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Pedobarography – a novel screening tool for diabetic peripheral neuropathy?

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Abstract. – AIM: To investigate the diagnostic significance of foot plantar pressure distribution abnormalities in patients with diabetic peripheral neuropathy (DPN).

PATIENTS AND METHODS: A total of 107 patients were divided into normal control (28 participants, 56 feet), non-DPN (56 patients, 112 feet), and DPN groups (23 patients, 46 feet). Foot plantar pressure was measured while patients walked at a constant speed over a flat floor using F-Scan pressure insoles. Recordings of six middle strides were averaged to evaluate the characteristics of foot plantar pressure distribution.

RESULTS: Compared with the normal group, the time of contact (TOC) was longer in non-DPN ($p < 0.05$) and DPN groups ($p < 0.01$). The foot to floor force-time integral (FTI) was increased in DPN group ($p < 0.01$). The forefoot plantar force ratio increased in non-DPN and DPN patients ($p < 0.05$). Moreover, in DPN patients, the ratio of lateral foot plantar force increased ($p < 0.05$). The examination of the correlations between biomechanical parameters of the foot plantar and electrophysiological parameters of the lower limbs showed foot plantar biomechanical abnormalities correlated with abnormal sensory conduction of the sural nerve and motor conduction of the common peroneal nerve. Receiver operating characteristic (ROC) analysis showed the area under FTI curve was 0.714 ($p < 0.001$).

CONCLUSIONS: The plantar pressure was shifted towards the side of the forefoot in DPN patients. The foot plantar biomechanical changes were closely correlated with lower limb paresthesia and contraction abnormalities of lower-limb extensor muscles. Foot plantar pressure measurement might be used as a screening tool for early diagnosis of DPN.

Key Words:
Diabetes mellitus, Diabetic peripheral neuropathy, Foot plantar pressure.

Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus. The lesions are usually symmetrically present in the lower limbs. A small portion of patients have severe limb pain, which can significantly affect their work and daily life activities. Moreover, DPN can lead to the occurrence and development of foot ulcers. Therefore, early diagnosis and treatment of DPN is critical.

According to the diagnostic criteria for diabetic neuropathy recommended by American Diabetes Association (ADA) in 2010[1], DPN (a type of distal symmetric polyneuropathy, DSPN) is the most common complication of diabetes (accounting for approximately 95%) and is the most typical type of diabetic neuropathy. Neuroelectrophysiological examination has been used as a gold standard for DPN diagnosis; however, it is not a routine exam, and its results are influenced by the limb temperature. In addition, because more than 50% of DSPN patients are asymptomatic[2], various simplified scoring scales used in the clinic, such as the Neuropathy Impairment Score in the Lower Limbs (NIS-LL), Diabetic Neuropathy Examination (DNE) score, and Toronto Clinical Scoring System (CSS) score, which are mostly carried out based on patients' clinical signs and symptoms, usually have a poor sensitivity for disease screening. The more comprehensive scoring systems, such as the Neuropathy Deficit Score (NDS) and Michigan Neuropathy Screening Instrument (MNSI), are time-consuming. Therefore, the establishment of a simple, easily operated screening tool will bring certain clinical value.

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The relationship between foot plantar pressure distribution and DPN has gained attention in recent years. Caselli et al[3] found that DPN patients had abnormal foot plantar pressure distribution, in which the pressure was shifted toward forefoot and the forefoot-to-rearfoot plantar pressure ratio was increased. Lee et al[4] found that DPN patients had an unstable pressure difference between two feet when walking on a force plate. Greenman et al.[5] found that muscular atrophy occurred in a portion of foot muscles even before clinical diagnostic criteria were met in DPN patients, which partially explained the pathophysiological mechanism of DPN-induced foot plantar pressure abnormalities. To effectively investigate in-shoe pressure during patients' daily activities, this study used pressure insoles to measure the changes in in-shoe pressure in diabetic patients walking over a flat floor, and evaluated the characteristics of in-shoe foot plantar pressure in DPN patients.

Patients and Methods

Study Subjects

The data from 79 patients with type 2 diabetes mellitus admitted to the Endocrinology Inpatient Unit at Shanghai First People's Hospital (South Branch) from June 1, 2012 to May 31, 2013 were included in this study. The control group included 28 patients without history of acute or chronic disease or trauma surgery. Type 2 diabetes mellitus was diagnosed according to the diagnostic criteria issued by the World Health Organization (WHO) in 1999. The diagnosis of DPN was based on the diagnostic criteria recommended by the ADA in 2010, in which the abnormal nerve conduction velocity (NCV) is considered the gold standard, along with one or more of the following conditions: (1) the presence of symptoms of DSPN, which were mostly distal and symmetric sensory abnormalities; (2) the presence of clinical signs of DSPN, including the ankle reflex, pressure sensation (using a 10 g monofilament), vibration perception (using a 128-Hz tuning fork), and pain and temperature sensation; (3) excluding neuropathy caused by other diseases, such as cervical and lumbar spine diseases, cerebrovascular diseases, uremia, and toxic peripheral neuritis. The exclusion criteria were (1) foot deformities, including flat feet, cavus feet, varus feet, and valgus feet, etc.; (2) foot infection and significant swelling; (3) corpus callosum; (4) history of lower-limb surgery, including hip surgery; and (5) gait instability caused by severe basic diseases.

The data of 107 subjects with 214 qualified feet were included in this study. They were divided into three groups according to the above criteria: DPN group (23 patients, 46 feet), non-DPN group (NDPN; 56 patients, 112 feet) and control group (NC; 28 subjects, 56 feet).

Study Methods

General Information Collection

Information on age, gender, size of regularly used shoes, and history of smoking (subjects who had quit smoking were included in the smoking group). Height, weight, waist circumference, hip circumference, and blood pressure were measured. The waist-to-hip ratio was calculated, and the body mass index (BMI) was calculated as the body weight/square of height (kg/m^2). Special conditions such as plantar calluses, foot deformity, infection, and surgery were also evaluated.

Laboratory Assessments

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and uric acid (UA) were measured in a biochemistry lab using a Hitachi 7600 automatic biochemistry analyzer (Chiyoda, Tokyo, Japan). Glycosylated hemoglobin (HbA1c) was examined using high-performance liquid chromatography (Bio-Rad VARIANT 1, Hercules, CA, USA). Diabetic nephropathy was defined by a 24-hour urinary albumin excretion greater than 30 mg in two separate tests. Diabetic retinopathy was evaluated by ophthalmologists. Atherosclerosis was determined by examining the carotid artery, internal carotid artery, femoral artery, popliteal artery, and dorsalis pedis artery using Doppler ultrasound. Hypertension was defined as ongoing administration of antihypertensive medications or systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg at rest (the mean systolic and diastolic blood pressure were obtained from three measurements using a mercury sphygmomanometer).

Measurement of NCV

A four-channel electromyograph (Medtronic Keypoint, Skovlunde, Denmark) was applied to examine the motor nerve conduction velocity

(MCV), sensory nerve conduction velocity (SCV), and F response of the tibial nerve in both lower limbs. The tested motor nerves included tibial nerves and common peroneal nerves. The stimulation electrodes for the tibial nerve were placed at the popliteal fossa and medial malleolus, respectively; the recording electrode was placed on the abductor hallucis (AH) muscle. The stimulation electrodes for the peroneal nerve were placed at the fibular head and the middle of the ankle joint, respectively; the recording electrode was placed on the extensor digitorum brevis (EDB). The latent period (unit: ms) and MCV (unit: m/s) were measured. The tested sensory nerves were the sural nerves of both lower limbs. The stimulation electrode was placed on the calf muscle, and the recording electrode was placed in the lateral malleolus. A reversing method was applied to record sensory nerve action potentials (SNAPs), i.e., wave amplitude (unit: V) and SCV (unit: m/s), respectively. The F response was determined using the mean latency of the tibial nerve F wave (unit: ms).

Foot Plantar Pressure Measurement

F-Scan pressure insoles (Tekscan Inc., South Boston, MA, USA) were used to record the mechanical parameters of foot plantars. All enrolled patients wore the same type of running shoes of a suitable size. F-Scan pressure insoles of a suitable size were placed inside each shoe. Patients walked along a straight line with a natural gait. The six walking gait cycles in the middle of the walk were collected. The mean values from these six gait cycles were obtained using F-Scan analysis software, including the mean contact area (CA) (unit: cm^2), time of contact (TOC) (unit: ms), peak pressure (PP) (unit: kPa), percentage of maximum force in body weight (MxF) (unit: % BW), pressure time integral (PTI) (unit: kPa·s) and force time integral (FTI) (unit: % BW·s).

The foot plantar area includes the first to fifth toes (T1-T5), the first to fifth metatarsal head (M1-M5), midfoot (MF), medial heel (MH), and lateral heel (LH). The foot plantar area was divided into the following regions in this study: (1) forefoot: including the first to fifth toe and first to fifth metatarsal head; (2) heel: including the medial heel and lateral heel; (3) lateral foot: including the lateral heel, midfoot, the fourth and fifth metatarsal heads, and the fourth and fifth toes; (4) medial foot: including medial heel, the first to third metatarsal head, and the first and third toes; (5) lateral forefoot: including the fourth and fifth metatarsal heads and the fourth and fifth toes; (6) medial forefoot: including the first to third metatarsal head and the first to third metatarsal toe.

Statistical Analysis

SPSS 13.0 statistical software was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Measurement data with a normal distribution are expressed as means ± standard deviation ($x \pm s$), and the t-test was used for comparison between groups. Numerical data are expressed as composition ratio (n/n), and the chi-squared test was used for comparison between groups. Pearson's correlation coefficient was used for the parametric correlation analysis. Two-sided tests were performed for all data analyses. $p < 0.05$ was considere statistically significant.

Results

General Clinical Characteristics

Compared with the NC group, only cholesterol significantly increased in the NDPN group, while cholesterol, TG, and UA all significantly increased and HDL-C significantly decreased in the DPN group ($p < 0.05$) (Table I). Compared with the NDPN group, both the proportion of smoking patients and the occurrence of diabetic retinopathy in the DPN group were significantly higher ($p < 0.05$ for both). The prevalence of diabetic nephropathy in the DPN group was also higher than in the NDPN group, but the difference was not statistically significant. There was no significant difference in the proportion of atherosclerotic patients between these two groups (Table I).

Comparison of Foot Plantar Pressure Parameters

The data from the walking recordings showed that TOC in the DPN group (756 ± 123 ms) was significantly longer than in NDPN patients (719 ± 79 ms, $p < 0.05$) and the control group (682 ± 102 ms, $p < 0.01$). In addition, the DPN patients had a significantly greater FTI (63.6 ± 11.0% BW·s, $p < 0.01$). However, the differences in CA, PP, MxF and PTI were not statistically significant between the groups (Table II).

The forefoot plantar force was significantly higher in diabetic patients (including DPN and NDPN patients) compared with the NC group ($p < 0.05$), with a corresponding reduction in foot

Table I. Comparison of general information of participants.

Groups		DPN	NDPN	NC
Number of patients	–	23	56	28
Male/female	n/n	17/6	33/23	15/13
Age	$x \pm s$, years	52.6 ± 11.4	50.1 ± 14.5	48.4 ± 13
Disease duration	$x \pm s$, months	68.6 ± 66.1	56.3 ± 73.1	–
Smoking	Yes/no, n/n	13/10#	15/41	8/20
BMI	$x \pm s$, kg/m^2	23.4 ± 3.1	24.6 ± 3.1	21.5 ± 3.8
Waist-to-hip ratio	$x \pm s$	0.90 ± 0.18	0.92 ± 0.10	0.89 ± 0.12
Hypertension	Yes/No, n/n	9/14	21/35	–
UA	$x \pm s$, mol/L	341 ± 128*	285 ± 84.6	244 ± 34
TC	$x \pm s$, mmol/L	4.53 ± 1.17*	4.42 ± 0.99*	3.36 ± 1.13
TG	$x \pm s$, mmol/L	2.89 ± 4.37*	1.78 ± 2.03	1.14 ± 2.48
HDL-C	$x \pm s$, mmol/L	1.03 ± 0.20*,#	1.22 ± 0.35	1.23 ± 0.27
LDL-C	$x \pm s$, mmol/L	2.65 ± 1.13	2.59 ± 0.73	2.22 ± 0.73
HbA1c	$x \pm s$, %	9.48 ± 2.48	9.76 ± 2.37	5.10 ± 0.32
Diabetic nephropathy	Yes/no, n/n	7/16	5/51	–
Diabetic retinopathy	Yes/no, n/n	9/14#	9/47	–
Atherosclerosis	Yes/no, n/n	12/11	25/31	–

*$p < 0.05$ compared with NC group; #$p < 0.05$ compared with NDPN group.

heel force. The plantar force of the lateral foot was significantly higher in the DPN group compared with the NDPN group ($p < 0.05$). The proportion of lateral forefoot plantar pressure was significantly larger in the DPN group compared with both the NC group ($p < 0.01$) and NDPN group ($p < 0.05$) (Table II).

Correlations Between Foot Plantar Biomechanical and Neuroelectrophysiological Parameters

The lower-limb electrophysiological exam was performed in diabetic patients. The motor nerve exam included the detection of the latent period and conduction velocity of the tibial nerve and

Table II. Comparison of foot plantar pressure parameters ($x \pm s$).

Group	DPN	NDPN	NC
N	46	112	56
CA (cm^2)	78.9 ± 31.3	69.6 ± 22.3	67.0 ± 33.5
TOC (ms)	756 ± 123**,#	719 ± 79*	682 ± 102
PP (kPa)	472 ± 224	459 ± 180	468 ± 195
MxF (% BW)	117.8 ± 19.2	113.8 ± 19.2	114 ± 19.7
PTI (kPa·s)	77.7 ± 25.5	78.3 ± 22.2	81.6 ± 29.1
FTI (% BW·s)	63.6 ± 11.0**,##	57.7 ± 10.3	54.8 ± 7.9
Forefoot force ratio, %	53.9 ± 7.0*	54.8 ± 7.0*	50.0 ± 6.8
Heel force ratio, %	39.1 ± 6.6**	40.2 ± 7.2*	44.9 ± 7.0
Midfoot force ratio, %	6.9 ± 4.9*,#	4.9 ± 3.2	5.0 ± 4.5
Medial force ratio, %	57.0 ± 7.7#	59.9 ± 6.2	58.1 ± 7.6
Lateral force ratio, %	42.9 ± 7.7#	40.1 ± 6.2	41.0 ± 7.6
Lateral forefoot force ratio, %	17.9 ± 5.0**,#	15.7 ± 4.4	14.3 ± 4.4

*$p < 0.05$, **$p < 0.01$ compared with the NC group; #$p < 0.05$, ##$p < 0.01$ compared with the NDPN group. Forefoot force ratio: MxF(T1+T2+T3+T4+T5+M1+M2+M3+M4+M5)/MxF(T1+T2+T3+T4+T5+M1+M2+M3+M4+M5+MF+MH+LH); Heel force ratio: MxF (MH+LH)/MxF (T1+T2+T3+T4+T5+M1+M2+M3+M4+M5+MF+MH+LH); Medial foot force ratio: MxF (T1+T2+T3+M1+M2+M3+MH)/MxF (T1+T2+T3+T4+T5+M1+M2+M3+M4+M5+MF+MH+LH); Lateral foot force ratio: MxF (T4+T5+M4+M5+MF+LH)/MxF (T1+T2+T3+T4+T5+M1+M2+M3+M4+M5+MF+MH+LH); Medial forefoot force ratio: MxF (T1+T2+T3+M1+M2+M3)/MxF (T1+T2+T3+T4+T5+M1+M2+M3+M4+M5+MF+MH+LH); Lateral forefoot force ratio: MxF (T4+T5+M4+M5)/MxF (T1+T2+T3+T4+T5+M1+M2+M3+M4+M5+MF+MH+LH).

Table III. Correlation between plantar mechanical parameters and neuroelectrophysiological parameters.

Compared parameters	Pearson's correlation coefficient	*p*
TOC and MCV of the common peroneal nerve	-0.242	0.038
TOC and wave amplitude of the sural nerve	-0.255	0.002
TOC and SCV of the sural nerve	-0.316	< 0.001
FTI and wave amplitude of the sural nerve	-0.165	0.046
Lateral forefoot force ratio and wave amplitude of sural nerve	-0.179	0.031

common peroneal nerve. The sensory nerve exam included the SNAP amplitude and conduction velocity of the sural nerve. In addition, the mean F latent period of the tibial nerve was determined. Correlation analysis was carried out between the above electrophysiological parameters and foot plantar physical parameters (PP, MxF, TOC, PTI, FTI, and the force ratios of different foot plantar regions). Negative correlations were found between TOC and the conduction velocity of the lower-limb common peroneal nerve, the wave amplitude of the sural nerve, and the conduction velocity of sural nerve. FTI was also negatively correlated with the wave amplitude of the sural nerve. In addition, there was a negative correlation between the lateral forefoot force ratio and the wave amplitude of the sural nerve. No significant correlation was found between the foot plantar mechanical parameters and electrophysiological parameters (including F response) of the tibial nerves (Table III).

ROC curve of Foot Plantar Pressure for the Diagnosis of DPN

ROC curve (Figure 1) was applied to evaluate the DPN-diagnostic value of forefoot force ratio, lateral foot force ratio, lateral forefoot force ratio, TOC and FTI. The area under the curve (AUC) was calculated for each. The AUC of FTI was 0.714 ($p < 0.001$), indicating diagnostic significance.

Discussion

In this work, we found that the DPN group had a higher proportion of smoking patients and showed more severe microvascular diseases (including retinopathy and nephropathy), indicating that smoking and microvascular diseases might be closely correlated with neuropathy, consistent with most international studies[6,7]. Furthermore, patients in the DPN group had more serious abnormalities in lipid and purine metabolism. Because both lipid metabolism disorders and hyperuricemia[8] are considered risk factors for cardiovascular events, DPN patients who have more serious metabolic disorders might have a higher risk of cardiovascular diseases.

Ko et al[9] found that patients with diabetes mellitus walked at a slower pace without shoes (barefoot walking). We observed a significantly longer TOC of diabetic patients compared with controls walking with shoes at a constant speed along a straight line, which indicated that diabetic patients walked at a slow pace and took small steps. The TOC and FTI in the DPN group were both significantly higher than those in the NDPN and NC groups, indicating the patients with DPN

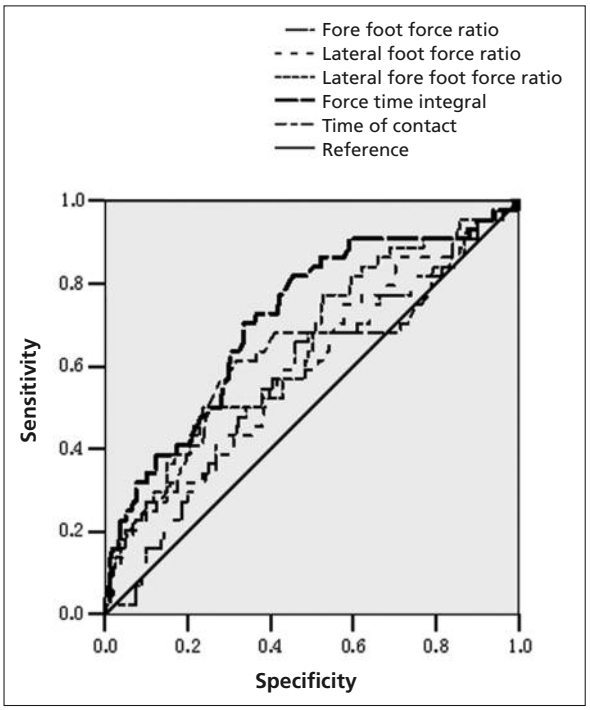

Figure 1. ROC curves for the diagnosis of DPN. The AUCs were 0.575 for fore foot force ratio ($p = 0.129$), 0.598 for latera foot force ratio ($p = 0.046$), 0.644 for lateral fore foot force ratio ($p = 0.003$), 0.623 for TOC ($p = 0.013$), and 0.714 for FTI ($p < 0.001$).

usually walk at a slower pace and take smaller steps. These findings suggest a gait instability in DPN patients[10,11]. However, we did not find that DPN patients had higher foot plantar pressure (PP). To exclude the effect of body weight on foot pressure, we then analyzed MxF, i.e., the percentage of maximal force in body weight, and found no difference in MxF between the three groups. This result indicates there is no difference in the absolute value of foot plantar pressure between the normal population, patients with diabetes, and patients with diabetes complicated with peripheral neuropathy. Simoneau et al[10] studied foot plantar pressure using a force plate and found no significant increase in the foot plantar PP values in patients with less severe DPN. The authors interpreted that finding as a mild neuropathy that was related to gait instability, while only a serious neuropathy could lead to increased PP and the occurrence of foot ulcers. This hypothesis might partially explain the findings of the present study. Although the PP values in our study are inconsistent with some international studies[12,13], they are consistent with domestic studies, which might be explained by racial differences.

To further study the characteristics of foot plantar pressure distribution in DPN patients, we divided the foot plantar area into several regions based on the anatomical features and analyzed the interregional ratios of foot plantar force. Our results demonstrate that in patients with diabetes, the forefoot plantar force ratio significantly increased, with a corresponding reduction of the force ratio in the heel. The lateral forefoot plantar force ratio was significantly higher in the DPN group, indicating that the regional distribution of foot plantar force changed in diabetic patients, with a rise in the force in the forefoot. We also found significant differences in the arch area and lateral forefoot area between the DPN group and the other two groups. Caselli et al[3] also showed, in a force plate experiment (barefoot), that the forefoot plantar pressure was greater than the rearfoot pressure in diabetic patients with peripheral neuropathy, with the pressure center of gravity shifting forward. By measuring in-shoe foot plantar pressure, we found that, in addition to the shift of the foot plantar force to the forefoot in diabetic patients, the foot plantar force tilted toward the lateral forefoot and arch area in DPN patients. The mechanical parameters of foot plantar force that showed relatively large differences among groups were selected for the ROC curve analysis. The area under the FTI curve was greater than 0.7, suggesting it has a certain diagnostic value for DPN.

We performed sensory and motor-neuroelectrophysiological examinations on both lower limbs in diabetic patients. The sensory exams were conducted on the sural nerve. The correlation analysis demonstrated that the wave amplitude of the sural nerve was negatively correlated with TOC, FTI, and the lateral forefoot plantar pressure ratio. The conduction velocity of the sural nerve was negatively correlated with TOC, indicating the changes in foot plantar mechanical parameters were closely related to lower limb paresthesia. The motor examinations were conducted on the tibial nerve and common peroneal nerve. The correlation analysis found that the conduction velocity of the common peroneal nerve was negatively correlated with TOC, but there was no correlation between motor electrophysiological parameters of tibial nerve and foot plantar physical parameters. The common peroneal nerves innervate the extensor muscles of the lower legs, while the tibial nerves innervate the flexor muscles of the posterior lower legs. Therefore, the abnormalities in the foot plantar pressure distribution might have been caused by the abnormal contraction of extensor muscles in the lower leg. The F-wave is generated by the pulse propagating along the proximal motor nerve fiber and then returning after the activation of the anterior horn neurons. F-response detection can be used to measure conduction velocity in the proximal nerve fibers. We did not find a correlation between the F-wave latency and foot plantar mechanical parameters, further indicating that changes in foot plantar mechanical parameters are more closely correlated with distal nerves of the lower limbs in diabetic patients.

However, NCV tests can only be used to determine the damage of large nerve fibers and are insensitive for the early detection of DPN that involves only peripheral nerves. The foot subcutaneous sensory fibers play an important role in maintaining the gait and static stability[14], but they cannot be effectively examined using NCV tests. Foot plantar pressure measurements can reflect the overall mobility performance of the lower limbs, including the damage to large fibers that can be determined by NCV tests and the damage to small fibers that cannot be detected by NCV tests. Therefore, to a certain extent, the foot plantar pressure measurement is more sensitive and suitable than NCV tests for the early detection of

DPN. The NCV test is still the gold standard for DPN diagnosis, but it cannot be used for routine screening due to complicated and time-consuming operation procedures. Foot plantar pressure measurement is easy to perform in clinical practice and is a painless method; therefore, it has certain advantages for use as a clinical screening tool. However, this method is still in the initial phase of development, and its applicability needs to be further confirmed in a larger sample. In addition, the biomechanical parameters and cut-off points that can be applied for clinical screening need to be further explored and optimized, which requires a close multidisciplinary collaboration.

Conclusions

Compared to the normal population, diabetic patients walk at a slower pace, take smaller steps, and have a greater forefoot plantar pressure during walking. In addition, in diabetic patients with neuropathy, the foot plantar pressure is shifted to the side of the foot, and the walking pace is even slower than in those without neuropathy. Therefore, the walking stability of diabetic patients with neuropathy is lower. Moreover, the changes in foot plantar pressure are closely correlated with lower limb paresthesia and abnormal contraction of the extensor muscles of the lower legs. Hence, detection of changes in foot plantar pressure distribution might be a potential screening tool for early DPN diagnosis.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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