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RESEARCH ARTICLE

The impact of diabetic peripheral neuropathy on pinch proprioception

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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. Target accuracy and precision was compared between groups using Kruskal–Wallis test. Sensation was tested through the two-point discrimination and Semmes–Weinstein monofilaments applied on the fingers. Sensory measures were correlated with 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 ($p=0.003$ and $p=0.006$, respectively) and the healthy groups (both $p=0.002$); no significant differences were found between T2D-only and healthy. Spearman's rank showed moderate ($r=0.45$–0.66, $p<0.001$) 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.

Keywords Index finger · Thumb · Joint position sense · Type 2 diabetes

Introduction

Sensory nerves carry important proprioceptive information about the position of our body parts in relation to each other and to the surrounding environment (Gandevia et al. 2002; Proske and Gandevia 2012; Roijezon et al. 2015). Proprioceptive signals are derived from mechanoreceptors located in the skin, joints, tendons, ligaments, and muscles (Levine 2007; Roijezon et al. 2015). In particular, muscle spindles play a major role in the sense of proprioception throughout the range of joint motion (Proske and Gandevia 2012; Proske et al. 2000). 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 (Levine 2007).

The sense of proprioception will be disrupted by any interference with the generation, transmission, and processing of the proprioceptive signals (Abbruzzese et al. 2014; Aman et al. 2014). The presence of proprioceptive deficits in the upper extremities with sensory deafferentation has been shown in a multitude of studies (Cardinali et al. 2016; Rothwell et al. 1982). 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 (Rothwell et al. 1982). 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 ablongata (Cardinali et al. 2016). In addition, severe cases of nerve damage to the CNS, such as multiple sclerosis and stroke, are associated with significant finger proprioceptive

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deficits. These deficits are mainly due to impairments in the processing of the proprioceptive signals received from, otherwise, intact mechanoreceptors and afferent nerve fibers (Connell and Tyson 2012; Duque et al. 2003; Wiblin and Guadagno 2017; Winward et al. 1999).

In a disease such as type 2 diabetes (T2D), peripheral nerves are susceptible to damage (Bales and Meals 2009; Matsutomo et al. 2005; Meijer et al. 2000) 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 (Dyck et al. 2011; Mahajan et al. 2016). Research has mostly shown proprioceptive deficits to occur in the lower extremities in individuals with T2D + DPN (Kamenov et al. 2010; Simoneau et al. 1996; van Deursen and Simoneau 1999). On the other hand, proprioceptive deficits in the upper extremities in subjects with T2D + DPN have not been as commonly studied. One study by Ochoa et al. (2016) 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 (Kamenov et al. 2010; Simoneau et al. 1996; van Deursen and Simoneau 1999). 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 (Han et al. 2016).

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 (Lincoln et al. 1991; Moberg 1983). In this test, the examiner would passively move the subject's finger to 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 (Connell and Tyson 2012; Ingemanson et al. 2016; Lincoln et al. 1991; Winward et al. 1999). 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) (Cordo et al. 2011; Proske and Gandevia 2012). 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 (Wycherley et al. 2005), wrist joint (Gay et al. 2010), and elbow joint (Elangovan et al. 2014). In addition, the precision pinch between the index finger and thumb are responsible for 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 the previous work, we tested a novel device designed to assess quantitatively the pinch proprioception in healthy participants under the effect of extensor tendon vibration and in two subjects with T2D + DPN (Yahya et al. 2018). 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 (Goodwin et al. 1972; Proske and Gandevia 2012; Proske et al. 2000; van Deursen et al. 1998). 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.

Methods

This is a cross-sectional study and all measurements were collected in 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 (Oldfield 1971). 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).

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 30 to 70 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 30–60 s. In the Tenile's sign, the examiner lightly tapped over the course of the median nerve at the wrist joint. Subjects were excluded if they had a positive sign that provoked symptoms of tingling or pins and needles from both tests (Szabo et al. 1999). 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, and stage 3; hand deformity at rest (Papanas and Maltezos 2010). Subjects were excluded if they had severe deformity at rest (stage 3).

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 have told them that they have T2D. In addition, following the American Diabetes Association guidelines (Davidson 2010), Glycated Hemoglobin A1c (HbA1c) testing was conducted (PTS Diagnostics Polymer Technology Systems A1CNow + ™ Systems (Lemke and Matthaei 2009)). This test was used 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) (Davidson 2010).

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 10 g 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 (Olaleye et al. 2001; Perkins et al. 2001). 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, 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) neuropathy (Olaleye et al. 2001; Perkins et al. 2001).

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 (Cederlund et al. 2009a). 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 respond verbally whenever they felt the touch of the monofilament on their fingers. There are five levels that represent the severity of the tactile 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 with 4 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 (Feng et al. 2009; Lee et al. 2003). 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 point 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 5 mm is considered normal, 6–10 mm is fair, and 11–15 mm is poor (Novak 2001).

Pinch proprioception testing

The device used to test for pinch proprioception is described in detail in our previous study (Yahya et al. 2018). In short, it included a modified goniometer with its fulcrum fixed on top of a small cardboard, Fig. 1. The goniometer arms extended out the cardboard's edge and included circular pads on its extremities attached perpendicularly for the fingers tip 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° and 15° 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 s, 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 (Hincapie et al. 2016).

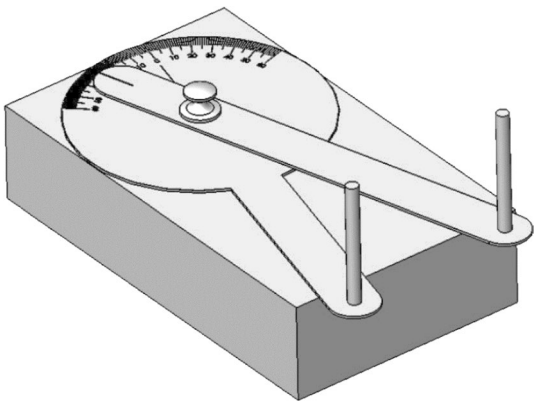

Fig. 1 Schematic representation of the pinch proprioception device. Used with permission: Yahya et al. (2018)

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 (Mathiowetz et al. 1985, 1984). Subjects were seated on an armless chair with shoulder abducted and neutrally rotated while the forearm was held at 90° of elbow flexion. Both the forearm and the wrist were held at neutral position (midway). Subjects were asked to use their thumb and index finger to press and hold the pinch gauge for at least 5 s using their maximum force. A break of 30 s 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.

Data analysis

Sample size was based on our preliminary study of pinch proprioception under the effect of extensor tendon vibration (effect size of 1.68) (Yahya et al. 2018) and another study investigating proprioception of the ankle joint in individuals with DPN (effect size of 0.55) (Simoneau et al. 1996). 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 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 were 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 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^2) 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.

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 of 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 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.

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

Table 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*
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**
SWME (threshold)	3.6 ± 0.4	3.6 ± 0.1	3.8 ± 0.7	0.058**
Trigger finger (*n*)	0	2[a]	1[a]	
History of carpal tunnel syndrome (*n*)	0	1[a]	1[b]	
Prayer sign (*n*)	4	5	7	
Pinch proprioception				
Accuracy (°)	0.67 ± 0.67	0.33 ± 1.67	3.67 ± 3.84	0.002**
Precision (°)	0.58 ± 0.42	0.58 ± 0.57	2 ± 3	0.003**
Pinch strength (Newton)	65.3 ± 22.2	59.7 ± 16.7	68.6 ± 17.9	0.53

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

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

[a]Non-dominant hand

[b]Dominant hand

*p value from an independent t test

**Data represented as median and interquartile range. p values from Kruskal–Wallis test

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 1, Fig. 2.

Spearman's rho was performed for all correlations presented below. As shown in Table 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 2, Fig. 3.

Table 2 Correlations between pinch proprioception, cognitive, and hand sensibility measures

Variables	*r* value[a]	*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

[a]Spearman's Rho test

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, the 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 et al. (1982) 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, Fig. 2. Similar to our study, Ochoa et al. (2016) 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 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 et al. (2016) shows no difference in proprioceptive performance between patients with T2D

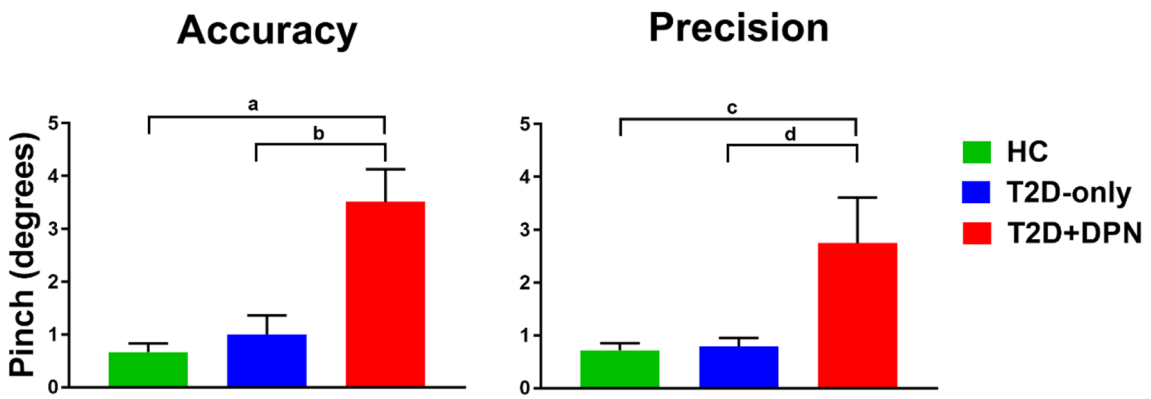

Fig. 2 Pinch proprioception measures. *HC* healthy control, *T2D-only* type 2 diabetes, *T2D + DPN* type 2 diabetes and diabetic peripheral neuropathy. The T2D + DPN group is significantly different from the other two groups for the accuracy and precision. [a]*p* value = 0.002), [b]*p* value = 0.003,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

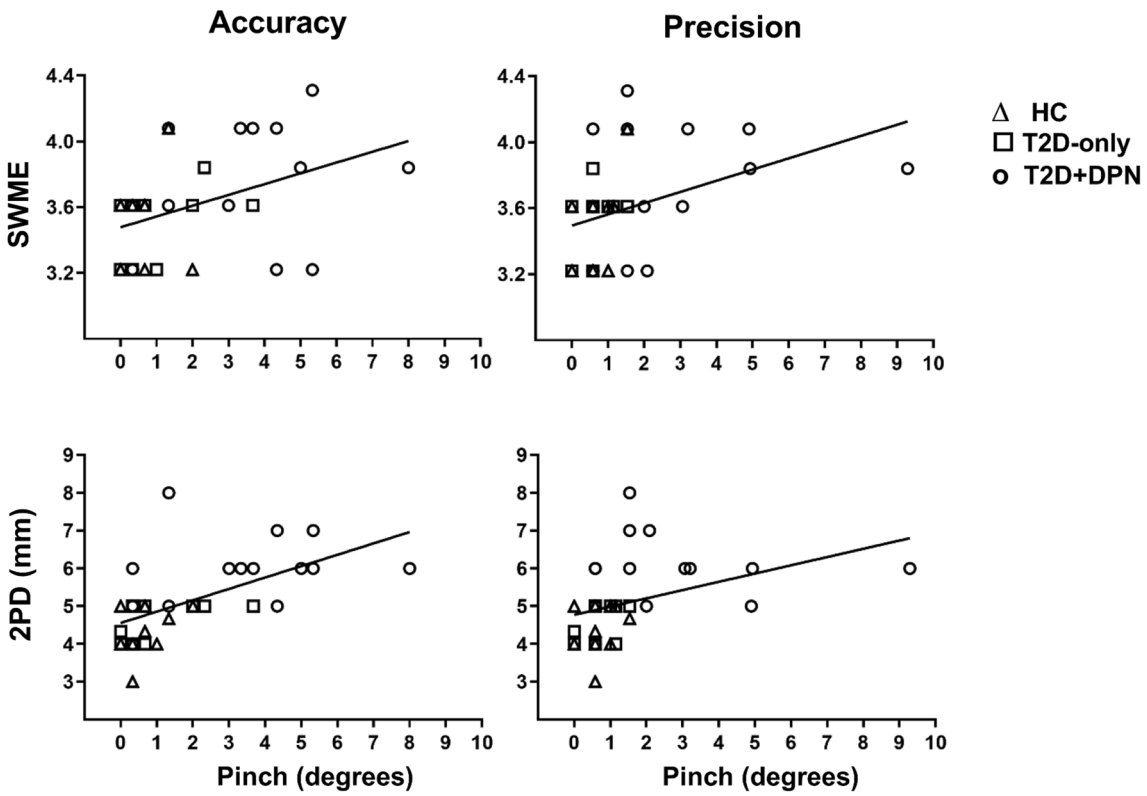

Fig. 3 Correlations between pinch proprioception (accuracy and precision), and cutaneous measures (SWME and 2PD). *SWME* Semmes–Weinstein monofilament examination, *2PD* 2-point discrimination. *HC* healthy control, *T2D-only* type 2 diabetes, *T2D + DPN* type 2 diabetes and diabetic peripheral neuropathy

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 subject's thumb of 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 cognitive system or on afferences from the forearm (muscle spindles). These were probably "less efficient" in T2D than those of the healthy subjects. Differently, in the present study, the subjects depended on afferences of the distal parts of the upper extremity and motor commands from the feedback system. Thus, patients with T2D without DPN had no problem in performing the task properly (i.e., similar to the 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 longer duration of DPN (Swash and Fox 1974). Our previous experiment (Yahya et al. 2018) 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 (Yahya et al. 2018). 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° 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 on areas innervated by the median nerve at the fingertips (Cederlund et al. 2009a). 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 2, Fig. 3. 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. In addition, 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 (Simoneau et al. 1996). 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 (Cederlund et al. 2009b; Papanas and Maltezos 2010; Schiavon et al. 2004). The majority of the musculoskeletal changes in T2D are strongly associated with the length of the disease (Cederlund et al. 2009b; Papanas and Maltezos 2010; Schiavon et al. 2004). 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, chronic incidence of carpal tunnel syndrome, and the limited range of motion as measured by the prayer sign, Table 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°–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 (Karagiannopoulos and Michlovitz 2016). 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 has functional relevance to 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 (de Freitas and Lima 2013; Shah et al. 2014) 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 (de Almeida Lima et al. 2017; Pfutzner et al. 2011). 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 (Dyck et al. 2011; Mahajan et al. 2016). 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, the past studies have shown moderate-to-strong (− 0.60 to − 0.80) associations between pinch strength and fine motor control (Beebe and Lang 2009; Lang and Beebe 2007). Our findings showed no significant differences in the pinch strength between healthy and diabetic groups which indicated that motor function is not affected (Table 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 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 (Hazari et al. 2015) and it has been suggested as a possible mechanism for impaired sensorimotor control (Ochoa et al. 2016). 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 (Selvarajah et al. 2006). This could result in a delay in central sensory processing (Connell and Tyson 2012), 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 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.

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.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest and this study was self-funded.

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