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Relationship between deep and superficial sensitivity assessments and gait analysis in diabetic foot patients

Mar Sempere-Bigorra[1] | **Lorenzo Brognara**[2] | **Iván Julian-Rochina**[1,3] | **Antonio Mazzotti**[2] | **Omar Cauli**[1,3]

[1]Nursing Department, Faculty of Nursing and Podiatry, University of Valencia, Valencia, Spain

[2]Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum University of Bologna, Bologna, Italy

[3]Frailty Research Organized Group, Faculty of Nursing and Podiatry, University of Valencia, Valencia, Spain

Correspondence
Omar Cauli, Nursing Department, Faculty of Nursing and Podiatry, University of Valencia, Avda Menendez Pelayo 19, 46010 Valencia, Spain.
Email: omar.cauli@uv.es

Abstract

Peripheral neuropathy is a prevalent complication of diabetes that can lead to gait impairment and its adverse consequences. This study explored the potential utility of different parameters of gait analysis using a single sensor unit as a simple tool to detect peripheral neuropathy in 85 diabetic patients (DP) with diabetic foot in whom different somato-sensitivity tests in the feet were performed. Gait spatiotemporal parameters were examined by sensor inertial measurement placed in the lumbar area, while the superficial sensitivity pathway was assessed by nociception tests and deep sensitivity was examined by light touch-pressure and vibration sensitivity tests. Correlations between each sensory test and gait parameters were analysed in a logistic regression model in order to assess if gait parameters are associated with two different sensory pathways. Impaired deep sensory pathways were significantly ($P < .05$) correlated with lower gait speed, reduced cadence, smaller stride length, longer stance periods, and a higher risk of falling on the Tinetti Scale, while all gait parameters were significantly ($P < .01$) correlated with the superficial sensory pathway. Type 2 diabetics have significantly ($P < .05$) higher impairment in vibratory sensitivity than type 1 diabetics, and the years with diabetes mellitus (DM) diagnosis have a significant ($P < .05$) association with reduced vibration sensitivity. These findings indicate relationships between the deep sensory pathway and gait impairments in DP measured by inertial sensors, which could be a useful tool to diagnose gait alterations in DP and to evaluate the effect of treatments to improve gait and thus the risk of falls in diabetic patients.

KEYWORDS

deep sensory pathway, gait parameters, peripheral diabetic neuropathy, superficial sensory pathway

Key Messages

- diabetic patients with peripheral neuropathy have gait impairment as measured by inertial measurement units

- the role of deep and superficial sensitivity alterations on gait alterations has not been evaluated in detail in diabetic patients
- impaired deep sensory pathway correlates with lower gait speed, reduced cadence, smaller stride length and longer stance periods
- inertial measurement units can be used to assess the efficacy of interventions aimed to improve peripheral neuropathy on gait

1 | INTRODUCTION

According to the International Diabetes Federation (IDF), diabetes mellitus (DM) is a very common disease with a prevalence of 9.3% and is suffered by 463 million people around the world, and it is estimated that these figures will increase to 700 million by 2045.[1] Diabetic peripheral neuropathy (DPN), defined by the American Diabetes Association (ADA) as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after the exclusion of other causes', is one of the most common complications, and its estimated prevalence ranges between 6% and 51% among the diabetic population.[2,3] Symmetric sensorimotor peripheral neuropathy progressively leads to reduced sensitivity, loss of ankle reflexes, a lower limb joint motion range and muscle weakness, which cause biomechanical changes in the lower limbs and significantly increase the risk of falling.[4-7] DPN is an independent risk factor for falls, which supposes a 20-fold increased likelihood of falling, compared with healthy people, affecting their quality of life.[8]

Sensory receptors on the cutaneous surface, joints and proprioceptor muscles of the lower limbs provide continuous somatosensory information about position and movement, which is used in the central nervous system to control the posture and gait.[9] Sensory loss is the most common manifestation of DM in the early stages and affects all sensory modalities, for example, pain and thermal sensation, vibration and light touch-pressure and proprioception.[10,11] In general, the first nerve fibres to be damaged are the small unmyelinated fibres, followed by the small myelinated fibres and lastly the large myelinated fibres.[12,13] However, this is open to controversy, and prospective longitudinal studies are needed to clarify the issue.[14] Quantitative sensory testing (QST) is non-invasive method to assess sensory nerve function and quantify perceptual thresholds.[15] For this purpose, the Pin-Prick test was used to assess nociception (superficial sensitivity pathway)[16,17] and the deep sensitivity pathway[17] was assessed by exploring the vibration sensation using a 128-Hz Rydel-Seiffer diapason and biothesiometer[18] and light touch-pressure using a Semmes-Weinstein monofilament (SWMT).[14,19]

Many studies have confirmed that reduced sensitivity in lower limbs is related to postural and gait disorders,[20-24] but few have studied the correlations between different alterations of sensory modalities and gait parameters. Changes in plantar sensitivity and tactile and vibratory sensitivity in lower limbs have been seen to alter human gait.[9] An impact on gait and posture due to increased vibration thresholds has been observed in patients with peripheral neuropathy.[20,21,24,25] Significant differences in gait parameters between DPN group and healthy subjects have been shown in two studies[20,21] and in both, peripheral neuropathy was quantified only by a vibration thresholds assessment. The presence of PN based on vibration perception thresholds affects postural control regardless of the cause of the peripheral neuropathy.[24] The cutaneous plantar surface has been defined as a 'sensory map' with skin receptors providing information about the posture of the body to the central nervous system and playing an important role in maintaining balance during standing and ambulation.[7,19] DPN patients with tactile and vibratory sensitivity impairments have slower gait speed, reduced cadence and shorter step lengths.[26] Modification of the plantar skin sensitivity by means of anaesthesia or cooling has also been seen to cause changes in gait parameters.[27-29] In contrast, no studies about gait parameter modifications and reduced pain have been found; however, increased gait variability was associated with neuropathic pain.[30-32]

Several reports have recently analysed the spatiotemporal parameters of gait in patients with DPN, using different sensors and methods.[33-37] Most of them perform gait analysis in laboratories using methods such as stereophotogrammetry, force platforms and dynamic surface electromyography. Although they are validated and precise systems, their high cost, large size and transport limitations make their use in clinical practice difficult. Inertial wearable sensors are an excellent alternative to these systems: they have a low production cost, are portable thanks to their small size, and they can be applied outside laboratories, enabling gait analysis in any environment, even at home.[38] Diabetic patients with peripheral neuropathy are characterised by having a slower gait speed, shorter step and stride lengths, reduced cadence, a longer duration of double support and a reduced duration

of single support compared with healthy subjects.[33-40] Subjects with diabetic neuropathy have a longer duration of the stance phase, in which the foot is in contact with the ground, a shorter duration of the swing phase, and a longer duration of the gait cycle than the control group.[34,35] A longer stance phase increases plantar pressure and with other mechanisms, contributes to the development of plantar ulcers, and when these are present, the gait is altered even further, perpetuating the formation of ulcers and hindering their healing.[41]

Despite efforts to study gait disturbances in DPN, the relationships between gait parameters and the impairment of different sensory modalities have not been clarified. The aim of this study was therefore to analyse associations between gait spatiotemporal parameters and deep and superficial somatic sensitivity and to determine the role of clinical variables and comorbidities related to diabetes manifestations and diabetic control.

2 | MATERIALS AND METHODS

A cross-sectional study was carried out in diabetic patients to explore relationships between gait parameters measured by sensors and peripheral neuropathy variables. The study was conducted at the diabetic foot consultation unit in the Rizzoli Orthopaedic Hospital in Bologna, Italy, between September and December 2021. The study was conducted with the approval of the University of Bologna Ethics Committee for Human Research (Reference: 659/2021/Sper/IOR). The participants were recruited through a research proposal to the University of Bologna under the agreement established with the University of Valencia for research purposes. All the procedures were realised in accordance with the ethical requirements of the Helsinki Declaration. All the hospital's diabetic patients were contacted by telephone to explain the objectives of the study and the procedure, and they signed the informed consent before joining the study.

The inclusion criteria were as follows: (1) individuals of both genders; (2) individuals aged 18 years or older; (3) type 1 or type 2 diabetics. The exclusion criteria were: (1) subjects without severe cognitive impairment or poorly controlled psychiatric problems; (2) presence of active ulcers on the feet; (3) cancer patients; (4) subjects with retinopathy; (5) subjects with Charcot foot; (6) subjects with lower limb injuries or fractures in the previous 6 months; (7) a history of orthopaedic lower limb surgery in the last year. In addition, they were told to bring a blood test performed within the last 3–4 months and their usual medication. A clinical, gait and peripheral neuropathic assessment was carried out on each participant.

2.1 | Clinical data

Age, gender, marital status and the patient's cohabitation or otherwise, type of diabetes, its treatment and time evolution, smoking habit and mean number of cigarettes per day, body mass index, and presence of arterial hypertension were recorded. The history of foot ulcers and lower limb amputations was noted. A podiatric examination of foot deformities such as hallux valgus and claw toes was performed.

The blood analysis provided by the patient was also collected, and we were mainly interested in parameters related to renal function, glycemic and lipid status (creatinine, glomerular filtration rate, HbA1c, glycemia, LDL and HDL cholesterol and triglyceride). The participants were classified into two renal function categories based on their glomerular filtration rate according to the American Journal of Kidney Disease: (1) renal insufficiency (<90 GFR) and (2) normal function (90–119 GFR).[42]

2.2 | Gait assessment

Two scales were used to evaluate the risk of falls: the Tinetti Scale and the Downton Index. The Tinetti Scale is one of the most useful tools for assessing the functional level of the population and examines two aspects: balance and gait. The gait part of the test contains seven items with a total score of 12 points, while in the balance part, there are nine items with a total score of 16 points. The final score of the scale is 28 points, and the interpretation is as follows: 25–28 = low risk of falls; 19–24 = moderate risk of falls, and <19 = high risk of falls.[43,44] The Downton Index assesses items grouped in five categories that are related to the risk of falls: previous falls, medication, sensory deficit, mental state, and ambulation.[45] A total score of 3 or more indicates a risk of falls. This is an instrument with high sensitivity for predicting fall risks, and as such, it is very useful in preventive programs.[46]

The system used to analyse gait parameters was Wiva Science, a wearable inertial system that contained a sensor (inertial measurement unit [IMU]). This sensor consists of a tri-axial accelerometer, a tri-axial gyroscope, and a magnetometer for detecting several spatiotemporal parameters, as well as a micro-electro-mechanical system (MEMS) designed to capture motion and translate mechanical energy into electrical energy by applying an algorithm.[33,47] The sensor was placed in the lumbar area on the L5 spinal segment using an elastic band, according to the manufacturer's recommendations, and the patients were asked to walk at their usual speed for 15 m. This 15-m walk included back and forth. When the patients

reached the halfway point, they had to remain immobile for 3 s in the standing position, turn around, let another 3 s pass, and start walking again towards the starting point. After this procedure, the Wiva Science sensor sent the information collected to a computer via Bluetooth, and the data were stored in the Biomech Study 2011 v.1 software package. Many other studies have been carried out using these sensors with similar methodologies for studying gait disturbances in different pathologies and disorders.[47-52] The following parameters are thereby obtained: gait speed, cadence, stride length, gait cycle duration, stance and swing duration phases, double and single support duration, step length, stance period, variability, maximum velocity of acceleration, gradient acceleration, and gradient deceleration. Table 1 shows the description of each gait parameter.[53,54]

2.3 | Neuropathic assessment

The evaluation of superficial and deep sensitivity by means of different tests provides valuable information about the integrity of the two sensory pathways: the dorsal column–medial lemniscal system or deep sensitivity pathway and the anterolateral system or superficial sensitivity pathway, which can be useful in the diagnosis of diabetic neuropathy. The superficial sensitivity pathway was examined by assessing nociception using the Pin-Prick test (Neuropen)[16] and deep sensitivity was evaluated by analysing light touch-pressure with the 5.07 Semmes-Weinstein monofilament (SWMT) (10 g), and the vibration perception threshold (VPT) using two instruments: biothesiometer Polyneuro^{+} (Diabetik Foot Care Pvt Limited, India) and 128-Hz Rydel-Seiffer diapason (Podoservice, Spain). Two different instruments were used to assess the sensation of vibration because vibration is perceived through two main types of mechanoreceptors, the Meissner corpuscles (MCs) and Pacinian corpuscles (PCs) associated with large fibres (Aβ fibres). MCs are located in hairless superficial skin, and they detect low-frequency vibrations of between 30 and 50 Hz, while PCs are present in subcutaneous tissue, muscles and joint capsules, and their function is to detect deep pressure and high-frequency vibration of between 100 and 400 Hz.[32] The sensory signals coming from both structures are transmitted in the same way and in the same large nerve fibres (Aβ) until they reach the primary somatosensory area of the cortex,[32] but they are structurally different receptors, their locations are also different, and they are sensitive to different frequency ranges. For this reason, although vibratory stimuli arrive at the same destination in the same way, their origin, where they are

TABLE 1 Definitions of spatiotemporal parameters of gait by inertial sensor.

Parameters	Definitions
Gait speed (m/min)	Ratio between the length and duration of the gait cycle.
Cadence (step/min)	Number of steps per minute.
Stride length (cm)	Distance between two successive contacts with the ground of the same foot. It is composed of two-step lengths, left and right.
Gait cycle duration (s)	Time interval between the first contact of two footsteps of the same foot.
Stance duration (%)	This is the phase of the gait in which the foot is in contact with the ground. It begins when the foot touches the ground for the first time, and ends when the same foot rises from the ground. This phase accounts for approximately 40% of the gait cycle.
Swing duration (%)	This is the phase of the gait in which the foot is oscillating in the air and is not in contact with the ground. It begins when the foot rises from the ground, and ends when the same foot comes into contact with the ground again. It accounts for approximately 60% of the gait.
Double support duration (%)	This is the period in which the 2 ft are in contact with the ground, between the initial contact by the first foot and the last contact by the second foot. It accounts for 10% (twice in the same gait cycle).
Single support duration (%)	This is when only one foot is in contact with the ground. It accounts for 40% of the gait cycle.
Step length (cm)	The distance between initial contact by one foot and the initial contact of the opposite foot.
Stance period (s)	The time interval during which the foot is in contact with the ground.
Variability (%)	The standard deviation of the gait cycle duration
Max. velocity of acceleration (m/sec^2)	Peak acceleration
Gradient acceleration	Variation of the acceleration during the gait between two points of a certain distance.
Gradient deceleration	Variation of the deceleration during the gait between two points of a certain distance.

generated, is different, and their affectation could also be different. For a broader study of deep sensitivity pathway impairment, two instruments with the ability to stimulate the same sense in different ways were therefore used. SWMT, which is used to assess light touch and pressure, evaluates the sensitivity of three receptors: Meissner corpuscles, Merkel cell–neurite complexes and Pacinian corpuscles. By analysing the VPT and using the SWMT, we can assess the dorsal column–medial lemniscal system and identify large fibre neuropathy.[19,55,56]

Prior to the assessment of each sensation, the patients were reminded that when they perceived the stimulus, they had to express this verbally. They were reminded of this procedure as many times as necessary during the examination, and we avoided asking if they noticed it every time we stimulated an area, as this could pressure the patients to answer 'yes' and misrepresent the results of the investigation. The procedure of each test was explained before the assessment, and a demonstration was performed on the participants' hands so that they could identify the sensation. The patients had to be lying or sitting with their feet raised, without shoes or socks, and with a screen to prevent them from looking at their feet during the examination.

2.3.1 | Superficial sensitivity

The Pin-Prick test protocol was carried out on six sites: the plantar fingertip of the first toe, the first and fifth metatarsal heads, the outer plantar edge of the foot, the medial arch and a dorsal area of the hallux, near to the nail fold. Previously, we performed a demonstration with the blunt end of the instrument and with the sharp tip so that the patients would be able to distinguish between the tactile and the painful sensations. The instrument was pressed perpendicularly onto the skin plantar surface at each location until the sharp tip retracted, and the patients indicated if they detected a sensation of pain by raising their hand.[16,57] The Pin-Prick test was considered abnormal when the patients did not notice the painful stimulus in the dorsal area of the hallux near the nail fold.[18,58]

2.3.2 | Deep sensitivity

Semmes-Weinstein monofilament was applied at 10 locations, 9 on the plantar surface and 1 on the dorsum of the foot, which coincide with the different foot dermatomes: the plantar fingertips of the first, third and fifth toes; the first, third and fifth metatarsal heads; the outer plantar edge of the foot, the medial arch, the heel and the dorsal interdigital area (between the first and second toes). The instrument was placed perpendicular to the skin surface, and pressure was applied until the monofilament buckled. This pressure was maintained for 1 second, and the instrument was then removed and the patients' possible response was awaited. This procedure was carried out on both feet.[18,57,59] Application of the monofilament directly on ulcers, scars, callus and necrotic tissue was avoided.[60] The test was classified as abnormal when the patients did not detect the pressure at 4 of 10 locations, following the evidence.[61,62]

The VPTs were measured with both instruments at the same five bone prominences on the right and left feet: on the distal dorsal area of the big toe, first and fifth metatarsal heads and medial and lateral malleolus.[60,63,64] For the assessment with the diapason, the examiner hit the 128-Hz Rydel-Seiffer tuning fork against the palm of his hand to make it vibrate, and it was applied perpendicularly to the different sites. The test started with a maximum vibration of 8 to 0. The patients were asked to state when they stopped feeling the vibration, and the vibration was then quantified. The test was considered abnormal on the distal dorsal area of the big toe for values ≤ 6 in the population younger than 60 years, and for values ≤ 4 in patients older than 60 years.[18] With the biothesiometer, we started by applying a 25 V vibration: if the patients did not detect that vibration intensity, it was gradually raised until they detected it or until it reached its maximum (50 V). However, when the patients felt the 25 V vibration, it was decreased until they stopped feeling it. We recorded the number immediately before the voltage was detected, that is, the vibration intensity at which the patients stopped feeling. According to the evidence, not feeling values greater than 25 V in the dorsal area of the big toe is associated with an ulceration risk, and it has demonstrated high levels of sensitivity and specificity in the detection of distal symmetric polyneuropathy.[58,63-65]

After the whole examination, the presence of sensory diabetic neuropathy (SDN) was established with the results of the light touch-pressure using the monofilament and the vibration sensation using the biothesiometer, according to the recommendations of the International Working Group of the Diabetic Foot (IWGDF).[66]

2.4 | Statistical analysis

In the descriptive analyses, the mean, standard error mean, maximum and minimum were obtained for quantitative variables, and frequencies and proportions were obtained for categorical variables. The Kolmogorov–

Smirnov test (n > 50) was used for analysing the data distribution. In general, they showed non-normal data distribution for all neuropathic test variables and for most gait parameters and clinical and sociodemographic data. Depending on the result of normality test, parametric or non-parametric tests were applied in bivariate analysis. When analysing the relationships between numerical variables, we used the non-parametric test of the Spearman correlation coefficient and the parametric test of the Pearson correlation coefficient, while the associations between the quantitative variables and categorical variables were analysed by the *U* Mann–Whitney non-parametric test and the Student's t parametric test. A binary logistic regression analysis was used to predict which variables of gait were related to alterations of sensory modalities in diabetic patients. Logistic regression (LR) is used as a predictive model to simultaneously examine some independent variables that are supposedly related to the dependent variable. In our research, five binary regression analyses were performed with a backward model for each dependent variable related to sensory alterations. We used gait parameters analysed by sensors and the results of the Tinetti and Downton scales as independent variables.

A confidence level of 95% with a statistical significance of $P < .05$ was used throughout the analysis. The data were analysed using the IBM SPSS 25.0 statistical software package.

3 | RESULTS

3.1 | Description of the sample

A total of 85 diabetic participants with a mean age of 68.1 (±1.3) years (aged between 20 and 87 years), participated in the study. The sociodemographic and clinical characteristics are presented in Table 2. Of these participants, 25 (29.4%) lived alone, 3 (3.5%) with their children, 1 (1.2%) with their parents, 11 (12.9%) lived with the whole family, 43 (50.6%) lived with their wife, husband, or partner and 2 (2.4%) shared a home with someone. Among the 11 (12.9%) smokers participating, the mean number of cigarettes smoked per day was 14.2 (±3.7) with a minimum of 1 and a maximum of 45. The evolution time of type 1 diabetes was 32.4 years (±4.6) ranging from 4 to 63 years, while for the group of type 2 diabetics, it was 14.9 (±1.2) with a minimum of 2 years and a maximum of 41. 6 (7.1%) of the participants had no treatment for diabetes. 19 (22.4%) participants were taking took insulin, 40 (47.1%) oral anti-diabetic drugs and 20 (23.5%) had a combined treatment of both.

As regards foot complications, 6 (7.1%) patients developed ulcers in one of the feet during their diabetes, 2 (2.4%) developed bilateral ulcers, while 77 (90.6%) had no ulcers. 82 (96.5%) participants had no history of amputations and 3 (3.5%) had experienced unilateral amputations. 37 (43.5%) patients had no deformities, while 7 (8.2%) had unilateral deformities and 41 (48.2%) had bilateral deformities. 59 (69.4%) participants had no history of Hallux Valgus; however, 7 (8.2%) had it unilaterally and 19 (22.4%) bilaterally. In addition, 35 (41.2%) had claw toes, compared with 50 (58.8%) who did not.

On the Tinetti scale, 6 (7.1%) individuals had a high risk of falls, 34 (40.0%) had a moderate risk of falls and 45 (52.9%) individuals had low risk of falling. On the Downton scale, 39 (45.9%) participants were found to be at risk of falls compared with 46 (54.1%) who were not.

TABLE 2 Sociodemographic and clinical characteristics of diabetic patients.

Age (years)	Mean ± SEM: 68.1 ± 1.3 (Minimum 20 - Maximum 87)
HbA1c (mmol/mol)	Mean ± SEM: 52.9 ± 1.3 (Minimum 33 - Maximum 86)
Glycemia (mg/dL)	Mean ± SEM: 128.7 ± 4.5 (Minimum 63 - Maximum 261)
Gender	46 males; 39 females
Marital status	Single: 12 (14.1%) Married: 49 (57.6%) Widow/Widower: 13 (15.3%) Divorced: 11 (12.9%)
Type of diabetes	Type 1: 18 (21.2%) Type 2: 67 (78.8%)
Smoking habit	Non-smoker: 74 (87.1%) Smoker: 11 (12.9%)
BMI	Normal (18.5–24.9): 26 (30.6%) Overweight (25–29.9): 39 (45.9%) Obese ≥30: 20 (23.5%)
Arterial hypertension	No: 33 (38.8%) Yes: 52 (61.2%)
Renal function impairment	Normal function (90–119 GRF): 17 (25.4.%) Renal insufficiency (<90 GFR): 50 (74.6%)
Digital deformities	37 (43.5%) with deformities 48 (56.6%) without deformities

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; SEM, standard error mean.

TABLE 3 Sensory neuropathy evaluation (both feet).

Superficial sensitivity	Painful sensitivity: 11 of 85 altered (12.9%) versus 74 normal (87.1%)
Deep sensitivity	Light touch-pressure: 16 of 85 altered (28.6%) versus 68 normal (81%)
	Vibratory sensation (DP): 20 of 85 altered (23.8%) versus 64 normal (76.2%)
	Vibratory sensation (BTM): 33 of 85 altered (38.8%) versus 52 normal (61.2%)
Presence of SN	15 individuals of 85 with SN (17.6%) versus 70 individuals without SN (82.4%)

Abbreviations: BTM, biothesiometer; DP, diapason; SEM, standard error mean; SN, sensory neuropathy.

A sensory neuropathy evaluation was conducted using different tools on the feet to that end (Table 3).

3.2 | Analysis between gait parameters and sensory evaluation

We next evaluated which gait parameters are related to different impairments of sensory modalities in a binary logistic regression model. Regression logistic analyses showed which gait parameters are more significantly associated with the different somatosensitive neuropathies. Lower light touch-pressure sensitivity was significantly associated with reduced gait speed (OR = 0.52, 95% IC = 0.31–0.88, $P = .015$), lower cadence (OR = 12.9, 95% IC = 2.57–65.15, $P = .002$), reduced stride length (OR = 1.39, 95% IC = 1.07–1.82, $P = .014$) and increased stance period (OR = 1.17, 95% IC = 1.04–1.32, $P = .012$). Lower vibratory sensitivity measured by diapason was significantly associated with lower cadence (OR = 8.80, 95% IC = 1.88–41.11, $P = .006$), increased stride length (OR = 1.61, 95% IC = 1.13–2.29, $P = .009$), increased mean step length (OR = 0.41, 95% IC = 0.21–0.88, $P = .014$) and a longer stance period (OR = 1.22, 95% IC = 1.07–1.39, $P = .004$). Lower vibratory sensitivity measured by biothesiometer was significantly associated with reduced cadence (OR = 2.61, 95% IC = 1.04–6.51, $P = .040$) and a longer stance period (OR = 1.09, 95% IC = 1.01–1.19, $P = .034$). Finally, the presence of sensory neuropathy (SN) was significantly associated with a lower gait speed (OR = 0.48, 95% IC = 0.27–0.85, $P = .011$), reduced cadence (OR = 20.82, 95% IC = 3.25–133.32, $P = .001$), reduced stride length (OR = 1.46, 95% IC = 1.09–1.95, $P = .010$) and a longer stance period (OR = 1.21, 95% IC = 1.05–1.38, $P = .007$). The main significant differences in gait parameters between patients with and without sensitivity impairments are shown in Figure 1.

In contrast, painful sensitivity was not significantly associated with any of the gait parameters analysed. The following gait parameters did not show any relationship with sensitivity alterations: gait cycle duration, stance duration, swing duration, single and double support duration, variability, maximal velocity of acceleration, gradient acceleration and gradient deceleration (data not shown).

Interestingly, worse scores on the Tinetti scale (but not the Downton scale) were significantly associated with lower light-touch pressure (OR = 0.59, 95% CI = 0.41–0.85, $P = .005$), lower vibratory sensitivity measured by diapason (OR = 0.72, 95% CI = 0.53–0.97, $P = .032$) and with the presence of peripheral neuropathy (OR = 0.59, 95% CI = 0.40–0.88, $P = .009$).

3.3 | Associations between neuropathy measurements and age, sex and comorbidities

Regression-logistic analyses were performed in order to evaluate which clinical variables (age, gender, type of diabetes, years since DM diagnosis, smoking, arterial hypertension, overweight/obesity, reduced renal glomerular filtration rate and foot ulcer history) could be associated with lower sensitivity and the presence of neuropathy. Compared with patients with type I diabetes, those with type II diabetes had more impaired vibratory sensitivity in both the diapason test (OR = 20.19, 95% CI = 1.54–265.10, $P = .022$) and with the biothesiometer (OR = 13.52, 95% CI = 1.60–114.10, $P = .017$). The number of years since the DM diagnosis was significantly associated with reduced vibratory sensitivity measured with the biothesiometer (OR = 1.08, 95% CI = 1.03–1.14, $P = .003$) and with the presence of neuropathy (OR = 1.06, 95% CI = 1.0–1.13, $P = .047$). As expected, a previous history of foot ulcers was significantly associated with all types of sensitivity, for example, reduced light touch-pressure (OR = 9.4, 95% CI = 1.49–59.66, $P = .017$), reduced vibration sensitivity measured with the diapason test (OR = 14.44, 95% CI = 1.79–116.79, $P = .012$) and with the biothesiometer (OR = 8.33, 95% CI = 1.3–67.33, $P = .047$), reduced painful sensitivity (OR = 6.75, 95% CI = 1.21–37.63, $P = .029$) and with the presence of sensory neuropathy (OR = 12.10, 95% CI = 1.82–80.52, $P = .010$). In contrast, age, gender, overweight/obesity, arterial hypertension and reduced renal glomerular filtration rate were not significantly associated with any sensitivity impairment variables (data not shown).

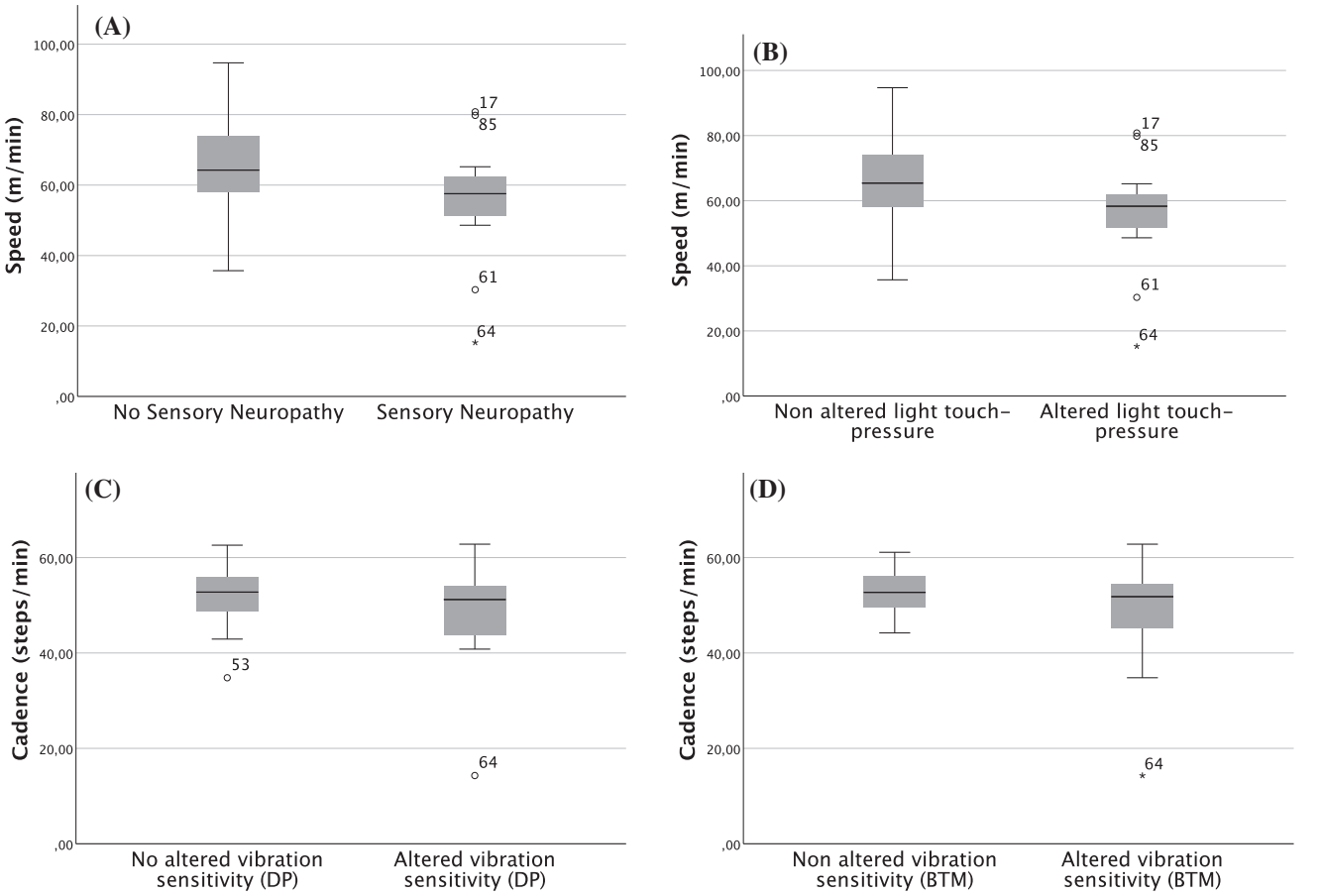

FIGURE 1 Significant differences in gait speed between patients with and without sensory neuropathy (A), in speed between patients with and without altered light touch-pressure (B), in cadence between patients with and without altered vibration sensitivity as measured by diapason (DP) (C) and by biothesiometer (BTM) (D).

4 | DISCUSSION

Our findings confirm the relationship between deep sensitivity impairment and some gait parameters in diabetic patients as measured by inertial measurement units (IMUs), a convenient tool for measurement of feet motion outside laboratory settings because of their low cost and ease of use.[38] However, no correlation was found with superficial sensitivity. This pattern of nerve involvement suggests that proprioception sense is damaged simultaneously to the sensory modalities (light touch-pressure and vibration sensation) that are transmitted by the same pathway and by the same types of fibres (large myelinated Aβ fibres), which reinforces the importance of vibratory and cutaneous plantar sensory afferences for walking, as other authors have indicated.[7,9,19] Of all the parameters studied, only gait speed, cadence, stride and step length and stance period maintained the relationship with sensory loss in a simultaneous analysis model. The damage of light touch-pressure and vibration sensitivity was correlated with a slower gait velocity, shorter stride length, lower cadence and a longer stance period. These results for gait parameters are consistent with previous studies performed in diabetic patients.[33-40] Altered deep sensitivity measured by diapason was correlated with shorter stride and step lengths, but stride and step lengths were increased when these parameters were analysed in the presence of sensory neuropathy (SN) and with light touch-pressure. Other studies[48,67] have suggested an increase in cadence as a compensation for reduced step and stride lengths and lower gait speed. In our case, it is possible that the length of the steps may be increased to compensate for loss of speed and cadence, but we suggest that correlations between these reduced gait parameters and altered light touch-pressure and the presence of SN are stronger because they include the association of two sensory assessment tests.

Our findings coincide with those of Menz HB et al.[26] who showed a significant relationship between gait speed and step length with vibration and tactile sensitivity in DPN patients; however, no superficial sensory modalities were analysed, and only one measure of deep sensory pathway has been considered. On the other hand, the analysis of both sensory pathways performed in our study

has allowed us to show the relationship that deep sensitivity damage has on the balance and gait, proposing of future research lines and clinical interventions in the sensory and walking field.

Although few studies have been dedicated to this question, some of them reinforce the relationships between gait parameters and specific sensory losses that have been found in this study, especially in the case of vibratory sensitivity. Brown S et al.[20] showed that diabetics with DPN develop balance impairment during movement, predominantly in the medial-lateral plane, and they found a positive correlation between medial-lateral dynamic sway and reduced vibratory sensation measured with a biothesiometer. Allet L et al.[21] found abnormalities in gait parameters even before sensory loss was clinically detected, in this company by a Rydel-Seiffer diapason in this case. In our case, the differences were found in results between neurothesiometer and diapason measures: we observed a closer relationship between altered gait parameters and sensory vibration loss measured by the neurothesiometer in bivariate analysis. A recent study[68] concluded that there was no difference between the Rydel-Seiffer diapason and the neurothesiometer in the polyneuropathy diagnosis for both clinical and research purposes, although diabetic patients were not included in this research. Of all the sensory variables considered in our study, 'the presence of sensory neuropathy,' established by the combination of monofilament and VPT by neurothesiometer, was the variable that was related to the most gait abnormalities, which reinforces the importance of both deep sensory modalities during walking.

Our results have shown correlations between an increased risk of falls quantified by the Tinetti Scale and light touch-pressure, altered vibratory sensitivity measured by diapason and the presence of sensory neuropathy. We suggest that deep sensory pathway impairments lead to balance impairment, and changes in gait become necessary to avoid falls. In fact, shorter step and stride lengths are widely reported in populations with a risk of falls[38,48] and it has been considered a compensatory strategy to maintain a closer control of mass centre and reduce the risk of falling.[20,69,70]

The somatosensitive impairment that seems to develop in the early stages of DPN is followed by dysfunction of the neuromuscular system, leading to muscle atrophy and muscular weakness.[71] In addition, hyperglycemia seems to lead to increased tendon stiffness, reduced extensibility of the Achilles tendon and finally, limited dorsiflexion ankle mobility.[72] All these factors favour the development of bony deformities and plantar pressure increase, and eventually foot ulcers. In this context, it has been suggested that the mechanical pressures exerted on the sole of the foot during gait are a key factor in the development of plantar ulcers.[73] The stance period, which is the time when the foot is in contact with the ground, has been proposed as an important factor in the formation of foot ulcers. As other studies have shown, a longer stance period has been observed in diabetics.[37,38,73] In fact, Fernando M et al.[41] showed that diabetic patients with higher plantar pressures and active ulcers had a longer stance period.

We observed a greater frequency of large-fibre neuropathy than small-fibre neuropathy, which is contrary to the results of other studies. It has previously been argued that small-fibres and unmyelinated fibres are more susceptible to damage from metabolic changes than large myelinated fibres, with an earlier appearance of small-fibre neuropathy during diabetes.[12,13,74-77] Nevertheless, a recent prospective study conducted on type 2 diabetics[78] failed to show that nerve damage during DPN begins affecting small fibres and progresses to affect large fibres, as has been suggested to date, and in line with our results, they detected a large proportion of patients with large-fibre neuropathy.

As for clinical variables, a 'previous history of foot ulcers' was the only clinical variable associated with small fibre neuropathy (superficial sensitivity pathway) determined by pain sensitivity. In fact, painful neuropathy has been associated with diabetic foot[79] which is the clinical entity resulting in widespread neuropathy-based injury among patients with diabetes uncontrolled for long periods of time.[80,81] The clinical variables that were associated with impaired deep sensitivity were type II diabetes and the number of years since the DM diagnosis. Likewise, impaired vibratory sensitivity assessed in malleolus and hallux has been reported as higher in type 2 diabetic patients than in type 1 diabetic patients,[82-85] as it was found in 40% of type 2 diabetics and in approximately 12% of type 1 diabetic patients,[83,85] and in another study,[84,85] a reduced vibration sense was not significant in type 1 diabetics, thereby reinforcing the data on higher threshold values in type 2 patients than in type 1 patients. The risk of developing peripheral neuropathy increases with a longer duration of diabetes, as observed in both type 1[86,87] and type 2 diabetics.[87-89]

This study also has some limitations. First, the sample of type 1 diabetics was insufficient to make a comparison with type 2 diabetics. We believe it is important to study the differences in peripheral nervous impairment between the two types of diabetes to improve understanding of the pathology and its treatment.[85] Studies with a larger sample are required. Second, it is possible that the use of a particular type of footwear by all the participants would yield more reliable results for gait parameters. Measures of motor neuropathy, which plays an important

role in gait alteration, were not included in this study. After some questions about the relationships between sensory damage and gait parameters have been clarified, further studies should evaluate muscle function and damage and gait parameters in diabetic patients, as deep sensitivity can also alter motor responses.

In conclusion, the deep sensitivity pathway impairment seems to have a significant implication in gait alterations, as evidenced by the fact that the score of the Tinetti scale was significantly associated with presence of sensory neuropathy in this study. Gait speed, cadence, stride length, step length and stance period are the main gait parameters associated with deep sensitivity alteration. Larger studies are needed to clarify the course of nerve fibre impairment in DPN and to expand knowledge of the influence of this damage on gait and posture. Clarifying these issues will enable improved planning of the diagnosis and management of diabetes complications related to gait impairment.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mar Sempere-Bigorra https://orcid.org/0000-0003-4161-276X
Lorenzo Brognara https://orcid.org/0000-0002-5660-9419
Iván Julian-Rochina https://orcid.org/0000-0002-1782-0019
Antonio Mazzotti https://orcid.org/0000-0001-9974-4787
Omar Cauli https://orcid.org/0000-0001-5669-4943

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