Original Article

Neurophysiological assessment of peripheral neuropathy through whole plantar nerve conduction in type 2 diabetes mellitus and healthy control subjects

Dario Ricciardi[1,#], Raffaele Galiero[2,#], Vincenzo Todisco[1], Gioacchino Tedeschi[1], Giuseppe Loffredo[2], Alfredo Caturano[2], Luca Rinaldi[2], Giovanni Cirillo[3,§], Ferdinando Carlo Sasso[2,§]

[1]Division of Neurology and Neurophysiopathology, University of Campania "Luigi Vanvitelli", Naples I-80138, Italy.
[2]Division of Internal Medicine, University of Campania "Luigi Vanvitelli", Naples I-80138, Italy.
[3]Neuronal Networks Morphology Lab, Division of Human Anatomy, University of Campania "Luigi Vanvitelli", Naples I-80138, Italy.
[#]Co-first authorship.
[§]Co-last authorship.

Correspondence to: Prof. Ferdinando Carlo Sasso, Dr. Raffaele Galiero, Division of Internal Medicine, University of Campania "Luigi Vanvitelli", Piazza Luigi Miraglia 2, Naples I-80138, Italy. E-mail: ferdinandocarlo.sasso@unicampania.it; raffaele.galiero@unicampania.it

Abstract

Aim: To neurophysiologically characterize the innervation of the sole and assess the diagnostic efficacy of whole plantar nerve (WPN) conduction study in type 2 diabetes mellitus (T2DM) patients and healthy control subjects.

Methods: This single-center prospective observational case-control study involved 51 individuals with T2DM and 34 healthy controls. All subjects underwent validated screening tests for peripheral neuropathy (PN), including proximal and distal sural nerve conduction study and WPN.

Results: The median amplitude of the compound nerve action potentials (CNAPs) and the sensory conduction velocity (SCV) recorded by WPN conduction were significantly lower in patients with T2DM as compared to healthy controls. Sural nerve conduction revealed that both proximal and distal sensory nerve action potentials

amplitude and SCV were significantly lower in subjects with diabetes, as compared to healthy controls. As compared with sural nerve conduction, WPN shows a Sensitivity of 77% and a negative predictive value (NPV) of 77%.

Conclusions: WPN conduction study is helpful in characterizing the most distal nerve fibers in patients with T2DM and healthy controls. WPN may represent a useful tool in the diagnosis of length-dependent diabetic polyneuropathy.

Keywords: Whole plantar nerve conduction study, sural nerve conduction, type 2 diabetes mellitus, peripheral neuropathy

INTRODUCTION

Approximately 500 million people suffer from type 2 diabetes mellitus (T2DM), one of the most common chronic diseases in Western countries and a leading cause of death[1]. Peripheral neuropathy (PN), retinopathy and nephropathy represent the major microvascular complications of the diabetic disease, and severely impact the patient's prognosis[2]. PN, in particular, affects 70% of subjects with T2DM and is often present by the time of the diagnosis. Early diagnosis of PN, therefore, is of outstanding importance for its prognostic value and prevention of severe complications (i.e., limb amputation)[3]. The pathophysiology of diabetic PN is not completely known: inflammatory distress, metabolic dysfunction, oxidative damage, and small-vessel (vasa nervorum) ischemia seem to be involved[4,5]. Damage of the nerve fibers (large, small and/or autonomic fibers) might be present at various levels (nerves, plexus, and roots), with different clinical distribution (focal, multifocal or generalized) and clinical manifestations[6-9]. The most frequent clinical presentation of diabetic PN is a symmetric sensory-motor axonal neuropathy, characterized by large nerve fiber impairment and a length-dependent pattern, with initial involvement of sensory nerves. This damage thus involves primarily the longest fibers (e.g., sciatic and sural nerve) with a centripetal axonal degeneration from the lower limb extremities to nerve roots[10]. Patients usually complain of paresthesia and distal tingling and neurological examination could show decreased perception of thermo-nociceptive and vibratory stimuli, distal muscle weakness and atrophy[11].

Clinical neurological examination supports PN diagnosis also through useful questionnaires for the evaluation of classical symptoms, like the Neuropathic Pain 4 Questions (DN4), and validated clinical scores such as the Michigan Neuropathy Screening Instrument (MNSI) and the Neuropathy Disability Score. However, nerve conduction study (NCS), through the observation and calculation of potential action amplitudes, velocity, and latency, evaluates peripheral nerve function directly and objectively. Moreover, the electrophysiological study of the sural nerve represents the diagnostic gold standard. In few cases, the diagnostic algorithm is completed by skin biopsy, especially in unclear conditions and when a small fiber neuropathy is suspected[12,13].

Whole plantar nerve (WPN) conduction study permits the simultaneous registration of both lateral and medial plantar nerves, the two nerves of the foot sole, providing the conduction parameters (amplitude, latency and conduction velocity) of a compound nerve action potential (CNAP). This latter is the summation of the two single plantar nerve amplitudes[14,15]. Consistent with the above-described pathophysiology of PN in diabetes, it is expected that WPN, evaluating the most distal nerve extremities, could represent a sensitive technique in detecting patients affected by length-dependent neuropathy. This result could be verified by comparing expected high CNAP amplitudes obtained from healthy subjects with expected lower nerve conduction amplitudes obtained from subjects with T2DM. Moreover, it is expected that neurophysiological differences between the two populations could be consistent with population

differences obtained through the gold standard evaluation, sural nerve conduction study[14,15]. Here, we demonstrate the capability of WPN in detecting nerve conduction impairment, by comparing nerve conduction parameters obtained in two different groups of subjects. Therefore, we aim to assess the reliability of WPN conduction in the evaluation of foot-nerve sole innervation in a population of T2DM patients and healthy controls (HCs).

MATERIALS AND METHODS

Study design

This single-center prospective observational case-control study was carried out in 51 T2DM patients and 34 HC subjects referred to the Internal Medicine Unit of the University of Campania "Luigi Vanvitelli" between October 2019 and October 2020. Pregnant women, subjects < 18 years old, and those affected by any other form of either diabetes or suspected neuropathy were instead excluded (e.g., type 1 diabetes, alcoholic, vasculitic, nutritional and drug-induced/toxic neuropathies, tarsal tunnel). The study was approved by our local Ethics Committee and is in accordance with the Declaration of Helsinki and its later amendments. All HCs and T2DM individuals provided written informed consent for the use of clinical data for research purposes.

Endpoints of the study

The primary endpoint is the assessment of the capability of WPN conduction study in characterizing the innervation of the foot sole in a population of T2DM patients and HCs.

The secondary endpoints were: the assessment of WPN conduction study accuracy in the early detection of diabetic PN, through the assessment of the diagnostic accuracy and agreement of WPN as compared to the gold standard, distal sural nerve conduction.

Clinical evaluation

Clinical history assessment, physical examination, and routine laboratory tests were obtained for each subject. Anamnestic data and clinical and laboratory exams, according to the most recent guidelines, allowed the diagnosis of dyslipidemia, hypertension, retinopathy, and renal failure[16-19]. Neurological examination, MNSI, DN4 and Neurotensiometer [vibration perception threshold (VPT)] analysis were performed to screen PN.

The neurological examination included evaluation of sensory (decreased or loss of proprioception, vibration and pain sensation, hypoesthesia at soft touch), motor (reduced/absent reflexes, weakness, and muscle atrophy), and autonomic (thermoregulatory mechanisms alteration) symptoms and signs. MNSI evaluated the presence of foot deformities and ulcers, with one point/foot assigned in the presence of deformities while another one in the case of ulcers. To complete MNSI, we also performed: (a) ankle reflex (0.5 points if decreased, 1 if absent); (b) vibration sensitivity through a 128 Hz diapason (0.5 or 1 point in the case of decreased or absent perception, respectively); (c) 10 g monofilament in order to evaluate tactile sensitivity (0.5 if the perception was absent on at least one of 4 points of stimulation at dorsal and sole of the foot, 1 point if the stimulus was not perceived at all points of stimulation). MNSI overall score ≥ 2.5 allowed a probable diabetic PN[12].

DN4 includes a neurological examination in case of suspicion of neuropathic pain, comprising 10 items, 7 of which on symptoms (pins and needles, numbness, itching, burning, painful cold, electric shocks, tingling) and 3 on signs (hypoesthesia at the touch, hypoesthesia at prick, brushing). If the total score is higher than 4, the test is recognized as positive[12,20].

All subjects underwent VPT evaluation. The stimulus was transmitted on the medial malleolus and distal joint of the toe, and results were adjusted for the age of subjects[21,22].

Neurophysiological evaluation
Synergy electromyography machine (Synopo, Milan, Italy) was used to perform all procedures, following the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) guidelines[23]. Neurophysiological tests were performed with subjects in a supine position, and foot skin had been cleaned with alcohol to decrease impedance and skin temperature at the plantar surface had been kept at 32 °C.

Cup electrodes for recording and disposable surface strip electrodes (Natus Neurology Incorporated) were applied to perform WPN conduction study orthodromically, simultaneously stimulating both the medial and plantar nerves [Figure 1A][14]. The cathode was placed on the sole at a variable distance from the active recording electrode, with the stimulating anode placed distally and parallel to it. The active recording electrode was positioned at the ankle, proximally to the flexor retinaculum, with the reference electrode 3 cm proximally. The ground electrode was applied between the stimulating and recording electrodes. Due to the individual variability of the foot length, the application of the fixed previously reported distance of 14 cm between the active electrode and the stimulating one was not ever permitted[14]. Thus, we placed the cathode at three-quarters of the sole and the anode 2 cm distally, and measured conduction parameters including CNAP amplitude [in microvolts (mV)] and sensory conduction velocity (SCV) (in m/s).

For sural nerve conduction (SNC), we obtained sensory nerve action potential (SNAP) amplitude and SCV of the proximal (sural region-lateral malleolus, distance 12 cm) and distal nerve segment (lateral malleolus-V metatarsal bone, distance 8 cm) [Figure 1B]. Proximal and distal sural SNAP amplitudes were used to calculate the proximal to distal ratio (P/D R).

Statistical analysis
Continuous variables were expressed as the median and interquartile range (IQR), assessed by the Shapiro-Wilk test, while categorical variables were expressed as numbers and percentages according to their distribution.

The Fisher Exact Test or the Chi-square test, with Yates correction, as appropriate, assessed group differences. Student's *t*-test or non-parametric Mann-Whitney U test was performed for continuous variables, according to their distribution. In addition, we also tested the accuracy of WPN with respect to the gold standard (distal sural nerve conduction) by computing Sensitivity and Specificity, negative predictive value (NPV) and positive predictive value (PPV). Linear Regression analysis was performed to evaluate the associations between WPN outcomes (amplitudes and velocities) and clinical variables in the overall population (T2DM subjects and HCs). A *P* value < 0.05 was considered statistically significant. All analyses were performed with SPSS 24 software (IBM, Armonk, New York), RStudio® and STATA 15.5 software (StataCorp. 2019. College Station, TX: StataCorp LLC).

RESULTS
General and clinical characteristics of the study population
34 HCs and 51 T2DM patients were finally included. The two sub-populations were homogeneously distributed for age and sex, and, as expected, median levels of glycemia (116 mg/dL *vs.* 82 mg/dL, *P* < 0.001) and HbA1c (6.9% *vs.* 5.6%, *P* < 0.001) were significantly higher in T2DM patients as compared to HCs. Likewise, as for renal function, median levels of creatinine (0.8 mg/dL *vs.* 0.7 mg/dL, *P* < 0.001) were significantly higher in T2DM individuals, while median estimated glomerular filtration rate (eGFR)
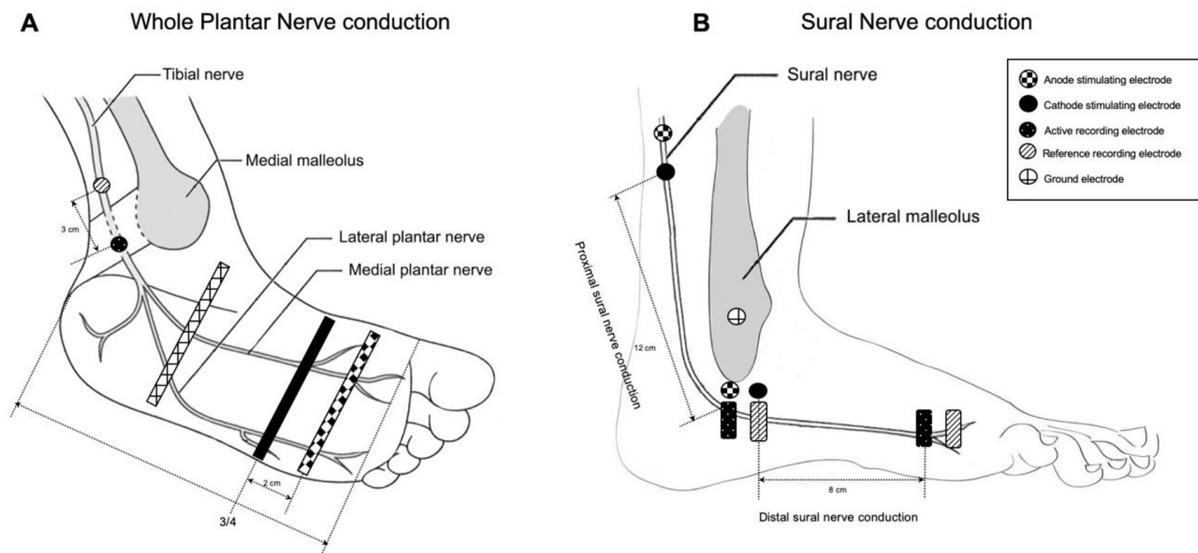
Figure 1. Neurophysiological techniques. Schematic representation of the neurophysiological setup for (A) WPN and (B) SNC. WPN: Whole plantar nerve; SNC: sural nerve conduction.

significantly lower in subjects with T2DM (80 mL/min/1.73 m^2 *vs.* 98.5 mL/min/1.73 m^2, $P < 0.001$). Moreover, T2DM patients showed an increased prevalence of systemic hypertension (77% *vs.* 47%, $P < 0.009$) and a significant difference in median HDL cholesterol. All results are shown in Table 1.

Assessment of PN in the study population
Neurophysiological results
WPN conduction study revealed significantly lower CNAP amplitude [1.8 (0.5-3.7) μV *vs.* 5.1 (2.2-9.9) μV, $P = 0.001$] and not significantly lower SCV [41.3 (35.6-45.7) m/s *vs.* 43.6 (39.2-48.0) m/s, $P = 0.06$] in patients with T2DM as compared to HCs [Figure 2 and Table 2].

Proximal SNC revealed that both SNAP amplitude [8.1 (3.8-12.2) μV *vs.* 13.0 (7.3-17.2) μV, $P < 0.001$] and SCV [49.5 (44.4-54.8) m/s *vs.* 53.6 (49.0-56.2) m/s, $P < 0.001$] were significantly lower in subjects with diabetes, as compared to HCs.

Similar findings were also obtained for distal SNC: both SNAP amplitude [3.2 (1.8-5.6) μV *vs.* 5.6 (3.1-8.4) μV, $P = 0.001$] and SCV [40.4 (35.5-45.2) m/s *vs.* 43.3 (38.5-46.9) m/s, $P = 0.010$] were lower in T2DM group [Figure 2 and Table 2].

Analysis of P/D R did not show any significant difference between the two groups [Table 2]. In agreement with SNC results, WPN conduction study shows significant differences between the two groups.

Clinical results
Analysis of the clinical test scores revealed that both MNSI and DN4 positivity were significantly more prevalent among individuals with T2DM as compared to HCs (23.4% *vs.* 3.0%, $P < 0.001$ and 35.4 % *vs.* 5.9%, $P < 0.001$, respectively). A similar result was observed for VPT (40.9% *vs.* 8.8%, $P = 0.002$).

Accuracy and clinical efficacy of the WPN technique
As the secondary endpoint of the study was to assess the diagnostic accuracy of WPN in identifying T2DM

Table 1. General and clinical-laboratoristic features of the study population

Parameter	HC (*n* = 34)	T2DM (*n* = 51)	*P*
Age (yrs.), median (IQR)	61 (25-74)	63 (29-81)	0.171
Sex, *n* (%)			0.827
M	17 (50)	27 (53)	
F	17 (50)	24 (47)	
BMI (kg/m^2), median (IQR)	25.1 (23.0-29.9)	29.0 (24.0-33.2)	0.055
Glycemia (mg/dL), median (IQR)	82 (63-102)	116 (71-180)	< 0.001
HbA1c (%), median (IQR)	5.6 (5.4-5.8)	6.9 (6.5-8.5)	< 0.001
T2DM duration (yrs.), median (IQR)	-	10 (1-40)	N.a.
Creatinine (mg/dL), median (IQR)	0.7 (0.7-0.8)	0.8 (0.8-1.1)	< 0.001
eGFR (mL/min), median (IQR)	98.7 (90.4-110.0)	80.0 (60.4-98.4)	< 0.001
Blood pressure (mmHg), median (IQR)			
Systolic	120 (100-150)	130 (100-180)	0.263
Diastolic	72 (55-85)	80 (55-90)	0.022
Hypertension, *n* (%)	16 (47)	36 (77)	< 0.009
Cholesterol (mg/dL), median (IQR)			
Total	170.5 (143.5-203.2)	156.0 (124.5-186.0)	0.270
HDL	45.5 (41.5-57.7)	41.0 (35.5-51.0)	< 0.031
LDL	96.5 (77.7-125.2)	99.0 (73.5-123.5)	0.053
Triglycerides (mg/dL), median (IQR)	116.0 (96.5-143.8)	109.0 (85.5-155.0)	0.924

HC: Healthy controls; T2DM: type 2 diabetes mellitus; IQR: interquartile range; M: male; F: female; BMI: body mass index; HbA1c: glycosylated hemoglobin; n.a.: not applicable; eGFR: estimated glomerular filtrate; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

subjects with PN, we used CNAP and SNAP amplitude cut-offs, respectively, for WPN and sural nerve conduction, previously obtained by our research group[15]. As a result, WPN conduction study identified 29 (57%) neuropathic patients, while distal sural nerve examination identified 22 (43%) neuropathic individuals [Figure 3]. We thus assessed the accuracy of WPN with respect to the gold standard distal sural nerve conduction study: the comparison of the outcomes of these two techniques displayed 17 true positives, 12 false positives, 17 true negatives, and 5 false negatives. Therefore, we reported a Sensitivity of 77%, a Specificity of 58%, a PPV of 58%, and a NPV of 77%. Figure 3 shows the confusion matrix of WPN *vs.* SNC.

A linear regression analysis was obtained to evaluate the effects of clinical variables on neuropathy according to WPN parameters [Supplementary Materials]. Both in T2DM subjects and HCs, increases in age and HbA1c seem significantly associated with a reduction in WPN amplitudes ($P = 0.001$; $P = 0.016$) [Supplementary Table 1]. An increase in HbA1c seems significantly associated with a reduction in WPN velocity ($P = 0.006$) [Supplementary Table 2].

DISCUSSION

In this paper, we aimed to assess the role of WPN conduction study in characterizing the foot-sole nerves in a population of T2DM patients and HCs. Although homogeneously distributed for age and sex, significant differences emerged between the two populations, as for both clinical characteristics and neurophysiological evaluation. Consistent with SNC results, WPN conduction study shows lower CNAP amplitude and SCV in T2DM subjects.

PN has been reported in about one-third of patients with T2DM and this percentage can increase to 50% of patients after a 4-year period of follow-up, independently of the treatment for diabetes[7,11]. Several risk
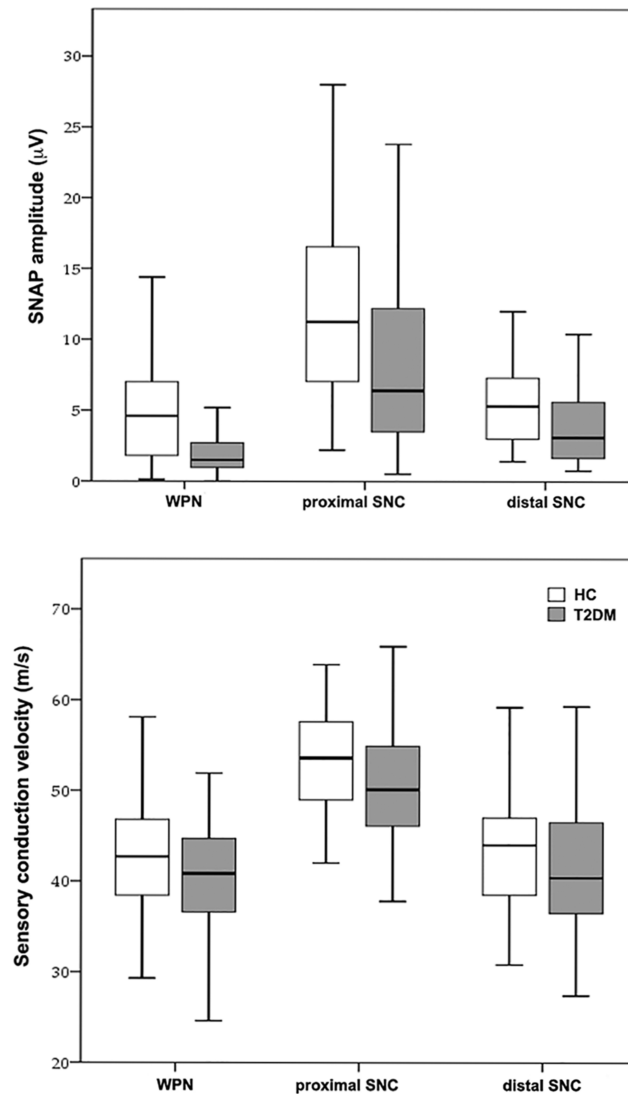
Figure 2. Neurophysiological results. Box plots showing SNAP amplitude and SCV with WPN (CNAPs), proximal and distal SNC. SNAP: Sensory nerve action potential; SCV: sensory conduction velocity; WPN: whole plantar nerve; CNAPs: compound nerve action potentials; SNC: sural nerve conduction.

factors seem associated with the onset of PN in T2DM patients [e.g., age, diabetes duration, HbA1c, dyslipidemia, body mass index (BMI), smoking habit, and neurosensorial damage][21,24,25]. As recently described, individuals with T2DM have more than twice the risk of lower extremity amputations compared to subjects without diabetes, despite selection bias regarding study populations across different research[26]. To prevent this complication, an early clinical evaluation of PN signs and symptoms at the time of the diagnosis is the only proven effective countermeasure. However, painful PN could be referred by patients and assessed through clinical scores in 25% of diabetes patients, highlighting the need for a tool that enables early diagnosis of PN, even in the absence of clear clinical manifestations[11]. Moreover, emerging evidence describes the presence of distal symmetric polyneuropathy also in subjects with prediabetes[12,27]. For this reason, the international position statement recommends screening for neuropathy individuals with impaired glucose tolerance and symptoms of PN[12]. Consistently, in our sample size, DN4 revealed PN symptoms in 35% of T2DM subjects, while MNSI and VPT revealed positive tests in 25% and 40.9% of T2DM cases, respectively, thus confirming the usefulness of these tests as screening tools and as reliable

Table 2. Clinical and neurophysiological assessment of diabetic neuropathy: sub-groups differences

Parameter	HC (*n* = 34)	T2DM (*n* = 51)	*P*
Age (yrs.), median (IQR)	61 (25-74)	63 (29-81)	0.171
WPN, median (IQR)			
CNAP amplitude (µV)	5.1 (2.2-9.9)	1.8 (0.5-3.7)	< 0.001
SCV (m/s)	43.6 (39.2-48.0)	41.3 (35.6-45.7)	0.063
Proximal SNC, median (IQR)			
SNAP amplitude (µV)	13.0 (7.3-17.2)	8.1 (3.8-12.2)	< 0.001
SCV (m/s)	53.6 (49.0-56.2)	49.5 (44.4-54.8)	< 0.001
Distal SNC, median (IQR)			
SNAP amplitude (µV)	5.6 (3.1-8.4)	3.2 (1.8-5.6)	< 0.001
SCV (m/s)	43.3 (38.5-46.9)	40.4 (35.5-45.2)	0.010
P/D amplitude ratio, median (IQR)	2.0 (1.8-2.3)	2.3 (1.7-2.9)	0.075
MNSI score, median (IQR)	0 (0-0.4]	2 (0.9-3.0)	< 0.001
MNSI score, *n* (%)			< 0.001
Positive	1 (3.0)	21 (23.4)	
Negative	33 (98.0)	27 (76.6)	
DN4 score, median (IQR)	0 (0-2)	2.0 (1-4)	< 0.001
DN4 score, *n* (%)			< 0.001
Positive	2 (5.9)	17 (35.4)	
Negative	32 (94.1)	31 (64.6)	
VPT, *n* (%)			0.002
Positive	3 (8.8)	18 (40.9)	
Negative	31 (91.2)	26 (59.1)	

HC: Healthy controls; T2DM: type 2 diabetes mellitus; IQR: interquartile range; WPN: whole plantar nerve; CNAP: compound nerve action potential; SCV: sensory conduction velocity; SNC: sural nerve conduction; SNAP: sensory nerve action potential; P/D: proximal/distal; MNSI: Michigan Neuropathy Screening Instrument; DN4: Neuropathic Pain 4 Questions; VPT: vibration perception threshold.

WPN vs Distal Sural Nerve

51 patients	Sural -	Sural +
WPN -	17	5
WPN +	12	17

Sensitivity: 17/17+5= 77 %

Specificity: 17/12+17= 58%

Positive predictive value: 17/17+12 = 58%

Negative predictive value: 17/17+5 = 77%

Figure 3. Accuracy of WPN with respect to the gold standard, distal sural nerve conduction. WPN: Whole plantar nerve.

components of the diagnostic workup. However, as compared with these tests, electrophysiological studies (e.g., WPN and sural nerve conduction study) are recognized as more sensitive and specific. NCS permits to study districts inaccessible to clinical examination, to give a quantitative assessment and qualitative

information on the type of damage (myogenic and axonal/myelin damage), which are useful to evaluate prognosis and follow-up, acute denervation and signs of reinnervation, and could also be performed in the uncooperative patient[20,28,29]. NCS, which highlights a progressive amplitude reduction of both SNAPs and compound motor action potentials (CMAPs), has shown that diabetic PN is mainly characterized by a progressive axonal degeneration process with a length-dependent pattern[30,31]; a slight reduction of sensory and motor conduction velocity may also be observed, related to large fibers axonal loss[32]. Electrophysiological tests are coherent with histopathological studies, demonstrating the degeneration of both large myelinated and small unmyelinated fibers[30-32]. For these reasons, nerve conduction studies are still considered as the gold standard for evaluating PN[20,28,29].

In the assessment of diabetic PN, NCS allows the evaluation of both the sensory (sural and superficial peroneal SNAPs) and motor (deep peroneal and posterior tibial CMAPs) nerves of the lower limbs[32]. In particular, SNAP amplitude reduction of the sural nerves is the main marker of PN in T2DM. Neurophysiological evaluation of the plantar nerves could increase the diagnostic efficacy of the NCS in a PN with length-dependent pattern, just like diabetic neuropathy, and enable an early diagnosis[33-35]. However, plantar nerve evaluation with classical electrodes has been limited by technical hitches and small amplitude of the SNAPs, even among HCs[32,36-38]. Recently, medial plantar nerve conduction revealed greater SNAP amplitudes and greater sensitivity than the SNC in both symptomatic and non-symptomatic individuals with diabetes[39]; however, positioning the near-nerve recording needle in the interdigital space, this instrument caused discomfort for patients, limiting its adoption as a diagnostic technique[39]. Amplitudes of the medial plantar nerve also revealed a statistically significant difference between T2DM patients and HCs. Moreover, this study was performed in a younger population, using a surface bar recording electrode, and is consistent with our results regarding the sensitivity of distal nerve studies in the detection of PN[40]. Recently, WPN technique allowed the collection of higher CNAP amplitudes in HCs, thus suggesting this tool is a potentially useful neurophysiological instrument to assess the distal sensory fibers in length-dependent neuropathies[14]. WPN conduction study, in fact, enables the simultaneous recording of CNAPs from the distal sensory fibers of the plantar nerves and could be useful in the early detection of diabetic length-dependent PN[14].

As compared to previous works, here we have assessed the clinical application of WPN in a population of patients affected by T2DM, and in a larger, although older, group of HC subjects[14,15]. As expected, WPN conduction study demonstrated a statistically significant reduction of the CNAP amplitude in subjects with T2DM as compared to HCs, thus confirming the presence of axonal damage of the more distal sensory nerve fibers of the sole[36]. Thus, in individuals with T2DM, we can observe a significant reduction of SNAP amplitudes and SCV, also in the absence of clinical signs and regardless of the achievement of established cut-offs useful to diagnose PN through nerve conduction studies[36]. This general nerve impairment could be linked to the endothelial dysfunction described in subjects with diabetes, and could be recognized as an epiphenomena of the "inflammation status" described in individuals with diabetes[41].

Moreover, significant differences between HCs and T2DM patients were detected at SNC, thus confirming the diagnostic efficacy of sural conduction in diabetic PN[42,43]. Consequently, to evaluate the diagnostic efficacy of WPN in identifying neuropathic subjects among individuals with T2DM, we performed a sub-analysis by comparing results from WPN with gold standard distal sural nerve conduction amplitudes evaluation (SNAP). As compared with sural nerve conduction, WPN results revealed a good sensitivity (77%) and NPV (77%), while specificity and PPV were both 58%. These findings suggest that results from WPN are consistent with those obtained from the gold standard SNC. Moreover, due to its capability to study the overall more distal fibers and to discriminate individuals with T2DM from HCs, WPN could be a

useful tool to early diagnose diabetic length-dependent polyneuropathy[36,37,44-46].

This study presents some limitations. First, WPN CNAP amplitudes in HCs and T2DM patients are smaller than those previously reported. However, a progressive age-related reduction of SNAP amplitude has also been generally reported in HCs[14]. Accordingly, to confirm this issue, the calculated Linear Regression analysis shows that age is negatively associated with nerve conductivity [Supplementary Materials]. As expected, the same association also seems significant for HbA1c levels. Thus, the difference could represent a hallmark of our whole study population, remarkably older. Secondly, we did not perform a NCS of the medial plantar nerve to compare our findings, because we aimed to compare WPN with the SNC study[12,13,39]. Finally, the sample size of both HCs and T2DM patients is quite small and does not enable a reliable assessment of the non-inferiority of WPN as compared to the gold standard. A larger sample size of HCs and individuals with T2DM would also be useful to better generalize and support results.

CONCLUSION

To the best of our knowledge, this is the first study comparing WPN performances in subjects with T2DM and HCs. Taken together, our findings show that WPN conduction study enables the neurophysiological characterization of plantar nerve conduction in a population of both healthy individuals and subjects with T2DM. The study also demonstrates the capability of WPN to accurately differentiate electrophysiological characteristics between healthy individuals and subjects with diabetes. Moreover, we confirmed the WPN accuracy in identifying subjects with PN, as compared with the gold standard sural nerve conduction study, thus permitting an early diagnosis.

As described above, some authors suggest that PN could also be present in individuals with prediabetes, thus suggesting the usefulness of screening evaluations and electrophysiological studies also in those subjects. From literature, there are no studies that describe the role of WPN in screening subjects with prediabetes. However, given the role of WPN in HCs and subjects with diabetes, we could also hypothesize its usefulness in this setting. From a future perspective, other investigations would be needed to describe the role of WPN and other electrophysiological studies in individuals with prediabetes.

In this regard, future studies would be necessary to better evaluate and confirm this association.

DECLARATIONS

Acknowledgments

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Ricciardi D, Galiero R, Todisco V, Loffredo G, Cirillo G, Sasso FC
Performed data acquisition, as well as providing administrative, technical, and material support: Ricciardi D, Galiero R, Todisco V, Tedeschi G, Loffredo G, Caturano A, Rinaldi L, Cirillo G, Sasso FC

Availability of data and materials

Authors declare that the data are deposited into data repositories.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
All patients provided written informed consent for the use of clinical data in research. The study was approved by our Local Ethics Committee (AOU Università della Campania Vanvitelli, CET Campania 2, DGR n. 224) and is in accordance with the 1976 Declaration of Helsinki and its later amendments.

Consent for publication
Not applicable.

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