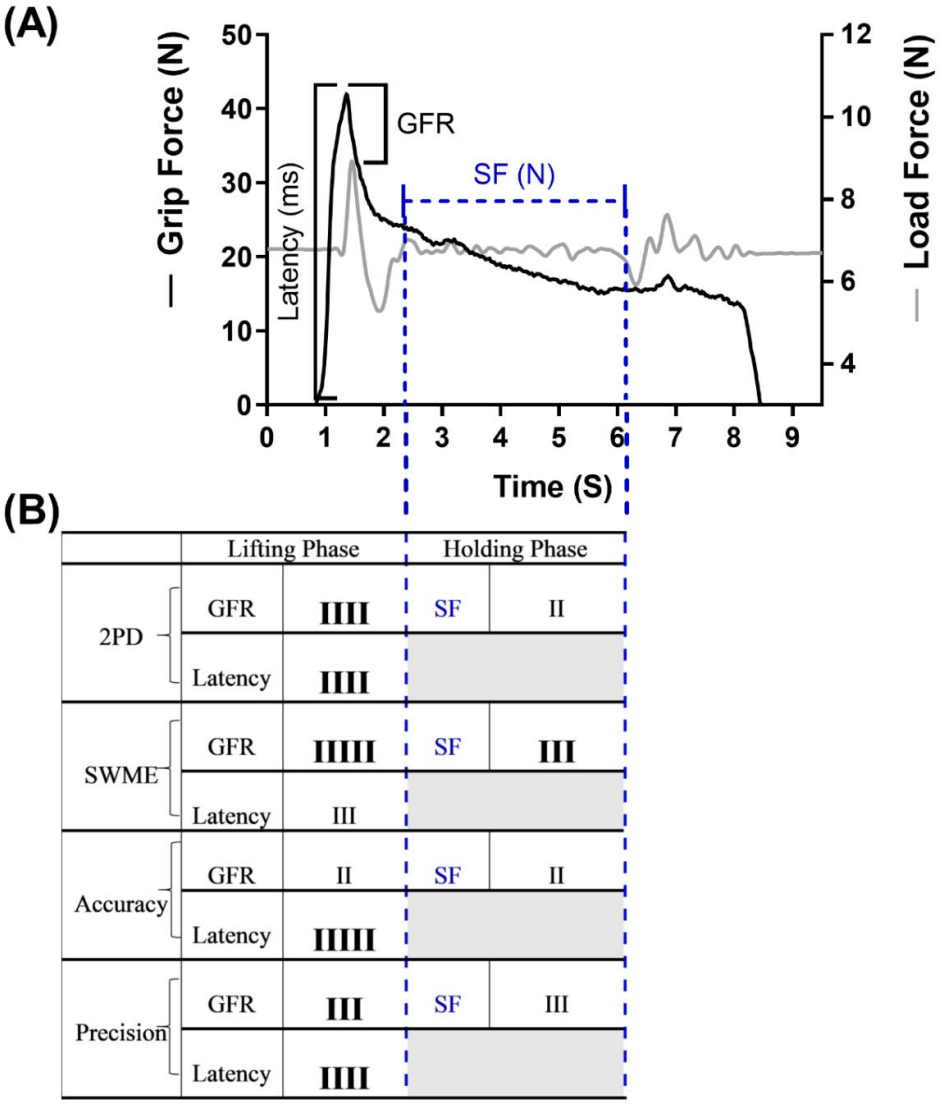

Figure 5.3. Part (**A)** represent grip and load force traces from a subject with T2D+DPN. The parameters of grip force control during lifting and holding phases are indicated: grip force ratio (GFR), and static force (SF). Part **B** represents a visual illustration of the correlations between sensory (2-point discrimination (2PD), Semmes-Weinstein monofilament examination (SWME), accuracy, and precision) and grip force control parameters. Bold vertical lines (**III, IIII, IIIII; for approximate r values of 0.3, 0.4, and 0.5, respectively**) represent significant correlations while regular vertical lines (II, III; for approximate r values of 0.2 and 0.3, respectively) represent non-significant correlations. Notice the higher correlations between sensory (tactile and proprioceptive) and grip force control parameters during the lifting phase while they fade away during the holding phase except for the SWME.

5.4.3. Relationships between GFC and hand dexterity tests.

Table 5.4 and Figure 5.4, show significant positive correlations between MPUT and GFR (r = 0.44, p = 0.007), latency (r = 0.40, p = 0.015), and SF (r = 0.43, p = 0.009). JTHFT was positively and significantly correlated with GFR (r = 0.58, p < 0.001) and latency (r = 0.35, p = 0.038) while approaching significance with SF (r = 0.32, p = 0.059).

Table 5.4- Correlations between Grip Force Control and Hand Dexterity Measures

Variables	MPUT	JTHFT
GFR	r = 0.44**	r = 0.58***
Latency	r = 0.40*	r = 0.35*
SF	r = 0.43**	r = 0.32

GFR, grip force rate; SF, static force; MPUT, Moberg pickup test; JTHFT, Jebsen-Tailor hand function test.
r values calculated from Spearman's Rho test
* P-values < 0.05
** P-values < 0.01
*** P-values < 0.001

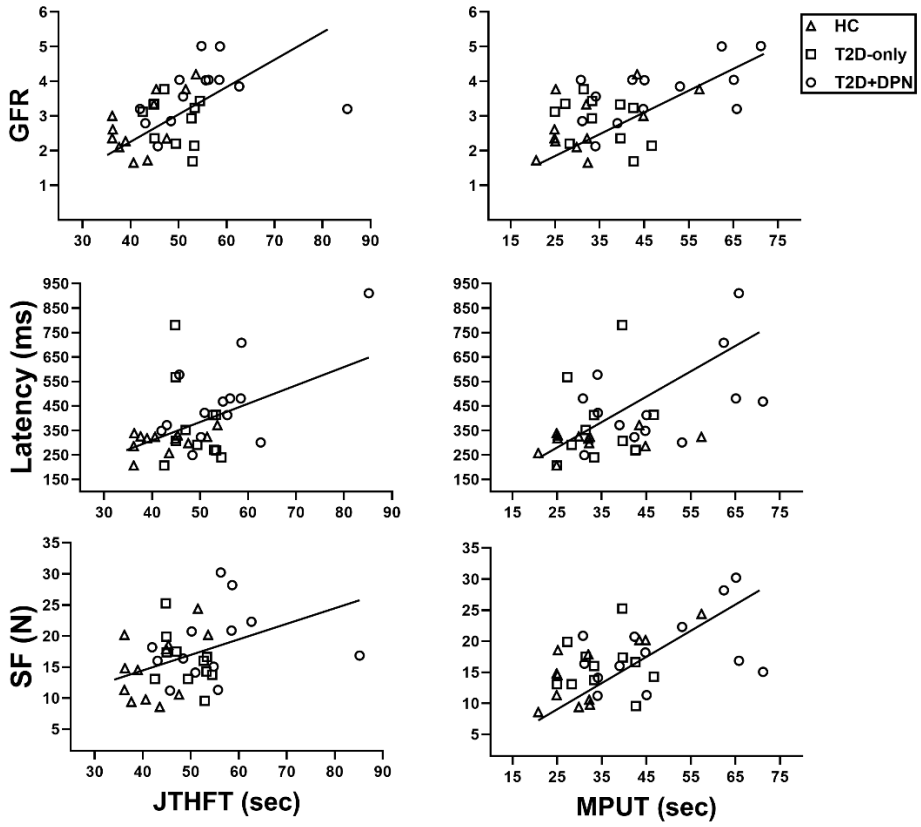

Figure 5.4. Moderate correlations between grip force control and hand dexterity measures. HC, healthy control; T2D-only, type 2 diabetes; T2D+DPN, type 2 diabetes and diabetic peripheral neuropathy; GFR, grip force ratio; SF, static force; JTHFT, Jebsen-Tailor hand function test; MPUT, Moberg pickup test.

5.5. Discussion

This study aimed to investigate the relationship between hand dexterity, sensory, and GFC variables. The results confirm our hypotheses that there are relationships between the outcomes of commonly used dexterity and sensory tests and parameters of GFC in individuals with T2D and DPN.

5.5.1. Relationships between hand dexterity and sensory measures

The current study revealed that relationships exist between the outcomes of sensory and hand dexterity measures. The contribution of tactile sensory deficits to the dexterity impairments associated with T2D is still controversial. For instance, Gorniak and colleagues [35] showed that tactile sensory deficits in the presence of T2D explained part of the dexterity impairments, whereas Redmond and colleagues [102] showed that worsening of tactile sensory deficits were not associated with dexterity decline over a two-year period. Furthermore, different studies have suggested the presence of other mechanisms responsible for the dexterity impairments besides the tactile sensory deficits [35, 102, 160]. DPN can lead to not only tactile sensory deficits, but also to proprioceptive impairments [115, 116]. Previously, we have shown that finger proprioception might be disrupted in the presence of T2D and DPN using a novel device and methods [116]. In the current study, MPUT showed higher correlations with precision and accuracy as compared to the JTHFT. This supports the view that proprioceptive deficits in subjects with T2D+DPN might be responsible for hand dexterity deficits since MPUT are performed without visual feedback, and the subjects heavily depended on the finger proprioception [93]. Because muscle spindles play a major role in the sense of proprioception [48, 67, 73, 175], the current findings may indicate that damaged muscle spindles contribute to deficits in hand dexterity. The combination of proprioceptive deficits associated with DPN and hand dexterity impairments which might increase the risk of hand injury or hinder the performance of many activities such as administering an insulin injection and picking up pills.

5.5.2. Relationships between GFC parameters and sensory measures

This study demonstrated moderate correlations between GFC parameters and sensory measures. Thus, during the lifting phase, GFR showed moderate and positive correlations with 2PD, SWME, and accuracy. Latency, on the other hand, showed moderate and positive correlations with accuracy, precision, and 2PD.

Few studies suggested the presence of other mechanisms different from tactile sensory feedback that are responsible for GFC deficits in people with T2D [35, 160]. While in the current study, we showed proprioceptive deficits were correlated with GFC deficits, it is important to notice that tactile sensory deficits were correlated as well. The reason for the different findings in our study from the ones reported in the literature could be related to differences in the experimental setup. For instance, both studies by Gorniak [35] and Ochoa [160] utilized a feedback system where subjects would match a predetermined grip force magnitude by pulling on a lever to match a line that appears on a computer screen. This is similar to the holding phase in our study but with a small difference. In our study, we did not provide visual feedback from a computer screen, and the subjects derive grip force magnitude on their own based on the physical properties of the object and the demands of the task.

In addition, tactile sensory feedback appears to influence the grip force magnitude (GFR), where the brain relies more on information about slippage of the object off the fingers during the lifting phase [110]. The findings of the current study revealed that the GFR was higher in individuals with T2D+DPN as compared to T2D without DPN and healthy controls. Unnecessarily higher GFR during object manipulation has been reported in individuals with type one diabetes [95] as well as patients with central and peripheral neurological diseases [98, 188]. During the holding phase, however, static force showed moderate and positive correlations only

with SWME but approached significance with precision. Monofilament testing was suggested to provide limited information about the tactile sensory encoding of lifting and holding phases during object manipulation [44].

Nonetheless, we still observed a similar pattern in the current study to findings from neurophysiological studies of tactile sensory encoding [61, 196]. For instance, fast adapting type I and II nerve fibers transmit signals about the mechanical changes from the first contact between the fingertips and the object during the lifting phase while slow adapting type I and II nerve fibers continue to fire during the holding phase [196]. The monofilament testing has been shown to be more reflective of fast adapting type I (Meissner's corpuscles), and slow adapting type I (Merkel endings) sensory nerve fibers and hence the correlations between the monofilament testing during the lifting phase were higher in comparison to the holding phase [197].

In contrast, 2PD was correlated with GFR and latency during the lifting phase while it was not correlated with static force during the holding phase. These findings echo the exact theoretical basis of the 2PD. The 2PD reflects the density of slowly adapting type I nerve distribution at the fingertips [198]. Therefore, the lower the density of nerve distribution, the worse the ability to detect object slippage during object manipulation, and as a result, the higher the GFR and latency during the lifting phase. In the holding phase, however, the nerve density as measured by the 2PD does not seem to play an important role (no correlations between 2PD and static force, and moderate correlations between SWME and static force during the holding phase). Perhaps, this is due to the presence of less mechanical events or perturbations as compared to the lifting phase.

It is interesting that accuracy and precision were more strongly correlated with latency than GFR during the lifting phase. It was suggested that proprioceptive feedback could support

or replace tactile sensory feedback from the grasping digits [76, 89]. Latency represents the efficiency in processing the sensorimotor signals and hence it measures the time delay to reach the grip force peak [88] while GFR represents the ability to efficiently scale the grip force based on the load force changes, and hence it measures the ratio between peak of grip and load forces [95, 98, 188]. Therefore, proprioception might play a role in optimizing the sensorimotor process, but it does not seem to directly drive any changes in the grip force production [199-201]. Similar findings from the lower extremities also suggest that anticipatory muscle activity was delayed as a result of altered proprioceptive sense due to vibration [202]. Nevertheless, most of the significant correlations observed in the current study were in the lifting phase; i.e., during the anticipatory phase. Several studies are showing that long term deficits affecting the sensory feedback from the fingers may disrupt the feedforward mechanisms of the motor control while the feedforward mechanisms might stay unaltered in short term deficits, such as in digital anesthesia [79, 84, 85, 187, 203]. However, it is not known when or how the brain integrates proprioceptive and tactile sensory feedback from the grasping digits.

Furthermore, our findings are in agreement with the suggestion brought forward by Johansson and Westling [204]. It was suggested that the cortical drive during the static phase is reduced compared to the lifting phase. In particular, the parameters of the motor output during the early lifting phase are based on the physical properties of the object. These parameters are closely adjusted by cortical control [205]. Once the parameters are established, the subcortical mechanisms take over the function of maintaining a stable grip during the static phase [204, 205].

5.5.3. Relationships between GFC and hand dexterity measures

Significant correlations between MPUT and GFC parameters (GFR, latency, and static force) were observed, while JTHFT showed significant correlations with GFR, latency, and

approaching significance with static force. Many studies in the literature reported GFC and hand dexterity deficits in subjects with T2D and DPN, but the deficits in the motor control system related to these deficits are yet to be elucidated. This can be the result of analyzing the GFC data solely based on a specific phase (whether lifting or holding phase) from the manipulative task. For instance, the holding phase was more commonly investigated in people with T2D [35, 97, 160], while the lifting phase was only investigated in subjects with type 1 diabetes [95, 96]. In the current study, common parameters of GFC were analyzed from the lifting and holding phases and were correlated to common dexterity measures.

Similar, but stronger correlations between GFC and hand dexterity deficits were observed in people with hand osteoarthritis [93]. In this study, the individuals who took longer to perform the MPUT showed longer latencies to liftoff the object from the table [93]. While we cannot directly relate to the findings from the osteoarthritis population, similar parameters can clarify the similarities between different diseases. Osteoarthritis patients showed stronger correlations than the ones we observed in the current study between latency and MPUT, $r = 0.85$, as compared to $r = 0.40$ in the current study. This can be the result of differences in the severity and the nature of the disease itself. The majority of the subjects in our study showed mild to moderate neuropathy with no reported symptoms of osteoarthritis [116]. In addition, significant correlations were observed in our study between GFR and MPUT and JTHFT, while the study by Nunes [93] showed no significant correlations between MPUT and grip force peak (GFP). Although GFP and GFR are both parameters derived from the lifting phase, the GFR represents the ratio between GFP and load force peak (LFP) and hence, that might explain the differences between our findings. Nevertheless, whether the disease has a neurological or musculoskeletal origin, correlations do exist between the temporal and magnitude of GFC parameters and hand

dexterity measures. Longer latency and higher GFR might be responsible for hand dexterity deficits. Such deficits can be the result of damage to sensorimotor integration due to tactile and proprioceptive damage, as discussed above in the previous sections. Therefore, different stages of GFC should be considered to better understand the nature of the main problem. Finally, our study has limitations, mostly related to the sample size and the generalizability to other populations. Nevertheless, majority of the correlations were moderate, and the significance was substantial. Thus, it is likely our findings would be identified in other populations.

5.6. Conclusion

The main outcome of this study was the observed positive correlations between sensory (tactile and proprioceptive) and parameters from GFC during the lifting phase and hand dexterity tests. The majority of the dexterity measures reported in the literature use time as an indicator of impairment; i.e., more time needed to perform a task is an indication of hand dexterity impairments. Our findings provide additional information on possible causes of hand dexterity deficits utilizing GFC parameters and in relation to sensory deficits. For instance, proprioception is essential for the human movement to have a proper interaction with the surrounding environment during a manipulative task. Clinicians should be aware of the nature of the problem and hence, they might be able to provide a guideline focused on improving hand function. Hand rehabilitation programs designed for people with T2D and DPN should investigate proprioceptive and GFC training strategies to improve hand function.

Chapter 6: Discussion and conclusions

6.1. Summary of findings

This dissertation work was primarily undertaken to help clarify and characterize the impact of T2D and DPN on hand function. This research was focused on developing new methods to measure proprioception of the fingers in a manner that is very similar to a variety of tasks performed during everyday life such as pinching with the thumb and index fingers diversified small objects or using pair of scissors. Further, this research expands on the contribution of sensory damage to grip force control and hand dexterity. The findings of the present study suggest that DPN might be responsible for deteriorating hand function. Possible reasons for this will be further discussed in the next sections. These findings are important to guide the rehabilitation and screening process of the disease. It is hoped that through this work and the follow-up studies, we will attain a better understanding of the exact nature of the hand deficits in people who suffer from T2D and DPN and hence improve their quality of life.

Chapter 2. Pinch Aperture Proprioception: Reliability and Feasibility study

The main purpose of the three experiments undertaken in Chapter 2 was to develop a new strategy that would enable us to measure proprioception in a functional manner. If proprioception was defined as the awareness of body parts and its movement in relation to each other and to the surrounding environment, then testing methods should consider the fact that we use more than one finger when we reach out to lift a glass of water or administer an insulin injection or use a pencil to write. Experiment 1 demonstrated the reliability of a novel device and methods developed to test the pinch proprioception between the index finger and thumb in healthy subjects over two consecutive days. Experiment 2 was undertaken to demonstrate a model of proprioceptive damage via the use of vibration to resemble neurological diseases. Finally, experiment 3 demonstrated possible pinch proprioceptive damage in 2 subjects with T2D+DPN.

Thus, it was concluded that the device and methods were not only reliable to test the sense of proprioception, but also capable of detecting proprioceptive changes under the influence of extensor tendon vibration and possibly in subject with T2D+DPN.

Chapter 3. The Impact of Type 2 Diabetes and Diabetic Peripheral Neuropathy on Pinch Proprioception

To further investigate whether DPN was the primary complication associated with T2D that leads to pinch proprioceptive deficits, three groups of subjects matched by age were tested; T2D+DPN, T2D-only, and healthy controls. It was expected that the neuropathy group would be most affected by deteriorations in the pinch proprioception. Further, it was speculated that damage to muscle spindles could be a major contributing factor to deficits in pinch proprioception. This speculation can be supported if we could exclude other factors such as tactile sensory and mechanical deficits known to contribute to the sense of proprioception. It was found that healthy subjects and those with T2D-only were similar in their performance, while T2D+DPN subjects showed significant deteriorations to their pinch proprioception sense. Also, the moderate correlations between pinch proprioception and tactile sensory measures indicated it is very likely that possible damage to muscle spindles might be the main contributing factor to pinch proprioceptive deficits.

Chapter 4. The impact of Type 2 Diabetes and Diabetic Peripheral Neuropathy on Reactive and Anticipatory Grip Force Control

The main objective of chapter 4 was to analyze the precision grip force control during object manipulation utilizing a lifting and holding task in people with T2D and DPN. As such, grip force control was analyzed on the bases of reactive and anticipatory nature of motor actions,

which will help differentiate the source of potential motor control deficits, whether peripheral or central in origin. Our results provide some of the first evidence that grip force magnitude during object manipulation is mainly disrupted in people with T2D+DPN while the temporal coordination (time lag between load force peak and grip force peak) is well preserved, suggesting that grip force control deficits are most likely to be peripherally driven. This will be discussed further in the next few sections.

Chapter 5. The Associations between Grip Force Control, Sensory, and Hand Dexterity Measures in People with Type 2 Diabetes and Diabetic Peripheral Neuropathy

Fine motor function requires intact integration of sensorimotor processes. While previous chapters have shown that pinch proprioception and grip force control are disrupted, chapter 5 focuses on drawing any associations between hand dexterity, sensory, and grip force control measures. The dexterity measures included common tasks performed during everyday life such as writing a sentence, flipping cards, lifting heavy and light objects, and simulated feeding. The sensory measures include tactile (protective and discriminatory sense from the fingertips) and proprioceptive signals. Grip force control parameters were chosen from the lifting and the holding phases of a manipulative task. Three main objectives were explored in this chapter. First, the correlations between sensory deficits and hand dexterity measures, which generally clarify whether sensory damage (tactile or proprioceptive) can be correlated with common dexterity measures, were investigated. Our findings showed that both tactile and proprioceptive sensory deficits contributed to changes in hand dexterity measures. Second, the correlations between sensory deficits and grip force control parameters which will clarify what aspects of sensory damage contributed most to changes in grip force control. Our findings showed moderate correlations between sensory and grip force control measures. For instance, the time to lift the

object was more correlated with proprioceptive deficits, while tactile sensory deficits were more correlated with the magnitude of grip force, which was unnecessarily higher. Finally, the correlations between grip force control and hand dexterity measures will better determine which sensorimotor deficit has contributed most to deteriorations in hand dexterity. A moderate correlation was found between hand dexterity and grip force control parameters indicating that deficits in temporal delay and magnitude of grip force could indeed be what contributed most to the delays detected by hand dexterity measures.

6.2. Overall Discussion

It is very well documented that sensory feedback derived from the tactile mechanoreceptors located at the fingertips is essential for learning and maintaining intact anticipatory grip force control [44, 81, 90, 206]. For instance, Meissner's corpuscles only fire in response to important mechanical events such as when we make contact with an object with our fingers, and when we let go of it, and the action potentials travel through fast adapting type I nerve fibers [60]. On the other hand, Merkel corpuscles respond to skin indentations [61], and they continue firing and sending nerve impulses through the slowly adapting type I afferent nerve fibers as long as the object is still in contact with the fingertips [60]. T2D impacts the normal function of these different receptors and their nerve fibers and disrupts the anticipatory grip force control [43]. Our findings showed that the GFR was significantly higher in the T2D+DPN group, while the time lag showed no significant differences between the groups. Data shows that timing is controlled centrally while GFR is dependent on continuous sensory feedback to scale grip force based on load force changes [81, 206]. This is further supported by the associations we observed between tactile sensory and grip force control parameters during the lifting and holding phases. Tactile sensory feedback was associated with higher grip force

magnitude. Increased grip force in the presence of somatosensory deficits in pathological diseases [98, 99] might be a strategy adopted by the subjects to prevent object slippage [98]. As a result, grip forces will increase to secure the object as a safety precaution [98].

On the other hand, there is evidence to suggest that proprioceptive afferents exhibit low sensitivity to mechanical events between the object and the grasping fingers [44, 199-201, 207]. For instance, the contribution of muscle spindle to anticipatory and reactive grip force control mechanisms was investigated via direct afferent nerve recordings from healthy subjects [200]. The recording electrodes were inserted into the median and ulnar nerves of the proximal long flexor muscles (regardless of the exact origin, whether muscle spindles or tendon organs) [200]. The authors reported that no response was recorded before the onset of automatic grip force response as a result of load force changes, but during liftoff, the afferent discharge peaked. However, during the holding phase, a tonic discharge was sustained. In addition, no response was recorded from any of the distal muscles (lumbricals, dorsal interossei, opponens pollicis, and flexor pollicis brevis). It was concluded that muscle spindle mechanoreceptors played no role in the automatic grip force adjustments based on load changes, and the forward/anticipatory model is in play. Note that the subjects who were recruited for this study were healthy; hence, the contribution of damaged muscle spindles was not investigated. In addition, the afferent nerve recordings were collected from flexor muscle groups (the agonists in this case). Data suggest that the signals from muscle spindles of the antagonist muscles (extensor muscles, in this case) play a greater role in joint position sense, and they even precede the onset of agonist contraction [115, 208-210]. Therefore, the findings by Macefield and colleagues [200] might have been clouded by the fact that they did not measure muscle spindle discharge from the antagonist muscles (the

extensor muscles) and hence their findings cannot be conclusive in excluding the role of proprioception in anticipatory phase during the lifting task.

The majority of the evidence that opposes the importance of proprioceptive signals during object manipulations rises from neurophysiological studies of tactile sensory encoding on healthy subjects [199-201, 207]. On the other hand, the evidence that highlights the importance of proprioceptive signals during object manipulation is based on cases with severe proprioceptive impairments [89, 152, 153]. For instance, the evidence from studies on subjects with complete sensory deafferentation can be conflicted to whether proprioception or tactile sensory deficits contributed most to grip force control deficits [89]. Nevertheless, our findings provided further evidence on the contribution of proprioceptive feedback during the anticipatory phase of grip force control.

Many studies support the idea that the cerebellum is the main location for the internal model; i.e., the cerebellum plays a major role in constructing the anticipatory grip force in advance of the actual gripping and lifting movement to compensate for the natural delay in the sensory feedback [79-82]. Our data showed that time lag was not affected, which indicates that the temporal coupling between grip and load forces is intact. Additionally, the T2D+DPN showed longer latencies to achieve the grip force peak during the lifting phase. There is evidence to suggest that the cerebellum delays the efference copy of the motor command to match the actual sensory feedback [211]. Worse accuracy and precision of the pinch proprioception were correlated with longer latencies to reach the grip force peak during the lifting phase. If the proprioceptive feedback processed by the cerebellum does not match the efference copy, then it is possible that longer latencies observed in the T2D+DPN group during the anticipatory phase of the lifting task is based on the difficulty faced by the cerebellum trying to filter the

proprioceptive noise generated by damaged muscle spindles in those subjects [211-213]. In accordance with this statement and considering our findings, we can speculate that if proprioception is affected, then it will generate a noise in the background of the motor activity causing more delays in the sensorimotor process. Our results echoed previous findings in the literature suggesting that proprioception does not have a direct contribution to reactive changes in grip force control during a manipulative task [199-201, 207], but rather deteriorate the sensorimotor process in general.

6.3. Limitations

6.3.1. Neuropathy Screening

It is widely known that DPN advances from distal to proximal parts of the upper and lower extremities [30]. DPN mainly affects small sensory fibers first and correlates with the severity of the disease itself [31-33]. In addition, even before the presence of small fiber neuropathy, changes in motor function might still exist without noticing (asymptomatic manifestations) [34, 35]. Therefore, diagnosing DPN comes with challenges, and the subclinical signs of neuropathy might still exist in the T2D-only group. The gold standard measures of neuropathy are nerve conduction studies and skin biopsies [27, 214]. The latter can be used to study small nerve fiber neuropathies as compared to the former, which mainly investigates neuropathy affecting large nerve fibers [27, 214]. Nevertheless, both tools are invasive and hard to implement for this current dissertation project. To account for such difficulty, the priority was given to subjects with a known diagnosis of DPN. As such, all our subjects in the T2D+DPN group had already been diagnosed by a neurologist using nerve conduction studies and skin biopsies. Regarding the T2D-only group, ruling out neuropathy was challenging, knowing that there might be a chance of having subclinical signs of neuropathy. Nevertheless, all the clinical testing for neuropathy was performed for both diabetic groups (T2D-only and T2D+DPN). This

includes using a 10g monofilament (protective sensation), superficial pain sensation, and vibration by on-off method on the big toe to screen for neuropathy [134, 135]. Other clinical examinations included position sense of the big toe (up or down test), bilateral knee and ankle reflexes, and temperature sensation. In specific, temperature sensation, which is part of our thorough screening process might capture small fiber neuropathy [214]. Regardless of the presence of deficits in small fibers of the sensory system, the present study does not confirm the presence of subclinical signs in terms of hand dexterity and precise motor control in patients with T2D without "apparent" neuropathy.

6.3.2. Nerve Damage to the Central Nervous System

In a systemic disease such as T2D, CNS damage has been documented [10, 12, 13, 16], and it has been suggested as a possible mechanism for impaired sensorimotor control [160]. For instance, diffuse axonal degeneration and demyelination of the sensory nerves in the spinal cord and brain stem have also been observed in people with DPN [16]. This could result in a delay in central sensory processing [54], which might affect the sensorimotor integration and hence the hand function. Furthermore, damage to peripheral sensory and motor nerves may reflect differences in central processing; i.e., confounding the real source of the problem as if it is central while it is peripheral at the origin. To investigate the status of the central processing, we screened for the cognitive function via Montreal cognitive assessment (MoCA) for all the subjects. MoCA is a valid and sensitive test for mild cognitive dysfunction [215]. The results showed no significant differences between the groups. Although we can conclude that our subjects showed no cognitive dysfunction, there is the possibility that MoCA did not capture all central nerve involvement in the T2D and DPN populations. Therefore, we cannot conclusively exclude the involvement of CNS as a possible explanation for our findings due to the complexity

of the disease itself and the difficulty of ruling out the CNS involvement simply based on subjective screening.

6.3.3. Other limitations

The sample size is an obvious limitation in this dissertation although our primary outcome variables were well-powered. A larger sample size will be needed to further support the current findings. For instance, the index of grip force adjustments (newly developed outcome measure) approached significance when comparing groups with a trend of more deficits in the T2D+DPN group. Perhaps, a larger sample size would have diminished the variability in the neuropathy group. Furthermore, the design of the lifting task used in this dissertation might have limited our findings. For instance, the time during the holding phase was 5 seconds on average, which is the common procedure available in the literature. However, this time window might still be too short to capture the subtle decline in grip force during the holding phase, and hence, the index of grip force adjustments failed to capture the exact and natural steepness of the grip force curve. Also, the current protocol that was designed to investigate the grip force control among the groups is only focused on understanding motor behavior and not motor learning. Nonetheless, it is an important first step to study motor behavior in order to understand the motor learning process.

In addition to larger sample size and study design, perhaps a wider range of disease severity could have better differentiated the group differences. In the current dissertation, the majority of our subjects did have mild to moderate neuropathy based on the neuropathy scale we utilized [134, 135]. However, including more severe cases can be challenging when interpreting the results due to the vast range of complications associated with T2D and DPN, affecting joints,

skin, muscles, and nerves to different degrees [40, 177, 216]. This would make it very difficult to match groups based on the subjects' characteristics.

6.4. Clinical Implications

It is important to have a comprehensive understanding of the sensorimotor integration during object manipulation in order to improve hand function. The cumulative knowledge from previous research and of the current dissertation is applicable in screening and, hopefully, rehabilitation of hand deficits. The moderate correlations between grip force control and hand dexterity measures helped clarify possible mechanisms that contributed most to deteriorations in hand dexterity, providing a good target for rehabilitation programs. For instance, if we were to design a rehabilitation program focused on improving hand function in people with T2D+DPN with similar clinical characteristics, the present data suggest that proprioceptive and tactile sensory deficits contributed to exaggerated grip force magnitude and time delay during the lifting phase of a hand-held object. Therefore, clinicians should provide finger proprioceptive training when dealing with patients with T2D and DPN. Also, clinicians should be aware of the unnecessarily high grip force applied during object manipulation and inform their patients to be careful when lifting fragile objects to avoid causing damage and possibly injuring their hands. In the next paragraphs, few ideas are provided to help clinicians provide treatment plans focused on improving hand function in people with T2D and DPN.

In addition to the deficits we observed during the lifting phase, there were no significant differences between the groups in grip force control parameters during the holding phase. If solely based on the interpretation of this finding, it can be concluded that subjects with T2D+DPN might still be able to adjust their grip force when they are provided with more time. In other words, this should be a fair trade if safety is paramount when performing a task, but the

opposite might put subjects at risk if time is of the essence. One way to overcome such difficulty is to highlight the importance of visual feedback. For instance, if proprioception sense is diminished or absent, it has been suggested that visual feedback can compensate for such deficits and can have a critical role in motor learning [152, 217]. This is of utmost importance to be used as a preventative strategy; i.e., subjects with proprioceptive deficits should be made aware of their problem and should be advised to pay more attention (guided hand movements with direct visual feedback while avoiding distractions as much as possible) when performing activities with their hands.

An alternative approach to enhance the sense of proprioception is to maximize the sensory feedback by engaging more skin mechanoreceptors. While the muscle spindles are the primary mechanoreceptor responsible for the sense of proprioception, skin mechanoreceptors are also known to contribute to the sense of proprioception. For instance, wearing compression garments has been shown to improve the sense of proprioception by maximizing and enhancing signals originating from skin mechanoreceptors [218]. Knowing that our groups did not differ significantly in their light touch perception, it is plausible that subjects with T2D+DPN can improve their sense of proprioception utilizing this approach.

6.5. Future directions

The long-term goal of this work is to characterize the contribution of disease status (T2D with and without DPN) to deficits in sensorimotor process of grip force control and hand dexterity. In specific, this will establish the foundation to possibly use our novel design and methods as part of neuropathy screening and hand rehabilitation for people with T2D and DPN and other neurological populations.

6.5.1. Motor learning

The current dissertation work focused on understanding the *motor performance* in subjects with T2D and DPN; future work is still needed to understand the process of *motor learning* in the presence of proprioceptive deficits in this population. Previous research has shown that proprioceptive disruption via the use of vibration did not impact motor learning [219]. However, this conclusion is yet to be identified in subjects with T2D and DPN. Therefore, the question of what magnitude the motor learning can take effect in subjects with diabetes is a good premise for future work. Furthermore, the fact that motor learning was still possible in more severe cases of peripheral deafferentation and central damage such as in stroke [152, 217, 219] provides hope that diabetic subjects, in comparison, might be at better odds considering the nature of the disease is much less severe.

6.5.2. Grip force control as a rehabilitation tool

Future studies should investigate the application of biofeedback force tracking devices [220-222] during a grip lifting task to reduce the excessive force utilized by subjects with T2D and DPN. The biofeedback tracking devices provide visual feedback of the *actual* grip force trace during object manipulation along with a *target* grip force trace so that the subjects should try to match during practice [220-222]. In fact, research shows that even temporal parameters, as well as the trajectory (proprioceptive), can be improved if a large number of trials were allowed, more than 50 for the temporal aspects and more than seventy for the trajectory of anticipatory grip force control [81, 82, 206]. Finally, a longer time should be provided during the holding phase (up to 20 seconds, [187]) in order to investigate the index of grip force adjustments.

6.5.3. More future directions

It is important to establish the sensitivity and the specificity of grip force control paradigm and pinch proprioception device against gold-standard measures such as nerve

conduction studies and magnetic resonance imaging techniques. In addition to a larger sample size, different study designs, and wider range of disease severity, future studies should investigate the implementation of the current design and methods of pinch proprioceptive testing on different populations such as stroke. It has been reported in stroke survivors that the more severe the proprioceptive deficits, the greater the impact on motor learning [217]. While the proprioceptive testing took place primarily at the shoulder joint for this study [217], it is as important or even more to investigate how pinch proprioceptive deficits contribute to grip force control and motor learning at the hand in stroke survivors.

6.6. Conclusions

It has long been believed that DPN associated with T2D affects mainly the lower extremities. The work presented in this dissertation indicates that this is not the case. Even people with mild-moderate DPN associated with T2D demonstrated pinch proprioceptive, grip force control, and hand dexterity deficits. One of the major contributions of the current work was categorizing the role of tactile and pinch proprioception during grip force control paradigm. This finding provides additional evidence to support the role of proprioception in anticipatory grip force control. In addition, the temporal delays were associated with hand dexterity measures, which indicate that reducing the temporal delays might improve the hand dexterity for this population. Overall, the tactile sensory deficits appear to affect the force production, while proprioceptive deficits seem to affect the temporal aspects of the grip force control. While temporal delays might contribute to the slowness in hand dexterity measures, higher grip forces might cause hand fatigue or damage to delicate objects. Physical and occupational therapy interventions are very limited in terms of improving tactile sensory function in the presence of T2D and DPN. However, developing interventions focused on improving hand function might

benefit greatly by integrating proprioception training as part of the treatment plan. Future studies such as those outlined above aimed at improving hand sensorimotor control screening and rehabilitation strategies might benefit by using our device and methods to establish such plans.

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