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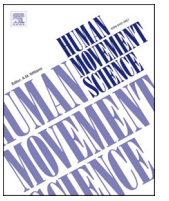

Full Length Article

Grip and load force control and coordination in individuals with diabetes in different manipulation tasks

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ABSTRACT

The study aimed to investigate the control and coordination of grip force (normal component) and load force (tangential component) in three different manipulation tasks in individuals with diabetes with and with no diagnosis of diabetic peripheral neuropathy (DPN) and healthy controls. Twenty-four individuals with type 2 diabetes mellitus, 12 with no (nDPN) and 12 with DPN (wDPN), and 12 healthy controls performed three manipulation tasks (*static holding*, *lifting and holding*, and *oscillation*) with the dominant hand, using an instrumented handle. Relative safety margin (% of GF exerted above the minimum GF needed to hold the object) was measured in all tasks. Individuals with diabetes from the nDPN and wDPN groups set lower relative safety margin than controls only in the *static holding* task. No other group effect was revealed, except a lower coefficient of friction between skin and object surface in individuals with DPN. The coordination between grip and load force and grip force control was not affected by the diabetes during dynamic manipulation tasks (*lifting and holding* and *oscillation*). However, when individuals with diabetes without and with DPN performed a manipulation task in which the inflow of cutaneous information was small and stable (*static holding*), grip force control was affected by the disease. This finding indicates that individuals with type 2 diabetes mellitus not diagnosed with DPN, already show mild impairments in the nervous system that could affect grip force control and that could be one of the first signs of neuropathy caused by the diabetes.

1. Introduction

Diabetic peripheral neuropathy (DPN) is one of the commonest comorbidities of the diabetes mellitus (DM) (Papanas & Ziegler, 2014; Tesfaye et al., 2010) altering the nerve conduction velocity (NCV), the tactile sensitivity, and the overall movement performance (Boulton, 2005; Dunnigan et al., 2014; Ferris, Inglis, Madden, & Boyd, 2020). Recently, we found that while individuals with diabetes without DPN present similar hand function (i.e., strength and dexterity) than healthy controls (de Freitas & Lima, 2013), individuals with DPN, show a considerable reduction in hand and finger dexterity (Lima, da Silva Borges, Hatanaka, Rolim, & de Freitas, 2017). Additionally, we demonstrated, that individuals with diabetes with and with no diagnosis of DPN apply approximately half of the magnitude of grip force (GF) compared to healthy individuals when they are asked to simply hold a vertically oriented handle using a five-digits grasp (de Freitas & Lima, 2013; Lima et al., 2017). This fact could be a sign that individuals with diabetes with and with no

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DPN are in higher risk of letting handheld objects to slip off from the hand. In this context, GF is defined as the normal force component acting on the interaction between the digits' skin and the object surface. To hold a vertically oriented object without dropping it, the individual must exert GF equal to or greater than the ratio between the tangential force component acting on the digits-object interaction (load force, LF) and the coefficient of friction of this interaction (GF $\geq$ LF/COF) (de Freitas, Krishnan, & Jaric, 2008; Westling & Johansson, 1984). However, the individuals implement a safety margin (SM), producing an amount of GF above the minimum required to prevent object slippage (Johansson & Westling, 1984; Westling & Johansson, 1984).

Earlier reports have shown that individuals with neurological disorders affecting primarily the central nervous system have altered GF control during object manipulation. For instance, individuals with Parkinson's Disease (Fellows, Noth, & Schwarz, 1998; Ingvarsson, Gordon, & Forssberg, 1997; Nowak & Hermsdörfer, 2002, 2006), multiple sclerosis (Iyengar, Santos, Ko, & Aruin, 2009; Krishnan, De Freitas, & Jaric, 2008; Marwaha, Hall, Knight, & Jaric, 2006), cerebellar degeneration (Brandauer, Timmann, Häusler, & Hermsdörfer, 2010; Müller & Dichgans, 1994), and post-stroke (Allgöwer & Hermsdörfer, 2017; Hermsdörfer, Hagl, Nowak, & Marquardt, 2003) exert a larger magnitude of GF than healthy individuals while performing different manipulation tasks (e.g., lifting and holding and oscillation). In addition, individuals with peripheral neurological disorders such as carpal tunnel syndrome also exert an increased GF when manipulating objects (Afifi, Santello, & Johnston, 2012; Lowe & Freivalds, 1999; Zhang et al., 2011). However, our recent study (Lima et al., 2017) was the first that showed that a group of individuals with a known peripheral neurological disorder (i.e., DPN) exerted less GF while manipulating an object, instead of producing more GF than controls. We found that the GF produced while holding an object was approximately 33% lower in individuals with DPN than controls. When the GF produced was normalized by the minimum GF required to hold the object (i.e., relative safety margin, SM_{Rel}), this difference was even higher (56%). An important difference between our studies (de Freitas & Lima, 2013; Lima et al., 2017) and the ones in which individuals with central and peripheral neurological disorders exerted a higher GF than controls was the manipulation task performed. While in our studies, the individuals simply hold the object after its complete stabilization (i.e., *static holding task*), in the other studies they perform more complex tasks, such as *lifting and holding* (the holding part was immediately preceded by the object lifting) and *oscillation* tasks.

An obvious follow-up to our previous studies is to assess individuals with diabetes with and with no diagnosis of DPN in different manipulation tasks to confirm our previous findings in the *static holding* task and test whether this difference is task specific. We hypothesized that individuals with diabetes without and with DNP would exert lower GF (i.e., set a lower SM) than controls during the

Table 1
Medical, physical, screening tests, and anthropometric characteristics from healthy individuals (Controls), individuals with diabetes with no diabetic peripheral neuropathy (nDPN) and individuals with diabetes with diagnosis of diabetic peripheral neuropathy (wDPN).*

	Controls	nDPN	wDPN
	(mean ± SE)	(mean ± SE)	(mean ± SE)
N	12	12	12
Medication			
Participants without medication	6	0	0
Number of medications prescribed per person	0.8 ± 0.2	4.6 ± 1.3	6.8 ± 2
Participants on medication for diabetes	0	12	12
Participants on medication for hypertension	5	9	11
Participants on medication for dyslipidemia	1	2	4
Participants on medication for neuropathy	0	0	3
Physical and clinical aspects			
Age (years)	65.1 ± 0.9	65.4 ± 1.2	65.5 ± 1.3
Time since diagnosis of T2DM (years)	–	14.8 ± 2.4	20 ± 1.6
Carpal tunnel syndrome *(n)*	0	0	0
Screening tests			
MNSI Score ($\geq$ 6)	–	1.25 ± 0.4	6.5 ± 0.5
DPN-Check amplitude (μV)	13.1 ± 2.5	10.7 ± 2.2	3.6 ± 0.3
DPN-Check nerve conduction velocity (m/s)	48.8 ± 1.4	44.9 ± 1.2	42.9 ± 2.6
Blood pressure			
Systolic (mmHg)	136.3 ± 5.9	135.4 ± 5.6	140.7 ± 7.5
Diastolic (mmHg)	82.5 ± 4	77 ± 3.2	81.7 ± 4
Anthropometric measurements			
Body mass (kg)	71.9 ± 4.2	74.2 ± 4.3	79.6 ± 4.07
Body height (m)	1.63 ± 0.03	1.65 ± 0.03	1.63 ± 0.03
BMI (kg/m^2)	27.02 ± 1.6	27.7 ± 1.8	30 ± 1.2
Body fat (%)	29.3 ± 1.93	28.14 ± 1.13	34.5 ± 2.16
Lean mass (kg)	49.3 ± 3.3	51.5 ± 3.5	53.4 ± 3
Basal metabolic rate	1498 ± 99	1529 ± 110.7	1624 ± 91
Glycemic Control *(n)*	**5–12**	**12–12**	**9–12**
Fasting capillary glycemia (mg/dL)	91.8 ± 1.15	134.6 ± 1	157.2 ± 25.5
Fructosamine (μmol/L)	195.44 ± 21.5	295 ± 19.5	333.6 ± 29

* Standard Error (SE); Type 2 Diabetes Mellitus (T2DM); Diabetic Peripheral Neuropathy (DPN); Michigan Neuropathy Screening Instrument (MNSI), Body Mass Index (BMI).

simple holding task, but individuals with diabetes without and with DPN would not be different from each other. For the *lifting and holding* and *oscillation* tasks, we would expect that both groups of individuals with diabetes would exert lower GF than controls, but the difference between individuals with diabetes without and with DPN and healthy controls would be smaller (i.e., show lower effect sizes).

2. Methods

2.1. Participants

Thirty-six individuals participated in the study. We allocated twenty-four individuals with diagnosis of type 2 diabetes mellitus (T2DM) in two groups depending on the presence or not of DPN: 12 T2DM with no associated DPN (6 males and 6 females, nDPN group) and 12 with clinical diagnosis of DPN (6 males and 6 females, wDPN group). We also recruited twelve age- and sex-matched healthy individuals (control group) to participate in this study. We defined the sample size based on the results of our previous studies (de Freitas & Lima, 2013; Lima et al., 2017). Specifically, the effect sizes of the differences between individuals with diabetes (nDPN) and controls (de Freitas & Lima, 2013) and between individuals with DPN (wDPN) and controls (Lima et al., 2017), as well as, an alpha value of 0.05 and a power of 0.8 were used to determine the sample size for this study. The results indicated that we would find a group effect with a sample of six participants in each group. To increase the power of other outcome variables from the *lifting and holding* and *oscillation* tasks, we decided to test 12 participants on each group.

All participants were right-handed according to their answer to the Edinburgh Handedness Inventory (Oldfield, 1971). Table 1 shows anthropometric, demographic, and healthy status information of the participants of each tested group. All participants signed the informed consent form before starting their participation in the study. The study protocol and the informed consent form were approved by the human research ethics committee from the Universidade Cruzeiro do Sul, Sao Paulo, Brazil. The research protocol and experimental procedure were in accordance with the Declaration of Helsinki.

2.2. Eligibility criteria

All participants with T2DM allocated in the wDPN group had to have the clinical diagnosis of DPN made by a neurologist. In addition, at least two of the following four criteria were required for individuals with diabetes to be included in the wDPN group: (*a*) to present a score equal to or greater than six in the Michigan Neuropathy Screening Instrument (Feldman et al., 1994); (*b*) to show loss of protective foot sensibility detected by application of the 10.0 gf monofilament (98.1 mN) of the Semmes-Weinstein monofilament examination (SWME) kit on the volar portion of the hallux; (*c*) to show alteration of the vibratory perception tested by a tuning fork of 128 Hz applied to the head of the proximal phalanx of the hallux; and (*d*) to have a reduction in the amplitude and/or in the neural conduction velocity (NCV) of the sural nerve evaluated by NC-stat™ DPNCheck™ (Neurometrix Inc.), a portable and validated equipment for the identification of DPN signs (Kong, Gozani, Hayes, & Weinberg, 2006; Lee et al., 2014).

To be included in the nDPN group, the participants should have diagnosis of T2DM and not show (1) positive results in the criteria "a" and "b" described above and (2) either not show or show positive result in only one of the two other criteria ("c" and "d") used to characterize the DPN group. When reductions in one of the two parameters (signal amplitude and sural NCV) from the NC-stat DPNCheck™ was associated with at least one of the other criteria described above individuals from the nDPN and control groups were excluded from the sample. This criterion was adopted because the reductions in amplitude and/or NCV are seem in individuals with DPN but may also occur because the natural aging processes (e.g., Jain et al., 2008). As the average age of the participants in this study was around 65 years of age (see Table 1), we considered prudent to adopt this precaution.

Finally, to be included in the control group, the participants should have no previous diagnosis of DM, do not present alteration in the first three criteria ("a", "b", and "c") presented earlier, and do not show high glycemic level after a fast of 4 h (>135 mg/dL).

2.3. Experimental procedures

Besides performing the SWME in the feet to determine the presence of DPN in our sample, we also did the SWME in the five digits of the dominant hand used to perform all the manipulation tasks. Thus, it was possible to provide a score of the cutaneous sensitivity of the tip of all digits involved in the manipulation tasks (Lima et al., 2017). For each digit, when the participant was able to feel the monofilament of 0.05 gf he/she received a zero score; when he/she was not able to feel the 0.05 gf but feel the 0.2 gf monofilament he/she received a score of 1, and so on. Participant not able to feel any monofilament applied to determined location received a score of six. The sum of the scores obtained on each digit resulted in a single cutaneous sensitivity score for each participant, ranging from 0 to 30. The scores between 0 and 2 would represent a "normal cutaneous sensitivity" and between 3 and 7 would indicate a "diminished cutaneous sensitivity" with difficulty in fine discrimination. The scores between 8 and 12 would indicate a "diminished protective sensitivity", meaning than the individual has a decreased protective sensibility of the hand, with enough sensibility remaining to prevent injury but issues in discriminating between shapes and temperatures. Yet, scores between 13 and 17 would indicate "loss of protective sensitivity" in the hand. In this situation the individual is not able to discriminate between cold and hot and becomes more susceptible to skin injury. Scores above 18 would represent a severe impairment of cutaneous sensitivity of the tip of the digits.

After, the cutaneous sensitivity assessment, the participants performed three manipulation tasks using a free-moving instrumented handle: (1) *static holding* task; (2) *lifting and holding* task; and (3) *oscillation* task. The same instrumented object was used in all three tasks (de Freitas & Lima, 2013; Lima et al., 2017) and it is depicted in Fig. 1. This object was formed by two aluminum bars connected

by a compression-tension force sensor (LPM-530, Cooper Instruments and Systems, USA) and two aluminum pieces and a multi-axis force and torque (F/T) sensor (Mini40, ATI, USA) in between forming the base of the handle. A cylindrical mass was attached underneath the object to increase its total mass, which was in total 647 g (W = 6.35 N). The object aperture was 5 cm and the external surface of it was covered with extra fine sandpaper (320 grit), which provided a moderate to high coefficient of friction between the digits skin and the object surface. All participants were required to have normal or corrected-to-normal vision to perform the manipulation tasks.

In all experimental conditions, the participants were instructed to sit comfortably in a fixed chair without arm support, keeping the dominant arm at the side of the body with the shoulder in internal rotation around 60°, elbow flexed at 90°, wrist in a neutral position, metacarpophalangeal joints at approximately 90°, and extended interphalangeal joints. This body configuration enabled the participants to maintain the center of the instrumented object aligned with their body midline and positioned just above the umbilicus. Before starting each manipulation task, the participants cleaned the volar portion of their fingertips with alcohol swabs to remove residues that could artificially alter the coefficient of friction between the digits skin and object contact surface. Despite the following order of presentation, the participants performed the three manipulation tasks in a random order.

2.3.1. *Static holding task*

The *static holding* task performed in this study was identical to the one performed in our previous one (de Freitas & Lima, 2013; Lima et al., 2017). The participants were instructed to grasp the instrumented object using the tip of the five digits of the dominant hand and hold it as stable as possible as they would do when holding a glass full of water. The object was given to the participants by the experimenter after they have positioned their hands in the testing position. After the experimenter assured that the stability of the object was achieved (approximately 10 s from grasping the object), the data recording started. The participants were also instructed to keep their heads upright and look forward, avoiding looking to the object. No command about the amount of GF that should be used in this phase of the *static holding* task was given to the participants.

The participants were also instructed to open their digits slowly and gradually until the object slipped off from the hand after hearing a beep sound (at the 10th s of data recording). The handle was caught by the experimenter after it dropped from the participant's hand. The object dropping part was performed so we could identify the minimum GF needed to hold the free-moving object (GF_{min}) and calculate the coefficient of friction between the skin and object surface and the SM_{Rel} adopted by the participants during all manipulation tasks (Savescu, Latash, & Zatsiorsky, 2008; Westling & Johansson, 1984).

Each participant performed few familiarization trials (between 3 and 7) before performing 5 valid trials. The task was done only with the dominant hand. Resting intervals of 30 s between trials were given to avoid possible effects of muscle fatigue.

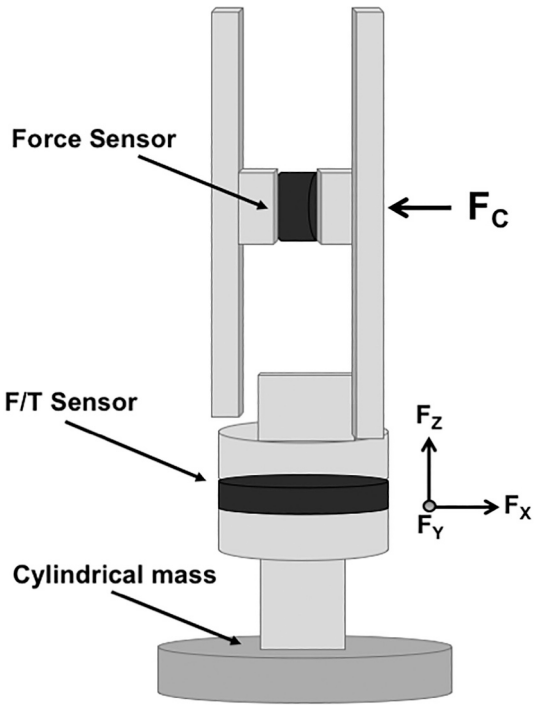

Fig. 1. Illustration of the free-moving instrumented object used in the manipulation tasks. Compression force (F_C) was recorded by the central force sensor (top black rectangle) and the vertical (F_Z) and horizontal (F_Y and F_X) force components recorded by the multiaxial (F/T) force sensor.

2.3.2. Lifting and holding task

In the *lifting and holding* task, the instrumented handle was placed in front of the participant's midline on a height-adjustable table and the forces sensors were zeroed before each trial. The participants were first asked to place their digits around the object without touching it. This was done to prevent that a reaching movement would create any extra tangential force and affect the GF exerted. Next, they were instructed to grasp and immediately lift the object up for approximately 5 cm after hearing a beep sound. This beep sound was presented 3 s after the beginning of the data recording. The participants were also instructed to keep the object in the air as stable as possible until they hear a second beep sound that signed them the moment to place the object back on the table. The interval between the first beep (at the 3rd s) that signed the participant to grasp and lift the object and the second beep (at the 15th s) was 12 s. It allowed the participant to hold the object in a stable position for at least 10 s after having lifted it.

The participants performed five trials lasting 15 s each, using the dominant hand. The first two trials were used for familiarization with the task and object. The last three trials were used for data analysis. Resting intervals of 30 s between trials were given to avert possible effects of muscle fatigue.

2.3.3. Oscillation task

For the *oscillation* task, the participants were instructed to grasp the object, position it in front of the umbilicus, and move it continuously upward and downward for approximately 20 cm at 1 Hz following a metronome set at 120 bpm (a beat for the upward

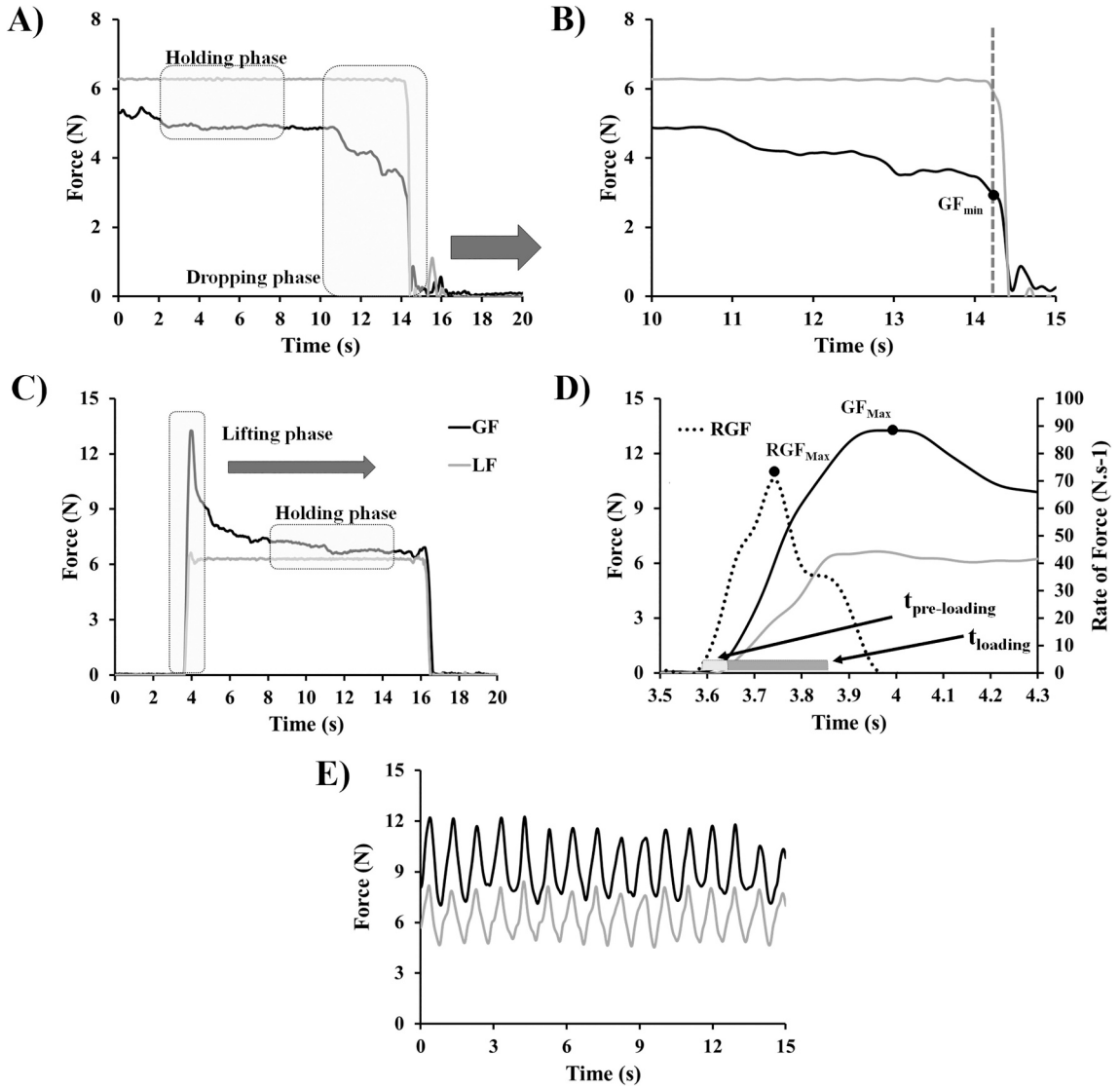

Fig. 2. The force signals from load force (LF) and grip force (GF) obtained from representative trials of an individual with diabetes with no diagnosis of DPN. (A) A complete trial and (B) the dropping phase from the *static holding* task. (C) A complete trial and (D) the lifting phase from the *holding and lifting* task. (E) *Oscillation* task.

and the next for the downward object position). Five trials lasting 15 s each were performed using the dominant hand and a rest interval of 30 s between the trials was provided. The first two trials were used for familiarization and the last three were used for data analysis.

2.4. Data processing and analyses

Force signals were recorded at 200 Hz and processed using two routines written in LabVIEW (Version 2010, National Instruments, Austin, TX, USA). Offline data processing started with force signals being digitally filtered by a 4th-order, zero-phase lag, low-pass Butterworth filter with a cut off frequency of 20 Hz. The GF exerted was provided by the uniaxial force sensor positioned between the aluminum bars in which the digits were placed. The LF in the static *holding* task was the weight of the object as the object was kept stationary and, in the *lifting and holding* and *oscillation* tasks LF was calculated based on the vertical (F_Z) and horizontal (F_X) forces components applied tangentially to the object surface ($LF = \sqrt{(F_Z^2 + F_X^2)}$), measured by the multi-axis force sensor placed in the object.

The *static holding* task was divided into two phases, the holding phase and the dropping phase (Fig. 2A). In the dropping phase, we calculated the coefficient of friction between the skin and object surface based on the value of GF_{min}. The GF_{min} was estimated as the GF measured at the moment immediately before the object's acceleration, which was automatically determined when F_Z (vertical force component) was smaller than the average minus two standard deviations of the F_Z in the holding phase (Fig. 2B). After defining GF_{min}, the coefficient of friction (COF) was calculated ($COF = LF/GF_{Min}*2$) (Johansson & Westling, 1984).

In the holding phase, we used the central 6 s to calculate the dependent variables. The first and last two seconds were excluded from the analysis after the signals filtering. The first two seconds were excluded to ensure that object was kept in a static position and the final two seconds were excluded because the participants could be influenced by the expectation of the beep sound that determined the starting of the dropping phase. In the holding phase, the ratio between GF and LF (GF-LF ratio) and the SM_{Rel} were computed. The mean value of GF (GF_{mean}) calculated in the holding phase was divided by the weight of the object (LF). The SM_{Rel} was calculated considering the value of GF_{min} in the object dropping phase and GF_{mean} exerted in the object in the holding phase (6 s central), using the following equation: $SM_{Rel} = 100*((GF_{mean}\text{-}GF_{min})/GF_{min})$.

In the *lifting and holding* task, we analyze two temporal variables: the pre-loading duration ($t_{pre\text{-}loading}$) and the loading duration ($t_{loading}$). The $t_{pre\text{-}loading}$ was defined as the interval between the first contact with the object (GF $\geq$ 2% of the maximum GF value) and the moment in which the participant started exerting force upward (LF $\geq$ than 2% of the maximum LF value). The $t_{loading}$ was defined as the interval between the moment in which the participant started exerting force upward and the moment in which the object started being lifted off from the table (LF $>$ weight of the object: 6.35 N).

The pre-programmed GF control during the loading and lifting phases was determined by the maximum values of the rate of GF (RGF_{Max}) and GF (GF_{Max}). The RGF_{Max} was determined as the maximum value of the first derivative of GF and the GF_{Max} was the maximum value of the GF time-series during the lifting phase.

The control of GF magnitude in the holding phase of the *lifting and holding* task (immediately after the object lifting) was assessed by the GF-LF ratio and by the SM_{Rel}. First, the GF_{mean} was calculated during the 6 s of the holding phase, starting 4 s after GF_{Max}, which was enough to assure that the object was being kept in a stable position. Then the GF-LF ratio was calculated by dividing GF_{mean} by LF (object weight = 6.35 N) (Fig. 2). Finally, SM_{Rel} was calculated using the same equation used in the *static holding* task: $SM_{Rel} = ((GF_{mean}\text{-}GF_{min})/GF_{min})*100$.

In the oscillation task, we analyzed the central 13 s of trials of 15 s. We removed the first and last second of each trial after filtering the data. Task performance was assessed by the object's predominant oscillation frequency and mean of the LF peaks. The predominant frequency was determined as the corresponding value on the x-axis (frequency) of the highest power spectral density (PSD) of the F_Z (vertical) signal. This variable was calculated to confirm that the handle's oscillation was performed at the requested frequency. The mean of the LF peaks was calculated by obtaining the LF peak within each oscillation cycle and averaging them.

The control of GF magnitude was assessed by the GF-LF ratio and SM_{Rel}. The GF-LF ratio was calculated by dividing the GF_{mean} by the averaged LF (LF_{mean}). The SM_{Rel} was calculated from the GF average produced during the object oscillation using the same equation employed previously ($SM_{Rel} = ((GF_{mean}\text{-}GF_{min})/GF_{min})*100$). The GF_{min} was the one obtained in the dropping phase of the *static holding* task and the GF_{mean} was the average value of the GF exerted during the oscillation task.

Finally, to assess the directional and temporal coupling between GF and LF, two variables were calculated: (*i*) maximum value of the cross-correlation coefficient (r_{max}), determined by the maximum value of the cross-correlation function between GF and LF and (*ii*) time-lag, determined by the temporal difference (phase) between the time-series of GF and LF. The negative (positive) temporal difference meant that changes in GF happened before (after) changes in LF. Values of r_{max} close to 1 and temporal difference close to zero were interpreted as a strong coupling between GF and LF. Due to the known non-normal distribution of r_{max}, this variable was Fisher-z transformed before performing statistical tests.

2.5. Statistical analyses

For cutaneous sensitivity, the non-parametric Kruskal-Wallis test was applied to test for group effect on the cutaneous sensitivity score. If significant, non-parametric *post-hoc* tests (Mann-Whitney U) were performed to test for specific differences between groups.

After assuring that the outcome variables from the manipulation tasks had normal distribution and that the variance was homogeneous (Shapiro-Wilk test and Levene test, respectively), we performed one-way analyses of variance (ANOVA) to test for effects of group (wDPN, nDPN, and control). Post-hoc tests with Bonferroni adjustment were carried out when necessary. Eta squared (η^2) values were calculated and presented as an indication of effect size. Values of η^2 below 0.06, between 0.06 and 0.14, and above 0.14 indicate

respectively small, medium, and large effect sizes (Cohen, 1988).

3. Results

Initially, we depict the results from the cutaneous sensitivity test. Next, the results of the three manipulation tasks (i.e., *static holding*, *lifting and holding*, and *oscillation* tasks) are presented.

3.1. Cutaneous sensitivity

The results of the cutaneous sensitivity from the tip of the digits of the dominant hand revealed that no individual with DPN (wDPN) presented preserved cutaneous sensitivity; four individuals with DPN had diminished cutaneous sensitivity; six had diminished protective cutaneous sensitivity, and two had loss of protective sensitivity. Also, no individual with T2DM and no DPN (nDPN) showed normal cutaneous sensitivity. Nine of them (out of 12) had diminished sensitivity, and three presented diminished protective sensitivity. A single individual from the control group showed normal cutaneous sensitivity, four presented diminished sensitivity, and seven diminished protective sensitivity.

The Kruskal-Wallis test revealed a main effect of group on the cutaneous sensitivity score ($X^2 = 6$, df = 2 $p = 0.048$). The median score (25th-75th percentile) for the wDPN group was 8.5 (7–11), for the nDPN group was 6.5 (4.75–8), and for the control group was 8 (6.5–9). Post-hoc Mann-Whitney *U* tests were performed and revealed a significant difference between the nDPN and wDPN group (z = 2.47, $p = 0.013$, Cohen's d = 1.35) and no difference between the nDPN and the control group (z = 0.85, $p = 0.398$, d = 0.36) and between the wDPN and control group (z = 1.46, $p = 0.144$, d = 0.65).

3.2. Manipulation tasks

Table 2 depicts across-group averaged (± 95% confidence intervals) for each dependent variable calculated in the three manipulation tasks. Furthermore, Table 3 shows the statistical results of the analyses performed for the manipulation tasks. In the *static holding* task, ANOVA revealed effect of group on COF, GF-LF ratio, and SM_{Rel}. The COF between digits' skin and object surface was lower for the wDPN group as compared to the nDPN and the control groups that were not different from each other. The GF-LF ratio and SM_{Rel} were higher for the control group than for the wDPN and nDPN groups. No differences between the wDPN and the nDPN groups were revealed for GF-LF ratio and SM_{Rel}.

In the *lifting and holding* task, ANOVA revealed no effect of group on any calculated outcome variable. Similarly, in the *oscillation* task, no effect of group on any dependent variable was revealed by the ANOVA. In terms of performance in the *oscillation* task, all participants were able to move the object at approximately 1 Hz (1.01 Hz, 95% confidence interval: 0.99:1.03), producing peaks of LF of 7.55 N (7.44:7.66 N), with no effect of group.

Table 2
Mean and 95% confidence interval (CI) of each tested group (nDPN, wDPN, and Control) of all outcome variables calculated during the *static holding*, *lifting and holding* and *oscillation* tasks.

Static holding Task			Lifting and holding Task			Oscillation Task		
Outcome	Group	Mean (95% CI)	Outcome	Group	Mean (95% CI)	Outcome	Group	Mean (95% CI)
COF	wDPN	0.93 (0.88:0.97)[b]	**$t_{preloading}$ (ms)**	wDPN	58.0 (31.6:84.4)	**GF-LF ratio**	wDPN	1.85 (1.57:2.13)
	nDPN	1.06 (1.01:1.11)[a]		nDPN	66.0 (39.8:92.1)		nDPN	1.51 (1.19:1.83)
	Control	1.05 (0.98:1.13)[a]		Control	77.2 (37.4:117.1)		Control	1.62 (1.33:1.90)
GF-LF ratio	wDPN	1.06 (0.84:1.27)[b]	**$t_{loading}$ (ms)**	wDPN	392.7 (277.8:507.6)	**SM_{Rel} (% GF_{Min})**	wDPN	242.2 (194.3:290.1)
	nDPN	0.87 (0.75:0.99)[b]		nDPN	274.4 (212.9:335.9)		nDPN	211.7 (147.3:276.1)
	Control	1.34 (1.13:1.54)[a]		Control	388.2 (258.5:517.9)		Control	232.8 (176.2:289.4)
SM_{Rel} (% GF_{Min})	wDPN	91.3 (59.2:123.3)[b]	**GF_{Max} (N)**	wDPN	13.6 (10.6:16.5)	**r_{max} (Fisher)**	wDPN	1.25 (1.05–1.45)
	nDPN	79.6 (62.5:96.7)[b]		nDPN	13.2 (9.5:16.9)		nDPN	1.16 (0.99–1.33)
	Control	181.1 (147.3:214.9)[a]		Control	16.2 (10.9:21.4)		Control	1.20 (0.98–1.42)
			RGF_{Max} (N/s)	wDPN	49.7 (36.6:62.8)	**Time lag (ms)**	wDPN	−42.6 (−69.3:-15.9)
				nDPN	48.7 (34.1:63.2)		nDPN	−57.3 (−84:-30.5)
				Control	55.0 (39.6:70.5)		Control	−26.7 (−57.2:3.7)
			GF-LF ratio	wDPN	1.77 (1.35:2.18)			
				nDPN	1.71 (1.24:2.18)			
				Control	1.91 (1.34:2.48)			
			SM_{Rel} (% GF_{Min})	wDPN	224.1 (152.8:295.3)			
				nDPN	255.9 (165.2:346.7)			
				Control	287.4 (188.3:386.5)			

Note: nDPN: individuals with diabetes with no diagnosis of diabetic peripheral neuropathy; wDPN: individuals with diabetes with diagnosis of diabetic peripheral neuropathy, COF: coefficient of friction; GF: grip force; LF: load force; $SM_{Rel:}$ relative safety margin; GF_{Min}: minimum GF; $t_{pre\text{-}loading}$: time of pre-loading; $t_{loading}$: time of loading; GF_{Max}: maximum grip force ; RGF_{Max}: maximum rate of grip force; r_{max} = maximum coefficient of cross-correlation.
"a" is significantly higher than "b".

Table 3
ANOVA statistical results.

Task	Outcome	$F_{(2,33)}$	p. value	η^2
Static holding	COF	8.970	0.001*	0.35
	GF-LF ratio	7.891	0.002*	0.32
	SM_{Rel}	18.197	<0.001*	0.52
Lifting and holding	$t_{preloading}$	0.457	0.637	0.03
	$t_{loading}$	1.932	0.161	0.1
	GF_{Max}	0.746	0.482	0.04
	RGF_{Max}	0.273	0.763	0.02
	GF-LF ratio	0.206	0.815	0.01
	SM_{Rel}	0.630	0.539	0.04
Oscillation	GF-LF ratio	1.682	0.202	0.09
	SM_{Rel}	0.368	0.695	0.02
	r_{max} (Fisher)	0.247	0.783	0.01
	Time lag	1.440	0.251	0.08

4. Discussion

In this study, we tested two hypotheses. The first was that individuals with T2DM with no and with diagnosis of DNP would exert lower GF and would set lower SM than controls during the *static holding* task, but individuals with T2DM with no and with diagnosis of DPN would not be different from each other. The first hypothesis was confirmed since we found that individuals with T2DM with and with no diagnosis of DPN exerted lower GF and set lower SM than individuals from the control group during the *static holding* task. The confirmation of this hypothesis was expected based on our previous studies (de Freitas & Lima, 2013; Lima et al., 2017). The second hypothesis was that in the *lifting and holding* and *oscillation* tasks, both groups of individuals with T2DM would exert lower GF than controls, but the difference between individuals with T2DM (without and with DPN) and healthy controls would be smaller (i.e., lower effect sizes than the one measured in the *static holding* task). This second hypothesis was rejected, as the results showed no difference among groups for GF exerted and SM set during these tasks.

Furthermore, the results showed that, in general, the participants presented reduced cutaneous sensitivity of the digits of the dominant hand that is consistent with the participant's age. None of the T2DM groups were different from the control group in terms of sensitivity, indicating no apparent influence of the T2DM in the cutaneous sensitivity. There was a group difference between the two groups of individuals with diabetes, with individuals with neuropathy showing lower cutaneous sensitivity than the group with no neuropathy. In addition, no effect of group on GF control and GF-LF coordination in the dynamic manipulation tasks: *lifting and holding* and *oscillation*. No differences among groups were found in the time spent from touching the object to lifting it up ($t_{preloading}$ and $t_{loading}$), in the maximum GF, and in the maximum rate of GF during the *lifting and holding* task. Moreover, no differences across groups were found in the directional (r_{max}) and temporal (time-lag) coupling between GF and LF. The only group effect observed besides the difference in GF and SM_{Rel} during the *static holding* task was on the coefficient of friction (COF). Specifically, COF was higher in the wDPN group when compared to the nDPN and control groups.

The most important finding of the present study is that the GF exerted and the SM set by individuals with T2DM, no matter whether they have diagnosis of DPN, is remarkably different from the SM set by the healthy controls in the holding phase of the *static holding* task, but not different in the holding phase of the *lifting and holding* task (holding immediately preceded by the object lifting). The first information necessary to discuss these findings is that the GF exerted and the SM set during both holding phases were different regardless the group assessed. For instance, the relative SM set by healthy controls in the holding phase during the *static holding* task was on average 1.8-fold of the GF_{Min}, whereas in the holding phase following the object lifting, the SM for the same group was on average 2.8-fold ($p = 0.026$). For individuals with T2DM (nDPN and wDPN) the increase in the SM during the holding phase after the object lifting was approximately threefold.

A plausible explanation for the difference in GF exertion and in the relative SM between the two holding phases would be related to the magnitude of the tactile stimuli triggered by the contact and interaction of the digits with the object in the different tasks. In the *lifting and holding* task, the holding phase was immediately preceded by the initial contact with the object, the pre-lifting (parallel increase of LF and GF), and the lifting phases (LF > object's weight). The initial contact phase is the moment that the cutaneous information regarding the characteristics of the object's surface is obtained and processed (Johansson & Flanagan, 2007). During this phase, the number of tactile mechanoreceptors activated and their firing rate is high and all four types of mechanoreceptors (i.e., fast-adapting, FAI and FAII, and slow-adapting, SAI and SAII) are activated at the same time. This information gathered and processed triggers the next action leading to the object's lifting (Johansson & Flanagan, 2007; Johansson & Westling, 1987a).

In the pre-lifting phase, the activation level of the mechanoreceptors remains high but lower than in the initial contact phase. However, as soon as the object is removed from the table (lifting phase), a burst of activation of the cutaneous mechanoreceptors, mainly of the Pacinian corpuscles of fast adaptation (FAII), is observed due to the lateral deformation of the skin caused by the object's weight. Again, a large influx of somatosensory (mainly tactile) information is sent to the supraspinal centers. After a few moments, at the beginning of the holding phase until its end, there is a predominance of activation of slow adaptation receptors and a pause in the activation of fast adaptation receptors, but just before that in the transition between the lifting and holding phases there is another burst of tactile information when the moving object is stopped and the skin is stretched due to inertial forces (Macefield, Häger-Ross, & Johansson, 1996, Johansson & Flanagan, 2007; Johansson & Westling, 1987a, 1987b). We suggest that the amount of information

collected and processed throughout the phases preceding the holding phase provides a sufficient amount of information to the GF controlling centers, which, in turn, is sufficient to trigger an increased SM by all three groups. Therefore, differences among them were not observed. Instead, in the holding phase, not immediately preceded by an object lifting (i.e., in the *static holding* task where the object was handed by the experimenter instead of lifting up), the information obtained with the object's first contact and lifting would not be strong enough and would be dissipated by the time spent from the first contact with the object until the beginning of data recording. Consequently, individuals would only have available small amounts of information originated from the periphery, mainly from slow adapting receptors as information that would be provided by the FAI and FAII receptors would be not triggered and used to control the amount of GF during the *static holding* tasks. Hence, the ability of an individual with diabetes without and with DPN to properly control the magnitude of GF in this particular task would be impaired as they would have difficulty to have a proper estimation of the amount of GF needed to safely perform the task (de Freitas & Lima, 2013).

Other findings supporting the idea that the cutaneous stimulus intensity and information inflow, defined by the number of receptors activated and their firing rate, could be responsible for this task dependent difference between healthy individuals and those with diabetes is the lack of difference in the initial contact time and in the pre-lifting time across the groups. They indicate that when individuals with diabetes with and without DPN are provided with a large inflow of tactile information they can detect, transmit, and process sensory information apparently with no delay, indicating that the processing of sensory information would depend on the amount of information that reaches the supraspinal centers (Fellows et al., 1998; Nowak & Hermsdörfer, 2006). When the somatosensory information exceeds a certain threshold, information would be processed satisfactorily and the system would use this information flow to adjust the magnitude of GF appropriately. Similarly, as with the *lifting and holding* task, the *oscillation* task would also generate a large number of cutaneous stimuli during cyclical changes in GF and LF. Studies have shown that the CNS can obtain a large amount of information, originating mainly from FAI tactile receptors, about the change in tangential force direction acting on the fingertips from cutaneous mechanoreceptors (Birznieks, Jenmalm, Goodwin, & Johansson, 2001; Saal, Vijayakumar, & Johansson, 2009). Therefore, the large influx of cutaneous and other somatosensory information to the CNS in the *oscillation* task is sufficient to GF control centers to detect the constant changes in the levels of GF and LF and, consequently, adjust the SM to a level similar to that of healthy individuals.

Yet, we still do not know whether the difficulty of individuals with diabetes in dealing with low amounts of cutaneous information to control GF in the *static holding* task is due to changes in either the peripheral or the central nervous system or in both. Specifically, is it due to the reduced amount of information triggered by the task associated with the individuals with diabetes' impaired tactile acuity (Dunnigan et al., 2014; Ochoa, Gogola, & Gorniak, 2016; Said, 2003) and/or because structural changes in the CNS regions responsible for receiving, transporting, and processing somatosensory information (Eaton et al., 2001; Ferris et al., 2020; Selvarajah et al., 2006; Selvarajah et al., 2014; Xia, Chen, & Ma, 2017)? Our findings of cutaneous sensitivity may speak against the former, as we found no difference between both groups of individuals with diabetes and healthy controls in the SWME. Nevertheless, the results of the SWME should be interpreted cautiously due to the involvement of conscious discrimination and its limitation in terms of resolution and may not directly reflect the use of cutaneous information during object manipulation. Alternatively, alterations in the CNS and, specifically, in the capacity of processing cutaneous information in the primary somatosensory cortex, may play the most important role on the changes in GF control observed in individuals with diabetes. There are strong evidences, reviewed and discussed by Ferris et al. (2020), that several areas of the CNS are affected by the diabetes that directly disturb the control of movements. For example, the primary somatosensory cortex where the cutaneous information from the tip of the digits is integrated and processed is structurally and functionally affected in individuals with diabetes (Ferris et al., 2020; Selvarajah et al., 2014; Xia et al., 2017). However, the results of the present study do not allow us to go beyond speculation in determining the contribution of the peripheral and central nervous system to the changes in GF control observed in this study. Next studies could aim to disambiguate between the peripheral or central origin of GF control alteration in individuals with diabetes seems in the *static holding* task associating neuroimaging and biomechanical measurements.

A question that still remains is why the group of individuals with diabetes is the only one among those suffering of neurological disorders to show a reduction in GF and safety margin. For instance, individuals with Parkinson's disease (Fellows et al., 1998; Nowak & Hermsdörfer, 2002), multiple sclerosis (Iyengar et al., 2009; Krishnan et al., 2008; Marwaha et al., 2006), and individuals after a stroke (Hermsdörfer et al., 2003) exert much higher amounts of GF when compared to age- and sex-matched healthy individuals in a number of manipulation tasks. It is suggested that the GF control system is able to detect structural and functional changes in its components and adopt a conservative and compensatory GF control strategy increasing GF in order to prevent slippage that could be caused by unexpected changes in load force. We believe that the peripheral and/or central changes in individuals with diabetes are very mild indeed and, therefore, not sufficient to trigger the use of compensatory GF control strategies as they are in individuals with diseases affecting the parts of CNS and in individuals with moderate and more severe loss of cutaneous sensitivity. However, this very mild sensory impairment is sufficient to disrupt the processing and proper use of sensory information in this population, causing an error in the estimation of GF needed during object manipulation (de Freitas & Lima, 2013). Also, there is another aspect that should be mentioned. As we stated in the introduction section, an important difference between our studies (de Freitas & Lima, 2013; Lima et al., 2017) and the ones in which individuals with central and peripheral neurological disorders exerted a higher GF than controls is the manipulation task performed. While in our studies, the individuals simply hold the object after its complete stabilization (i.e., *static holding* task), in the other studies they perform more complex tasks, such as lifting and holding, point-to-point, and oscillation tasks. Therefore, it is possible that individuals with central and peripheral neurological disorders could show similar outcome to ours (i.e., lower GF in individuals with diabetes than in healthy controls) if the *static holding* task would be performed. Hence, future studies with individuals with different types of neurological diseases should include the *static holding* task, following the procedures of this study. There is also a need for the findings of this study to be confirmed by other research groups to proof the veracity of this phenomenon.

With the lifting and oscillation tasks, it was also possible to determine whether the predictive neural control mechanism involved in GF-LF coordination is preserved in individuals with diabetes with and with no peripheral neuropathy. For the lifting task, the results showed no group effect on the GF control variables: GF_{Max} and RGF_{Max}. It is known that the magnitude of these two variables is pre-programmed based upon the information about the object (e.g., weight and friction) obtained in previous manipulations of the same object (Johansson & Westling, 1984; Westling & Johansson, 1984). With the oscillation task, the GF-LF coordination was examined by the directional and temporal coupling between the GF and LF (de Freitas, Krishnan, & Jaric, 2007; Flanagan & Wing, 1995), and no group effect was found as well. Based on these results we could conclude that individuals with diabetes are able to predict the effects of upper limb cyclic movements on LF and adjust GF to changes in this force component.

Another important finding of this study was that the coefficient of friction (COF) between the digits' skin and the object surface was lower for individuals with diabetes with DPN when compared to those with no DPN and with healthy ones. This reduction in the COF in individuals with DPN was probably due to structural changes in the skin of these individuals. Previous studies have shown that the skin's hydration level affects COF between the skin and the objects' surface. Specifically, more hydrated skins have a higher friction coefficient with different surfaces when compared to less hydrated skins (André, Lefèvre, & Thonnard, 2009; Smith, Cadoret, & St-Amour, 1997). Recent data from a systematic review (de Macedo, Nunes, & Barreto, 2016) showed that a reduction in sweating and, consequently, skin hydration, is a common manifestation of the progression of the DM. These results are corroborated by other studies that showed that the increase in skin dryness in T2DM is even greater after the individuals with diabetes are diagnosed with DPN (Chiu et al., 2014; Gorniak, Khan, Ochoa, Sharma, & Phan, 2014; Ochoa et al., 2016). Supporting these findings, Thames and Gorniak (2017) revealed a reduction in the frictional properties of the fingertip skin of individuals with T2DM when compared to healthy individuals, after performing a task very similar to the one used in this study (Thames & Gorniak, 2017).

One of the main aspects of GF control is the ability of the CNS to estimate COF between the digits' skin and the object surface using cutaneous afferent information (Johansson & Westling, 1984, 1987a; Westling & Johansson, 1984). This ability is important because the GF control center can confront what was predicted, based on previous experiences with the manipulated object, with the information extracted after the initial contact with it and, consequently, triggers the sequence of actions the object lifting subtasks (de Freitas et al., 2008; Johansson & Flanagan, 2007; Johansson & Westling, 1984, 1987a; Westling & Johansson, 1984). Thus, information about the COF between the skin and the object's surface must be incorporated in the determination of the safety margin by the individual. From a methodological standpoint, the difference in COF across groups of subjects is normalized when we use the SM_{Rel} instead of simply using the GF magnitude (de Freitas et al., 2008; Johansson & Westling, 1984, 1987a, 1987b; Westling & Johansson, 1984). Thus, we may suggest that the reduction in the SM_{Rel} in the *static holding* task in individuals with diabetes and neuropathy was not only due to mechanical aspects involving the COF but decreased sensory acuity and most probably due to structural changes in parts of the CNS responsible for processing sensory information (for review, see Ferris et al., 2020). Whether this reduction in tactile acuity is caused by deficits either in the peripheral or in the central nervous system or both should be investigated by a new study.

In addition, we have also found a difference in the COF between the two groups of individuals with diabetes. Individuals with neuropathy (wDPN) presented a higher COF than individuals with no neuropathy (nDPN). Even with a different COF, the individuals with neuropathy presented similar relative safety margin, which is the exerted GF adjusted by the COF, to individuals with diabetes with no neuropathy. The most plausible explanation for this finding is that individuals with neuropathy are still able to capture and interpret the changes of their skin characteristics and the effect of them in the skin-object surface's friction and use this information to set a proper safety margin. Recently, Khamis et al. (2021) showed that object slips provide useful information about skin and object surface friction that could not be obtained otherwise. The familiarization trials of the *static holding* task, which included objects slips at the end, and in the dynamic tasks (*lifting and holding* and *oscillation* tasks) could have provided information about friction to the participants that were implemented by the GF controller of individuals with neuropathy to adjust GF to skin-object frictional characteristics.

5. Conclusion

In conclusion, this study indicates that GF control in individuals with type 2 diabetes mellitus is affected by the amount somatosensory information triggered during the action. In dynamic manipulation tasks, in which the amount of information received and processed by the CNS is relatively large, individuals with type 2 diabetes mellitus can use it to set an appropriate safety margin to perform the task safely, whereas when this amount of information is small, the control system is not able to estimate properly the magnitude of GF necessary to perform the task and a low magnitude of GF is selected. Also, the findings indicate that the overall lack of difference between individuals with and with no diagnosis of DPN indicates that individuals with no clinical signs of neuropathy could already present changes in either the peripheral or central nervous system or both.

Authors' contribution

KCAL and PBF conceived and designed the research. KCAL, GOS, SSVD, and LB performed the experiments and analyzed the data. EH provided the reagents and ideas for the analyses. KCAL, LB, EH, and PBF interpreted the results and wrote the manuscript. All authors read and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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