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Effects of Type 2 Diabetes Mellitus and Peripheral Neuropathy on Mechanosensitivity of Lower Extremity Neurodynamic Testing

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by

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ABSTRACT

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Background: Type 2 Diabetes Mellitus (T2DM) and diabetic symmetrical polyneuropathy (DSP) impact multiple types of sensation including light touch, temperature, position sense and vibration perception. No study to date has examined the mechanosensitivity of peripheral nerves during limb movement in this population. **Objective:** The objective was to determine the unique effects T2DM and DSP have on nerve mechanosensitivity in the lower extremity. **Design:** This cross-sectional study included 43 people with T2DM and 20 age-matched controls without diabetes. **Methods:** Straight leg raise neurodynamic tests were performed with ankle plantar flexion (PF/SLR) and dorsiflexion (DF/SLR). Hip flexion range of motion (ROM), lower extremity muscle activity and symptoms were measured at rest, first onset of symptoms (P1) and maximally tolerated symptoms (P2). **Results:** The reduction in hip flexion ROM that ankle dorsiflexion induced at P2 was approximately 50% smaller in the T2DM group compared to the control group. Individuals in the T2DM group with signs of severe DSP had no difference in hip flexion ROM between PF/SLR and DF/SLR at P1 or P2. DF/SLR did not trigger the same global increase in protective muscle guarding and did not increase symptom intensity by the same magnitude in the T2DM group compared to

the control group. **Limitations:** This study did not assess the effects of sex on neurodynamic assessments. **Conclusions:** These findings support the hypothesis that increased neural loading during DF/SLR induces protective muscle guarding, reduced hip flexion motion and increased symptom intensity in healthy individuals. The SLR to the onset of symptoms is a valid assessment tool that allows for structural differentiation and is an appropriate end point for lower extremity neurodynamic testing in healthy individuals. Our study findings call into question the appropriateness of performing SLR neurodynamic testing in people with T2DM and signs of severe DSP. Without the ability to respond to the increased neural loading associated with neurodynamic testing, this population is at potential risk for harm and the information gathered will be of questionable clinical value.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SECTION A

INTRODUCTION

Clinical neurological examinations are an integral part of clinical decision making for determining the involvement of the nervous system in altered physical function and activity participation. One aspect of a standard neurological examination involves assessment of the sensitivity of peripheral nerves to limb movement, termed mechanosensitivity, through the use of neurodynamic tests. The most common neurodynamic test in the lower quarter is the passive straight leg raise (SLR) test.[1, 2] The base SLR test has been described previously[3] and includes passive hip flexion from a supine position with the knee held in full extension.

A recent systematic review of the SLR test found a lack of standardization in the literature including the use of various criteria for determining the end of the test.[2] The authors of this review reintroduce standardized methodology proposed by Brieg et al. in 1979 including the use of the first onset of "pain" as the end point to movement during the SLR test.[2]

Interpretations of neurodynamic examination findings are based primarily on expert consensus.[4] The proposed interpretations of a "positive" test includes considerations for whether the test 1) reproduced the patients symptoms, 2) asymmetry of testing involved and uninvolved limbs or significant deviation from normal range of motion, and 3) symptoms were altered by distant joint movement that doesn't impact local non-neural tissue.[4] The third consideration is critical to identify the source of limitations to movement as either neural or non-neural and is termed structural

differentiation. This is accomplished through use of additional limb movements as sensitizing maneuvers, in conjunction with the base test. The additional movements are chosen based on knowledge of how they alter the mechanical stresses of the peripheral nerves being tested.

Ankle dorsiflexion is a common sensitizing maneuver used with the SLR test.[5-7] Studies in rats and dogs have demonstrated that the sciatic nerve at the proximal thigh undergoes increased strain (elongation) when ankle dorsiflexion is added to the SLR test.[8, 9] Further support for the use of ankle dorsiflexion as a sensitizing maneuver is provided by findings from a cadaveric study, in which pre-positioning the ankle in dorsiflexion created distal movement in the tibial nerve at the knee and ankle.[6] Clinically, pre-positioning the ankle in dorsiflexion leads to a reduction of available hip range of motion during the SLR test when taken to maximal resistance in people with low back pain and healthy controls.[5]

The SLR test without ankle fixation provoked medial hamstring and gluteal muscle activity when the hip was held at the point of first onset of tension.[10] Both medial and lateral hamstring muscle activity occurred at the maximum hip flexion range (determined by the tester) with relative electrical silence through the rest of the range.[11] Pre-positioning in ankle dorsiflexion induced medial hamstring muscle activation earlier in the range of hip flexion during the SLR test.[7] The muscle activity provoked during the sensitized SLR test is thought to provide a protective mechanism to restrict further movement of the limb and help prevent overstretching and nerve injury.[10] This is consistent with findings during passive upper limb motions where electromyographic (EMG) activity was induced and contractile force of muscles adjacent to the nerves were

measured during neurodynamic testing.[12-15]

No study to date has simultaneously explored the differences in range of motion, symptoms, and muscle responses for the SLR with sensitizing maneuvers at both the onset of symptoms and the maximally tolerated position of the SLR in healthy individuals. It is important to understand the specific effects of sensitizing maneuvers at each of these testing end points to guide clinical decision-making and help validate standardized testing methodology. Additionally, no study has used non-invasive in vivo ultrasound imaging during the straight leg raise to quantify movement of the sciatic nerve and its distal branches. In this study we elucidated the specific effects of the ankle dorsiflexion sensitizing maneuvers on the mechanosensitivity of lower extremity posterior neural structures.

The aims of this study are to determine the quality, location and intensity of symptoms, hip range of motion, and muscle activity during two versions of the SLR (to include ankle dorsiflexion sensitization) at both the positions of onset of symptoms and the maximally tolerated position. Additionally, we identified biomechanical alterations to the nerves in the popliteal fossa associated with the SLR test through in vivo ultrasound imaging. Finally, we analyzed the reliability of neurodynamic testing. We hypothesized that ankle dorsiflexion would alter the intensity, location and quality of symptoms, increase muscle activity and reduce hip flexion range of motion during the SLR test. We further hypothesized that testing to the position of first onset of symptoms is the safest point at which to end a SLR test while still obtaining clinically relevant information from sensitizing maneuvers.

METHODS

This cross sectional study included 20 healthy control subjects recruited from the local medical and academic communities. Exclusion criteria included low back or leg pain lasting > 3 consecutive days in the past 6 months, peripheral neuropathy, diabetes mellitus, complex regional pain syndrome, lumbar spine surgeries, chemical dependence or alcohol abuse, a history of trauma to the nerves of the lower extremity, or chemotherapy in the past year. Participants had to meet flexibility requirements of hip flexion ≥ 90°, full knee extension, ankle dorsiflexion ≥ 0° and plantar flexion ≥ 30°. Institutional review boards at UCSF, SFSU and the General Clinical Research Center's Advisory Committee at UCSF approved this study. Written informed consent was obtained from subjects prior to testing. All subjects attended a single clinical assessment session. A subset of five subjects returned within 1-2 weeks for a second identical clinical assessment session for purposes of repeated measures reliability testing. A separate subset of five participants attended an ultrasound imaging session. One examiner (BB) performed all physical examinations.

Clinical assessment sessions

Questionnaires

Participants completed a medical history questionnaire and the Modified Baecke Questionnaire (MBQ), which is a self-report questionnaire on physical activity during work, recreation/sport, and leisure time.[16] In addition, the subjects were instructed in the use of a visual symptom reporting card, which included a body chart, qualitative descriptors adapted from the McGill Pain Questionnaire[17] and a visual analog symptom intensity scale (VAS) (Figure 1).

Sensory Testing

Vibration perception thresholds (VPT) and vibration extinction thresholds (VET) were measured bilaterally at medial malleoli and the plantar surface of the distal pad of the hallux using a biothesiometer. The medial malleoli were tested in sidelying and the halluces were tested in prone with the leg supported in 90° knee flexion and neutral ankle. The tip of the 60-Hz biothesiometer (Bio-Medical Instrument Company, Newbury, OH) was balanced on the testing site to ensure consistent contact pressure similar to methods described by Simoneau et al.[18] The voltage was slowly increased to a maximum of 50 V then reduced to 0 V position at variable speeds to avoid subject anticipation. The subject was instructed to report both the first feeling of vibration (VPT) and when the vibration sensation disappeared (VET). These measurements were repeated twice at each site on each limb.

Vibration perception was also tested using a tuning fork (128 Hz) on the great toes.[19] With the subject's eyes closed, the tuning fork was placed distal to the hallucis interphalangeal joint (dorsal surface) and the subject indicated when vibration sensation ceased. The subject's vibration perception was scored as present (<10-second discrepancy between subject and tester sensation), diminished (≥10-seconds discrepancy) or absent (unable to feel vibration).[20]

Sensation was evaluated bilaterally with a 10-gram monofilament on the dorsum of the great toe distal to the interphalangeal joint. Ten repetitions were performed and were scored as normal (≥8 correct responses), decreased (<8 correct responses), or absent (0 correct responses).[20]

Sharp and dull sensory testing was evaluated bilaterally distal to the hallucis

interphalangeal joint (dorsal surface) using a Neuro-Tip (Owen Mumford Ltd., Brook Hill, England). Five repetitions were performed and were scored as present (≥3 correct responses) or absent (<3 correct responses).[20]

Deep Tendon Reflexes

Deep tendon reflexes were assessed in sitting. A standard reflex hammer was used for patellar and calcaneal reflexes in the lower extremities and biceps and triceps reflexes in the upper extremities.[20] Reflexes were scored as present, present with reinforcement and absent. Reinforcement for the lower extremity reflexes consisted of looking away from the testing side and gripping hands and pulling apart, and for the upper extremity reflexes pressing the feet together and lightly clenching the jaw.

Muscle Strength Testing

Muscle strength was assessed with manual resistance for finger abduction, great toe extension and ankle dorsiflexion. Muscle strength was scored according to the method of Feldman et al. as normal strength, mild to moderate weakness, severe weakness or inability to perform the test (complete loss).[19]

Straight Leg Raise (SLR) Testing

The subject was positioned in supine with a 1-inch foam head support. Additional pillows were provided if requested. A blood pressure cuff bladder was centered under the subject's low back and during the test was pumped up to 40 mm Hg. Changes in cuff pressure were documented at end of movement during the SLR test. The subject's right ankle was placed in a customized ankle brace to maintain a fixed ankle position in either plantar flexion (30º) for the base SLR test (PF/SLR) or in neutral (0º) dorsiflexion for the sensitized SLR test (DF/SLR) (Figure 2A).

EMG Setup

Standard 1 cm circular bipolar Ag/AgCl surface electromyography (EMG) electrodes with an interelectrode distance of 2 cm (Noraxon USA Inc, Scottsdale, AZ) were placed over the gluteus maximus (GluM), semitendinosus (SemT), biceps femoris (BicF), medial gastrocnemius (MedG), soleus (Sol), rectus femoris (RecF), vastus medialis (VasM), and tibialis anterior (TibA) muscles of the right lower extremity (Figure 2B). Skin preparation and location of electrode placement was in accordance with the surface electromyography for non-invasive assessment of muscles (SENIAM) guidelines.[21] A single reference electrode was placed over the patella. Skin preparation included cleaning the skin and vigorous rubbing with an alcohol soaked gauze pad. Three repetitions of five-second maximal voluntary isometric muscle contractions (MVC) were performed against manually provided resistance with the subject in supine with their limb near neutral for comparisons to muscle activity during the SLR test. EMG signals were amplified (2000x) and acquired with a bandwidth frequency of 50-500Hz and a sampling rate of 2000 Hz using a TeleMyo 900 System, NorBNC and an A/D USB converter (Noraxon USA Inc., Scottsdale, AZ) connected to a personal computer using MRXP Master Package software, Version 1.06.21 (Noraxon USA Inc., Scottsdale, AZ).

Goniometer Setup

Twin-axis electrogoniometers (Noraxon USA Inc, Scottsdale, AZ) were placed laterally across the hip and knee joints (Figure 2B).[1, 11, 22, 23] The hip goniometer was placed with the proximal end parallel to the subject's torso adjacent to the iliac crest and with the distal end on the lateral thigh in line with the lateral femoral condyle. The knee goniometer was placed with the proximal end aligned with the greater trochanter of the

femur and the distal end aligned with the lateral malleolus. Care was taken to ensure the middle of the goniometer coil was centered over the axis of rotation for each joint. The subjects were given a custom-built hand held electronic button (trigger), which was held in the dominant hand with both hands resting on the abdomen (Figure 2B). Goniometer and trigger data were acquired at 2000 Hz in synch with the EMG data using a 16-channel NorBNC panel and an A/D USB converter (Noraxon USA Inc., Scottsdale, AZ).

Testing Procedure

One instructional trial was performed on the left lower extremity prior to formal testing on the right lower extremity. In the formal test, each ankle position was tested twice in a randomly assigned order for a total of four SLR tests. A metronome and wall placard marked with 10º degree increments was centered about the subject's hip axis of rotation and used to facilitate SLR testing rate of approximately 5º of hip flexion per second (Figure 2B).[24] The tester placed the subject's knee in full extension without lifting the thigh off of the mat and the subject was instructed to indicate this start position (START) by pressing the trigger three times. While holding the knee in full extension, the subject's hip was moved passively into hip flexion while avoiding rotation, abduction or adduction of the femur. The subject indicated the onset of symptoms (P1) and the symptom limit (P2) during the SLR by pressing the hand held trigger once at each time point. The subject was also instructed to say, "stop" the moment P2 was reached. The P2 position was held for 5 seconds before the limb was returned to a resting position on the plinth. Two-minute rests were given between each SLR trial.

Data Processing

Surface EMG signals were converted using a root mean squared (RMS) formula with a 50 msec interval. Mean voltage for EMG and degrees of range of motion were obtained for a 100 msec window centered on each of the following three time points; START, P1 and P2. For each muscle, MVC measurements were averaged from the center 3-second window of each of three repeated 5-second maximal isometric muscle contractions. Surface EMG values obtained during the SLR test were converted into percent of MVC for each muscle at each of the three time points.

Goniometer Reliability Testing

The goniometers were tested using a rigid wood hinged model to test the reliability and validity of moving to 0°, 30°, 45°, 60° and 90° using standardized metal angles. Further reliability testing was performed on a subset of five subjects by performing ten repeated SLR tests to arbitrary but consistent predetermined hip flexion positions. Specifically, the beam from a laser level was aimed horizontally across the room at an angle perpendicular to the subject's limb at an arbitrary height within the subject's symptom free hip flexion range of motion. A second tester pressed the trigger when the subject's leg blocked the laser beam and the hip flexion angle was measured.

Ultrasound Imaging

Subjects were positioned in left sidelying with their right knee fully extended and their ankle in a relaxed position. Ultrasound images of the nerves in the popliteal fossa of the right leg were obtained at 7 frames/second with an 8-15 MHz linear probe and a Acuson Sequoia Ultrasound Machine (Siemens Medical Solutions USA, Inc., Malvern, PA). Imaging of the tibial and common fibular nerves in the popliteal fossa was recorded with active plantar flexion and then dorsiflexion, each to end of range. After a two-

minute rest period, the limb was moved passively into hip flexion to the onset of symptoms (P1) with full knee extension and ankle in a relaxed position (sidelying SLR). Ultrasound imaging and ankle movements were repeated in this position.

Ultrasound images were imported into Image J (National Institutes of Health, Bethesda, MD) and the tibial and common fibular nerves were traced in the following four positions; initial rest, end of range plantar flexion, end of range dorsiflexion, end rest for both the resting and P1 hip positions. Calculations were made for short-axis (transverse plane) images to identify the central pixel of the nerve image (centroid), which was then used to measure movement of the nerve in the X-axis (medial/lateral) and the Y-axis (superficial/deep), the distance between nerves and the angle of a line drawn through the center of the nerves (Figure 6). Additionally, we measured the angle of the best-fit ellipse, the circularity of the nerve, and the cross-sectional area for short axis (transverse plane) images. Long-axis (sagittal plane) images were examined for proximal and distal movement of the tibial nerve.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 14.0 (SPSS Inc, Chicago, IL). Repeated measures general linear models were used for within test differences between the START, P1 and P2 positions for EMG and ROM data. Symptom intensity was tested with non-parametric statistics, including Kruskal-Wallis tests for independent comparisons and Friedman's test for related comparisons due to non-normal distributions. Between test comparisons (DF/SLR to PF/SLR) were made using paired t-tests. Pearson correlation coefficients were calculated to assess relationships between demographic, clinical measures and SLR testing variables. Descriptive statistics were

used to describe symptom quality and location frequencies during the SLR and to report the vibration perception and extinction thresholds. Intraclass correlation coefficients (ICC) were used for repeated measures reliability analysis and are reported with 95% confidence intervals. All results are presented as means ± standard deviations except frequency descriptive statistics, which are reported as percentages. Significance was set at $p \leq 0.05$.

RESULTS

The average age of the 20 participants was 50.4 ± 12.0 years old (range 25-63) and included 14 women and 6 men (Table 1). Average height was 1.7 ± 0.1 meters (65.1 ± 3.6 inches), weight was 71.2 ± 24.8 kg (156.9 ± 54.7 pounds), and body mass index (BMI) was 25.9 ± 8.8.

Standard neurological testing

Reliability analysis (ICC) for repeated measures was 0.99 (0.98, 0.99) for vibration perception thresholds (VPT) and 0.98 (0.97, 0.99) for vibration extinction thresholds (VET) for all locations tested. Averaged VPT were 20.3 ± 12.4 volts for the right and 18.9 ± 10.5 volts for the left medial malleolus (Table 2). The halluces values were 18.1 ± 14.5 volts for the right and 17.6 ± 13.6 for the left. The averaged VET were 21.8 ± 10.7 volts for the right and 19.7 ± 10.2 volts for the left medial malleolus. The halluces values were 19.2 ± 13.6 volts for the right and 18.2 ± 12.0 for the left. Monofilament halluces sensory testing was rated as normal in 90% (right) and 95% (left) of subjects (Table 2). Sharp-dull halluces sensory testing was rated as normal in 90% (both sides) of subjects (Table 2). Tuning fork vibration halluces sensory testing was rated as normal or diminished in 75% (both sides) of subjects (Table 2). Deep tendon

reflexes were rated as present or present with reinforcement 85% of the time (both sides) at the quadriceps tendon, 85% (right) and 80% (left) at the achilles tendon, 95% (right) and 90% (left) at the biceps brachii, and 85% (right) and 80% (left) at the triceps brachii (Table 3). Muscle strength was rated as normal in 100% (both sides) of subjects for finger abduction, 85% (right) and 90% (left) for halluces extension, and 100% (both sides) for ankle dorsiflexion (Table 4).

Straight leg raise neurodynamic testing

The order of the four repeated SLR tests did not affect the hip range of motion for either DF/SLR or PF/SLR at either P1 or P2 ($p>0.05$). The average speed of the PF/SLR was 3.0±1.0°/second and the DF/SLR was 2.8±0.9°/second ($p=0.045$).

Goniometric Validity and Reliability Testing

Repeated gonimetric measures on the wooden hinged model were 0.3° ± 0.2° for the known 0° angle, 31.3° ± 0.5° for the known 30° angle, 47.8° ± 0.7° for the known 45° angle, 64.1° ± 0.8° for the known 60° angle, and 95.9° ± 1.3° for the known 90° angle. The range of variability with repeated goniometric testing on the wooden hinged model was from 0.0°±0.0° to 0.5°±0.2° for sagittal plane measures and 0.0°±0.0° to 0.7°±0.2° for coronal plane measures with an ICC of 1.00 (1.00, 1.00). Using a subset of 5 subjects, the range of variability with repeated goniometric testing of hip flexion to arbitrary but consistent positions in the symptom free range (up to a max of 40°) was from 1.0°±0.3° to 2.4°±0.7° with an ICC of 1.00 (0.99, 1.00).

Range of motion

Intraclass Coefficient Correlations for hip flexion ROM between trials were 0.87 (0.69, 0.95) for PF/SLR at P1, 0.96 (0.91, 0.99) for PF/SLR at P2, 0.78 (0.50, 0.91) for

DF/SLR at P1 and 0.88 (0.73, 0.95) for DF/SLR at P2. The hip range of motion to P1 and to P2 during the SLR test was greater than the START position for both DF/SLR and PF/SLR ($p<0.0005$) (Figure 3A). There was 13.9% less hip flexion ROM at P1 during DF/SLR compared to PF/SLR ($p=0.001$, Figure 3A). At P2 there was 14.9% less hip flexion ROM in DF/SLR compared to PF/SLR ($p<0.0005$). There were no significant differences in thigh abduction/adduction, knee flexion/extension and varus/valgus at P1 or P2 between PF/SLR and DF/SLR ($p>0.05$, data not shown). Repeated testing of hip flexion ROM was performed on a subset of 5 subjects 10.4 ± 4.3 days apart with an ICC of 0.87 (0.68, 0.95).

Muscle Activation

There was relative electromyographic silence of the muscles until muscle activation was triggered late in the hip range of motion (Figure 4). At P1 during PF/SLR semitendinosus and rectus femoris became activated (SemT, $p=0.031$; RecF, $p=0.044$) (Figure 3B). When the PF/SLR was taken to P2, a slightly different pattern of muscle activation was stimulated. The rectus femoris remained activated (RecF, $p=0.034$) while the semitendinosus was no longer active. In addition, the gluteus maximus, vastus medialis and medial gastrocnemius became activated (GluM, $p=0.045$; VasM, $p=0.014$; MedG, $p=0.047$).

At P1 during the DF/SLR, all but one of the muscles measured was activated (Figure 3B). These activated muscles included soleus, medial gastrocnemius, semitendinosis, biceps femoris, rectus femoris, vastus medialis and gluteus maximus (Sol, $p=0.031$; MedG, $p=0.004$; SemT, $p=0.023$; BicF, $p=0.47$; RecF, $p=0.033$; VasM, $p=0.017$; GluM, $p=0.037$). When the DF/SLR was taken to P2 fewer muscles were

significantly activated: soleus, medial gastrocnemius, semitendinosis, rectus femoris, and vastus medialis (Sol, p=0.037; MedG, p=0.004; SemT, p=0.040; RecF, p=0.027; VasM, p=0.002).

Symptom Intensity

As expected, the mean symptom intensity (VAS) at P1 and P2 was increased above resting levels for both versions of the SLR ($p<0.0005$) (Figure 3C). During PF/SLR the mean symptom intensity went from 0.1 ± 0.3 at the START position to 2.5 ± 1.6 at P1 and to 6.6 ± 2.1 at P2. In contrast, during DF/SLR the mean intensity went from 0.4 ± 0.9 at the start position to 3.2 ± 1.9 at P1 and to 7.0 ± 1.8 at P2. The mean intensity at P1 was significantly higher by 0.7 ± 0.9 points during the DF/SLR ($p=0.002$). There was no difference in mean intensity between PF/SLR and DF/SLR at the START position or at P2.

Symptom Location

The frequencies of symptom locations reported at P1 and P2 during SLR are presented in Figure 5. Symptoms reported in the START position included the right anterior leg (area D), posterior hip (area Q), posterior thigh (area R), or posterior leg (area S) (Figure 1). During PF/SLR, the most frequent symptom location for P1 was in the right posterior thigh followed by the right posterior leg. When this test was taken to P2, the right posterior thigh symptoms remained the most frequent symptom location, while the frequency of the right posterior leg symptoms increased. In contrast, during DF/SLR distal symptoms in the right posterior leg were more frequent at P1 and distal symptoms in the right posterior leg and plantar foot were more frequent at P2.

Symptom Quality

The frequencies of descriptors used by the subjects to report symptom quality during both versions of the SLR are presented in Table 5. Eighty-five percent of the subjects had no symptoms at the START position in both PF/SLR and DF/SLR. During PF/SLR, the most common descriptor used was stretch (75% at P1 and P2) and the next most frequent was tight/tension (25% at P1 and 35% at P2), followed by ache (15% at P1 and P2). During DF/SLR, the most frequent descriptor was also stretch (70% at P1 and 65% at P2), followed by tight/tension (50% at P1 and 40% at P2), and third most common was ache (10% at P1 and 15% at P2). Pain and numbness were reported infrequently during SLR and no subjects reported tingling or pins/needles. After two minutes of rest following the SLR test, 90% of the subjects reported no symptoms following PF/SLR and 70% reported no symptoms following DF/SLR. The symptom that remained after PF/SLR were most commonly ache (15%) and dull (10%) and after DF/SLR were most commonly ache (15%) and stretch (10%).

Lumbar spine and pelvic movement

Repeated measure reliability (ICC) of the lumbar pressure cuff measures taken at P2 was 0.87 (0.69, 0.95) for PF/SLR and 0.91 (0.78, 0.96) for DF/SLR. Lumbar pressure cuff measurements increased from 40 mmHg at START position to 67.6 ± 11.5 mmHg at P2 during PF/SLR and 66.5 ± 12.6 mmHg at P2 during DF/SLR. Pearson correlations between the lumbar pressure cuff measure and hip flexion ROM at P2 was 0.77 ($p<0.0005$) for the PF/SLR and 0.79 ($p<0.0005$) for the DF/SLR.

Ultrasound Analysis

Reliability analysis (ICC) for the tibial nerve was 0.48 (0.19, 0.69) for cross-sectional area, 0.44 (0.11, 0.68) for nerve circularity, 0.94 (0.88, 0.97) for X-axis

position, 0.97 (0.95, 0.99) for Y-axis position, 0.67 (0.45, 0.81) for angle of best-fit ellipse. For the common fibular nerve ICC values were 0.63 (0.32, 0.80) for cross sectional area, 0.51 (0.23, 0.71) for nerve circularity, 0.76 (0.51, 0.88) for X-axis position, 0.76 (0.53, 0.87) for Y-axis position, 0.39 (0.09, 0.62) for angle of best-fit ellipse.

The positions of the tibial and common fibular nerves were altered during the SLR (Figure 6B). At the resting position (18.9° ± 2.3° hip flexion), maximal dorsiflexion resulted in 3.8 ± 1.9 mm movement ($p=0.011$) of the tibial nerve and 3.0 ± 0.7 mm ($p=0.001$) of the common fibular nerve compared to their positions during maximal plantarflexion. When the moved into hip flexion to P1 (62.2° ± 16.6°), maximal dorsiflexion resulted in 3.9 ± 1.8 mm superficial ($p=0.008$) and 1.8 ± 0.3 mm medial ($p<0.0005$) tibial nerve movement and 1.6 ± 1.2 mm ($p=0.038$) total movement and 0.9 ± 0.7 mm ($p=0.050$) medial movement of the common fibular nerve compared to their positions during maximal plantarflexion.

The cross-sectional area of the common fibular nerve was 16.5% smaller ($p=0.025$) in plantar flexion in comparison to its size in dorsiflexion in the resting hip position and 12.8% smaller in plantar flexion ($p=0.019$) with the hip at P1.

No significant differences were found in the distance between the two nerves, the angle of best-fit ellipse, or the circularity of either nerve. The angle made by a line bisecting the center of the tibial and common fibular nerves did not change significantly when the ankle was moved in the neutral hip position ($p>0.05$). However, when the hip was placed in the P1 position, this angle changed from an angle of 25.9° ± 11.6° in plantar flexion to an angle of 13.6° ± 15.3° in dorsiflexion ($p=0.016$) (Figure 6B). Visual

inspection of long-axis views showed proximal movement of the tibial nerve during plantar flexion and distal movement during dorsiflexion.

DISCUSSSION

This study supports the use of ankle positions as sensitizing maneuvers to the base SLR test. Hip flexion range of motion was reduced during the dorsiflexion version of the SLR test at both the onset of symptoms and the maximally tolerated symptoms. In addition, dorsiflexion altered the intensity, quality and location of symptoms and triggered a broader muscular response than did the plantar flexion version. A previous study also identified significant reduction in hip range of motion by 9° by the addition of ankle dorsiflexion.[5] Our findings of 5.5° less hip flexion range of motion when in ankle dorsiflexion when SLR is taken to the onset of symptoms and 10.1° less hip flexion range of motion when the test is taken to the maximally tolerated symptoms help to further validate the use of ankle positions as sensitizing maneuvers. The SLR with ankle plantar flexion has not pre-loaded the sciatic, tibial and plantar nerves and the hip can move to a greater range of flexion before the nerve undergoes sufficient stress and strain to trigger a stop to the movement. The addition of dorsiflexion, increases stress and strain on the sciatic, tibial and plantar nerves that occurs during dorsiflexion,[6] which is then exposed to additional stress and strain when the hip is flexed during the SLR.

Some researchers have discussed the first movement of the pelvis as the end point for the SLR test.[25-28] However, our study suggests that pelvis and lumbar spine movement are unavoidable during the SLR test. The strong relationship found in our study between hip range of motion and the amount of pressure measured under the low back at P2 is represented by the high correlation coefficients of 0.77-0.79. One research study found

pelvic movement occurred simultaneously during the SLR test even when the pelvis was strapped to the table.[29] Another study found that pelvic motion began after the first 10° and that the lumbar lordosis began to decrease after 30° of hip flexion motion during the SLR.[10]

Our study investigated two end points of SLR that were reliant upon reported symptoms (P1 and P2). Both of these end points are driven by multi-factorial influences. All outcomes of the SLR test will be influenced by the subjects understanding of the testing procedure, their personal history with pain, the instructions given to them on test day, and recent activities that could influence their physiological, emotional and cognitive responses. The symptoms reported are an interpretation and value judgments of the subject of the sensory information received from their limbs. Previous research has identified the importance of cognitive understanding of nerve health on the physical outcome measures such as the SLR.[30] In Moseley and associates study, subjects with chronic low back pain that underwent a neurophysiology education class had immediate improvements in their hip range of motion during the SLR compared to a control group.

A recent study has identified the frequent report of deep symptoms during a SLR and ankle dorsiflexion sensitizing maneuvers in people with lower limb radicular pain that may follow a myotomal or scleratomal pattern.[31] Our study has demonstrated that ankle dorsiflexion induced increased intensity and more frequent reported distal symptoms during SLR and these effects were specific to the test end point (P1 or P2).

We found a number of muscles activated during the DF/SLR test compared to the PF/SLR. At P1, DF/SLR induced more proximal muscle contractions of the hip extensors (gluteus maximus and biceps femoris), additional knee extensor activity (vastus medialis)

and triggered distal ankle plantar flexors (medial gastrocnemius and soleus) that were not active in PF/SLR. At P2, DF/SLR created the additional distal ankle plantar flexor activity (soleus) that was not present in PF/SLR and conversely, the proximal hip extensor (gluteus maximus) was only active in PF/SLR. This muscle response is not likely due to volitional changes in muscle activation as the subjects were instructed to remain relaxed throughout the SLR testing and were unaware of the muscle activation. This response is thought to be a protective reflexive mechanism of the local muscle tissue to stop further stress and strain of the nerves by limiting further motion. This protective response has been demonstrated in the upper limb, where surface EMG measurement showed increased activity of the upper trapezius muscle during motions of the upper limb neurodynamic test that are known to elongate the brachial plexus and median nerve.[12, 13] Increased contractile force in the muscles that elevate the shoulder was measured during a similar neurodynamic testing procedure, supporting the concept of increased upper trapezius activity with brachial plexus stretch.[14, 15] Furthermore, people with lower extremity radiculopathy have been shown to have significantly higher magnitude of medial hamstring muscle activity during the SLR test, which supports a greater mechanosensitivity in the injured state of a radiculopathy.[7]

What end point should be used for stopping neurodynamic tests that allow for sufficient information gathering and protection of the person being tested? Our study has shown excellent reliability of hip flexion measurements at the onset of symptoms (P1) on the same day (ICC = 0.78-0.96) and repeated testing in subsequent weeks in subjects with healthy nervous systems (ICC = 0.87). We found that the altered ankle position of only 30° between the PF/SLR and DF/SLR created differences in hip ROM, symptom

intensity and muscle activation that were measurable at P1. Taking the test to the maximally tolerated position (P2) did not provide additional clinically relevant information. While testing to P2 also had excellent repeatability it caries with it bigger risks, particularly when extrapolated to people in pain with suspected nerve injuries.

One limitation to extrapolation of our findings to the clinical setting is the precise measurement tools and standardized protocols required to determine small range of motion differences between PF/SLR and DF/SLR. The equipment used in this study is rarely available to the clinician and too time consuming to be feasible in patient care. However, precise standardized procedures can be used clinically to minimize the risks of confounding variables. Clinically, full ankle dorsiflexion range of motion can be used during SLR to increase the impact of sensitizing maneuvers on outcome measures. Care should be taken in extrapolating our findings to that of a clinical SLR test. For instance, it is not expected that clinicians can perceive the 5° difference in hip motion found in our study as this tends to exceed the within tester error of standard goniometry. However, a conceptual understanding of the impacts of sensitizing maneuvers on symptoms, mobility and muscle activity will assist with interpretation of SLR outcome measures. Another limitation is making definitive conclusions based on highly variable EMG data in a small sample. Further exploration is warranted of muscle responses in the lower extremity in various populations of people with pain during neurodynamic testing.

Performing the SLR to the first onset of symptoms is an assessment tool that allows for structural differentiation through altered ankle positions and may be warranted for patients with irritable conditions. Normal protective muscle guarding induced by the nervous system to avoid over stretch in healthy individuals should be considered when

assessing resistance felt during SLR testing and considered when prescribing muscle stretches. Physical therapists should design lower extremity muscle stretches that do not overload the nervous system to avoid reflexive increases in muscle tone.

SECTION B

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders that are characterized by hyperglycemia.[32] The Center for Disease Control (CDC) estimated the mean prevalence of DM in the United States (US) in 2005 was 7.0%, including 0.2% in those age <20, 9.6% in people age ≥20 and 20.9% in people age ≥60.[33] Distribution in adults was slightly higher in males compared to females.[33] Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is estimated to represent 90-95% of the US population with diabetes.[33] In 2002, the total estimated direct and indirect costs of DM medical care in the US was $132 billion.[34] The World Health Organization (WHO) estimated that 30 million people in the world had DM in 1985.[35] This estimate increased to 150 million people having DM in 2000 and 336 million are predicted to have DM in 2030.[36]

T2DM is characterized by insulin resistance at target tissues such as skeletal muscle. This insulin resistance reduces glucose uptake into cells and leads to hyperglycemia.[37, 38] Chronic hyperglycemia has adverse metabolic and vascular consequences for the peripheral nervous system.[32, 37] Distal symmetrical polyneuropathy (DSP) is the most common neural consequence of hyperglycemia and is present in 30%-60% of people with T2DM depending on the methodology for assessment.[32, 36, 39] The severity of DSP is related to the duration and severity of hyperglycemia.[36, 40]

DSP presents as distal, symmetrical sensory alterations that begin in the feet and progress into the legs and hands.[32, 36, 39-41] Multiple types of sensation are affected in DSP

including vibration sense,[42, 43] light touch sensation,[36, 41] position sense,[39, 41] temperature discrimination,[39-41] as well as diminished ankle reflexes.[36, 39-41] Pain can also be present.[32, 36, 39-41] Motor loss is usually minor or sub-clinical until advanced stages of the disease.[32, 36, 39, 40]

No study to date has examined the sensitivity of peripheral nerves in people with T2DM to the elongation and compression associated with limb movement, termed nerve mechanosensitivity. In fact, most studies examining nerve mechanosensitivity through neurodynamic testing specifically exclude people with T2DM. The presence and severity of DSP has been shown to affect multi-modal sensory, reflex and motor systems in the distal lower extremities[32, 36, 39-41] and we expect DSP to have an equivalent deleterious effect on nerve mechanosensitivity.

The objective of this study was to determine the unique effects of DSP on peripheral nerve mechanosensitivity in the lower extremity to enhance our understanding of appropriate activity guidelines and physical assessment considerations for people with T2DM and compare to age matched controls. We aimed to correlate muscle activity, flexibility and symptom presentation during a passive lower limb movement test with DSP severity. An additional aim was to compare biomechanical properties of peripheral nerves in the lower extremity during positioning and movement through in vivo ultrasound imaging.

METHODS

This cross sectional study included people with T2DM recruited from local medical and academic facilities (T2DM group). An aged matched group of people without diabetes (Control group) has been previously described and was used as a

comparison group (Section A). Exclusion criteria for the T2DM group included low back or leg pain lasting > 3 consecutive days in the past 6 months, complex regional pain syndrome, lumbar spine surgeries, chemical dependence or alcohol abuse, a history of trauma to the nerves of the lower extremity, or chemotherapy in the past year. Participants had to meet flexibility requirements of hip flexion ≥ 90°, full knee extension, ankle dorsiflexion ≥ 0° and plantar flexion ≥ 30°. Institutional review boards at UCSF, SFSU and the General Clinical Research Center's Advisory Committee at UCSF approved the study. Written informed consent was obtained from subjects prior to testing. All subjects attended a single clinical assessment session. A subset of five T2DM group participants attended an ultrasound imaging session. One examiner (BB) performed all physical examinations.

Clinical assessments

Questionnaires

Both groups completed 1) medical history questionnaire, 2) Brief Pain Inventory – Short Form (BPI-SF),[44] 3) Michigan Neuropathy Screening Instrument questionnaire (MNSIq), which has 15 questions addressing symptoms associated with neuropathy[19] and 4) Modified Baecke Questionnaire (MBQ), which is a self-report questionnaire on physical activity during work, recreation/sport, and leisure time.[16] In addition, all subjects were instructed in the use of a previously described visual symptom-reporting card, including symptom location, intensity and quality (Figure 1).

Vibration Sensory Testing

Vibration perception was measured bilaterally at medial malleoli and the distal plantar halluces using a 60-Hz biothesiometer (Bio-Medical Instrument Company,

Newbury, OH) as previously described (Section A). In brief, the first feeling of vibration (VPT) and when the vibration sensation disappeared (VET) were measured twice at each site on each limb. Hallux VPT has been previously used to estimate DSP severity.[43]

Clinical neuropathy examinations

Two scoring instruments of composite physical examinations were used as additional means of quantifying severity of DSP.[19] First, the Michigan Neuropathy Screening Instrument clinical examination (MNSIc) was performed, which included visual inspection for foot deformities or ulcerations, ankle deep tendon reflexes, tuning fork vibration perception (128-Hz) and monofilament sensory testing (10-gram) of the dorsal halluces.[19] Scoring for each examination has been described extensively elsewhere.[19, 20, 45] Briefly, ankle reflexes were scored as present, present with reinforcement or absent. Reinforcement consisted of looking away from the testing side and gripping hands and pulling apart. The subject's perception of vibration cessation was scored as present (<10-second discrepancy between subject and tester), diminished (≥10-seconds discrepancy) or absent (unable to feel). Monofilament testing was scored as normal (≥8 of 10 correct responses), decreased (<8 of 10 correct responses), or absent (unable to feel).

Second, the Michigan Diabetic Neuropathy Score (MDNS) clinical examination was performed, which included Achilles, patellar, biceps brachii and triceps brachii deep tendon reflexes, monofilament, vibration and sharp/dull sensation of the dorsal hallux and muscle strength of finger abduction, ankle dorsiflexion and hallux extension. Scoring for each examination has been described extensively elsewhere.[19, 20, 45] Reflexes, vibration and monofilament sensation were scored identically to the MNSIc. Reinforcement for the

upper extremity reflexes consisted of looking away while pressing the feet together and lightly clenching the jaw. Sharp/dull sensation was scored as present (≥3 of 5 correct responses) or absent (<3 of 5 correct responses). Muscle strength was assessed with manual resistance and scored according to the method of Feldman et al. as normal strength, mild to moderate weakness, severe weakness or inability to perform the test (complete loss).[19]

Straight Leg Raise (SLR) Testing

Straight leg raise (SLR) neurodynamic testing methodology has been described comprehensively for the control group (Section A). In brief, the subject was positioned in supine with standardized head support. Additional pillows were provided and documented if requested. A blood pressure cuff bladder centered under the subject's low back was used to documented changes in pressure during the SLR test.

Electromyography Setup

Standard surface electromyography (EMG) electrodes were placed over the biceps femoris (BicF), gluteus maximus (GluM), medial gastrocnemius (MedG), rectus femoris (RecF), semitendinosus (SemT), soleus (Sol), tibialis anterior (TibA) and vastus medialis (VasM) muscles of the right lower extremity (Figure 2B). Skin preparation and location of electrode placement was in accordance with the surface electromyography for non-invasive assessment of muscles (SENIAM) guidelines.[21] A single reference electrode was placed over the patella. To obtain comparisons to muscle activity during the SLR test, three repetitions of five-second maximal voluntary isometric muscle contractions (MVC) were performed against manual resistance with the subject in supine and the lower limb near neutral. EMG signals were amplified (2000x) and acquired with a

bandwidth frequency of 50-500Hz and a sampling rate of 2000 Hz using a TeleMyo 900 System, NorBNC and an A/D USB converter (Noraxon USA Inc., Scottsdale, AZ) connected to a personal computer using MRXP Master Package software, Version 1.06.21 (Noraxon USA Inc., Scottsdale, AZ).

Goniometer Setup

Twin-axis electrogoniometers (Noraxon USA Inc, Scottsdale, AZ) were placed laterally across the hip and knee joints in the same manner as described previously for the control group (Figure 2B). The subjects were given a custom-built hand held electronic button (trigger), which was held in the dominant hand, and both hands rested on the abdomen (Figure 2B). Goniometer and trigger data were acquired at 2000 Hz in synch with the EMG data using a 16-channel NorBNC panel and an A/D USB converter (Noraxon USA Inc., Scottsdale, AZ).

Testing Procedure

The subject's right ankle was placed in a customized ankle brace to maintain a fixed ankle position in either plantar flexion (30º) for the base SLR test (PF/SLR) or in neutral (0º) dorsiflexion for the sensitized SLR test (DF/SLR) (Figure 2A). One instructional trial was performed on the left lower extremity prior to formal testing on the right lower extremity. In the formal test, PF/SLR and DF/SLR were tested twice in a randomly assigned order to help control for order effects. The start position (START) included placing the subject's knee in full extension without lifting the thigh. While holding the knee in full extension, the subject's hip was moved passively into hip flexion while avoiding hip rotation, abduction or adduction. The subject indicated the onset of symptoms (P1) and the symptom limit (P2) during the SLR by using the hand held

trigger. The P2 position was held for 5 seconds before the limb was returned to the resting position on the plinth. Two-minute rests were given between each SLR trial.

Data Processing

Surface EMG signals were converted using a root mean squared (RMS) formula with a 50 msec interval. Mean voltage for EMG and degrees of range of motion were obtained for a 100 msec window centered on each of the following three time points; START, P1 and P2. For each muscle, MVC measurements were averaged from the center 3-second window of the maximal isometric muscle contractions. EMG data from the SLR was converted into percent of MVC.

Lab Testing

Subjects underwent a blood draw at UCSF. Blood samples were sent to Quest Diagnostics, Inc (San Jose, CA) for hemoglobin A1c (HbA1c) and mean plasma glucose (MPG) analysis, which estimate average blood glucose levels over the preceding 2-3 months.

Ultrasound Imaging

Subjects were positioned in left sidelying with the right knee fully extended and the ankle in a relaxed position. Ultrasound images of the nerves in the popliteal fossa of the right leg were obtained at 7 frames/second with an 8-15 MHz linear probe and an Acuson Sequoia Ultrasound Machine (Siemens Medical Solutions USA, Inc., Malvern, PA). Images of the tibial and common fibular nerves in the popliteal fossa were recorded with active plantar flexion and then dorsiflexion, each to end of range. After a two-minute rest period, the limb was moved passively into hip flexion with full knee extension and ankle in a relaxed position (sidelying SLR) up to the onset of symptoms

(P1). Ankle movements and ultrasound images were repeated in this position.

Ultrasound images were imported into Image J (National Institutes of Health, Bethesda, MD) software and the central pixel of the nerve image (centroid) was defined. The angle of the best-fit ellipse, the circularity of the nerve, and the cross-sectional area were calculated using the same procedures described previously for the control group (Section A), Comparisons of nerve locations between limb positions were made in the X-axis (medial/lateral) and the Y-axis (superficial/deep).

Statistical Analysis

All statistical analyses were performed using SPSS software, version 14.0 (SPSS Inc, Chicago, IL). Repeated measures general linear models were used for within test differences between the START, P1 and P2 positions for EMG and ROM data. Symptom intensity was tested with non-parametric statistics, including Kruskal-Wallis tests for independent comparisons and Friedman's test for related comparisons due to non-normal distributions. Between test comparisons (DF/SLR to PF/SLR) were made using paired t-tests. Pearson correlation coefficients were calculated to assess relationships between demographic, clinical measures and SLR testing variables. One-way ANOVA was used to examine the impacts of DSP measures on EMG, ROM, and symptom intensity data. Descriptive statistics were used to describe symptom quality and location frequencies during the SLR and to report the vibration perception and extinction thresholds. Intraclass correlation coefficients (ICC) were used for repeated measures reliability analysis and are reported with 95% confidence intervals. All results are presented as means ± standard deviations except frequency descriptive statistics, which are reported as percentages. Significance was set at $p \leq 0.05$.

RESULTS

The mean age of the 43 participants (21 females and 22 males) in the T2DM group was 56.3 ± 11.1 (range 21-75) years (Table 6). The average duration of T2DM was 7.0 ± 7.7 years. Average height was 1.7 ± 0.1 meters, weight was 94.0 ± 18.3 kg, and body mass index (BMI) was 32.8 ± 6.6 (Table 6). There was no difference in age or height between the T2DM and control groups. The weight was significantly greater in the T2DM group ($p<0.0005$) as was the BMI ($p=0.001$) compared to the control group. The HbA1c (MPG) results for the T2DM group were 7.4 ± 1.8% (183.7 ± 60.0 mg/dL) compared to 5.5 ± 0.3% (116.9 ± 12.2 mg/dL) in the control group ($p<0.0005$).

Clinical assessments and questionnaires

Repeated measures reliability (ICC) was 0.97 (0.96, 0.98) for vibration perception thresholds (VPT) and 0.98 (0.97, 0.98) for vibration extinction thresholds (VET) in the T2DM group. Averaged VPT for the medial malleoli in the T2DM group were 30.1 ± 12.6 volts for right and 32.7 ± 13.6 volts for left (Table 6). The halluces values were 30.1 ± 14.8 volts for right and 29.9 ± 15.6 for left. The averaged VET for the medial malleoli were 28.6 ± 11.4 volts for the right and 30.8 ± 12.6 volts for the left. The halluces values were 29.2 ± 13.9 volts for the right and 28.9 ± 15.0 for the left. All measures of VPT and VET were significantly higher in the T2DM group compared to the control group (Table 6).

Scores for the MNSIc were 3.9 ± 2.4 out of 10 for the T2DM group and 1.6 ± 1.4 for the control group ($p<0.0005$) (Table 6). MNSIq scores were 3.8 ± 2.4 out of 13 for the T2DM group and 0.7 ± 0.8 for the control group ($p<0.0005$). Scores for the MDNS were

13.8 ± 8.7 out of 46 for the T2DM group and 5.1 ± 6.0 for the control group ($p<0.0005$) (Table 6).

The Modified Baecke questionnaire total score was 7.9 ± 1.7 for the T2DM group compared to 9.1 ± 1.0 in the control group ($p=0.004$) (Table 6). Of the three subscales, the "sports" and "leisure" subscales score were significantly lower in the T2DM group ($p=0.007$ and $p=0.004$) compared to the control group but there was no difference in the "work" subscale ($p=1.00$).

From the BPI-SF, the reported average pain rating (Q5) on a 0-10 point scale was 3.0 ± 2.6 in the T2DM group compared to 0.5 ± 1.0 in the control group ($p<0.0005$). The reported pain "right now" (Q6) was 1.9 ± 2.2 in the T2DM group compared to 0.4 ± 1.9 in the control group ($p=0.007$).

Pearson correlations between clinical measures of signs of neuropathy and group membership (T2DM or control group) are presented in Table 7. Measures of signs of DSP had highly significant correlations with each other when considering both T2DM and control groups. The strongest such correlations were between MDNS and MNSIc (0.82, $p<0.0005$) and between MDNS and hallux VPT when averaged right and left (VPT-AVG) (0.76, $p<0.05$). Age also had high correlations with hallux VPT-AVG (0.57, $p<0.0005$) but did not correlate with maximal hip flexion ROM at P2 for PF/SLR (-0.23, $p=0.061$).

Straight leg raise neurodynamic testing

The order of the four repeated SLR tests did not affect the hip range of motion for either DF/SLR or PF/SLR at either P1 or P2 in the T2DM group ($p>0.05$). The average speed of hip flexion during PF/SLR was 2.3 ± 1.2°/second and DF/SLR was 2.1 ±

1.2°/second (p=0.002) in the T2DM group. The DM group had 0.7°/second slower PF/SLR (p=0.047) and DF/SLR (p=0.025) compared to the control group. In the T2DM group, 23.3% did not request any extra head support, 65.1% requested 1 pillow, 9.3% requested 2 pillows and 2.3% requested 3 pillows during the SLR testing. The number of pillows did not affect the hip range of motion for either DF/SLR or PF/SLR at either P1 or P2 in the T2DM group (p>0.05).

Range of motion

In the T2DM group, ICCs for hip flexion ROM between trials were 0.90 (0.82, 0.94) for PF/SLR at P1, 0.94 (0.90, 0.97) for PF/SLR at P2, 0.89 (0.80, 0.94) for DF/SLR at P1 and 0.96 (0.92, 0.98) for DF/SLR at P2. The hip range of motion to P1 and to P2 during SLR was greater than the START position for both DF/SLR and PF/SLR in the T2DM group (p<0.0005) (Figure 7A). Average hip flexion at P2 during PF/SLR was 13.3° less in the T2DM compared to the control group (p=0.027). There was 4.3 ± 6.5° less hip flexion ROM at P1 during DF/SLR compared to PF/SLR (P1 diff) (p<0.0005) (Figure 7A). At P2 there was 5.4 ± 4.9° less during DF/SLR compared to PF/SLR (P2diff) (p<0.0005) (Figure 7A). The P2diff was ~50% lower in the T2DM group compared to the control group (p=0.039).

ANOVA was used to investigate the effects of hallucis VPT-AVG score subgroups and group membership on hip flexion ROM during both SLR tests. Subgroup analyses included A) CON group compared to T2DM groups with B) 0-15V, C) >15-25V, D) >25-50V, and E) unable to perceive vibration (>50V) (Figure 8). There was no sub-group effect on hip flexion range of motion during PF/SLR, DF/SLR at P1, P2 or for P1diff. There was a significant effect of sub-groups on the difference in hip flexion ROM

between PF/SLR and DF/SLR at P2 (P2 diff). There was a significant reduction in P2diff in the people with T2DM who were unable to perceive the vibration up to 50V (0.9 ± 2.5°) compared to CON group (10.1 ± 9.7°) (p=0.001) and compared to people with T2DM who had VPT-AVG scores of >15-25V and >25-50V (p=0.021 and p=0.035). Within the T2DM group, the eta value for VPT-AVG subgroups was 0.54 with an eta^2 of 0.29, which indicates that VPT-AVG sub-groups explain 29% of the variability in the P2diff outcome measure.

There was 1.9 ± 4.5° more hip abduction at P2 during PF/SLR compared to DF/SLR in the T2DM group (p=0.008). There were no differences in hip abduction at P1, nor in knee extension or valgus at either P1 or P2 between PF/SLR and DF/SLR in the T2DM group (p>0.05, data not shown).

Muscle Activation

The T2DM group had soleus (p=0.011), gastrocnemius (p=0.011), semitendinosus (p=0.049), vastus medialis (p=0.002), and gluteus maximus (p=0.007) activation at P1 during PF/SLR (Figure 7B). When the PF/SLR was taken to P2, the biceps femoris (p=0.018), tibialis anterior (p=0.033) and rectus femoris (p=0.005) additionally became activated in the T2DM group.

Contrary to our expectations, fewer muscles were activated when the limb was taken to P1 during DF/SLR. These included the soleus (p=0.023), semitendinosus (p=0.034), and vastus medialis (p<0.0005) (Figure 7B). When the DF/SLR was taken to P2, the gastrocnemius (p=0.009), semitendinosis (p=0.002), biceps femoris (p=0.002), vastus medialis (p<0.0005), and gluteus maximus (p=0.008) were activated.

Sub-group ANOVA analyses revealed no sub-group effects on muscle activity (%MVC) during PF/SLR or DF/SLR at either P1 or P2 with the following exception. The gluteus maximus was significantly more active during PF/SLR at P1 in people with T2DM that had VPT-AVG scores of >25-50V compared to CON group ($p=0.003$).

Symptom Intensity

The mean symptom intensity at the START position was 0.7 ± 1.4 during PF/SLR in the T2DM group (Figure 7C). The T2DM group had symptom intensity increase to 2.8 ± 1.7 at P1 to 6.8 ± 2.0 at P2 during the PF/SLR ($p<0.0005$). During DF/SLR the mean intensity went from 0.8 ± 1.5 at the START position to 3.0 ± 1.8 at P1 and to 6.8 ± 2.0 at P2 ($p<0.0005$). The mean intensity at P1 was significantly higher by 0.3 ± 0.8 points during the DF/SLR ($p=0.043$). There was no difference in mean intensity at the START position, P2 or rest after SLR between PF/SLR and DF/SLR. Sub-group ANOVA analyses revealed no sub-group effects on symptom intensity during PF/SLR or DF/SLR at either P1 or P2.

Symptom Location

The frequencies of symptom locations reported at the START, P1 and P2 during SLR in the T2DM group are presented in Figure 9. More than 15% of the T2DM subjects had symptoms in both the dorsal and plantar surfaces of both feet at the START position for both PF/SLR and DF/SLR (Figure 9A & 9D). During PF/SLR at P1 and P2, the most frequent symptom location was reported in the right posterior thigh followed by the right posterior leg and then right posterior hip (Figure 9B & 9C). During PF/SLR, there was only a 7% increase in the frequency of reported symptoms in the right plantar foot at P2 compared to the START position. A similar pattern was seen during DF/SLR in the

T2DM group, including the right posterior thigh being the most frequent symptom location at P1 and P2, followed by the right posterior leg and then right posterior hip (Figure 9E & 9F). During DF/SLR, there was no change in the frequency of right plantar foot symptoms at P2 compared to the START position. Right posterior leg symptoms were 16.3% more frequent at P2 during DF/SLR compared to PF/SLR.

Symptom Quality

Frequencies of symptom descriptions are presented in Figure 10 for the T2DM group. Symptoms reported in <10% of participants are not presented. At the START position 58.1% of the T2DM subjects reported no symptoms during PF/SLR (Figure 10A). The main symptom reported in the START position during PF/SLR was tingling (14.0%). During PF/SLR to P1, the additional symptom of stretch was most commonly reported, followed by tightness/tension, then pain, and finally numbness (Figure 10B). When taken to P2, pain frequency increased and burning was additionally reported in 14% of the subjects (Figure 10C). Two minutes after testing while in the REST position, 51.2% of subjects reported no symptoms after PF/SLR while both numbness and tingling were present in 18.6% of subjects (Figure 10D).

In contrast, 48.8% of T2DM subjects reported no symptoms at the START position during DF/SLR (Figure 10E). Numbness and tingling were present in 18.6% at the START position during DF/SLR with an additional 11.6% reporting tension/tightness (Figure 10E). When DF/SLR was taken to P1 there was a similar response to PF/SLR where stretch was the most common symptom reported, followed by tightness/tension, then pain, numbness and finally tingling (Figure 10F). When taken to P2 during DF/SLR, the frequency of pain and numbness increased by 7% and 4.6% (Figure 10G). Two

minutes after testing while in the REST position, 46.5% reported no symptoms after DF/SLR while both numbness and tingling were present in 18.6% of subjects (Figure 10H).

Lumbar spine and pelvic movement

Repeated measure reliability (ICC) of the lumbar pressure measures taken at P2 in the T2DM group was 0.86 (0.75, 0.92) for PF/SLR and 0.90 (0.82, 0.95) for DF/SLR. Lumbar pressure measurements increased from 40 mmHg at START position to 65.8 ± 14.9 mmHg at P2 during PF/SLR and to 63.6 ± 15.3 mmHg at P2 during DF/SLR. Pearson correlations between the lumbar pressure measure and hip flexion ROM at P2 was 0.78 ($p<0.0005$) for the PF/SLR and 0.84 ($p<0.0005$) for the DF/SLR.

Ultrasound Analysis

The positions of the tibial and common fibular nerves were altered during the SLR in the T2DM group. At the resting hip position (20.7° ± 1.0° hip flexion), maximal dorsiflexion resulted in 3.6 ± 2.1 mm movement ($p=0.018$) of the tibial nerve with 2.9 ± 1.7 mm ($p=0.019$) of that movement being medial compared to the position during maximal plantar flexion. When the limb was moved into hip flexion to P1 (60.9° ± 15.1°), maximal dorsiflexion resulted in 3.1 ± 1.4 mm tibial nerve movement ($p=0.008$) with 2.9 ± 1.3 mm ($p=0.008$) of that movement being medial compared to maximal plantar flexion. In addition, in P1 the tibial nerve became more circular in dorsiflexion (0.90 ± 0.04) compared to plantar flexion (0.85 ± 0.03) ($p=0.003$), where a true circle would be a 1.00. No significant differences were found in the distance between the two nerves, the angle of best-fit ellipse, or the cross-sectional areas of either nerve in the T2DM group.

The main differences between the T2DM and control groups were the nerve cross-sectional area. These differences were most evident when the limb was placed in the hip flexion position of P1. For instance, the tibial nerve was larger in the T2DM group in maximal ankle plantar flexion (62.7 ± 9.8 mm^2) compared to the control group (45.2 ± 5.9 mm^2) ($p=0.009$). This size difference was also evident in maximal ankle dorsiflexion (Control group: 44.5 ± 6.1 mm^2; T2DM: 61.8 ± 14.1 mm^2; $p=0.035$). Lastly, the T2DM group had significantly less superficial movement of the tibial nerve during maximal dorsiflexion in hip P1 (Control group: 3.9 ± 1.7 mm; T2DM: 0.9 ± 0.8 mm; $p=0.008$).

DISCUSSION

Our study found that hip flexion range of motion during SLR neurodynamic testing in the lower extremity is different in people with Type 2 diabetes mellitus compared to age-matched controls without diabetes. Specifically, we found the overall range of hip flexion when tested to P2 during PF/SLR was dramatically reduced in the T2DM group by more than 13°compared to the control group. In addition, there was approximately a 50% reduction in the hip flexion range of motion difference between the ankle dorsiflexion and plantar flexion tests when taken to maximally tolerated symptoms (P2diff) in the T2DM group compared to the control group. Individuals with severe DSP had diminished symptomatology, and thus diminished capacity to perceive a difference in the SLR based on different ankle positions. It is hypothesized that the global loss of sensory perception in the lower limbs in these individuals includes diminished perception of nerve stretch in the tibial and plantar nerves that occurs with limb movement. This

would explain the lack of differentiation seen between the plantar flexion and dorsiflexion SLR tests at both P1 and P2.

Both the control and T2DM groups had activation of the semitendinosis muscle at P1 during the PF/SLR, but the T2DM group had additional activation of both distal plantar flexors (medial gastrocnemius and soleus) and the proximal hip extensor (gluteus maximus). This additional muscle activity in the T2DM group did not correlate with symptom intensity at P1 and was not influenced by the presence of resting symptoms. DF/SLR at P1 induced activation of all muscles measured except the tibialis anterior in the control group, whereas it only induced the semitendinosis, vastus medialis and soleus in the T2DM group. Although the authors cannot explain the paradoxical effect seen in the T2DM group, the findings support the hypothesis that the addition of ankle dorsiflexion in the T2DM group does not trigger the same general increase in protective muscle guarding seen in control group. Further analysis of the T2DM group did not find any effect of severity of signs of DSP on muscle activation.

Symptom intensity was not different between groups at either P1 or P2. However, within group analysis did identify that the control group had 0.7-point higher symptom intensities at P1 during DF/SLR compared to PF/SLR while the T2DM group only had 0.3-point higher symptom intensity during DF/SLR. Within the T2DM group, DSP severity did not alter symptom intensity reported. These differences are minimal and alone represent questionable clinical relevance. However, the symptom intensity differences fit the overall trend that the T2DM group does not respond to the addition of ankle dorsiflexion during SLR testing with the same magnitude of muscle response and range of motion reductions as seen in the control group.

This is further strengthened by the dramatic difference in symptom quality between the groups. At the START position, the T2DM group frequently reported symptoms associated with neurogenic sources, such as numbness and tingling.[46] These symptoms were absent at rest in the control group and rarely reported at any time point during SLR testing (≤5%). During limb movement, a large percentage of T2DM group reported pain (>20% at P1 and >30% at P2) compared to ≤ 10% in the control group.

Symptom location at rest was markedly different between groups. The T2DM group frequently reported symptoms on the dorsal and plantar surfaces of bilateral feet at rest. Interestingly, the T2DM group did not have a dramatic increase in distal foot symptoms reported at either P1 or P2 during either SLR test. The T2DM group also had a large increase in proximal symptoms reported in the right posterior hip that was most dramatic in P2 compared to P1 and not significantly different between PF/SLR and DF/SLR. In contrast, the control group rarely reported symptoms in either foot at rest and had more frequent right plantar foot symptoms that were greatest at P2 during DF/SLR. The control group had a much lower frequency of right posterior hip symptoms compared to the T2DM group.

One major limitation of our study is the small sample size reducing the power to detect differences between variables with smaller effect sizes and diminishing the ability to extrapolate findings to larger populations. However, the average age of our study participants closely resembles larger studies including studies by Fedele et al. examining prevalence in 8757 people in Italy with T2DM in (age = 55.8 ± 10.4) and by Rahman et al. examining multiple clinical measures of neuropathy (age=63.0 ± 7.8).[20, 43]

It has previously been found that gender has a significant impact on hip flexion range of motion during SLR testing, although Youdas et. al. did not use ankle fixation or alternate ankle positions.[47] We expected that females would have significantly more hip flexion range of motion, but that sex would not influence the reduction in hip flexion range associated with ankle dorsiflexion. In our study sex was not statistically associated with any hip flexion range of motion outcome measure. We cannot confidently conclude that sex had no impact due to our small sample size.

A potential covariate in our study is the impact of age on peripheral nerve health. We attempted to control for this confounding variable by matching the control and T2DM groups for age. Youdas et al. did not find any reduction in hip flexion ROM associated with increasing age when performing SLR as a hamstring length test without consideration for ankle positions.[47] Future study is warranted to examine the questions of sex and age effects of neurodynamic based SLR assessments.

Flexibility in the joints and musculature of the ankles has been found to be diminished in people with T2DM with signs of DSP.[48] Our study found diminished hip flexibility during SLR testing to maximally tolerated symptoms in ankle plantar flexion compared to healthy age matched controls. However, the body mass index was larger in the T2DM group compared to the controls in our study. This was also evident by the significantly higher mean weight in the T2DM group compared to the controls, although height was not different between groups. Multiple regression modeling found that BMI had no influence on any hip flexion range of motion during SLR in our study for either group. Future studies should investigate neurodynamic testing in stratified BMI groups

and BMI matched groups to further explore the effects of body mass on mechanosensitivity.

Reliance on muscle activity measures for decisive conclusions for mechanosensitivity is not reasonable due to the high variability of this type of measurement. Some individuals in each group had no muscle activation during SLR testing at P1 and P2, which is consistent with previous study findings.[10, 11] In our study, 10.0% of controls and 12.2% T2DM group had no muscle activity at P2 during PF/SLR and 5.0% of controls and 14.6% T2DM group had no muscle activity at P2 during DF/SLR. It has been suggested previously that a lack of induced muscle activity during upper extremity neurodynamic testing might be associated with highly flexible individuals,[12] but this was not the case in our study. We found no statistical correlation between maximal range of hip flexion (P2) during PF/SLR and muscle activation. The presence of these muscle "non-responders" warrants caution for using this as a means of conclusive clinical assessment. Further research needs to be done to identify characteristics of those who do not respond with muscle activation during SLR testing.

The difference of hip abduction range of motion at P2 during PF/SLR compared to DF/SLR in the T2DM group could have influenced the SLR outcome measures. The mean difference was less than 2° between the PF/SLR and DF/SLR but still represents a potential confounding variable that should be acknowledged in the interpretation of our study findings. Additionally, the 0.7°/sec slower SLR speed in the T2DM group compared to the control group could have influenced the results of our study. Despite strict standardized protocols in this research study, there is inherent error in manually controlling hip abduction/adduction positioning based on visual inspection during the hip

flexion of the SLR. This underscores the difficulty of consistency of neurodynamic testing and warrants the use of precisely controlled standardized procedures for clinical neurodynamic testing to minimize tester induced variability. We chose not to mechanically control hip abduction/adduction to be more consistent with the clinical performance of the SLR. Future studies should include the comparison of our methodology with the clinical assessments using standard clinical measures to improve generalizability to clinical settings.

Ultrasound imaging of peripheral nerve movement in the lower extremity during neurodynamic testing can help to improve our understanding of the mechanical impacts of limb movement on the peripheral nervous system. Ellis et. al. recently demonstrated ultrasound imaging is a reliable tool for assessing sciatic and tibial nerve movement in the lower extremity during limb movements.[49] The results of our preliminary study indicate the possibility of altered movement of the nervous system during lower limb movements and positioning in people with T2DM and warrants further investigation. Future studies should investigate the impact of DSP and T2DM on nerve mobility and the correlation to symptoms and mechanosensitivity in a larger sample.

Conclusions

Clinical recommendations for interpretation of neurodynamic tests rely in part upon the ability to determine a difference in symptoms, range of motion and resistance to movement when adding sensitizing maneuvers such as ankle dorsiflexion.[3, 4] We have provided evidence that the normal protective responses to neural loading during neurodynamic testing may be diminished in people with T2DM and absent in those who have signs of severe DSP. Additionally, we found increased frequency of resting

symptoms in people with Type 2 diabetes mellitus and the increased frequency of reported neurogenic related symptom qualities even without the addition of ankle dorsiflexion as a sensitizing maneuver. We found a diminished effect on range of motion reduction and diminished muscle protective guarding when ankle dorsiflexion is added during SLR in the T2DM group.

The findings of our study call into question the clinical decision of performing neurodynamic testing on people with signs of severe DSP. Without the ability to respond to the increases in neural loading associated with neurodynamic testing and sensitizing maneuvers, this population is at potential risk for injury from testing and the information gathered will be of questionable use to the clinician. Therefore, the authors recommend use of extreme caution when performing neurodynamic testing in people with T2DM that have multi-modal loss of distal sensation. In addition, it is recommended that clinicians perform a simple screen of sensation such as vibration perception testing or the MDNS prior to considering the appropriateness of neurodynamic assessments.

When neurodynamic testing is deemed appropriate in this population, additional considerations are necessary for test interpretation. It is paramount to clearly establish the person's resting symptom intensity, quality and location prior to performing SLR testing. Interpretation of symptoms provoked during SLR testing is only relative to these resting symptoms. Symptoms that are normally associated with neurogenic sources may be present bilaterally and overall range of motion may be reduced compared to similar age people without T2DM. The findings of our study highlight the difficulty of interpretation of neurodynamic test findings in the diabetic population. It is of utmost importance to consider the influences of T2DM on the health and sensitivity of the nervous system

when performing and interpreting SLR neurodynamic testing. It is further recommended that SLR neurodynamic testing should only be taken to the first onset of symptoms or first increase above resting symptoms (P1) in people with diabetes to avoid potential harm, as has been previously recommended in people without diabetes (Section A).

Lastly, our study findings influence patient education and therapeutic exercise instructions. People with T2DM and signs of DSP should be instructed to avoid activities that involve cumulative loading of the nervous system via multiple joints. This could include avoiding slumped postures with the feet elevated, altering specific activities of daily living such as forward bending to tie one's shoes, or avoiding specific movements or postures assumed during recreational activities such as yoga or pilates. An understanding of the health of the nervous system including its ability to respond to and protect against over stretch should be incorporated into clinical decision making for physical examination, exercise prescription and patient education in people with Type 2 diabetes.

FIGURE 1

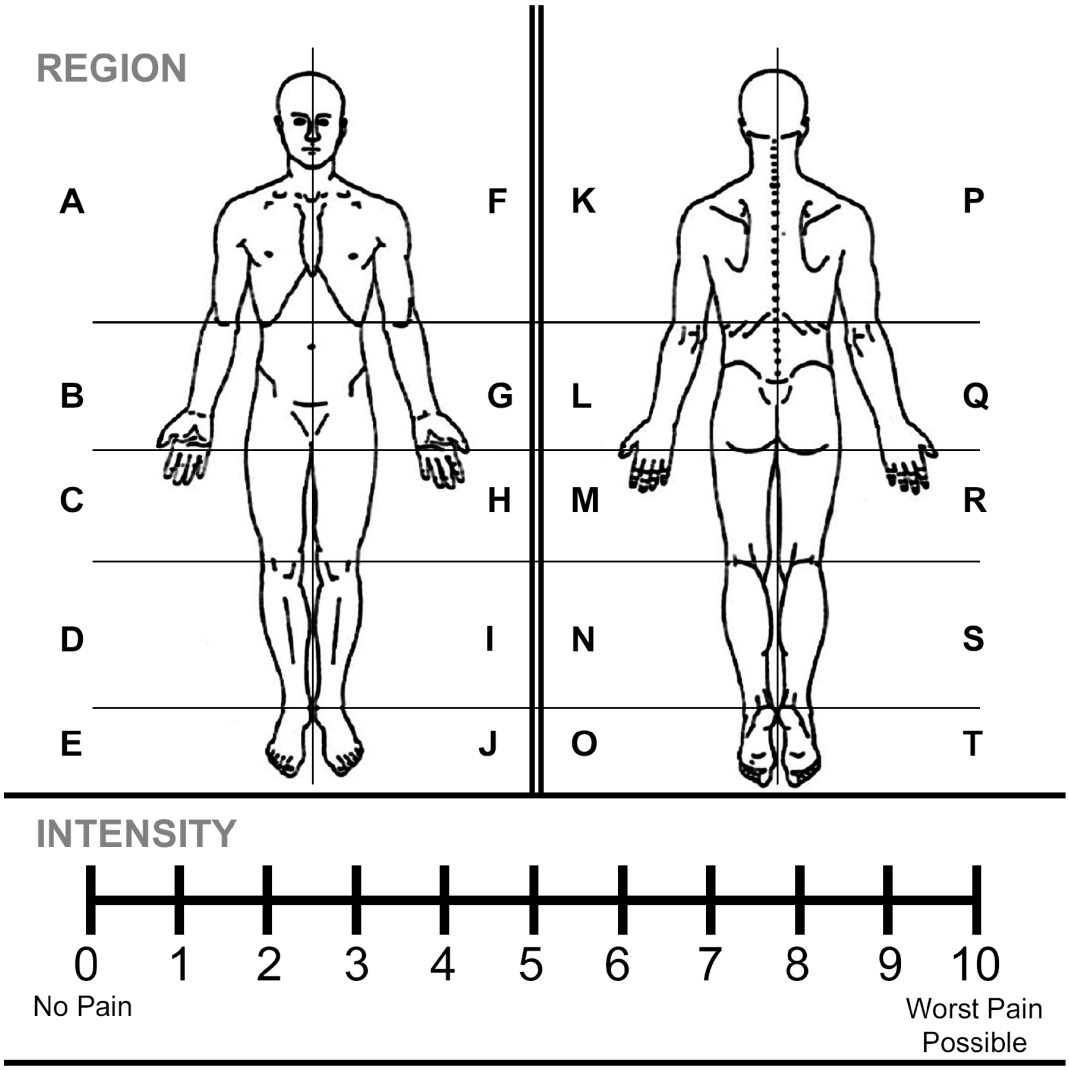


Figure 1. Symptom reporting placard used during neurodynamic testing procedures. The regions of the body chart were divided into sections identified by letters. Intensity was based on a 0-10 point visual analog scale with the anchors being no pain (0) and worst pain possible (10). A list of common descriptors of the quality of symptoms was taken from the McGill Pain Questionnaire and additional descriptors were added based on the clinical experience of the authors.

FIGURE 2

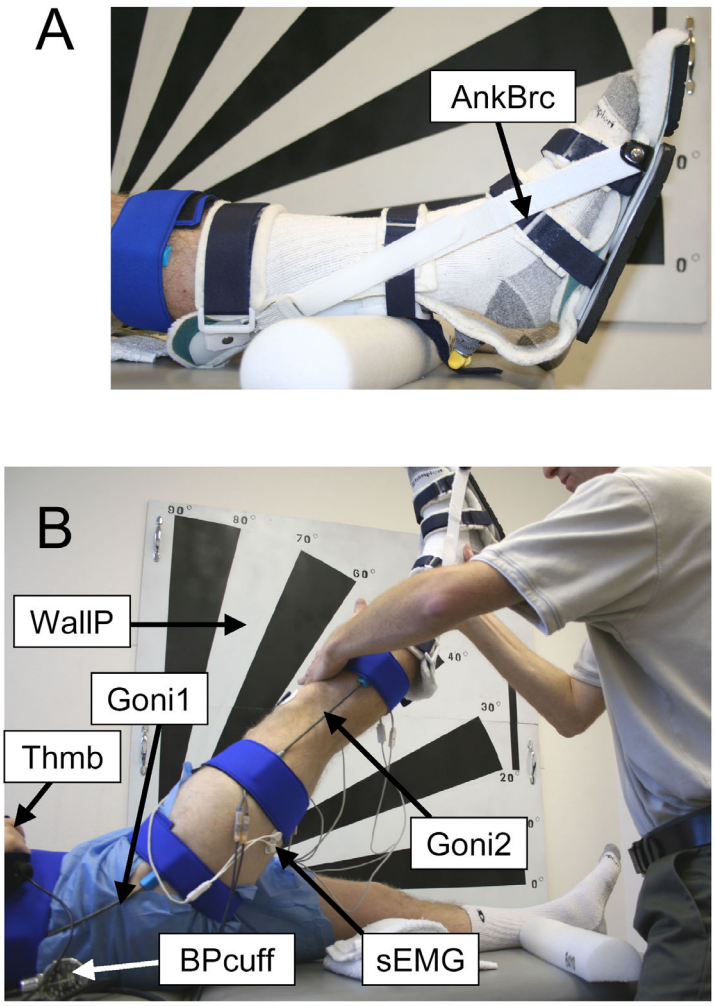


Figure 2. Neurodynamic testing set up for the straight leg raise. **A)** The subject's ankle was placed in an ankle brace (**AnkBr**) that could be adjusted to 30° of plantar flexion for the PF/SLR test or to a neutral ankle dorsiflexion for the DF/SLR test. **B)** Twin-axis electrogoniometers were placed on the lateral aspect of the hip joint (**Goni1**) and knee joint (**Goni2**) and were held in place with double-sided toupee tape and custom made neoprene straps (blue straps). Surface EMG electrodes (**sEMG**) were placed over eight right lower extremity muscles including; the gluteus maximus, semitendinosus, biceps femoris, medial gastrocnemius, soleus, rectus femoris, vastus medialis, and tibialis anterior following surface electromyography for non-invasive assessment of muscles (SENIAM) guidelines. A blood pressure cuff (**BPcuff**) was placed under the lumbar spine and inflated to 40 mmHg prior to performing the SLR. The subject was given a custom made joystick with a thumb trigger (**Thmb**) that was held with their hands resting on their stomach and for indicating the START position, the onset of symptoms (P1) and the maximum tolerated position (P2). The wall placard (**WallP**) provided the tester visual input of 10° increments painted on the board and was placed so that the axis of rotation was aligned with the subject's right greater trochanter.

FIGURE 3

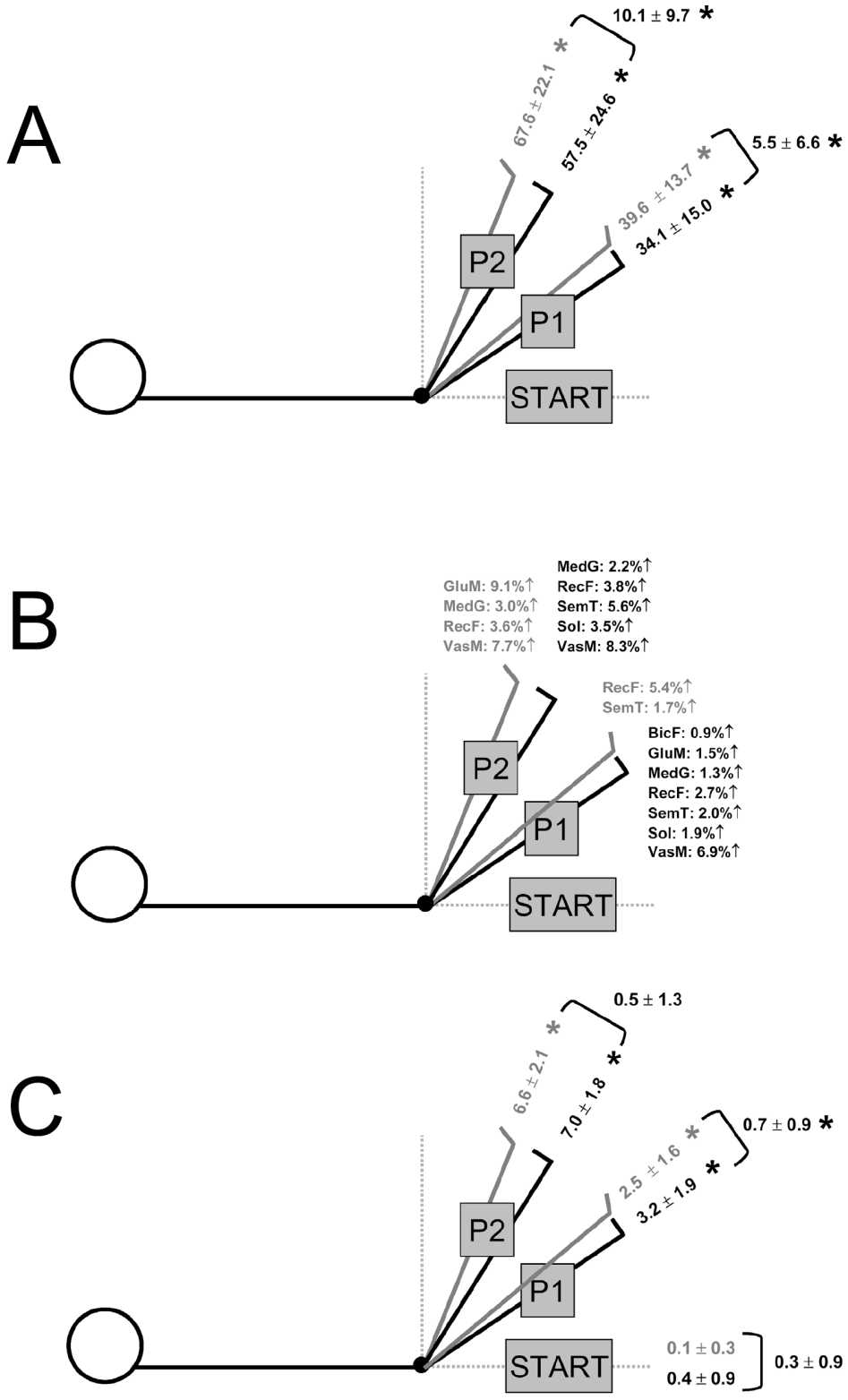
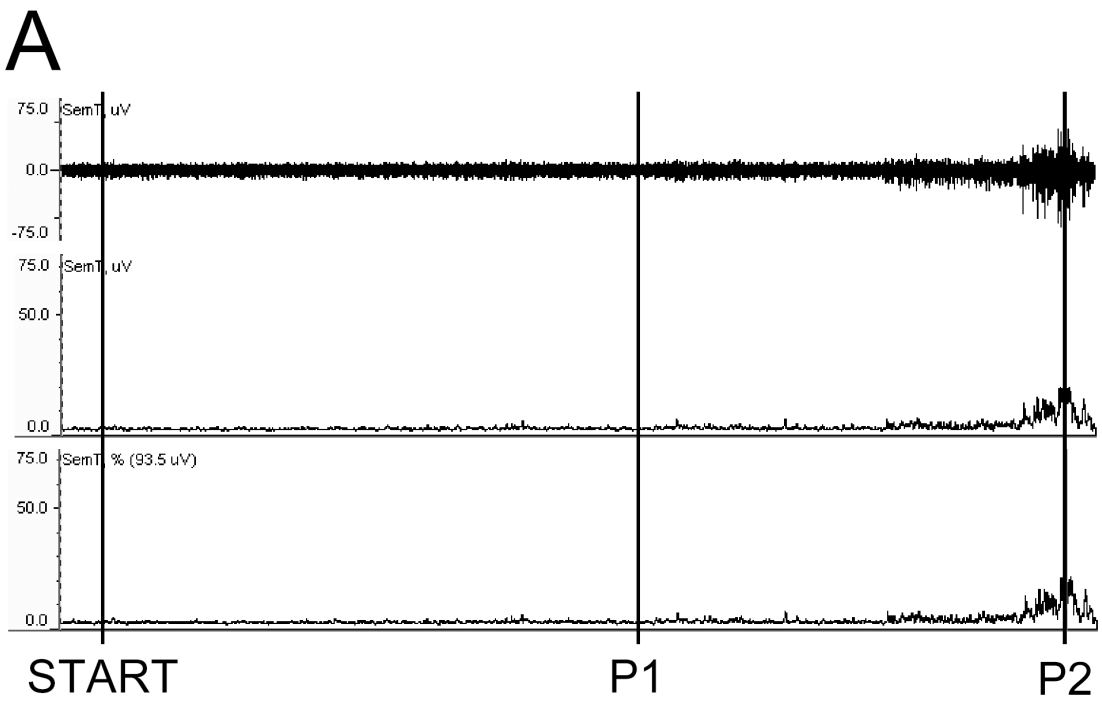

A
10.1 ± 9.7 *
67.6 ± 22.1 *
57.5 ± 24.6 *
5.5 ± 6.6 *
39.6 ± 13.7 *
34.1 ± 15.0 *
P2
P1
START
B
GluM: 9.1%↑
MedG: 3.0%↑
RecF: 3.6%↑
VasM: 7.7%↑
MedG: 2.2%↑
RecF: 3.8%↑
SemT: 5.6%↑
Sol: 3.5%↑
VasM: 8.3%↑
RecF: 5.4%↑
SemT: 1.7%↑
BicF: 0.9%↑
GluM: 1.5%↑
MedG: 1.3%↑
RecF: 2.7%↑
SemT: 2.0%↑
Sol: 1.9%↑
VasM: 6.9%↑
P2
P1
START
C
0.5 ± 1.3
6.6 ± 2.1 *
7.0 ± 1.8 *
0.7 ± 0.9 *
2.5 ± 1.6 *
3.2 ± 1.9 *
P2
P1
START
0.1 ± 0.3
0.4 ± 0.9
0.3 ± 0.9

Figure 3. Straight leg raise neurodynamic test results are presented for hip flexion range of motion (**A**), muscle activation patterns (**B**), and symptom intensity (**C**). Gray lined body diagrams represent the PF/SLR test and black lined body diagrams represent the DF/SLR test. Significance is indicated by an * and was set at $p \leq 0.05$. **A)** Hip flexion to the onset of symptoms (P1) and to the maximally tolerated position (P2) is significantly greater than the zeroed START position ($p<0.05$). The differences between the PF/SLR and the DF/SLR are 5.5° at P1 and 10.1° at P2 ($p<0.05$). **B)** Muscle activity is presented in percent of maximal isometric voluntary contractions (MVCs) and is only listed for the muscles that had significantly increased muscle activation over the resting levels in the START position. Muscle activity is presented for the gluteus maximus (GluM), semitendinosus (SemT), biceps femoris (BicF), medial gastrocnemius (MedG), soleus (Sol), rectus femoris (RecF), vastus medialis (VasM), and tibialis anterior (TibA) muscles of the right lower extremity. **C)** Symptom intensity on a 0-10 point scale is presented for each SLR test at both P1 and P2. Symptom intensity is significantly increased at both P1 and P2 over START position values ($p<0.05$). There was a 0.7-point significantly greater symptom intensity at P1 when in the DF/SLR test compared to the PF/SLR test.

FIGURE 4


A
75.0
SemT, uV
0.0
-75.0
75.0
SemT, uV
50.0
0.0
75.0
SemT, % (93.5 uV)
50.0
0.0
START
P1
P2

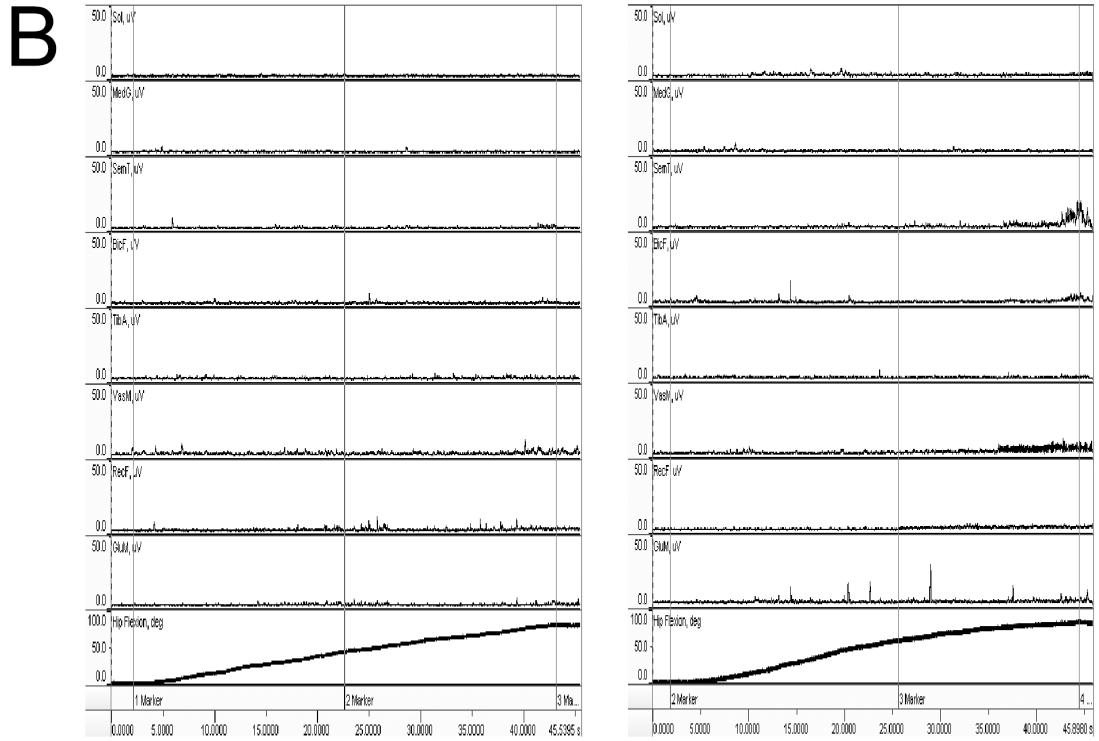

B
Sol, uV
MedG, uV
SemT, uV
BicF, uV
TibA, uV
VasM, uV
RecF, uV
GluM, uV
Hip Flexion, deg
1 Marker
2 Marker
3 Marker

Figure 4. Surface electromyographic (EMG) measures for each of eight right lower extremity muscles were taken during the SLR tests; gluteus maximus (GluM), semitendinosus (SemT), biceps femoris (BicF), medial gastrocnemius (MedG), soleus (Sol), rectus femoris (RecF), vastus medialis (VasM), and tibialis anterior (TibA). **A)** Representative EMG activity during DF/SLR for semitendinosis (SemT). First line represents the raw EMG signal and is reported in uV. Second line is the EMG signal rectified by use of a root mean squared (RMS) calculation using a 100 msec interval and is reported in uV. Third line represents the EMG signal normalized to the maximal voluntary isometric contraction (MVC) and is reported as %MVC. Vertical lines demarcate the START position, the onset of symptoms (P1) and the maximally tolerated position (P2). **B)** EMG signal for one subject comparing PF/SLR on left and DF/SLR on the right with all eight muscles measured (top 8 lines) and hip flexion range of motion (bottom line). Vertical lines demarcate the START position, the onset of symptoms (P1) and the maximally tolerated position (P2).

FIGURE 5

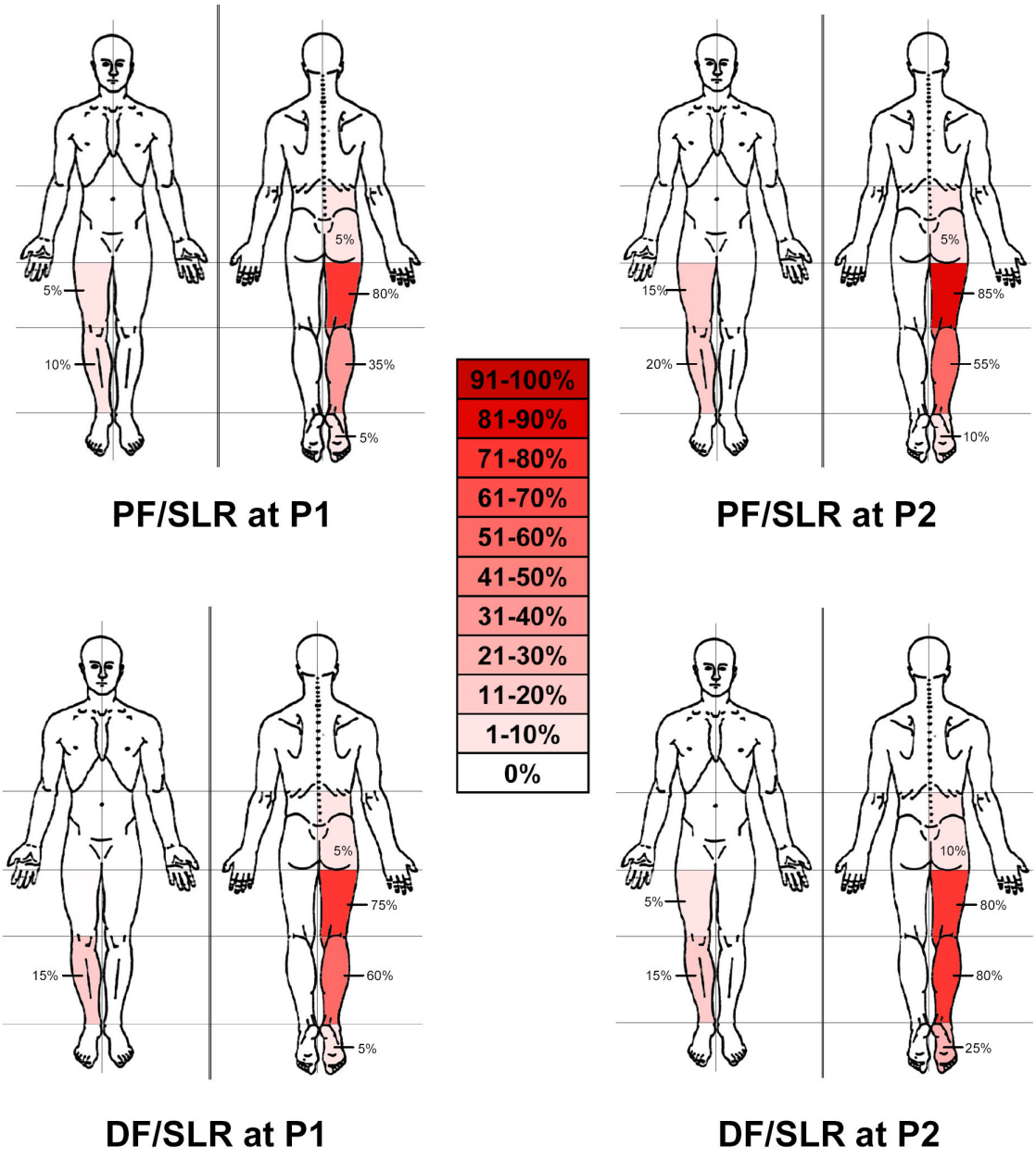


Figure 5. Body chart representations are presented for frequencies of symptom location reported during the PF/SLR and DF/SLR at both the onset of symptoms (P1) and the maximally tolerated position (P2). Frequencies are reported in 10% intervals from a white color of 0% frequency to 90-100% as dark red (see key in center of figure). There were more frequent distal symptoms in the DF/SLR test when compared to the PF/SLR for both the P1 and the P2 time points.

FIGURE 6

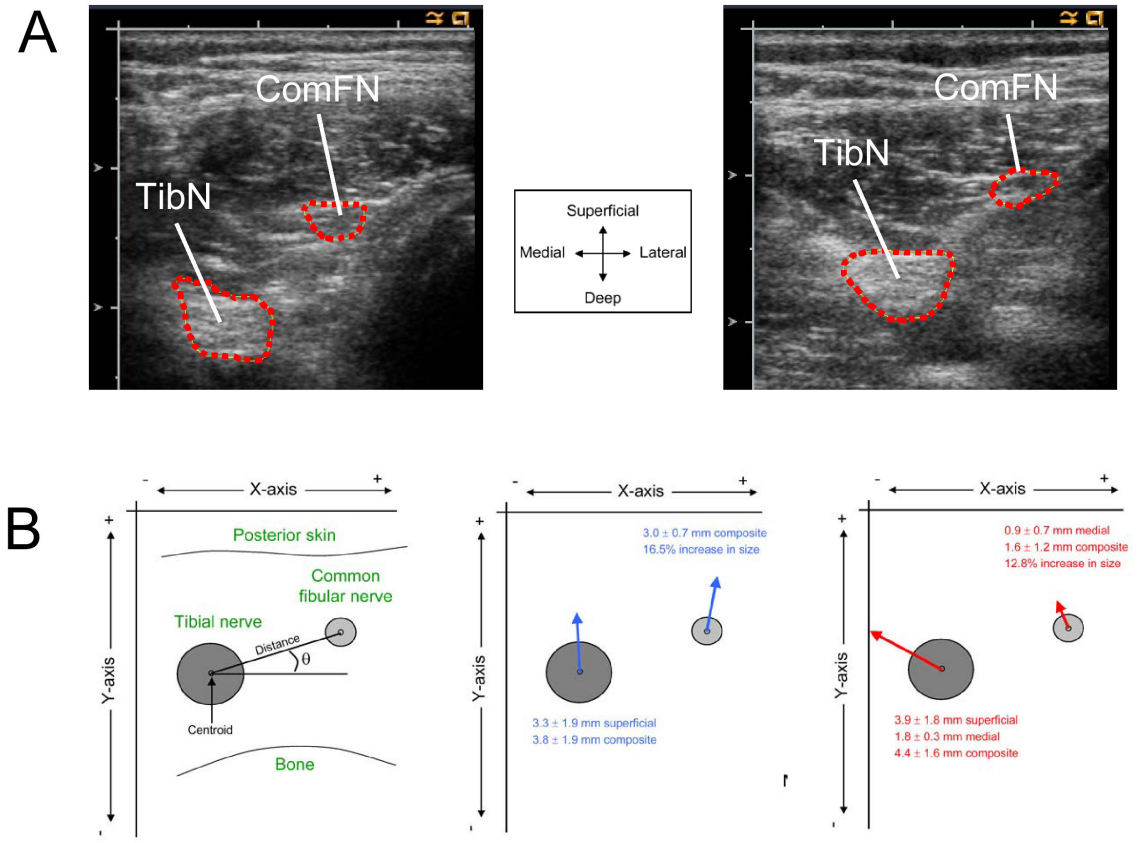


Figure 6. Ultrasound imaging sample images and schematic represent the position and movement of the tibial and common fibular nerve in the popliteal fossa when the ankle is moved from a position of end of range plantar flexion to a position of end of range dorsiflexion during the SLR test in a neutral hip position and at the onset of symptoms (P1). A) Representative sample images of tibial nerve (**TibN**) and common fibular nerve (**ComFN**) position at end of range PF (left) and DF (right) in the neutral hip position. B) Schematic of resting nerve positions (left) with measurements indicated for centroid (X and Y-axis position), distance between nerves, and angle of line between nerves (θ). Movements of each nerve represented in neutral hip (middle) and hip flexion to P1 (right) when moving to maximum dorsiflexion from maximum plantar flexion.

FIGURE 7

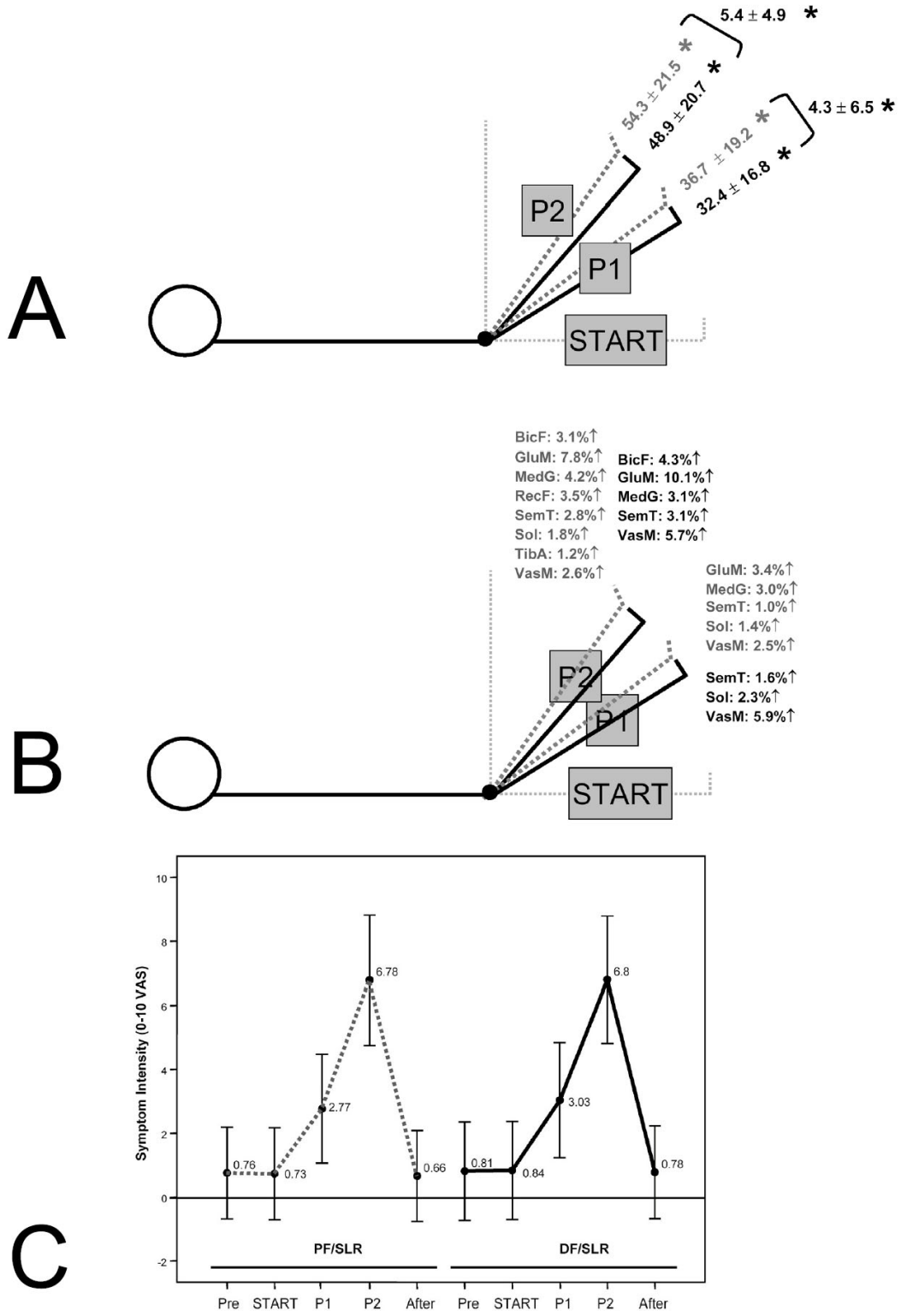

A
START
P1
P2
54.3 ± 21.5 *
48.9 ± 20.7 *
36.7 ± 19.2 *
32.4 ± 16.8 *
5.4 ± 4.9 *
4.3 ± 6.5 *
B
START
P1
P2
BicF: 3.1%↑
GluM: 7.8%↑
MedG: 4.2%↑
RecF: 3.5%↑
SemT: 2.8%↑
Sol: 1.8%↑
TibA: 1.2%↑
VasM: 2.6%↑
BicF: 4.3%↑
GluM: 10.1%↑
MedG: 3.1%↑
SemT: 3.1%↑
VasM: 5.7%↑
GluM: 3.4%↑
MedG: 3.0%↑
SemT: 1.0%↑
Sol: 1.4%↑
VasM: 2.5%↑
SemT: 1.6%↑
Sol: 2.3%↑
VasM: 5.9%↑
C
Symptom Intensity (0-10 VAS)
10
8
6
4
2
0
-2
0.76
0.73
2.77
6.78
0.66
0.81
0.84
3.03
6.8
0.78
PF/SLR
DF/SLR
Pre
START
P1
P2
After
Pre
START
P1
P2
After

Figure 7. Straight leg raise neurodynamic test results are presented for hip flexion range of motion (**A**), muscle activation patterns (**B**), and symptom intensity (**C**). Gray dotted lined body diagrams represents the PF/SLR test and black lined body diagrams represent the DF/SLR test. Significance is indicated by an * and was set at $p \leq 0.05$. **A)** Hip flexion to the onset of symptoms (**P1**) and to the maximally tolerated position (**P2**) is significantly greater than the zeroed **START** position ($p<0.05$). The differences between the PF/SLR and the DF/SLR are 4.3° at P1 and 5.4° at P2 ($p<0.05$). **B)** Muscle activity is presented in percent of maximal isometric voluntary contractions (MVCs) and is only listed for the muscles that had significantly increased muscle activation over the resting levels in the START position. Muscle activity is presented for the biceps femoris (**BicF**), gluteus maximus (**GluM**), medial gastrocnemius (**MedG**), rectus femoris (**RecF**), semitendinosus (**SemT**), soleus (**Sol**), tibialis anterior (**TibA**) and vastus medialis (**VasM**) muscles of the right lower extremity. **C)** Symptom intensity on a 0-10 point scale is presented for each SLR. The gray dotted line represents the PF/SLR test (left) and the black line represents the DF/SLR test (right). **Pre** position is supine lying in a relaxed position. **START** position is full manual knee extension prior to hip flexion. **P1** represents the moment of first onset of symptoms and **P2** represents the maximally tolerated symptom position. **After** is resting supine 2 minutes after the SLR test. Symptom intensity is significantly increased at both P1 and P2 over START position values ($p<0.05$). There was a 0.3-point significantly greater symptom intensity at P1 when in the DF/SLR test compared to the PF/SLR test.

FIGURE 8

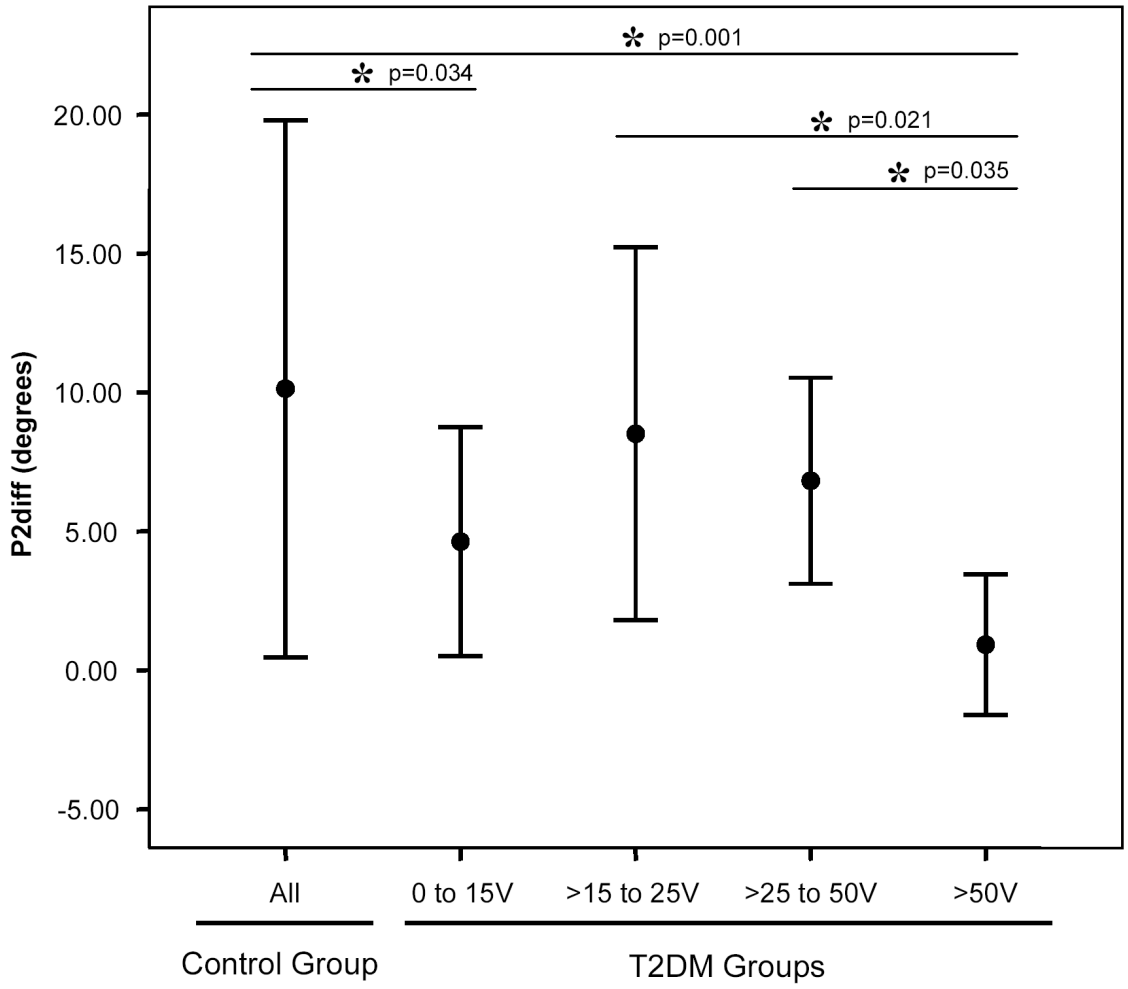


Figure 8. The difference in hip flexion range of motion between PF/SLR and DF/SLR at the maximally tolerated symptom position (P2) is presented on the Y-axis. Subgroups are presented on the X-axis and include the 1) Control group, 2) T2DM subjects who had a VPT-AVG of <15V, 3) T2DM subjects who had a VPT-AVG of 15V to <25V, 4) T2DM subjects who had a VPT-AVG of 25V to 50V, and 5) T2DM subjects who had a VPT-AVG of >50V. The control group had 10.1 degrees difference between PF/SLR and DF/SLR at P2 (P2diff). The subjects in the T2DM group that had a VPT-AVG of >50V had a significantly lower P2 diff compared to the controls and two of the other T2DM subgroups (15V to <25V and 25V to 50V). Significance is indicated by an * and was set at $p \leq 0.05$.

FIGURE 9

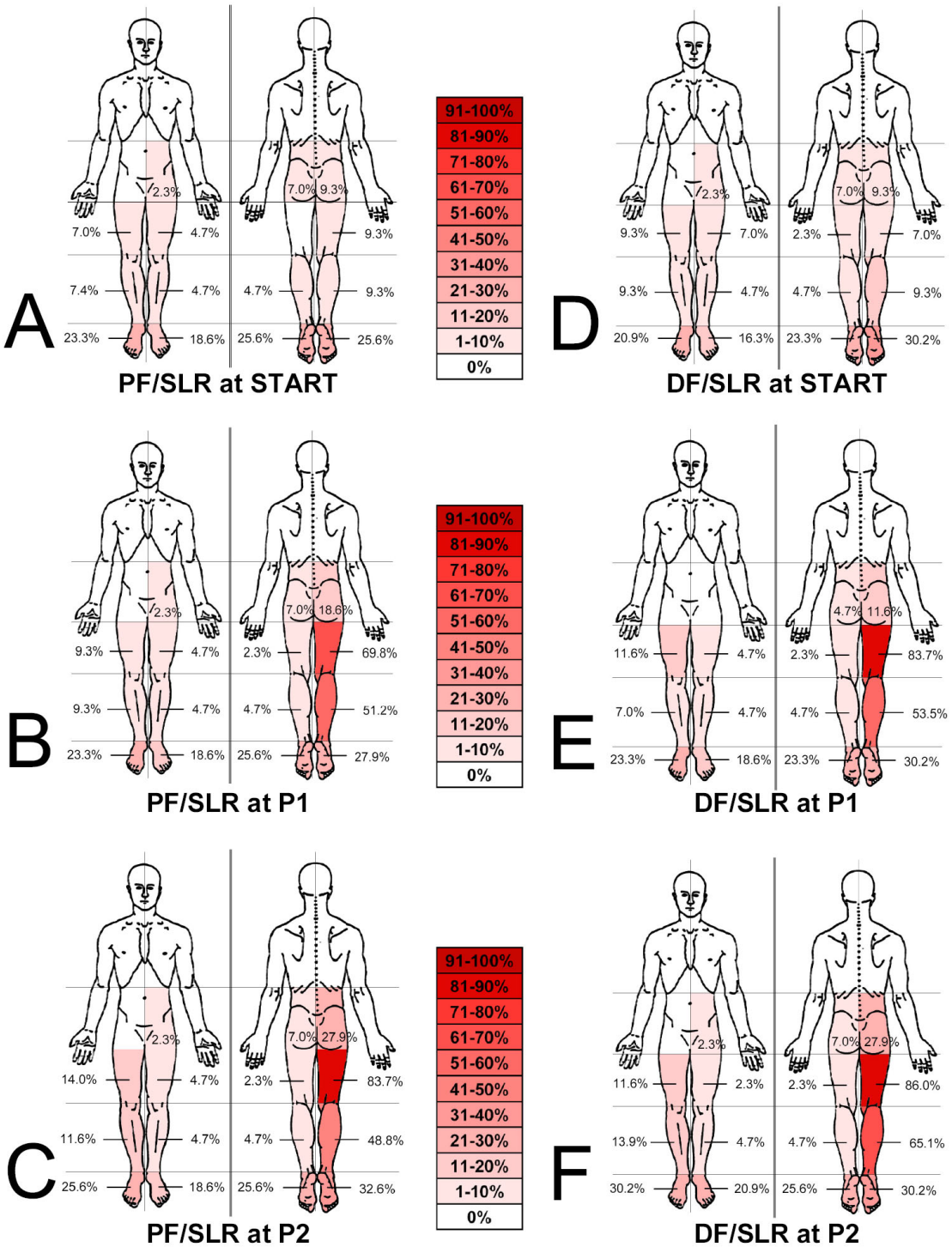

A
2.3%
7.0%
4.7%
9.3%
7.4%
4.7%
4.7%
9.3%
23.3%
18.6%
25.6%
25.6%
PF/SLR at START
91-100%
81-90%
71-80%
61-70%
51-60%
41-50%
31-40%
21-30%
11-20%
1-10%
0%
D
2.3%
7.0%
9.3%
9.3%
7.0%
2.3%
7.0%
9.3%
4.7%
4.7%
9.3%
20.9%
16.3%
23.3%
30.2%
DF/SLR at START
B
2.3%
7.0%
18.6%
9.3%
4.7%
2.3%
69.8%
9.3%
4.7%
4.7%
51.2%
23.3%
18.6%
25.6%
27.9%
PF/SLR at P1
E
4.7%
11.6%
11.6%
4.7%
2.3%
83.7%
7.0%
4.7%
4.7%
53.5%
23.3%
18.6%
23.3%
30.2%
DF/SLR at P1
C
2.3%
7.0%
27.9%
14.0%
4.7%
2.3%
83.7%
11.6%
4.7%
4.7%
48.8%
25.6%
18.6%
25.6%
32.6%
PF/SLR at P2
F
2.3%
7.0%
27.9%
11.6%
2.3%
2.3%
86.0%
13.9%
4.7%
4.7%
65.1%
30.2%
20.9%
25.6%
30.2%
DF/SLR at P2

Figure 9. Body chart representations are presented for frequencies of symptom location reported for the T2DM group. **A, B, C** represents PF/SLR at the START, onset of symptoms (P1) and the maximally tolerated position (P2), respectively. **D, E, F** represents DF/SLR at the START, onset of symptoms (P1) and the maximally tolerated position (P2), respectively. Frequencies are reported in 10% intervals from a white color of 0% frequency to 90-100% as dark red (see key in center of figure). There were >15% bilateral symptoms in the feet at the START position for both PF/SLR and DF/SLR. There were more frequent distal symptoms in the DF/SLR test when compared to the PF/SLR at P2.

FIGURE 10

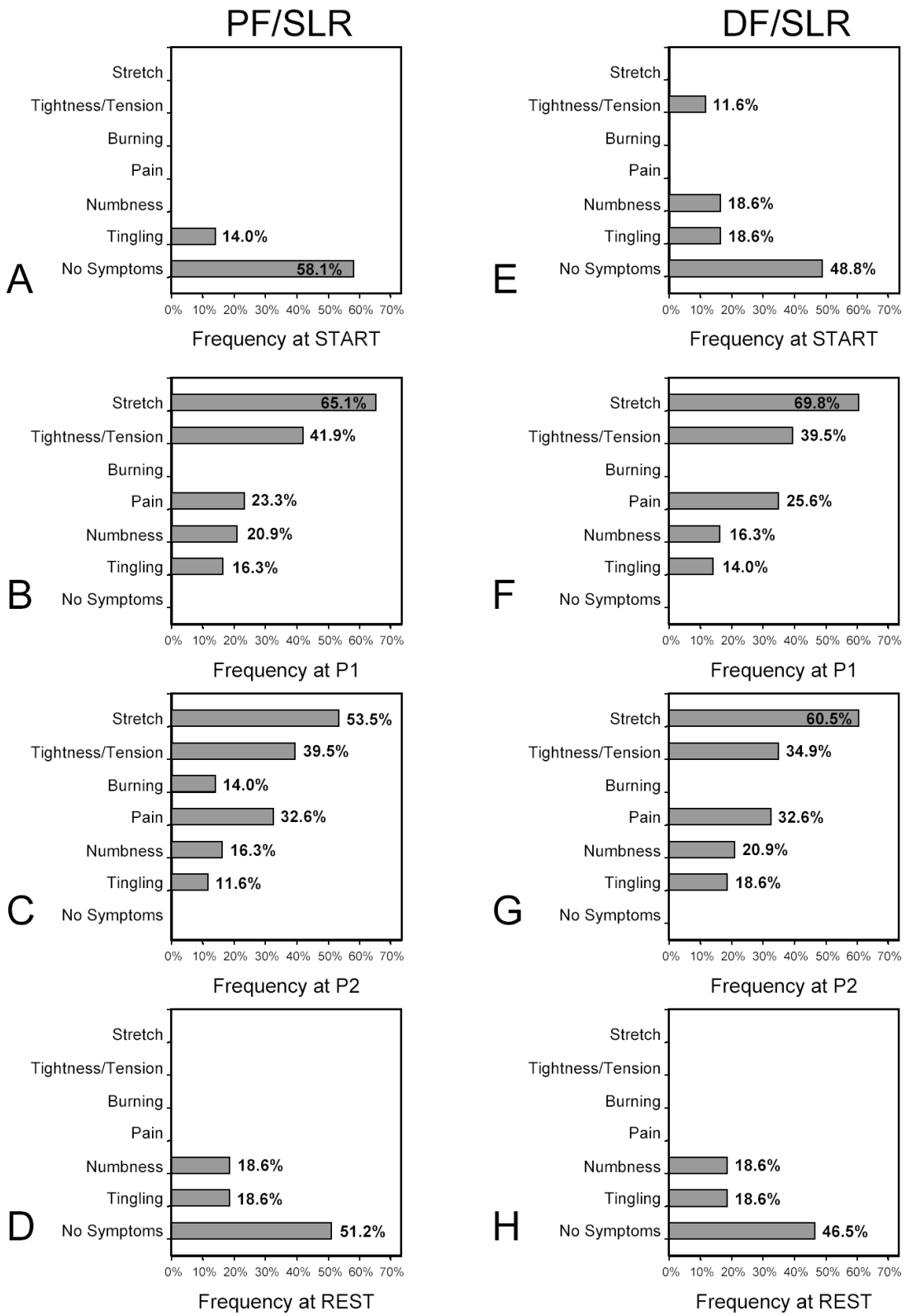

PF/SLR
DF/SLR
A
Stretch
Tightness/Tension
Burning
Pain
Numbness
Tingling
No Symptoms
14.0%
58.1%
0% 10% 20% 30% 40% 50% 60% 70%
Frequency at START
E
11.6%
18.6%
18.6%
48.8%
Frequency at START
B
65.1%
41.9%
23.3%
20.9%
16.3%
Frequency at P1
F
69.8%
39.5%
25.6%
16.3%
14.0%
Frequency at P1
C
53.5%
39.5%
14.0%
32.6%
16.3%
11.6%
Frequency at P2
G
60.5%
34.9%
32.6%
20.9%
18.6%
Frequency at P2
D
18.6%
18.6%
51.2%
Frequency at REST
H
18.6%
18.6%
46.5%
Frequency at REST

Figure 10. Histograms are presented for frequencies of symptom quality reported for the T2DM group. **A, B, C, D** represents PF/SLR at the START, onset of symptoms (P1), maximally tolerated position (P2), and at rest 2 minutes after resting, respectively. **E, F, G, H** represents DF/SLR at the START, onset of symptoms (P1), maximally tolerated position (P2), and at rest 2 minutes after resting, respectively. Symptoms reported in <10% of participants are not presented. The frequency of no symptoms at the START position was greater in the PF/SLR compared to the DF/SLR. The most common symptoms at the START position were numbness and tingling. Stretch and tightness/tension were the two most frequent reported symptoms at P1 and P2 during both SLR tests. Pain was also induced in >20% of the subjects at P1 and >30% of the subjects at P2 during both SLR tests.

TABLE 1

Subject Demographics

A. Subject Demographics	Mean	Std Dev	Range
Age	50.4	12.0	25-63
Height (m)	1.7	0.1	1.5-1.8
Height (in)	65.1	3.6	59-71
Weight (kg)	71.2	24.8	43.1-154.7
Weight (lb)	156.9	54.7	95.0-341.0
Body mass index (BMI)	25.9	8.8	18.1-58.1

B. Frequencies			
	Female	**Male**	
Gender	14	**6**	
	No pillows	**One pillow**	**Two pillows**
Number of additional pillows requested during SLR test	14	4	2

TABLE 2

Sensory Testing

Monofilament testing	Normal	Decreased	Absent
Right hallux	90%	10%	0%
Left hallux	95%	5%	0%

Sharp-dull testing	Present	Absent
Right hallux	90%	10%
Left hallux	90%	10%

Vibration testing (tuning fork)	Normal	Diminished	Absent
Right hallux	55%	20%	25%
Left hallux	60%	15%	25%

Vibration testing (biothesiometer)		
Averaged vibration perception thresholds (VPT)	**Right**	**Left**
Medial malleolus	20.3 ± 12.4 volts	18.9 ± 10.5 volts
Halluces	18.1 ± 14.5 volts	17.6 ± 13.6 volts

Averaged vibration extinction thresholds (VET)	Right	Left
Medial malleolus	21.8 ± 10.7 volts	19.7 ± 10.2 volts
Halluces	19.2 ± 13.6 volts	18.2 ± 12.0 volts

TABLE 3

Deep tendon reflex (DTR) testing

Quadriceps tendon	Normal	Present with reinforcement	Absent
Right	80%	5%	15%
Left	80%	5%	15%
Achilles tendon	**Normal**	**Present with reinforcement**	**Absent**
Right	75%	10%	15%
Left	70%	10%	20%
Biceps brachii tendon	**Normal**	**Present with reinforcement**	**Absent**
Right	95%	0%	5%
Left	90%	0%	10%
Triceps brachii tendon	**Normal**	**Present with reinforcement**	**Absent**
Right	65%	20%	15%
Left	65%	15%	20%

TABLE 4

Manual muscle strength testing

Finger abduction	**Normal**	**Mild to moderate weakness**	**Severe Weakness**	**Complete strength loss**
Right	100%	0%	0%	0%
Left	100%	0%	0%	0%
Great toe extension	**Normal**	**Mild to moderate weakness**	**Severe Weakness**	**Complete strength loss**
Right	85%	15%	0%	0%
Left	90%	10%	0%	0%
Ankle dorsiflexion	**Normal**	**Mild to moderate weakness**	**Severe Weakness**	**Complete strength loss**
Right	100%	0%	0%	0%
Left	100%	0%	0%	0%

TABLE 5

Symptom Quality Frequencies

	PF/SLR				DF/SLR			
	Start	P1	P2	Rest	Start	P1	P2	Rest
Ache	10%	15%	15%	15%	10%	10%	15%	15%
Annoying	---	---	5%	---	---	---	---	---
Burning	---	---	5%	---	---	15%	5%	---
Dull	5%	---	---	10%	5%	---	---	5%
Electric	---	---	---	---	---	5%	---	---
Hot poker	---	---	---	---	---	5%	5%	---
Intense	---	5%	5%	---	---	---	---	---
Knife cutting	---	5%	5%	---	---	5%	---	---
Loose	---	---	---	---	---	---	---	5%
Numbness	---	---	---	5%	---	---	---	---
Pain	---	5%	5%	---	---	10%	---	---
Pulling	---	---	---	---	---	---	5%	---
Radiating	---	5%	5%	---	---	5%	5%	---
Sharp	---	---	5%	---	---	10%	---	---
Sore	5%	5%	5%	5%	5%	5%	5%	5%
Spasm	---	---	5%	---	---	---	---	---
Stabbing	---	---	---	---	---	---	5%	---
Stiff	---	---	5%	---	---	---	---	---
Stretch	---	75%	75%	---	5%	70%	65%	10%
Tender	5%	---	5%	5%	5%	---	---	---
Throbbing	---	---	5%	---	---	5%	5%	5%
Tight/Tension	---	25%	35%	---	5%	50%	40%	5%
No symptoms	85%	---	---	90%	75%	---	---	70%

TABLE 6

Demographics and clinical measures

	Control Group (previously reported)	T2DM Group	p value
Demographics			
Age (years)	50.4 ± 12.0	56.3 ± 11.1	0.061
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.127
Weight (kg)	71.2 ± 24.8	94.0 ±18.3	<0.0005 *
BMI	25.9 ± 8.8	32.8 ± 6.6	0.001 *
Duration of T2DM (years)	------	7.0 ± 7.7	------
Gender	70% female / 30% male	49% female / 51% male	------
HbA1c	5.5 ± 0.3	7.4 ± 1.8	<0.0005 *
Vibration perception threshold (VPT)			
Right malleolus (volts)	20.3 ± 12.4	30.1 ± 12.6	0.005 *
Left malleolus (volts)	18.9 ± 10.5	32.7 ± 13.6	<0.0005 *
Right halluces (volts)	18.1 ± 14.5	30.1 ± 14.8	0.004 *
Left halluces (volts)	17.6 ± 13.6	29.9 ± 15.6	0.004 *
VPT-AVG for halluces(volts)	17.8 ±14.0	30.0 ±14.9	0.003 *
Vibration extinction threshold (VET)			
Right malleolus (volts)	21.8 ±10.7	28.6 ± 11.4	0.030 *
Left malleolus (volts)	19.7 ± 10.2	30.8 ± 12.6	0.001 *
Right halluces (volts)	19.2 ±13.6	29.2 ± 13.9	0.010 *
Left halluces (volts)	18.2 ±12.0	28.9 ±15.0	0.007 *
MNSIq	0.7 ± 0.8	3.8 ± 2.4	<0.0005 *
MNSIc	1.6 ± 1.4	3.9 ± 2.4	<0.0005 *
MDNS	5.1 ± 6.0	13.8 ± 8.7	<0.0005 *
ModBaecke Questionnaire			
Work subscale	2.5 ± 0.3	2.5 ± 0.5	1.000
Sports subscale	3.5 ± 0.7	2.7 ± 1.1	0.007 *
Leisure subscale	3.1 ± 0.6	2.7 ± 0.5	0.004 *
Total score	9.1 ± 1.0	7.9 ± 1.7	0.004 *

Significance set at $p \leq 0.05$ (*).
Abbreviations: Body mass index (BMI), hemoglobin A1c (HbA1c), Michigan diabetic neuropathy score (MDNS), Michigan neuropathy screening intstrument – clinical portion (MNSIc), Michigan neuropathy screening intstrument – questionnaire portion (MNSIq), Vibration perception threshold averaged for right and left halluces (VPT-AVG), and the Modified Baecke questionnaire total score (ModBaecke).

TABLE 7

Clinical measure correlations

	Group	Age	BMI	HbA1c	MDNS	MNSIc	MNSIq	VPT-AVG	ModBaecke
Group	-----	0.24	0.41*	0.53*	0.46*	0.46*	0.58*	0.37*	-0.36*
Age	0.24	-----	0.18	0.12	0.28*	0.49*	0.16	0.57*	-0.08
BMI	0.41*	0.18	-----	0.48*	0.33*	0.48*	0.45*	0.26*	-0.33*
HbA1c	0.53*	0.12	0.48*	-----	0.40*	0.49*	0.50*	0.28*	-0.61*
MDNS	0.46*	0.28*	0.33*	0.40*	-----	0.82*	0.51*	0.76*	-0.34*
MNSIc	0.46*	0.49*	0.48*	0.49*	0.82*	-----	0.65*	0.74*	-0.37*
MNSIq	0.58*	0.16	0.45*	0.50*	0.51*	0.65*	-----	0.42*	-0.42*
VPT-AVG	0.37*	0.57*	0.26*	0.28*	0.76*	0.74*	0.42*	-----	-0.24
ModBaecke	-0.36*	-0.08	-0.33*	-0.61*	-0.34*	-0.37*	-0.42*	-0.24	-----

Pearson product correlations are presented with significance set at $p \leq 0.05$ (*). Abbreviations: Body mass index (BMI), hemoglobin A1c (HbA1c), Michigan diabetic neuropathy score (MDNS), Michigan neuropathy screening intstrument – clinical portion (MNSIc), Michigan neuropathy screening intstrument – questionnaire portion (MNSIq), Vibration perception threshold averaged for right and left halluces (VPT-AVG), and the Modified Baecke questionnaire total score (ModBaecke).

REFERENCES

1. Coppieters, M., et al., *The impact of neurodynamic testing on the perception of experimentally induced muscle pain.* Man Ther, 2005. 10: p. 52-60.
2. Rebain, R., G.D. Baxter, and S. McDonough, *A systematic review of the passive straight leg raising test as a diagnostic aid for low back pain (1989 to 2000).* Spine, 2002. 27(17): p. E388-95.
3. Butler, D.S., *The sensitive nervous system*. 2000, Adelaide, Australia: Noigroup Publications.
4. Nee, R. and D.S. Butler, *Management of peripheral neuropathic pain: Integrating neurobiology, neurodynamics, and clinical evidence.* Physical Therapy in Sport, 2006(7): p. 36–49.
5. Boland, R. and R. Adams, *Effects of ankle dorsiflexion on range and reliability of straight leg raising.* Austral Journal of Physiotherapy, 2000. 46: p. 191-200.
6. Coppieters, M.W., et al., *Strain and excursion of the sciatic, tibial, and plantar nerves during a modified straight leg raising test.* J Orthop Res, 2006. 24(9): p. 1883-9.
7. Hall, T., M. Zusman, and R. Elvey, *Adverse mechanical tension in the nervous system? Analysis of straight leg raise.* Man Ther, 1988. 3(3): p. 140-146.
8. Babbage, C.S., M.W. Coppieters, and C.M. McGowan, *Strain and excursion of the sciatic nerve in the dog: biomechanical considerations in the development of a clinical test for increased neural mechanosensitivity.* Vet J, 2007. 174(2): p. 330-6.
9. Boyd, B.S., et al., *Strain and excursion in the rat sciatic nerve during a modified straight leg raise are altered after traumatic nerve injury.* J Orthop Res, 2005. 23(4): p. 764-70.
10. Goeken, L.N. and A.L. Hof, *Instrumental straight-leg raising: a new approach to Lasegue's test.* Arch Phys Med Rehabil, 1991. 72(12): p. 959-66.
11. McHugh, M.P., et al., *The role of mechanical and neural restraints to joint range of motion during passive stretch.* Med Sci Sports Exerc, 1998. 30(6): p. 928-32.
12. Balster, S.M. and G.A. Jull, *Upper trapezius muscle activity during the brachial plexus tension test in asymptomatic subjects.* Man Ther, 1997. 2(3): p. 144-149.
13. van der Heide, B., G.T. Allison, and M. Zusman, *Pain and muscular responses to a neural tissue provocation test in the upper limb.* Man Ther, 2001. 6(3): p. 154-62.
14. Coppieters, M., et al., *Reliability of detecting 'onset of pain' and 'submaximal pain' during neural provocation testing of the upper quadrant.* Physiother Res Int, 2002. 7(3): p. 146-56.
15. Coppieters, M.W., et al., *Aberrant protective force generation during neural provocation testing and the effect of treatment in patients with neurogenic cervicobrachial pain.* J Manipulative Physiol Ther, 2003. 26(2): p. 99-106.
16. Pols, M.A., et al., *Validity and repeatability of a modified Baecke questionnaire on physical activity.* Int J Epidemiol, 1995. 24(2): p. 381-8.
17. Melzack, R., *The McGill pain questionnaire: from description to measurement.* Anesthesiology, 2005. 103(1): p. 199-202.
18. Simoneau, G.G., et al., *Diabetic sensory neuropathy effect on ankle joint movement perception.* Arch Phys Med Rehabil, 1996. 77(5): p. 453-60.

19. Feldman, E.L., et al., *A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy.* Diabetes Care, 1994. 17(11): p. 1281-9.
20. Fedele, D., et al., *A multicenter study on the prevalence of diabetic neuropathy in Italy. Italian Diabetic Neuropathy Committee.* Diabetes Care, 1997. 20(5): p. 836-43.
21. Hermens, H.J., et al., *Development of recommendations for SEMG sensors and sensor placement procedures.* J Electromyogr Kinesiol, 2000. 10(5): p. 361-74.
22. Dingwell, J.B., et al., *Slower speeds in patients with diabetic neuropathy lead to improved local dynamic stability of continuous overground walking.* J Biomech, 2000. 33(10): p. 1269-77.
23. Pang, M.Y. and J.F. Yang, *Sensory gating for the initiation of the swing phase in different directions of human infant stepping.* J Neurosci, 2002. 22(13): p. 5734-40.
24. Medeiros, J.M., et al., *The influence of isometric exercise and passive stretch on hip joint motion.* Phys Ther, 1977. 57(5): p. 518-23.
25. Wang, S.S., et al., *Lower extremity muscular flexibility in long distance runners.* J Orthop Sports Phys Ther, 1993. 17(2): p. 102-7.
26. Raab, D.M., et al., *Light resistance and stretching exercise in elderly women: effect upon flexibility.* Arch Phys Med Rehabil, 1988. 69(4): p. 268-72.
27. Hsieh, C.Y., J.M. Walker, and K. Gillis, *Straight-leg-raising test. Comparison of three instruments.* Phys Ther, 1983. 63(9): p. 1429-33.
28. Girouard, C.K. and B.F. Hurley, *Does strength training inhibit gains in range of motion from flexibility training in older adults?* Med Sci Sports Exerc, 1995. 27(10): p. 1444-9.
29. Bohannon, R.W., *Cinematographic analysis of the passive straight-leg-raising test for hamstring muscle length.* Phys Ther, 1982. 62(9): p. 1269-74.
30. Moseley, G.L., M.K. Nicholas, and P.W. Hodges, *A randomized controlled trial of intensive neurophysiology education in chronic low back pain.* Clin J Pain, 2004. 20(5): p. 324-30.
31. Bove, G.M., A. Zaheen, and Z.H. Bajwa, *Subjective nature of lower limb radicular pain.* J Manipulative Physiol Ther, 2005. 28(1): p. 12-4.
32. Cameron, N.E., et al., *Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy.* Diabetologia, 2001. 44(11): p. 1973-88.
33. CDC. *Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2005.* 2005 [cited; Available from: http://www.cdc.gov/diabetes/pubs/factsheet05.htm.
34. Gooch, C. and D. Podwall, *The diabetic neuropathies.* Neurologist, 2004. 10(6): p. 311-22.
35. Valeri, C., P. Pozzilli, and D. Leslie, *Glucose control in diabetes.* Diabetes Metab Res Rev, 2004. 20 Suppl 2: p. S1-8.
36. Rathur, H.M. and A.J. Boulton, *Recent advances in the diagnosis and management of diabetic neuropathy.* J Bone Joint Surg Br, 2005. 87(12): p. 1605-10.

37. Groop, P.H., C. Forsblom, and M.C. Thomas, *Mechanisms of disease: Pathway-selective insulin resistance and microvascular complications of diabetes.* Nat Clin Pract Endocrinol Metab, 2005. 1(2): p. 100-10.
38. Kuzuya, T., et al., *Report of the Committee on the classification and diagnostic criteria of diabetes mellitus.* Diabetes Res Clin Pract, 2002. 55(1): p. 65-85.
39. Bansal, V., J. Kalita, and U.K. Misra, *Diabetic neuropathy.* Postgrad Med J, 2006. 82(964): p. 95-100.
40. *Peripheral neuropathy*. 4th ed, ed. P.J. Dyck and P.K. Thomas. 2005, Philadelphia: Saunders.
41. *Harrison's Principles of Internal Medicine*. 16th ed, ed. D.L. Kasper, et al. 2006: McGraw Hill.
42. Garrow, A.P. and A.J. Boulton, *Vibration perception threshold--a valuable assessment of neural dysfunction in people with diabetes.* Diabetes Metab Res Rev, 2006. 22(5): p. 411-9.
43. Rahman, M., et al., *How should peripheral neuropathy be assessed in people with diabetes in primary care? A population-based comparison of four measures.* Diabet Med, 2003. 20(5): p. 368-74.
44. Zelman, D.C., et al., *Validation of a modified version of the Brief Pain Inventory for painful diabetic peripheral neuropathy.* J Vasc Nurs, 2005. 23(3): p. 97-104.
45. Feldman, E.L. and M.J. Stevens, *Clinical testing in diabetic peripheral neuropathy.* Can J Neurol Sci, 1994. 21(4): p. S3-7.
46. Bouhassira, D., et al., *Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4).* Pain, 2005. 114(1-2): p. 29-36.
47. Youdas, J.W., et al., *The influence of gender and age on hamstring muscle length in healthy adults.* J Orthop Sports Phys Ther, 2005. 35(4): p. 246-52.
48. Kwon, O.Y., et al., *Comparison of muscle activity during walking in subjects with and without diabetic neuropathy.* Gait Posture, 2003. 18(1): p. 105-13.
49. Ellis, R., et al., *Reliability Of Measuring Sciatic And Tibial Nerve Movement With Diagnostic Ultrasound During A Neural Mobilisation Technique.* Ultrasound Med Biol, 2008.

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