

DIABETES AND PERIPHERAL NEUROPATHY ARE RELATED TO HIGHER PASSIVE TORQUE AND STIFFNESS OF THE KNEE AND ANKLE JOINTS

Jean P. Ferreira^{1,2}, Vanessa L. Araújo³, Ângela M. O. Leal⁴, Paula R. M. S. Serrão¹,
Julya P. M. Perea¹, Afonso H. A. Santune¹, Henrique Pott-Júnior⁴,
Ricardo A. S. Fernandes⁵, Gabriel D. A. Aranha^{5,6}, Isabel C. N. Sacco⁷, and Tania F. Salvini¹

¹Department of Physical Therapy, Federal University of São Carlos, SP, Brazil

²Department of Morphology, Faculty Morgana Potrich, Mineiros, GO, Brazil

³Department of Physical Therapy, Federal University of Minas Gerais,
Belo Horizonte, MG, Brazil

⁴Department of Medicine, Federal University of São Carlos, São Carlos, SP, Brazil

⁵Department of Electrical Engineering, Federal University of São Carlos, SP, Brazil

⁶Department of Computer Science, Federal University of São Carlos, SP, Brazil

⁷Department of Physical Therapy, Speech and Occupational Therapy,
School of Medicine, University of São Paulo, São Paulo, SP, Brazil

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Abstract:

The aim of this study was to investigate the ankle and knee stiffness and passive torque in individuals with diabetes mellitus type 2 (DM2), with and without diabetic peripheral neuropathy (DPN) at different speed of motion. Forty-nine male individuals of a similar age were studied (17 with DM2 without DPN, 15 with DM2 and DPN, and 17 controls). Knee and ankle flexion and extension passive torques were assessed on an isokinetic dynamometer at 5°/s, 30°/s, and 60°/s. Our results showed that the individuals with DM2 exhibited greater knee stiffness compared to the controls and the individuals with DPN presented greater ankle stiffness and passive torque compared to the controls and those with DM2 without DPN. The mechanical impairments at the ankle passive structures were most evident at low speeds while the knee alterations were at 30°/s and 60°/s. Although the presence of DPN was a key factor for the increased passive ankle stiffness and torque, it was not related to the increase in the knee passive stiffness. Preventive measures for avoiding stiffness and motion impairments at the ankle and knee could be adopted in the early stages of DM2.

Key words: ankle, knee, joint stiffness, passive torque, range of motion, diabetes mellitus

Introduction

Type 2 diabetes mellitus (DM2) is associated with connective tissue alterations, motion and physical functionality disorders (Gautieri, et al., 2017; Haus, Carrithers, Trappe, & Trappe, 2007). There are evidences linking DM2 to collagen aging, reduction in proteoglycan levels, and increased stiffness of passive musculoskeletal structures, as ligaments, cartilage (Atayde, et al., 2012) and fascia (D'Ambrogi, et al., 2003; Giacomozzi, D'Ambrogi, Uccioli, & MacEllari, 2005). These changes are related to collagen glycation (Andreassen, Seyer-Hansen, & Bailey, 1981), which leads to the accumulation of advanced glycation end products (AGEs) (Paul & Bailey, 1999; Vlassara & Palace, 2002).

High stiffness levels in musculoskeletal structures can increase the risk of musculoskeletal injuries (Lorimer & Hume, 2016), reduce joints' range of motion (RoM) and impair the performance of daily living activities (Lorentzen, et al., 2017; Semba, Bandinelli, Sun, Guralnik, & Ferrucci, 2010).

Although there is evidence of biochemical alterations in the collagen of DM2 individuals (Andreassen, et al., 1981; Atayde, et al., 2012; Paul & Bailey, 1999; Vlassara & Palace, 2002), their consequences for joint motion, stiffness and functionality are still unclear. Salsich, Mueller, and Sahrman (2000) did not find any changes in ankle plantar flexor passive torque and passive stiffness in individuals with DM2 at 60°/s compared to controls,

despite their clear reduction in the ankle RoM. In a subsequent study, Rao, Saltzman, Wilken, and Yak (2006) observed higher passive stiffness during ankle dorsiflexion in DM2 individuals, which was also associated with the reduced ankle RoM. However, in this study, the muscle activation was not controlled during testing, which could have biased the results (Araújo, et al., 2011; Lamontagne, Malouin, Richards, & Dumas, 1997; Leite, et al., 2012; Palmer, et al., 2015). In both studies analyzing stiffness in DM2 individuals (Rao, et al., 2006; Salsich, et al., 2000), the presence of diabetic peripheral neuropathy (DPN) was not taken into consideration, although this condition may result in further musculoskeletal impairments (Fernando, et al., 2013; Giacomozzi, D'Ambrogi, Cesinaro, Macellari, & Uccioli, 2008; Sacco, et al., 2009).

In addition to the musculoskeletal impairments due to DM2 that might be linked to increased joint stiffness, DPN progressively changes foot-ankle biomechanics during gait (Picon, Sartor, et al., 2012; Sacco, et al., 2015; Yi, Sartor, Souza, & Sacco, 2016), represented by the reduced ankle RoM in the sagittal and frontal planes (Deschamps, et al., 2013; Giacomozzi, et al., 2002) and altered muscle dynamics (Gomes, Ackermann, Ferreira, Orselli, & Sacco, 2017; Watari, et al., 2014). A recent study (Ferreira, et al., 2017) included the DPN as a factor in the analysis of lower limb joint torques and concluded that the concentric and isometric knee and ankle torques at 60°/s were altered in DM2 individuals, regardless the presence of DPN, while the eccentric torque was similar to controls. Taken together, these data (Ferreira, et al., 2017; Rao, et al., 2006; Salsich, et al., 2000) demonstrate that the coexistence of DM2 and DPN might explain the lingering controversy in clinical literature regarding joint stiffness results, and should be considered when planning further studies.

The global consensus is that individuals with DM2 and DPN should protect their feet at all times to minimize the risk of tissue damage (Schaper, et al., 2019). Because of this principle, protective strategies are preferred over therapeutic exercises to regain the lost functionality usually linked to DM2 and DPN progression (Schaper, et al., 2019). Restricted joint movement as a strategy implemented in clinical settings might additionally reduce the RoM of the foot-ankle joints (Schaper, et al., 2019), leading to changes in foot rollover, which is the main cause of alterations in plantar pressure – a well-known risk factor for foot ulcer development (Schaper, et al., 2020). A better understanding of both tissue and joint stiffness and passive torque would contribute to a better characterization of joint dynamics, and would add value to the next international guidelines recommendations (Schaper, et al., 2020). This would be supplemented by further discussion regarding the need to include a regime

of therapeutic exercises to preserve and improve foot-ankle mobility, since the elastic strain energy is an important component of distal joint torque during gait (Lai, et al., 2015; Lai, Schache, Brown, & Pandy, 2016; Lai, Schache, Lin, & Pandy, 2014). In addition, data on passive stiffness and passive torque in DM2 and DPN individuals would potentially contribute to biomechanical modeling studies aimed at calculating joint and muscle forces in these individuals (Gomes, et al., 2017; Santos, Gomes, Sacco, & Ackermann, 2017).

As the passive biomechanical properties change according to individuals' motion speed (Taylor, Dalton, Seaber, & Garrett, 1990), it would be interesting to analyze the passive torque at 5°/s (minimal velocity of the equipment), avoiding reflex muscle activation (Lamontagne, Malouin, & Richards, 1997), and also at 30°/s and 60°/s that is typically achieved during gait (Hsu, Tang, & Jan, 2003; Olney, Griffin, & McBride, 1994; Salsich, et al., 2000). Thus, this study aimed to investigate ankle and knee passive stiffness and torque in individuals with DM2, with and without DPN, at 5°/s, 30°/s, and 60°/s compared to those without diabetes. Our hypotheses were that: (1) the individuals with DM2, with and without DPN, will exhibit greater passive stiffness and passive torque than the controls, and (2) passive stiffness and passive torque will be higher in those with DPN when compared to the controls and those with DM2.

Methods

Participants

This study follows the Strobe Statement for observational studies (Vandenbroucke, et al., 2007). Male volunteers aged between 18 and 56 years were recruited. Given that stiffness is greater in men than in women (Morse, 2011), we opt to compare groups matched for only one sex. The study was conducted in line with human research guidelines and regulations (National Health Council Resolution 466 of 2012; Laws 11.794, 8.080 and 8.142) and approved by the Institutional Research Ethics Committee (protocol 1.930.043).

Inclusion and exclusion criteria

The participants were divided into three groups: (1) individuals with DM2 and no DPN, (2) individuals with DM2 and DPN, and (3) individuals without DM2 as controls. Those with self-reported osteoarticular diseases (osteoarthritis, history of fractures, herniated discs, previous orthopedic knee or ankle surgery) (Cruz-Jentoft, et al., 2010; Poberezhets, et al., 2020), prediabetes, non-diabetic neuropathies, history of peripheral artery disease (Cruz-Jentoft, et al., 2010) and body mass index (BMI) >35 kg/cm² (Stegeman & Hermens, 2007) were not included.

The sample size calculation resulted in 51 individuals (17 per group) to achieve a power of 0.80 and an α of 0.05 within an F-test design, using a medium effect size (0.45) calculated with the mean and standard deviation of the plantar flexion peak of passive torque levels obtained in a pilot study (Dalmaijer, Nord, & Astle, 2020). A total of 75 individuals were interviewed for eligibility. From them, 51 met the criteria, being included in the analysis and distributed into three groups: control (n=17), DM2 (n=17), and DPN (n=17) (Figure 1). The presence of DM2 was determined by an endocrinologist in accordance with the American Diabetes Association criteria (ADA, 2018), using the glycated hemoglobin test (HbA1c) and considering a DM2 individual with > 6.1%.

The groups were not different in terms of age, anthropometric characteristics, occupational physical activity, sports, or leisure-time exercise (Table 1) and the DM 2 groups did not differ regarding clinical characteristics (Table 1).

The presence of DPN was based on highly reliable and reproducible assessments of clinical parameters: (i) tactile sensitivity using a 10 g Semmes-Weinstein monofilament; (ii) vibratory perception

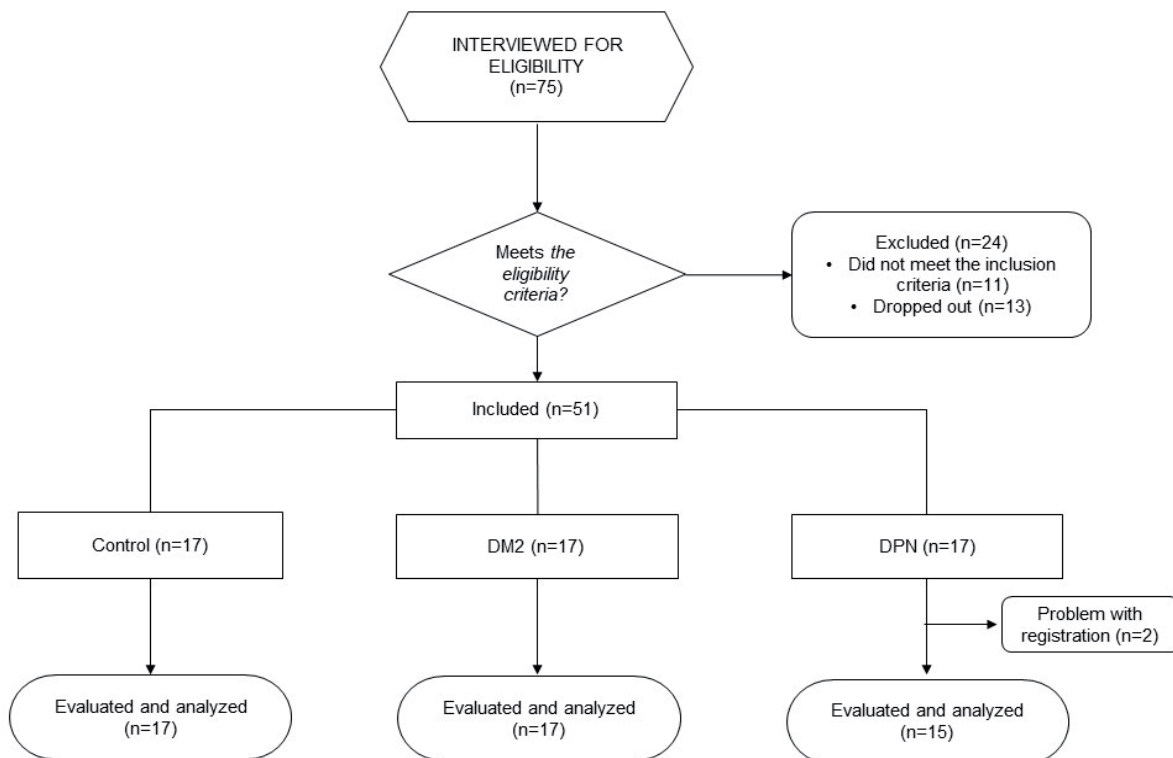
using a 128 Hz tuning fork, and (iii) typical DPN symptoms, which were assessed by the Michigan Neuropathy Screening Instrument (MNSI) (Bakker, Apelqvist, & Schaper, 2012; Boulton, et al., 2005; Sartor, Oliveira, Campos, Ferreira, & Sacco, 2018). To determine the presence of DPN, those three groups of variables were used as linguistic inputs in a fuzzy model, as described previously (Picon, Ortega, Watari, Sartor, & Sacco, 2012; Watari, et al., 2014). The fuzzy model combines each fuzzy set of input variables and assigns a score corresponding to the degree of DPN severity. A score > 2 was considered to constitute the presence of DPN (Suda, et al., 2017). This classification model presents a high accuracy receiver operating characteristic (ROC) curve= 0.91, which correlates highly with specialists' opinions (Pearson's correlation coefficient = 0.94) (Picon, Ortega, et al., 2012).

Given that exercise or physical activity can improve strength and flexibility, all participants answered a habitual physical activity questionnaire (Baecke) (Paffenbarger, Blair, Lee, & Hyde, 1993) validated for Brazilian Portuguese (Florindo & Latorre, 2003). The questionnaire summarized the participants' levels of habitual physical activity

Table 1. Clinical and demographic characteristics of participants

	Control (N=17)	DM2 (N=17)	DPN (N=15)	ANOVA
Age (years)	53.62 (8.74)	59.35 (6.55)	57.02 (7.25)	$P=0.08$; $F=2.54$
Time since diagnosis (years)	0 (0.00)	12.06 (7.87)*	11.13 (6.54)*	$P<0.01$; $F=21.06$
Body mass (kg)	85.47 (16.65)	81.49 (12.07)	91.83 (16.33)	$P=0.16$; $F=0.88$
Body Mass Index (kg/m ²)	26.4 (4.1)	27.8 (3.1)	30.7 (5.0)	$P=0.32$; $F=1.15$
Height (m)	1.73 (0.05)	1.69 (0.05)	1.73 (0.06)	$P=0.06$; $F=2.92$
HbA1C (%)	5.3 (0.3)	8.0 (2.5)*	8.1 (1.9)*	$P<0.01$; $F=12.32$
DPN severity fuzzy score	0.64 (0.02)	1.28 (0.71)	4.35 (2.63) *†	$P<0.01$; $F=26.24$
Michigan questionnaire score	0.47 (0.62)	2.52 (1.97)*	6.93 (2.31)*†	$P<0.01$; $F=55.05$
Vibration sensitivity right present/reduced/absent (number of patients)	17/0/0	17/0/0	9/2/4	-
Vibration sensitivity left present/reduced/absent (number of patients)	17/0/0	17/0/0	11/1/3	-
Occupational physical activity	6.39 (1.50)	5.83 (2.51)	5.94 (2.23)	$P=0.72$; $F=0.32$
Sports activity	1.32 (2.59)	1.32 (2.13)	0.55 (1.20)	$P=0.52$; $F=0.66$
Second sports activity	0.91 (2.18)	0.94 (0.58)	0.0 (0.0)	$P=0.14$; $F=2.04$
Total index of sports activities	2.44 (4.49)	1.51 (2.24)	0.55 (1.20)	$P=0.24$; $F=1.46$
Physical exercises in leisure score	4.95 (1.03)	4.72 (1.12)	4.44 (1.26)	$P=0.50$; $F=0.70$

Note. Data were expressed as mean (standard deviation). * $P<0.05$ in relation to controls. † $P<0.05$ in relation to DM2. m= meters, kg= kilograms. Control= control group; DM = Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy.



Note. Control = control group; DM2 = Type 2 diabetes; DPN = Type 2 diabetes with peripheral neuropathy.

Figure 1. Flowchart of the study design.

within the past 12 months, with the answers scored on a scale from 1 (never) to 5 (very often). The total score was determined by the sum of the scores from the categories of ‘physical activity in leisure’ and ‘leisure and locomotion activities (Florindo & Latorre, 2003).

The passive torque assessment protocol

Instruments. An isokinetic dynamometer (Biodex Multi-joint System 3, USA) was used to evaluate passive torque during knee and ankle flexion and extension at 5°/s – the recommended level for evaluating passive torque (Gajdosik, 2001) – and also at 30°/s and 60°/s (Hsu, et al., 2003; Olney, et al., 1994). The order of assessment for joints and velocities was randomized (Dallal, 2013).

To ensure the electrical silence of muscles during movement, electromyographic (EMG) signals of knee flexors (semitendinosus and biceps femoris), extensors (vastus lateralis, rectus femoris and vastus medialis), ankle dorsiflexors (tibialis anterior), and plantar flexors (soleus and medial gastrocnemius) were monitored by a Trigno™ Mobile EMG system (Delsys Inc., USA). Electrodes were attached to the skin following SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) recommendations (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000; Stegeman & Hermens, 2007).

Isokinetic assessments. All isokinetic assessments followed the standard guide of the dynamometer used in the study. Passive knee torque was evaluated with participants sitting on the dynamometer, guaranteeing electrode clearance over the seat (Figure 2 A and Figure 2 B).

The hips were stabilized at approximately 85° of flexion. Knee flexion at 90° was considered as the starting position. The axis of the dynamometer was aligned with the lateral epicondyle of the femur and the attachment fixed to the distal third of the shank (approximately 3 centimeters above the malleolus). For the test, the dynamometer moved the joint passively and recorded the torque. The knee was extended from 90° (i.e., starting position) up to 160° and flexed back toward 90°. The total RoM for the knee was 70° (Davies, 1992; Eng, Kim, & MacIntyre, 2002).

For the passive ankle torque assessment, participants were seated on the equipment with their hips and trunk stabilized at 70° of hip flexion. The shank was supported and maintained with the knee at 30° flexion, and the foot on a platform in a neutral position (i.e., position 0 was the one in which the foot was perpendicular to the shank) (Nielsen, et al., 2014). The axis of the dynamometer was aligned with the lateral malleolus. During ankle testing, the ankle moved from 10° of dorsiflexion until 35° of plantar flexion. Thus, the total RoM for the ankle was 35° (Nielsen, et al., 2014).

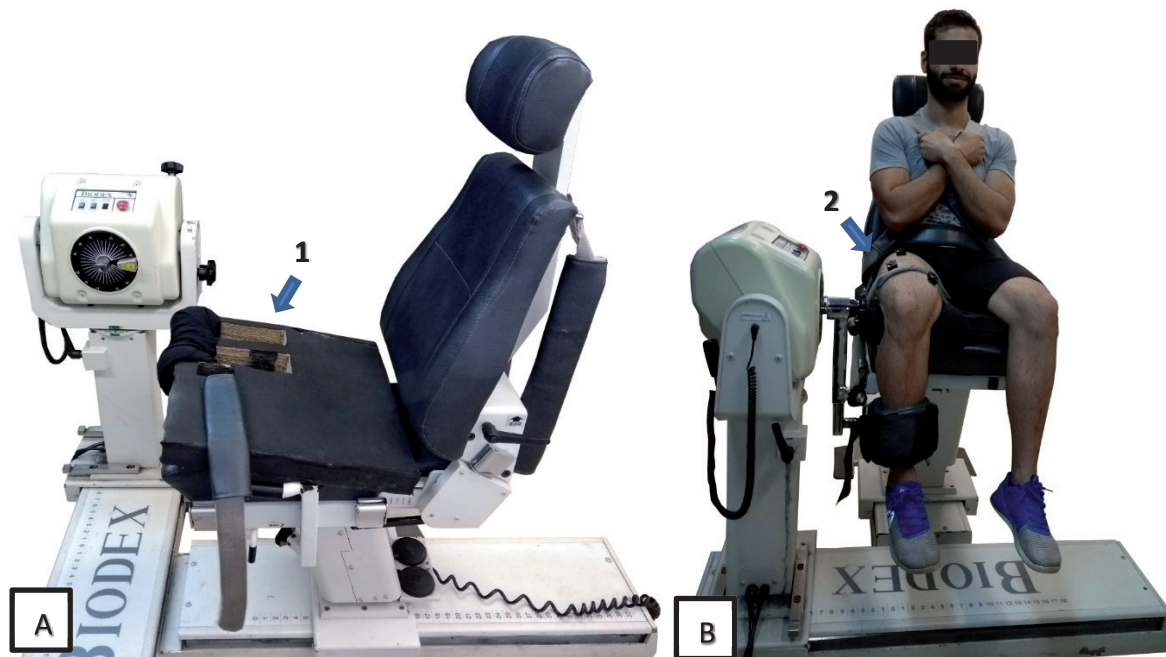


Figure 2. A: Adapted seat to assess surface electromyography of the hamstring muscles in the sitting position on an isokinetic dynamometer; 1: compartment to accommodate the sensors. B: Participant seated on the seat adapted to accommodate the electromyographic sensors during passive torque assessment; 2: Electromyographic sensors as accommodated by the adapted seat.

One repetition was performed just with the dynamometer attachment for both joints, and this register was used for passive torque processing (Gajdosik, 2001; Otoni, et al., 2011). Before the passive torque assessment, a set of five repetitions was performed for familiarization (Araújo, et al., 2011).

EMG assessment – monitoring muscle activation. EMG activity was measured at rest, before testing, and during the tests. After each repetition in the passive torque tests, the EMG signal was processed in real-time using MATLAB software (version 7.0.1, Matworks, USA) to monitor muscle activation. EMG signals were filtered using a 4th order band-pass Butterworth filter (zero-lag, 10Hz to 500Hz) (Otoni, et al., 2011). The signal during passive torque testing was compared to that obtained at rest in 100ms intervals. Muscle activity was deemed present when the mean of the signal was > 2 standard deviations of the resting signal (Lamontagne, et al., 1997). In the event of muscle activation, that repetition was disregarded and repeated (Gajdosik, 2001; Otoni, et al., 2011) until three valid repetitions were obtained.

Passive torque data processing. The passive torque and angular displacement data were processed using MATLAB software (version 7.0.1, Matworks, USA). The signal was filtered using a 4th order band-pass Butterworth filter (zero-lag) with a 1.25Hz cutoff frequency. The torque produced by the weight of the knee and ankle attachments was subtracted from total knee and ankle torque. Knee torque was calculated by subtracting the

torque generated by shank and foot weight from the total torque, while the ankle torque was obtained by subtracting the torque generated by foot weight from the total torque. The following calculation determined the torque of the shank and foot weight:

$$Nm = (Bw \times g) \times \% Bw \times m$$

where Nm = torque in newton meters; Bw = body weight; g = gravity; % Bw = percentage of the limb weight in relation to total body weight; and m = linear distance in meters between the center of mass and joint axis.

The proportion of the limb's weight in relation to total body weight was 4.65% and 1.45% for the shank and foot, respectively. The linear distance between the center of mass and the joint axis was measured as proposed by Dempster (Winter, 2015).

A time series of passive torque versus degree of motion was generated from the position where torque was equal to 0 N.m (the angle at which the elastic forces of agonist and antagonist muscles are neutral) to the end of the movement. The time series is presented as supplementary material for qualitative analysis. First, the peak of passive torque and total torque (mean torque produced during the entire RoM) were identified. Second, total stiffness was calculated as the slope of the curve torque versus angular displacement, as follows:

$$\frac{\Delta Nm}{\Delta JM}$$

where, Δ = variation; N.m = torque in newton meters; and JM = joint motion in degrees.

The peak of passive torque represents the maximal passive resistance evaluated at the final range of motion position. This parameter is important because it helps to understand the behavior of passive stiffness in activities that require a maximum range of motion. The mean of total torque (mean torque produced during the entire RoM) contributes to understanding of the passive resistance during the entire range of motion, including in the initial and intermediate degrees of motion that produce smaller passive tension (Souza, Fonseca, Gonçalves, Ocarino, & Mancini, 2009). Test-retest reliability was performed for all the three variables (peak torque, total torque, and total stiffness) with the sub-sample of seven controls for guaranteeing the reproducibility of the procedure. The intraclass correlation coefficients (ICC [2,1]) were excellent for knee flexion and extension and ankle dorsiflexion and plantar flexion at 5°/s, 30°/s, and 60°/s (Table 2).

Statistical analysis

A one-way analysis of variance (ANOVA) using Tukey's *post-hoc* test was conducted to compare each variable among the groups: clinical and demographic characteristics, total torque, peak of torque, and total joint stiffness during knee passive flexion and extension and ankle passive dorsiflexion and plantarflexion at 5°/s, 30°/s, and 60°/s. The differences were considered statistically significant when $\alpha < .05$. Moreover, the effect size (ES) and a confidence interval (CI) of 95% were calculated. The ES was calculated using Hedges' *g* test which classifies effect sizes as insignificant (0.00–0.19), small (0.20–0.39), medium (0.40–0.79), and large (>0.80).

The analyses were conducted using SPSS version 22 (IBM, Somers, USA) and R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

For knee extension, the individuals with DPN ($p < .01$; ES: 0.98; CI 95% 0.2–1.7) and DM2 ($p < .01$; ES: 0.78; CI 95% 0.0–1.4) showed greater mean total passive stiffness at 60°/s when compared to the controls, although there were no intergroup differences for mean and peak torque at 5°/s or 30°/s (Table 3). For knee flexion, there was no difference among the groups (Table 3).

For ankle plantar flexion, the DPN participants exhibited higher peak torque at 5°/s compared to the controls ($p = .02$; ES: 0.67; CI 95%, 0.0–1.3) and to DM2 participants ($p < .01$; ES: 0.79; CI 95% 0.0–1.5). The DPN group presented greater total passive stiffness than the controls ($p < .01$; ES: 1.29; CI 95% 0.5–2.0) at 60°/s (Table 4).

For ankle dorsiflexion, the peak torque at 5°/s was higher in the DPN group compared to the controls ($p = .04$; ES: 0.86; CI 95% 0.1 – 1.5) and DM2 ($p < .01$; ES: 1.05; CI 95% 0.3 – 1.7). Mean total torque at 5°/s was higher in the DPN group than in the controls ($p < .01$; ES: 1.24; CI 95% 0.4 – 1.9) (Table 4).

Analyzing qualitatively the time series, the groups showed a similar behavior of the passive torque curves for knee flexion and extension at 5°/s and 30°/s. However, the slope of the knee flexion torque at 60°/s seemed steeper at the end of the knee excursion in the DPN group (Figure 3). With respect to the ankle, both curves (dorsiflexion and plantar

Table 2. Intraclass correlation coefficient (ICC^{1,2}) and standard error of measurement (SEM) for knee and ankle passive torque and stiffness

Joint motion	Joint speed	Mean of total torque	Peak torque	Mean of total joint stiffness
Flexion	5°/s	ICC= 0.89; SEM= 0.39	ICC= 0.88; SEM= 1.52	ICC= 0.97; SEM= 0.01
	30°/s	ICC= 0.65; SEM= 0.75	ICC= 0.92; SEM= 1.07	ICC= 0.99; SEM= 0.00
	60°/s	ICC= 0.88; SEM= 0.61	ICC= 0.97; SEM= 0.67	ICC= 0.99; SEM= 0.00
Extension	5°/s	ICC= 0.88; SEM= 0.25	ICC= 0.89; SEM= 1.56	ICC= 0.45; SEM= 0.02
	30°/s	ICC= 0.57; SEM= 0.51	ICC= 0.96; SEM= 0.55	ICC= 0.99; SEM= 0.05
	60°/s	ICC= 0.63; SEM= 0.69	ICC= 0.93; SEM= 0.83	ICC= 0.88; SEM= 0.01
Dorsiflexion	5°/s	ICC= 0.94; SEM= 0.06	ICC= 0.56; SEM= 0.65	ICC= 0.96; SEM= 0.00
	30°/s	ICC= 0.63; SEM= 0.10	ICC= 0.87; SEM= 0.77	ICC= 0.95; SEM= 0.01
	60°/s	ICC= 0.58; SEM= 0.44	ICC= 0.77; SEM= 0.73	ICC= 0.90; SEM= 0.01
Plantar flexion	5°/s	ICC= 0.53; SEM= 0.30	ICC= 0.54; SEM= 0.86	ICC= 0.93; SEM= 0.00
	30°/s	ICC= 0.69; SEM= 0.59	ICC= 0.59; SEM= 0.57	ICC= 0.56; SEM= 0.01
	60°/s	ICC= 0.52; SEM= 0.54	ICC= 0.85; SEM= 1.67	ICC= 0.99; SEM= 0.13

Note. ICC value: poor (<0.4); moderate (0.4–0.75); excellent (>0.75). The confidence interval adopted was 95%.

Table 3. Passive knee torque and stiffness

	Control (N=17)			DM2 (N=17)			DPN (N=15)		
	5°/s	30°/s	60°/s	5°/s	30°/s	60°/s	5°/s	30°/s	60°/s
Knee flexion									
0 N.m angle (degree)	38.93 (12.81)	40.34 (12.91)	35.91 (10.43)	42.03 (13.86)	39.93 (20.25)	43.80 (15.88)	36.80 (10.40)	41.53 (12.44)	46.60 (14.55)
Mean of total torque (N.m)	1.36 (1.38)	1.35 (1.94)	1.15 (1.31)	0.98 (0.75)	1.14 (0.72)	1.15 (1.19)	1.41 (1.45)	1.70 (2.00)	1.72 (1.97)
Peak torque (N.m)	5.32 (1.63)	6.06 (1.72)	6.60 (1.04)	5.27 (1.81)	5.30 (2.28)	6.25 (1.49)	5.89 (2.21)	7.10 (2.34)	7.42 (1.78)
Mean of total joint stiffness	0.05 (0.02)	0.14 (0.05)	0.11 (0.05)	0.11 (0.18)	0.13 (0.07)	0.14 (0.07)	0.06 (0.05)	0.13 (0.06)	0.11 (0.06)
Knee extension									
0 N.m angle (degree)	48.26 (18.46)	58.78 (16.68)	57.43 (11.24)	50.60 (19.56)	58.47 (20.12)	56.93 (20.33)	54.54 (12.41)	62.16 (16.26)	67.14 (17.39)
Mean of total torque (N.m)	1.25 (1.02)	1.38 (1.32)	0.85 (0.56)	1.27 (1.16)	1.11 (0.83)	1.45 (1.15)	1.37 (1.41)	1.63 (1.51)	1.87 (1.41)
Peak torque (N.m)	4.65 (1.65)	4.37 (2.42)	4.58 (1.07)	4.99 (2.01)	4.19 (1.60)	5.00 (5.07)	5.20 (2.28)	4.63 (2.00)	4.56 (2.39)
Mean of total joint stiffness	0.08 (0.03)	0.09 (0.05)	0.05 (0.03)	0.11 (0.04)	0.36 (1.07)	0.14 (0.16)*	0.09 (0.05)	0.08 (0.03)	0.15 (0.14)*

Note. Data expressed as mean (standard deviation). *P<0.05 in relation to controls. N.m= newton meters. Control= control group; DM2= Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy. 0 N.m angle (degree) = neutral joint position.

Table 4. Passive ankle torque and stiffness

	Control (N=17)			DM2 (N=17)			DPN (N=15)		
	5°/s	30°/s	60°/s	5°/s	30°/s	60°/s	5°/s	30°/s	60°/s
Ankle dorsiflexion									
0 N.m angle (degree)	98.14 (5.98)	86.25 (20.70)	10.91 (3.05)	100.68 (5.16)	88.47 (20.12)	18.52 (24.07)	99.25 (6.32)	82.16 (16.26)	10.07 (4.07)
Mean of total torque (N.m)	0.49 (0.33)	0.96 (0.77)	1.25 (0.69)	0.45 (0.41)	0.50 (0.36)	1.22 (0.49)	0.93 (0.52)*†	0.73 (0.44)	1.27 (0.95)
Peak torque (N.m)	6.24 (1.62)	6.40 (1.61)	6.68 (1.03)	6.05 (1.48)	5.90 (1.42)	6.33 (1.19)	7.66 (1.57)*†	7.29 (1.01)†	7.40 (1.85)
Mean of total joint stiffness	0.18 (0.09)	0.21 (0.06)	0.23 (0.06)	0.21 (0.06)	0.23 (0.06)	0.26 (0.06)	0.25 (0.08)	0.26 (0.06)	0.28 (0.06)†
Ankle plantarflexion									
0 N.m angle (degree)	92.04 (5.18)	86.25 (20.70)	20.05 (3.08)	92.38 (3.46)	85.42 (13.25)	20.35 (2.43)	92.52 (5.10)	88.83 (5.27)	19.48 (3.62)
Mean of total torque (N.m)	1.04 (0.62)	0.98 (0.50)	0.83 (0.58)	0.98 (0.48)	0.61 (0.40)	0.52 (0.36)	1.06 (0.86)	0.82 (0.72)	1.06 (0.74)
Peak torque (N.m)	7.24 (1.07)	5.28 (1.20)	5.43 (1.31)	7.03 (0.93)	5.11 (1.36)	5.11 (1.17)	8.49 (1.77)*†	6.06 (1.45)	6.27 (1.67)
Mean of total joint stiffness	0.02 (0.02)	0.12 (0.15)	0.11 (0.05)	0.03 (0.01)	0.08 (0.05)	0.11 (0.04)	0.04 (0.01)*	0.08 (0.04)	0.11 (0.03)

Note. Data expressed as mean (standard deviation). *P<0.05 in relation to controls. †=P<0.05 in relation to DM2. N.m= newton meters. Control= control group; DM2= Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy. 0 N.m angle (degree) = neutral joint position.

flexion) of the DPN group showed a greater torque magnitude throughout RoM at 5°/s and a steeper slope at the end of the ankle excursion. This qualitatively change in the ankle pattern suggests that, although individuals with DPN show high stiffness

throughout the RoM, it is greatest at the end of the movement. In general, the DM2 group showed an intermediate behavior in relation to the control and DPN groups for almost all the movements, with a higher passive torque magnitude than the control

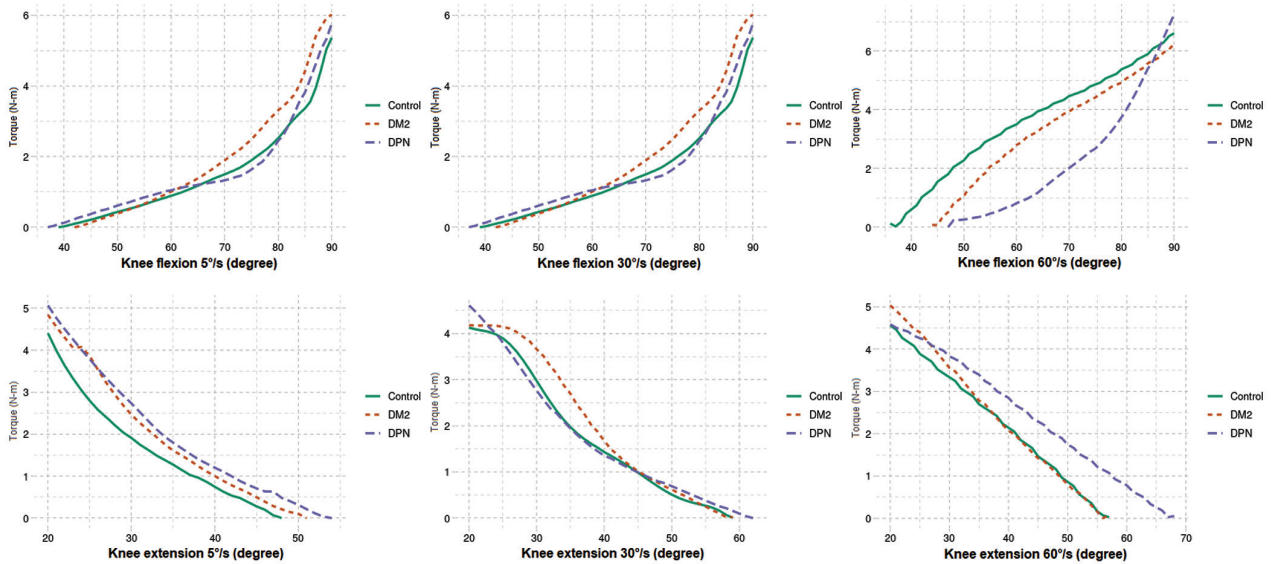


Figure 3. Passive torque time series for knee flexion and extension at 5%/s, 30%/s, and 60%/s. N.m= newton meters. Control= control group; DM2= Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy.

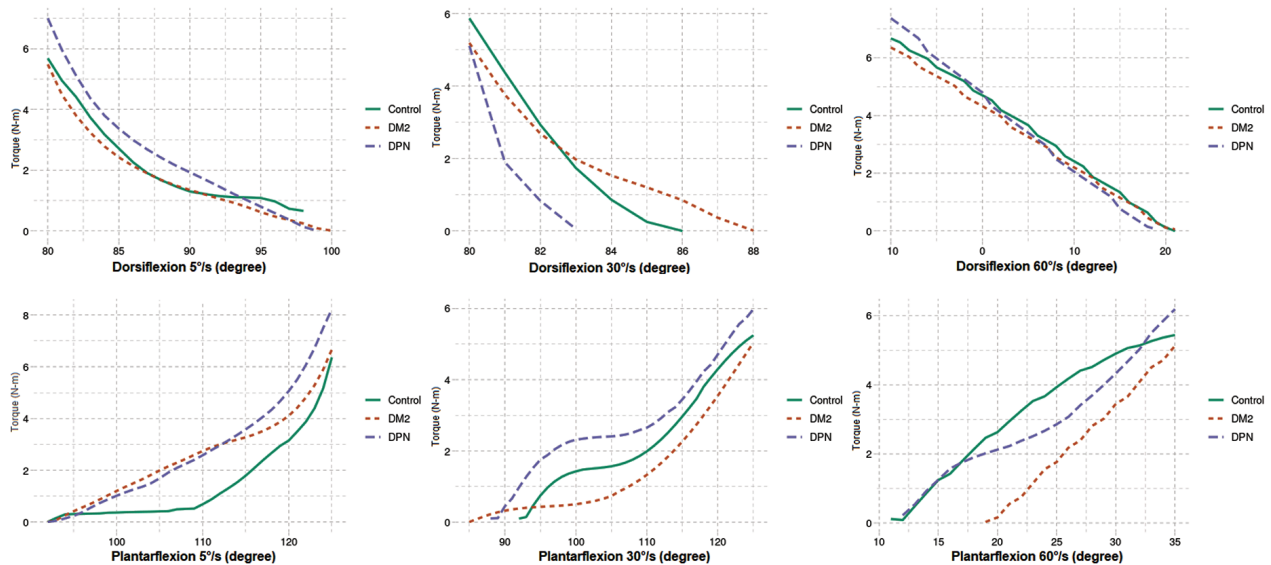


Figure 4. Passive torque time series for ankle dorsiflexion and plantarflexion at 5%/s, 30%/s, and 60%/s. N.m= newton meters. Control= control group; DM2= Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy.

group and lower than the DPN group (Figures 3 and 4).

Discussion and conclusions

This study compared ankle and knee passive stiffness and passive torque during sagittal motion at different speeds for the individuals with DM2, with and without DPN, and the control individuals. The main results confirmed our hypothesis that the individuals with DM2 and DPN exhibited greater passive stiffness and passive torque than the controls or the individuals with DM2 without DPN for ankle dorsiflexion and plantar flexion at 5%. These findings could explain the functional impair-

ments during locomotor activities usually observed in individuals with DM2 and DPN (Giacomozzi, et al., 2008; Gomes, et al., 2017; Picon, Sartor, et al., 2012; Sacco, et al., 2015; Yi, et al., 2016), probably because the increased passive stiffness can modify force transmission through the passive musculo-skeletal system, reducing active torque and power (Haus, et al., 2007), and changing gait mechanics. Clinically, increased passive stiffness also impairs the performance of daily living activities (Haus, et al., 2007) and reduces gait speed (Haus, et al., 2007; Semba, et al., 2010), as has also been observed in DM2 individuals (Fernando, et al., 2013).

Although Rao et al. (2006) already reported greater passive stiffness during ankle dorsiflexion

in DM2 subjects, our study was the first to investigate passive torque and passive stiffness in individuals with DM2 while also considering the presence or absence of DPN. The lack of difference in the ankle movements between the DM2 without DPN individuals and controls indicates that DPN status might be a key factor in the degree of passive ankle torque and stiffness. Although the length of time since diagnosis was the same between the two DM2 groups, the presence of DPN was a crucial factor for this difference. Thus, while the relationship between DPN and time since diagnosis is not necessarily direct, stiffness may be directly linked to neuro-motor impairments related to DPN and glycemic control. The increased passive torque and passive stiffness in the DPN individuals can be explained by the poor glycemic control that is known to lead to DPN (Pop-Busui, et al., 2017) and, at the same time, it can lead to non-enzymatic glycation of collagen (Gautieri, et al., 2017). The non-enzymatic glycation of collagen is a process that modifies collagen type, altering the elastic resistance of joint structures (Atayde, et al., 2012). Chronically, DM2 also results in an accumulation of AGEs (Gautieri, et al., 2017; Vlassara, 1990), contributing to early aging of the collagen matrix in these structures (Paul & Bailey, 1999; Vlassara & Palace, 2002). Our results suggest that musculoskeletal structures may become stiffer with the presence of DPN.

An increase in the ankle passive torque was observed only in the DPN group, while the knee changes occurred in the DM2 individuals with and without DPN. This could be related to the atrophy and changes in the mechanical properties of passive structures due to AGE accumulation that are likely more accentuated in the distal region of the limbs, as are the sensory and motor alterations in DPN (Giacomozzi, et al., 2008; Gomes, et al., 2017; Sacco, et al., 2015). Thus, changes in the torque and stiffness of the ankle of individuals with DM2 and DPN are consistent with sensorimotor changes in distal extremities. Several studies have indicated that DPN mainly compromises the distal joints (Giacomozzi, et al., 2008; Gomes, et al., 2017; Picon, Sartor, et al., 2012; Sacco, et al., 2015; Yi, et al., 2016). However, specifically for the knee – an intermediate joint – our results show that passive stiffness is altered in DM2 individuals, regardless of the presence of DPN. Williams, Brunt, and Tanenberg (2007) also found an important alteration in the knee moment of force during gait in individuals with DM2, but not DPN, suggesting a potential compensatory strategy for the lower ankle range of motion in DM individuals, as we also observed in our study.

Interestingly, the alterations in passive ankle torque and stiffness occurred in DPN individuals at 5°/s, while the alterations in passive knee torque

and stiffness occurred in DM2 and DPN individuals at 30°/s and 60°/s. The fact that the knee outcomes were altered in the DM2 and DPN individuals only during faster movements was unexpected. It is known that the viscoelastic components present greater tension at lower stretching speeds (McNair, Dombroski, Hewson, & Stanley, 2001), while the viscous component increases tension linearly with speed (McNair, Hewson, Dombroski, & Stanley, 2002). Although these components contribute greatly to passive resistance, passive torque represents the whole joint tissues and cannot differentiate between viscous or elastic structures and properties.

The greater passive torque and stiffness observed at the knee and ankle movements reinforces the need for preventive actions aiming to reduce joint impairments resulting from DM2 and DPN. To date, most biomechanical interventions have been based on using structured and cushioned shoes for all people with DM, regardless of their musculoskeletal condition. However, preventive therapeutic interventions involving active exercise, stretching, and joint mobility are highly recommended to delay or prevent the joint tissues alterations investigated here, thereby reducing the impact of this disease on mobility and quality of life (Sacco & Sartor, 2016).

The time series presented in the supplementary material for passive knee and ankle torque at different velocities might contribute to biomechanical modeling studies aimed at calculating joint and muscle forces in individuals with DM2, with and without DPN (Gomes, et al., 2017; Santos, et al., 2017), since research depends on *in vivo* values to implement models that are biomechanically similar to real individuals.

This study has certain limitations that should be considered. The cross-sectional design precludes establishing an association of causality for the effect of DPN on passive stiffness. Two participants from the DPN group did not complete the protocol, thus there was an uneven number of subjects in the groups and below sample size calculation for the DPN group. Moreover, this study evaluated only male subjects, and different results may be observed in women.

In conclusion, the individuals with DM2 and DPN exhibited greater passive knee and ankle stiffness and torque than control individuals and those with DM2 and no DPN. The mechanical impairments in ankle joint structures were most evident at low speeds, while knee alterations were observed only at faster speeds (30°/s and 60°/s). The characteristics of passive knee and ankle torque in individuals with DM2, with and without DPN, can contribute to the field of biomechanics by helping to model the mechanical properties of distal muscu-

loskeletal tissue in these populations. Although the presence of DPN was the key factor for greater passive ankle stiffness and torque, it was not a factor for increased passive stiffness of the knee. Based

on these findings, preventive measures for avoiding stiffness and motion impairment in the ankle and knee could be adopted during the early stages of DM2.

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Correspondence to:

Tania F. Salvini, P.T., M.S., Ph.D.

Department of Physiotherapy, Federal University of São Carlos, SP, Brazil

CEP: 13565-905

Phone: +55 16 33518345

E-mail: tania@ufscar.br

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