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

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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 Sahrmann (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 & 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).

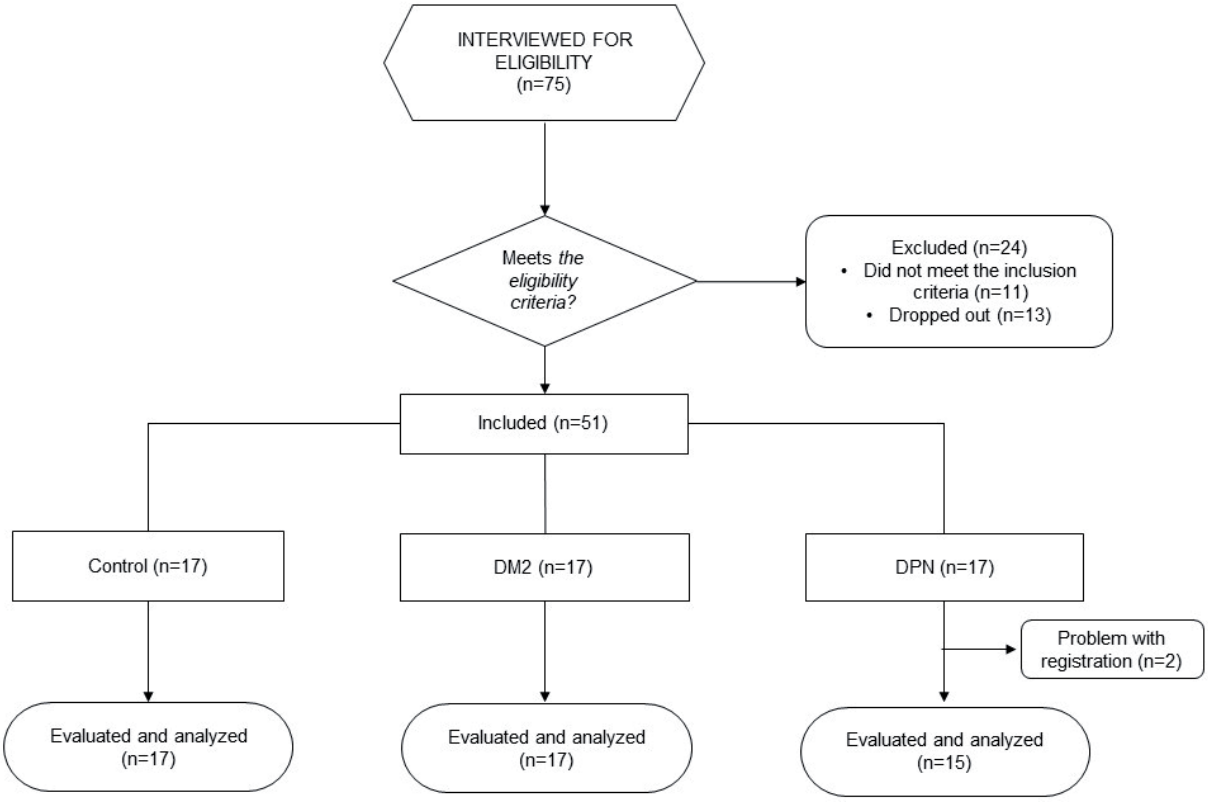
The presence of DPN was based on highly reliable and reproducible assessments of clinical parameters: (i) tactile sensitivity using a 10 g Semmes-Weinstein monofilament; (ii) vibratory perception using a 128 Hz tuning fork, and (iii) typical DPN symptoms, which were assessed by the Michigan Neuropathy 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 sincediagnosis (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/m²)	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

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.



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 90º 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 90º (i.e., starting position) up to 160° and flexed back toward 90º. The total RoM for the knee was 70° (Davies, 1992; Eng, Kim, & MacIntyre, 2002).

For 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

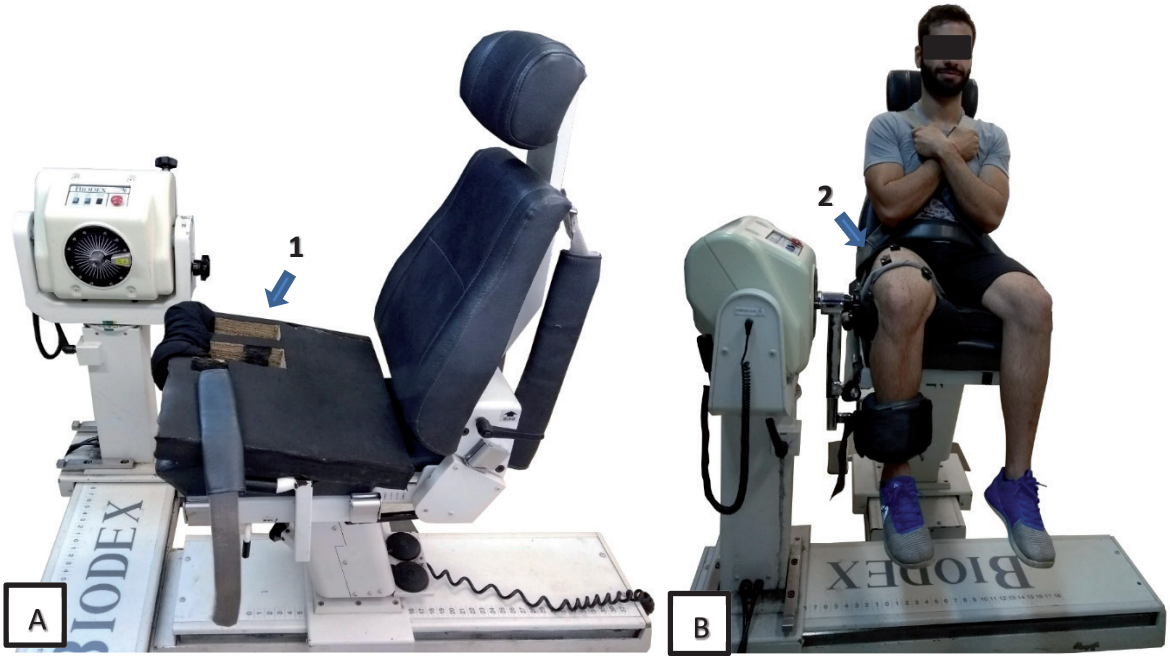


Figure 2. A: Adapted seat to assess surface electromyography of the hamstring muscles in the sitting positionon an isokinetic dynamometer;1:compartment to accommodate the sensors.B: Participant seated on the seat adapted to accommodate the electromyographic sensors during passive torque assessment; 2: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

plantar flexion. Thus, the total RoM for the ankle was 35° (Nielsen, et al., 2014).

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 movement. The time series is presented as supplementary material for qualitative analysis. First, the peak of passive torque and total torque (mean torque produced 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 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

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)*

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)

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

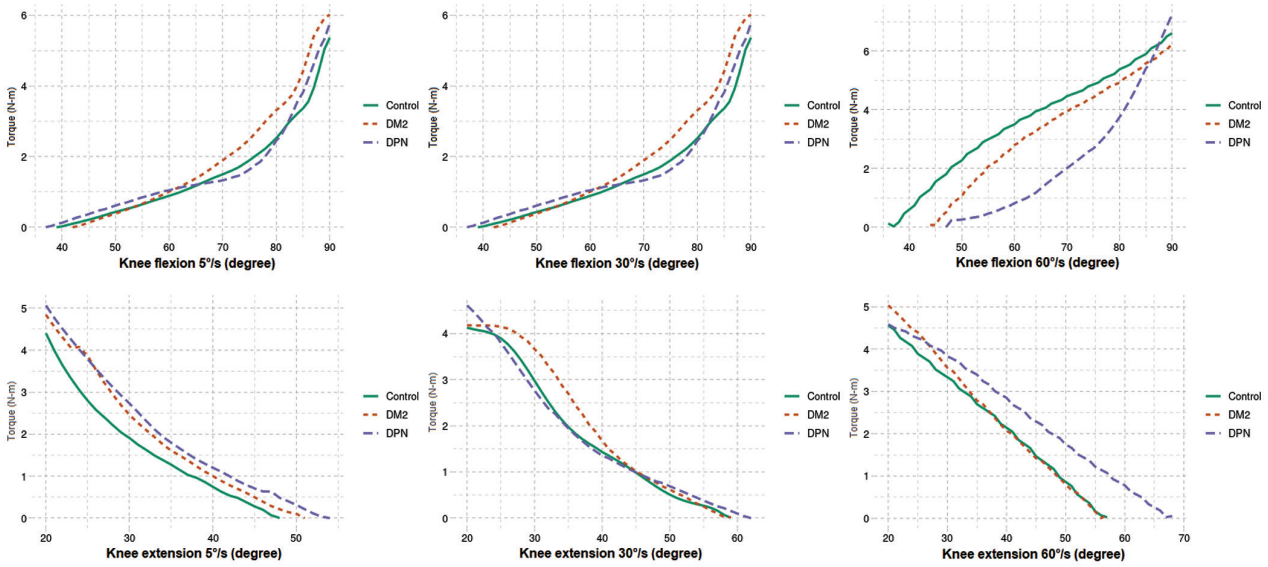


Figure 3. Passive torque time series for knee flexion and extension at 5°/s, 30°/s, and 60°/s. N.m= newton meters. Control= control group; DM2= Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy.

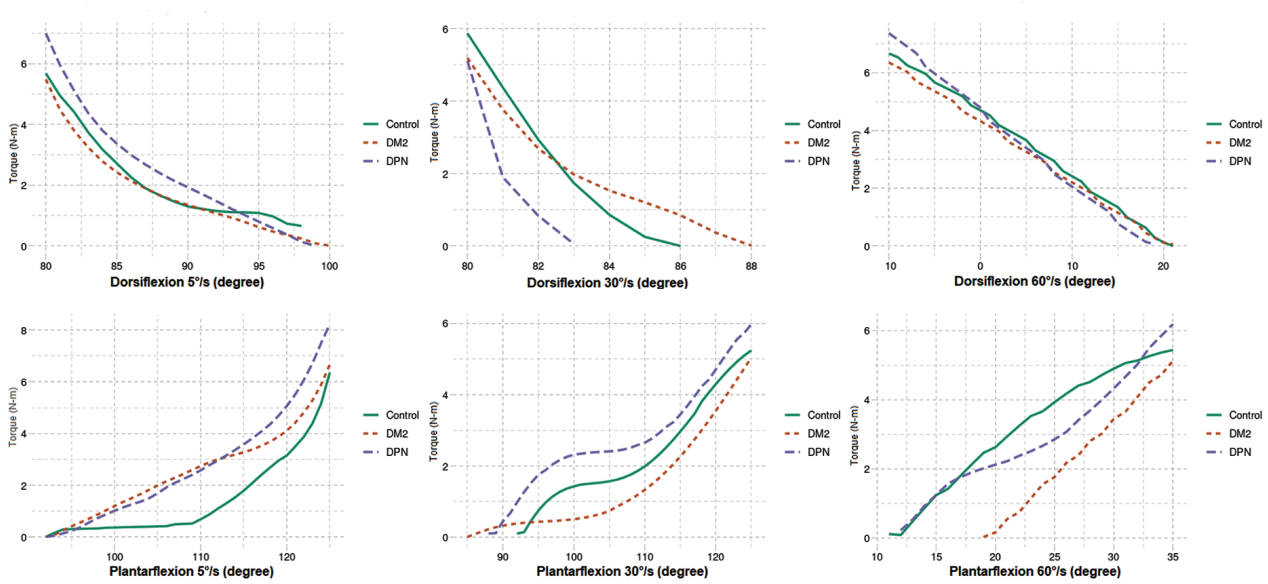


Figure 4. Passive torque time series for ankle dorsiflexion and plantarflexion at 5°/s, 30°/s, and 60°/s. N.m= newton meters. Control= control group; DM2= Type 2 diabetes patients without diabetic peripheral neuropathy; DPN= Type 2 diabetes patients with diabetic peripheral neuropathy.

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°/s. These findings could explain the functional impairments 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 musculoskeletal 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 neuromotor 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, & 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 musculoskeletal 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.

References

ADA – American Diabetes Association. (2018). 2. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2018. [Position statement] *Diabetes Care*, *41*(Suppl 1), S13-S27. https://doi.org/10.2337/dc18-S002

Andreassen, T.T., Seyer-Hansen, K., & Bailey, A.J. (1981). Thermal stability, mechanical properties and reducible cross-links of rat tail tendon in experimental diabetes. *Biochimica et Biophysica Acta*, *677*(2), 313-317.

Araújo, V.L., Carvalhais, V.O.C., Souza, T.R., Ocarino, J.M., Gonçalves, G.G.P., & Fonseca, S.T. (2011). Validity and reliability of clinical tests for assessing passive ankle stiffness. *Brazilian Journal of Physical Therapy*, *15*(2), 166-173. https://doi.org/10.1590/S1413-35552011000200013

Atayde, S.A., Yoshinari, N.H., Nascimento, D.P., Catanozi, S., Andrade, P.C., Velosa, A.P.P., …, & Teodoro, W.R. (2012). Experimental diabetes modulates collagen remodelling of joints in rats. *Histology and Histopathology*, *27*(11), 1471-1479. https://doi.org/10.14670/HH-27.1471

Bakker, K., Apelqvist, J., & Schaper, N.C. (2012). Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes/Metabolism Research and Reviews*, *28*(S1), 225-231. https://doi.org/10.1002/dmrr.2253

Boulton, A.J.M., Vinik, A.I., Arezzo, J.C., Bril, V., Feldman, E.L., Freeman, R., …, & Ziegler, D. (2005). Diabetic neuropathies: A statement by the American Diabetes Association. *Diabetes Care*, *28*(4), 956-962. https://doi.org/10.2337/diacare.28.4.956

Cruz-Jentoft, A.J., Baeyens, J.P., Bauer, J.M., Boirie, Y., Cederholm, T., Landi, F., …, & Zamboni, M. (2010). Sarcopenia: European consensus on definition and diagnosis. *Age and Ageing*, *39*(4), 412-423. https://doi.org/10.1093/ageing/afq034

D'Ambrogi, E., Giurato, L., D'Agostino, M.A., Giacomozzi, C., Macellari, V., Caselli, A., & Uccioli, L. (2003). Contribution of plantar fascia to the increased forefoot pressures in diabetic patients. *Diabetes Care*, *26*(5), 1525-1529. https://doi.org/10.2337/diacare.26.5.1525

Dallal, G.E. (2013). Randomization.com. Retrieved from http://www.randomization.com

Dalmaijer, E.S., Nord, C.L., & Astle, D.E. (2020). Statistical power for cluster analysis. *ArXiv*. Retrieved from http://arxiv.org/abs/2003.00381

Davies, G. (1992). Compendium of isokinetic in clinical usage and rehabilitation techniques. In *Database* (4th ed.). Onalaska, WI.

Deschamps, K., Matricali, G.A., Roosen, P., Nobels, F., Tits, J., Desloovere, K., …, & Staes, F. (2013). Comparison of foot segmental mobility and coupling during gait between patients with diabetes mellitus with and without neuropathy and adults without diabetes. *Clinical Biomechanics*, *28*(7), 813-819. https://doi.org/10.1016/j.clinbiomech.2013.06.008

Eng, J.J., Kim, C.M., & MacIntyre, D.L. (2002). Reliability of lower extremity strength measures in persons with chronic stroke. *Archives of Physical Medicine and Rehabilitation*, *83*(3), 322-328. https://doi.org/10.1053/apmr.2002.29622

Fernando, M., Crowther, R., Lazzarini, P., Sangla, K., Cunningham, M., Buttner, P., & Golledge, J. (2013). Biomechanical characteristics of peripheral diabetic neuropathy: A systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. *Clinical Biomechanics*, *28*(8), 831-845. https://doi.org/10.1016/j.clinbiomech.2013.08.004

Ferreira, J.P., Sartor, C.D., Leal, Â.M.O., Sacco, I.C.N., Sato, T.O., Ribeiro, I.L., …, & Salvini, T.F. (2017). The effect of peripheral neuropathy on lower limb muscle strength in diabetic individuals. *Clinical Biomechanics*, *43*, 67-73. https://doi.org/10.1016/j.clinbiomech.2017.02.003

Florindo, A.A., & Latorre, M. do R.D. de O. (2003). Validation and reliability of the Baecke questionnaire for the evaluation of habitual physical activity in adult men. *Revista Brasileira de Medicina do Esporte*, *9*(3), 129-135. https://doi.org/10.1590/S1517-86922003000300002

Gajdosik, R.L. (2001). Passive extensibility of skeletal muscle: Review of the literature with clinical implications. *Clinical Biomechanics*, *16*(2), 87-101. https://doi.org/10.1016/S0268-0033(00)00061-9

Gautieri, A., Passini, F.S., Silván, U., Guizar-Sicairos, M., Carimati, G., Volpi, P., …, & Snedeker, J.G. (2017). Advanced glycation end-products: Mechanics of aged collagen from molecule to tissue. *Matrix Biology*, *59*, 95-108. https://doi.org/10.1016/j.matbio.2016.09.001

Giacomozzi, C., Caselli, A., Macellari, V., Giurato, L., Lardieri, L., Uccioli, L., …, & Macellari, V. (2002). Walking strategy in diabetic patients with peripheral neuropathy. *Diabetes Care*, *25*(8), 1451-1457. https://doi.org/10.2337/diacare.25.8.1451

Giacomozzi, C., D'Ambrogi, E., Cesinaro, S., Macellari, V., & Uccioli, L. (2008). Muscle performance and ankle joint mobility in long-term patients with diabetes. *BMC Musculoskeletal Disorders*, *9*(1), 99. https://doi.org/10.1186/1471-2474-9-99

Giacomozzi, C., D'Ambrogi, E., Uccioli, L., & MacEllari, V. (2005). Does the thickening of Achilles tendon and plantar fascia contribute to the alteration of diabetic foot loading? *Clinical Biomechanics*, *20*(5), 532-539. https://doi.org/10.1016/j.clinbiomech.2005.01.011

Gomes, A.A., Ackermann, M., Ferreira, J.P., Orselli, M.I.V, & Sacco, I.C.N. (2017). Muscle force distribution of the lower limbs during walking in diabetic individuals with and without polyneuropathy. *Journal of Neuroengineering and Rehabilitation*, *14*(1), 111. https://doi.org/10.1186/s12984-017-0327-x

Haus, J.M., Carrithers, J.A., Trappe, S.W., & Trappe, T.A. (2007). Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. *Journal of Applied Physiology*, *103*(6), 2068-2076. https://doi.org/10.1152/japplphysiol.00670.2007

Hermens, H.J., Freriks, B., Disselhorst-Klug, C., & Rau, G. (2000). Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology*, *10*(5), 361-374. https://doi.org/10.1016/S1050-6411(00)00027-4

Hsu, A.-L., Tang, P.-F., & Jan, M.-H. (2003). Analysis of impairments influencing gait velocity and asymmetry of hemiplegic patients after mild to moderate stroke. *Archives of Physical Medicine and Rehabilitation*, *84*(8), 1185-1193. https://doi.org/10.1016/S0003-9993(03)00030-3

Lai, A., Lichtwark, G.A., Schache, A.G., Lin, Y.C., Brown, N.A.T., & Pandy, M.G. (2015). In vivo behavior of the human soleus muscle with increasing walking and running speeds. *Journal of Applied Physiology*, *118*(10), 1266-1275. https://doi.org/10.1152/japplphysiol.00128.2015

Lai, A., Schache, A.G., Brown, N.A.T., & Pandy, M.G. (2016). Human ankle plantar flexor muscle-tendon mechanics and energetics during maximum acceleration sprinting. *Journal of the Royal Society Interface*, *13*(121). https://doi.org/10.1098/rsif.2016.0391

Lai, A., Schache, A.G., Lin, Y.C., & Pandy, M.G. (2014). Tendon elastic strain energy in the human ankle plantar-flexors and its role with increased running speed. *Journal of Experimental Biology*, *217*(17), 3159-3168. https://doi.org/10.1242/jeb.100826

Lamontagne, A., Malouin, F., & Richards, C.L. (1997). Viscoelastic behavior of plantar flexor muscle-tendon unit at rest. *Journal of Orthopaedic and Sports Physical Therapy*, *26*(5), 244-252. https://doi.org/10.2519/jospt.1997.26.5.244

Lamontagne, A., Malouin, F., Richards, C.L., & Dumas, F. (1997). Impaired viscoelastic behaviour of spastic plantarflexors during passive stretch at different velocities. *Clinical Biomechanics (Bristol, Avon)*, *12*(7-8), 508-515.

Leite, D.X., Vieira, J.M.M., Carvalhais, V.O.C., Araújo, V.L., Silva, P.L.P., & Fonseca, S.T. (2012). Relationship between joint passive stiffness and hip lateral rotator concentric torque. *Revista Brasileira de Fisioterapia (Sao Carlos, Sao Paulo, Brazil)*, *16*(5), 414-421.

Lorentzen, J., Kirk, H., Fernandez-Lago, H., Frisk, R., Scharff Nielsen, N., Jorsal, M., & Nielsen, J.B. (2017). Treadmill training with an incline reduces ankle joint stiffness and improves active range of movement during gait in adults with cerebral palsy. *Disability and Rehabilitation*, *39*(10), 987-993. https://doi.org/10.1080/09638288.2016.1174745

Lorimer, A.V., & Hume, P.A. (2016). Stiffness as a risk factor for achilles tendon injury in running athletes. *Sports Medicine*, *46*(12), 1921-1938. https://doi.org/10.1007/s40279-016-0526-9

Mcnair, P.J., Dombroski, E.W., Hewson, D.J., & Stanley, S.N. (2001). Stretching at the ankle joint : Viscoelastic. *Medicine and Science in Sports and Exercice*, *33*(3), 354-358.

McNair, P.J., Hewson, D.J., Dombroski, E., & Stanley, S.N. (2002). Stiffness and passive peak force changes at the ankle joint: The effect of different joint angular velocities. *Clinical Biomechanics*, *17*(7), 536-540. https://doi.org/10.1016/S0268-0033(02)00062-1

Morse, C.I. (2011). Gender differences in the passive stiffness of the human gastrocnemius muscle during stretch. *European Journal of Applied Physiology*, *111*(9), 2149-2154. https://doi.org/10.1007/s00421-011-1845-z

Nielsen, R.H., Couppé, C., Jensen, J.K., Olsen, M.R., Heinemeier, K.M., Malfait, F., …, & Kjaer, M. (2014). Low tendon stiffness and abnormal ultrastructure distinguish classic Ehlers-Danlos syndrome from benign joint hypermobility syndrome in patients. *FASEB Journal*, *28*(11), 4668-4676. https://doi.org/10.1096/fj.14-249656

Olney, S.J., Griffin, M.P., & McBride, I.D. (1994). Temporal, kinematic, and kinetic variables related to gait speed in subjects with hemiplegia: A regression approach. *Physical Therapy*, *74*(9), 872-885. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8066114

Otoni, V., Araújo, V.L. De, Souza, T.R., Gomes, G., Gonçalves, P., Ocarino, J.D.M., & Fonseca, S.T. (2011). Validity and reliability of clinical tests for assessing hip passive stiffness. *Manual Therapy*, *16*(3), 240-245. https://doi.org/10.1016/j.math.2010.10.009

Paffenbarger, R.S., Blair, S.N., Lee, I.M., & Hyde, R.T. (1993). Measurement of physical activity to assess health effects in free-living populations. *Medicine and Science in Sports and Exercise*, *25*(1), 60-70. https://doi.org/10.1249/00005768-199301000-00010

Palmer, T.B., Akehi, K., Thiele, R.M., Smith, D.B., Warren, A.J., & Thompson, B.J. (2015). Dorsiflexion, plantar-flexion, and neutral ankle positions during passive resistance assessments of the posterior hip and thigh muscles. *Journal of Athletic Training*, *50*(5), 467-474. https://doi.org/10.4085/1062-6050-49.6.04

Paul, R.G., & Bailey, A.J. (1999). The effect of advanced glycation end-product formation upon cell-matrix interactions. *The International Journal of Biochemistry and Cell Biology*, *31*(6), 653-660.

Picon, A.P., Ortega, N.R.S., Watari, R., Sartor, C., & Sacco, I.C.N. (2012). Classification of the severity of diabetic neuropathy: A new approach taking uncertainties into account using fuzzy logic. *Clinics (Sao Paulo, Brazil)*, *67*(2), 151-156. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22358240

Picon, A.P., Sartor, C.D., Roveri, M.I., Pássaro, A.C., Ortega, N.R., & Sacco, I.C.N. (2012). Diabetic patients with and without peripheral neuropathy reveal different hip and ankle biomechanical strategies during stair descent. *Revista Brasileira de Fisioterapia (Sao Carlos, Sao Paulo, Brazil)*, *16*(6), 528-534.

Poberezhets, V., Skoczyński, S., Demchuk, A., Oraczewska, A., Tobiczyk, E., Mostovoy, Y., & Barczyk, A. (2020). Impact of comorbidities on the deterioration of skeletal muscle dysfunction among COPD patients. *European Respiratory Journal, 56*, 700). https://doi.org/10.1183/13993003.congress-2020.700

Pop-Busui, R., Boulton, A.J.M., Feldman, E.L., Bril, V., Freeman, R., Malik, R.A., …, & Ziegler, D. (2017). Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care*, *40*(1), 136-154. https://doi.org/10.2337/dc16-2042

Rao, S.R., Saltzman, C.L., Wilken, J., & Yak, H.J. (2006). Increased passive ankle stiffness and reduced dorsiflexion range of motion in individuals with diabetes mellitus. *Foot and Ankle International*, *27*(8), 617-622. https://doi.org/10.1177/107110070602700809

Sacco, I.C.N., Hamamoto, A.N., Gomes, A.A., Onodera, A.N., Hirata, R.P., & Hennig, E.M. (2009). Role of ankle mobility in foot rollover during gait in individuals with diabetic neuropathy. *Clinical Biomechanics*, *24*(8), 687-692. https://doi.org/10.1016/J.CLINBIOMECH.2009.05.003

Sacco, I.C.N, Picon, A.P., Macedo, D.O., Butugan, M.K., Watari, R., & Sartor, C.D. (2015). Alterations in the lower limb joint moments precede the peripheral neuropathy diagnosis in diabetes patients. *Diabetes Technology and Therapeutics*, *17*(6), 405-412. https://doi.org/10.1089/dia.2014.0284

Sacco, I.C.N., & Sartor, C.D. (2016). From treatment to preventive actions: Improving function in patients with diabetic polyneuropathy. *Diabetes/Metabolism Research and Reviews*, *32*, 206-212. https://doi.org/10.1002/dmrr.2737

Salsich, G.B.B., Mueller, M.J.J., & Sahrmann, S.A.A. (2000). Passive ankle stiffness in subjects with diabetes and peripheral neuropathy versus an age-matched comparison group. *Physical Therapy*, *80*(4), 352-362. Retrieved from http://ptjournal.apta.org/content/80/4/352.short

Santos, G.F., Gomes, A.A., Sacco, I.C.N., & Ackermann, M. (2017). Predictive simulation of diabetic gait: Individual contribution of ankle stiffness and muscle weakening. *Gait and Posture*, *58*, 208-213. https://doi.org/10.1016/j.gaitpost.2017.07.124

Sartor, C.D., Oliveira, M.D., Campos, V., Ferreira, J.S.S.P., & Sacco, I.C.N. (2018). Cross-cultural adaptation and measurement properties of the Brazilian Version of the Michigan Neuropathy Screening Instrument. *Brazilian Journal of Physical Therapy*, *22*(3), 222-230. https://doi.org/10.1016/j.bjpt.2017.10.004

Schaper, N.C., van Netten, J.J., Apelqvist, J., Bus, S.A., Hinchliffe, R.J., & Lipsky, B.A. (2020). Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes/Metabolism Research and Reviews*, *36*(S1), e3266. https://doi.org/10.1002/dmrr.3266

Schaper, N., Netten, J. van, Apelqvist, J., Bus, S., Hinchliffe, R., & Lipsky, B. (2019). *Guidelines on the prevention and management of diabetic foot disease IWGDF Guidelines*. Retrieved from www.iwgdfguidelines.org

Semba, R.D., Bandinelli, S., Sun, K., Guralnik, J.M., & Ferrucci, L. (2010). Relationship of an advanced glycation end product, plasma carboxymethyl-lysine, with slow walking speed in older adults: The InCHIANTI study. *European Journal of Applied Physiology*, *108*(1), 191-195. https://doi.org/10.1007/s00421-009-1192-5

Souza, T.R., Fonseca, S.T., Gonçalves, G.G., Ocarino, J.M., & Mancini, M.C. (2009). Prestress revealed by passive co-tension at the ankle joint. *Journal of Biomechanics*, *42*(14), 2374-2380. https://doi.org/10.1016/j.jbiomech.2009.06.033

Stegeman, D., & Hermens, H. (2007). Standards for surface electromyography: The European project Surface EMG for non-invasive assessment of muscles (SENIAM). *Línea). Disponible En: Http://Www. Med. ...*, (January), 108-112. Retrieved from http://www.seniam.org/%5Cnhttp://www.med.uni-jena.de/motorik/pdf/stegeman.pdf

Suda, E.Y., Madeleine, P., Hirata, R.P., Samani, A., Kawamura, T.T., & Sacco, I.C.N. (2017). Reduced complexity of force and muscle activity during low level isometric contractions of the ankle in diabetic individuals. *Clinical Biomechanics*, *42*, 38-46. https://doi.org/10.1016/j.clinbiomech.2017.01.001

Taylor, D.C., Dalton, J.D., Seaber, A.V, & Garrett, W.E. (1990). Viscoelastic properties of muscle-tendon units. The biomechanical effects of stretching. *The American Journal of Sports Medicine*, *18*(3), 300-309. https://doi.org/10.1177/036354659001800314

Vandenbroucke, J.P., von Elm, E., Altman, D.G., Gøtzsche, P.C., Mulrow, C.D., Pocock, S.J., …, & Egger, M. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *PLoS Medicine*, *4*(10), e297. https://doi.org/10.1371/journal.pmed.0040297

Vlassara, H. (1990). Advanced nonenzymatic tissue glycosylation: Cell-mediated interactions implicated in the complications associated with diabetes and aging. *Blood Purification*, *8*(4), 223-232. https://doi.org/10.1159/000169970

Vlassara, H., & Palace, M.R. (2002). Diabetes and advanced glycation endproducts. *Journal of Internal Medicine*, *251*(2), 87-101.

Watari, R., Sartor, C.D., Picon, A.P., Butugan, M.K., Amorim, C.F., Ortega, N.R.S., & Sacco, I.C.N. (2014). Effect of diabetic neuropathy severity classified by a fuzzy model in muscle dynamics during gait. *Journal of Neuroengineering and Rehabilitation*, *11*(1), 11. https://doi.org/10.1186/1743-0003-11-11

Williams, D.S.B., Brunt, D., & Tanenberg, R.J. (2007). Diabetic neuropathy is related to joint stiffness during late stance phase. *Journal of Applied Biomechanics*, *23*(4), 251-260. https://doi.org/10.1123/jab.23.4.251

Winter, D.A. (2015). Frontmatter. In *Biomechanics and motor control of human movement* (pp. i-xiv). Hoboken, NJ: John Wiley & Sons. https://doi.org/10.1002/9780470549148.fmatter

Yi, L.C., Sartor, C.D., Souza, F.T., & Sacco, I.C.N. (2016). Intralimb coordination patterns in absent, mild, and severe stages of diabetic neuropathy: Looking beyond kinematic analysis of gait cycle. *PloS One*, *11*(1), e0147300. https://doi.org/10.1371/journal.pone.0147300

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