

# The impact of lower extremity neuropathy and artery disease on gait characteristics in type 2 diabetic individuals

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## Original investigation

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# Abstract

## Background

It is generally believed that gait characteristics of diabetic neuropathic patients differ from non-diabetic ones. However, it is still unclear whether these changes during walking could also be extended for different conditions of type 2 diabetes mellitus (T2DM), especially diabetic individuals with lower extremity complications.

## Methods

In this investigation, gait was examined among 1861 participants with or without T2DM from three study centers. Subjects with NGT (normal glucose tolerance) and IGT (impaired glucose tolerance) were taken as control groups, patients with T2DM were divided into 4 groups: DM (no chronic complications), DPN (DM complicated with diabetic peripheral neuropathy), LEAD (DM complicated with lower extremity artery disease) and DPN + LEAD. Analyses of variance were employed to verify possible differences of gait parameters between these groups.

## Results

Results showed lowered cadence, increased step time and decreased walking speed in diabetes with lower extremity neural and/or vascular complications (all  $p < 0.05$ ). Increased duty factor\_double stance was displayed in participants with LEAD alone (32.51%,  $p < 0.05$ ). And the results displayed lower  $SD_A$  (1.32 vs. 1.57,  $p < 0.01$ ) and  $SD_B$  (0.38 vs. 0.51,  $p < 0.01$ ) of subjects with both DPN and LEAD. All these indicated the subjects with diabetic lower extremity complications showed much more conservative gait pattern. Stepwise multivariate regression models showed that independent variables were sex, age and leg length ( $p < 0.01$ ). While, VPT was listed as significant independent predictor of cadence, step time,  $SD_A$  and  $SD_B$  ( $p < 0.05$ ). And ABI was documented as significant independent predictor of stride length, duty-factor\_Double stance,  $SD_A$  and  $SD_B$  ( $p < 0.05$ ). Binary logistic regression analysis revealed a significant positive association between decreased stride length and the lowest ABI group (OR = 112.19, 95% CI: 3.11- 4040.13,  $p = 0.01$ ). ROC analysis showed a significant discriminatory power of step time for occurrence of DPN. The AUC value was 0.752 (95% CI: 0.721–0.782,  $p < 0.01$ ).

## Conclusions

In total, the cut-off point was 526.13 ms for predicting DPN. Maybe, this non-invasive and non-irritating gait examination could be an alternative measurement that could help distinguish diabetic neuropathy conveniently.

## Background

Gait analysis provides an objective means of measuring walking [1], and presents biomechanical differences depending on individual characteristics, such as morphological nature, physical activity, age and the presence of some diseases. Based on the results of other researches, altered gait pattern is apparently observed among individuals with diabetic peripheral neuropathy [2–6]. It is generally believed that up to 50% of people with diabetes will develop significant peripheral neuropathies [7]. The presence of diabetic peripheral neuropathy, could cause abnormal alterations during gait, leading to an increased number of repetitive falls compared with individuals without diabetes [7]. There were many recent studies implicated that the main abnormalities in gait parameters among diabetic peripheral neuropathy include decreased walking speed, shorter steps, and greater variability of step timing [8], exhibiting a more conservative gait pattern, which resulted from peripheral sensory loss rather than from vision or lower-limb muscle strength, and the differences were particularly evident on the irregular surface. However, different researches yielded different results because of various examining devices and diverse subjects. For instance, other researchers found gait patterns did not differ significantly when diabetes compared with patients suffering from neuropathy [9].

In addition to DPN, LEAD is another common co-morbidity of diabetes, which also has distinct effect on walking patterns, such as a much more conservative walking style, so what is the effect of lower extremity vascular disease on gait? Findings showed that symptomatic peripheral artery disease patients with hypertension displayed a slower cadence and shorter stride length during a constant-load, sub-maximal treadmill test [4]. Possible mechanisms may be the inflammation, mitochondria dysfunction, and reduced muscle perfusion caused by vascular dysfunction [10]. In this investigation, both symptomatic and asymptomatic patients with LEAD were included, we would try to generalize the effect among the whole population with LEAD.

Though emerging evidence focused on specific diabetes complications, a wealth of studies have been designed to investigate the possible relationships between gait and diabetes. It has been well documented that gait pattern can be dramatically altered in persons with diabetes, diabetes has been recorded to be associated with slowed gait speed, shorter steps, prolonged double support time, and increased step width, as well as gait variability [11]. A cross-sectional study of patients with DPN (n = 20), diabetes (n = 26), and age-gender-BMI matched control patients (n = 20) that was conducted by Yavuzer and colleagues [12], showing diabetic patients had slower gait, shorter steps, limited knee and ankle mobility, and lower plantar flexion moment and power than the control group. Of course, there was also trial proved no difference between diabetic patients with and without neuropathy [9].

Although dictated by the specific matching procedure, the relatively small sample size could be considered as a limitation of these studies. Moreover, it is still unknown if these gait parameter changes are also present for non-diabetes during the usual daily living condition, especially among IGT individuals. A comprehensive study focused on gait characteristics has never been accomplished on subjects with healthy and IGT controls, type 2 diabetes, DPN, LEAD, DPN complicated with LEAD patients

in the same clinic trial. Based on this consideration and those controversies, we believe it is urgent to explore the impact of different conditions of diabetes, particularly the lower extremity neural and vascular complications, on gait. Thus, the aim of the study was to determine whether gait components were affected by impaired blood glucose, diabetes and diabetic complications. We hypothesized that the altered gait parameters are associated with diabetes related complications, and aimed to verify this idea by analysed the baseline data from our mutiple-centered clinical trial.

## Subjects And Methods

### Subjects

A cross-sectional and observational study was conducted. Totally, 1861 individuals (922 males and 939 females) were enrolled from the Shanghai Clinical Medical Center of Diabetes, the First Affiliated Hospital of Anhui Medical University and West China Hospital of Sichuan University; 49.5% were male, with a mean age of  $60.95 \pm 9.25$  years. Participants were recruited into one of six groups: subjects with normal diabetic tolerance (NGT, n = 282); subjects with impaired diabetic tolerance (IGT, n = 70); diabetes with no history of peripheral neuropathy or LEAD (DM, n = 1266 ); diabetes with peripheral neuropathy (DPN, n = 144) ; diabetes with lower extremity artery disease (LEAD, n = 50) ; diabetes with DPN and LEAD ( n = 49). All the individuals were diagnosed as NGT, IGT or T2DM based on 1999 World Health Organization criteria and American Diabetes Association standards [13]. Diabetes status were self-reported. Peripheral neuropathy was confirmed if the Vibration Perception Threshold (VPT) was  $> 25$  V in combination with a positive Neuropathy Deficit Score (NDS) [14]. Lower extremity artery disease was confirmed if the Ankle Brachial Index (ABI) was  $< 0.9$  [10]. For co-morbid conditions, chronic heart disease was defined by having one of the following conditions: a history of coronary atherosclerotic stenosis or symptoms of exertional angina. Patients who had: 1) a history of myocardial infarction; 2) surgery of coronary stents or coronary artery by-pass graft were excluded. Cerebral infarction was defined by having one of the following conditions:1) a history of old cerebral infarction; 2) physical activity was not affected by cerebral infarction. Patients with any other cerebrovascular accident were excluded. Other exclusion criteria were the presence of any orthopedic, visual, neurological or other disturbance that might affect gait, including current pain, injury, history of diabetic foot, acute cerebral infarction within three months, Parkinson's disease, moderate and severe lumbar disease, active ulceration or amputation. The prevalence of HP (hypertension), CHD (chronic heart disease), CI (cerebral infarction) and smoking between these groups were compared. The study was approved by the Ethics Committee of the Shanghai Sixth People's Hospital, and written informed consents were obtained from all the participants.

### Procedures

All subjects' sex, age, BMI, diabetes duration, and history of DPN, LEAD, HP, CHD and CI were collected. BMI was calculated as body weight (in kg) divided by the square of the height (in m). The history of smoking was recorded based on self-report of all subjects. The analysis of levels of fasting plasma glucose and 2-h postprandial blood glucose were estimated by the glucose oxidase method. HbA1c

(glycosylated hemoglobin) was determined by high-pressure liquid chromatography using the Variant® II machine (Bio-Rad Inc., Hercules, CA).

A neuropathic assessment of VPT was performed by the same technician using a neurothesiometer (BioThesiometer; Bio-Medical Instrument Co., Newbury, OH). The operational approaches were based upon the International Working Group on the Diabetic Foot of the International Diabetes Federation. The higher value of VPT in either limb was selected for our analysis. The ankle-brachial index (ABI), the ratio of ankle systolic pressure to arm systolic pressure, was opted according to the standard protocols noted by the International Diabetes Federation. The lower value of ABI in either limb was opted for our analysis.

A commercially available LPMS (LP-RESEARCH Motion Sensor, 100 Hz, Japan) was attached over the skin of the 4th lumbar vertebra. Participants were asked to walk over a 10-m walkway free of obstacles at comfortable walking pace with a pair of their comfortable shoes. Participants started at a static position at the zero-point, came to a complete stop at the 10-m line. Two successful walks were conducted for each participant. All parameters of the gait cycle are registered and can be analyzed using Vicon 512 Motion Analysis System (Oxford Metrics Ltd., Oxford, England) in great detail. Descriptive statistics of the spatiotemporal gait parameters for both 10 m level walks were calculated and analyzed: cadence, step time, stride length, walking speed, duty-factor\_double stance and walk ratio (step length-cadence ratio). Phase plot description of gait included  $SD_A$ ,  $SD_B$ , Aratio and  $\Delta\text{angle}\beta$ .  $SD_A$  (spatiotemporal variability) means the spatial and temporal variability of the vertical trunk movement during walking, but also is influenced by the magnitude of vertical trunk movement.  $SD_B$  (temporal variability) reflects the symmetry of trunk movement from stride to stride. Aratio was described by the ratio between  $SD_A$  and  $SD_B$ .  $\Delta\text{angle}\beta$  (symmetry) was calculated as the angle difference between the  $SD_A$  vector and  $45^\circ$ . We calculated and analyzed the spatiotemporal and phase plot variables per group in the middle section of the walkway, avoiding acceleration and deceleration periods during gait.

## Data analysis

Categorical variables were expressed as percentages, and continuous variables were given as mean  $\pm$  SD values. Comparison of continuous variables among the six groups was performed using one-way analysis of variance (ANOVA). Non-parametric testing was accomplished by the Kruskal-Wallis test. Associations between gait parameters and other variables were evaluated with stepwise multiple regression analysis. A receiver operating characteristic (ROC) curve was employed to find a cut-off of step time to indicate the presence of DPN. Logistic regression analysis was performed to evaluate the odds ratio (OR), with the purpose to figure out the risk of lower ABI on stride length. The odds ratio (OR, 95% CI) was calculated in four logistic regression models: a non-adjusted model, a leg length-adjusted model, a leg length and sex-adjusted model, and a leg length, sex and age-adjusted model. Statistical analyses were performed using SPSS version 24.0 software (SPSS Inc., Chicago, IL were expressed).  $P < 0.05$  was considered statistically significant.

## Results

# Clinical characteristics

All patients in DM, DPN, LEAD, and DPN complicated with LEAD groups presented type 2 diabetes. Descriptive characteristics for these six groups are listed in Table 1. As shown, differences of gender, age, height, leg length and diabetes duration were shown among these groups ( $p < 0.01$ ). Males were subject to suffer from diabetes related complications ( $p < 0.05$ ). Compared to other groups, subjects with lower extremity diseases were getting obviously older (64.12 years vs. 60.54 years,  $p < 0.05$ ). Although the height was not the tallest, participants with DPN showed the longest leg length ( $p < 0.05$ ). Diabetes duration more than 10 years indicated the higher incidences of DPN and/or LEAD. All the individuals shared a similar BMI ( $p > 0.05$ ). Diabetic participants exhibited a poorer condition of health, they were more likely to have hypertension, CHD and CI (all  $p < 0.05$ ), as well as they took a greater number of smokers ( $p < 0.05$ ), especially in the subjects with lower extremity complications. Apparently, the highest value of VPT (36.43V) was detected among DPN complicated with LEAD ones ( $p < 0.05$ ), followed by DPN individuals. Lowest ABI were present for LEAD ones, with and without DPN (0.74 and 0.75,  $p < 0.05$ ). No pronounced difference of ABI among the rest groups was found ( $p > 0.05$ ). Gradually elevated FPG, PPG and HbA1c were displayed ( $p < 0.05$ ). Generally, these groups manifested an obvious uptrend of age, a higher prevalence of complications and relatively worse condition.

Table 1  
Comparison of Descriptive Characteristics among Different Glucose Metabolism Groups.

	NGT	IGT	DM	DPN	LEAD	DPN+ LEAD	P
<b>Patients(n)</b>	282	70	1266	144	50	49	-
<b>Sex(M, M%)</b>	104, 36.9%	23, 32.9%	639, 50.5%	93, 64.6%	31, 62.0%	32, 65.3%	0.000
<b>Age(years)</b>	61.07 ± 7.93	59.84 ± 10.46	60.41 ± 9.59	64.32 ± 6.37*#a	66.56 ± 6.91*#a	63.91 ± 9.34 <sup>bc</sup>	0.000
<b>Height(cm)</b>	162.52 ± 7.44	163.39 ± 8.94	164.67 ± 8.19*	165.24 ± 8.11*#a	167.24 ± 7.41*	165.52 ± 7.58*#a	0.000
<b>Leg length(cm)</b>	91.17 ± 4.76	91.47 ± 5.29	91.93 ± 5.34*	93.61 ± 5.69*#a	92.41 ± 4.67	92.80 ± 5.21*#a	0.000
<b>BMI(Kg/m<sup>2</sup>)</b>	24.16 ± 3.03	24.98 ± 3.19	24.67 ± 3.31	24.99 ± 3.13	24.92 ± 3.43	24.19 ± 3.61	0.099
<b>DM duration</b>	-	-	9.35 ± 7.03	11.18 ± 7.59 <sup>a</sup>	12.93 ± 8.45 <sup>ab</sup>	14.81 ± 7.11 <sup>ab</sup>	0.000
<b>Percentage(%)</b>							
Smokers	7.0	8.6	27.9*#	36.6*#a	51.9*#ab	46.5*#ab	0.000
HP	27.0	25.7	46.4*#	60.7*#a	66.7*#ab	58.1*#ac	0.000
CHD	1.8	7.1*	13.2*#	22.3*#a	24.1*#a	14.0*#bc	0.000
CI	3.9	0.0*	11.1*#	18.8*#a	35.2*#ab	4.7#abc	0.000
<b>VPT(V)</b>	12.00 ± 1.01	11.50 ± 2.08	14.30 ± 4.30*#	31.98 ± 8.83*#a	16.60 ± 3.70*#ab	36.43 ± 13.26*#ab	0.000
<b>ABI</b>	1.10 ± 0.12	1.13 ± 0.14	1.12 ± 0.09	1.13 ± 0.11	0.75 ± 0.17*#ab	0.74 ± 0.25*#abc	0.000
<b>HbA1C(%)</b>	-	6.10 ± 0.50	7.49 ± 1.60 <sup>#</sup>	7.24 ± 0.96 <sup>#</sup>	8.02 ± 1.75 <sup>#</sup>	7.52 ± 2.26 <sup>#abc</sup>	0.252

Data are mean ± SD values.

\*  $P < 0.05$ , compared with NGT; #  $P < 0.05$ , compared with IGT; <sup>a</sup>  $P < 0.05$ , compared with DM; <sup>b</sup>  $P < 0.05$ , compared with DPN; <sup>c</sup>  $P < 0.05$ , compared with LEAD. NGT, normal glucose tolerance; IGT, impaired glucose tolerance. VPT, vibration perception threshold; ABI, ankle-brachial index; CHD, Chronic Heart Disease; CI, cerebral infarction; HP, hypertension; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, 2-h postprandial blood glucose.

	NGT	IGT	DM	DPN	LEAD	DPN + LEAD	P
FPG(mmol/l)	5.50 ± 0.73	6.50 ± 0.92*	8.23 ± 2.41*#	8.58 ± 2.61*# <sup>a</sup>	8.34 ± 3.04*#	8.90 ± 2.57*#	0.000
PPG(mmol/l)	-	9.70 ± 2.82	11.45 ± 3.55#	12.08 ± 4.15#	11.92 ± 3.87	12.58 ± 6.32# <sup>abc</sup>	0.076
Data are mean ± SD values.							
* $P < 0.05$ , compared with NGT; # $P < 0.05$ , compared with IGT; <sup>a</sup> $P < 0.05$ , compared with DM; <sup>b</sup> $P < 0.05$ , compared with DPN; <sup>c</sup> $P < 0.05$ , compared with LEAD. NGT, normal glucose tolerance; IGT, impaired glucose tolerance. VPT, vibration perception threshold; ABI, ankle-brachial index; CHD, Chronic Heart Disease; CI, cerebral infarction; HP, hypertension; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, 2-h postprandial blood glucose.							

## Alterations Of Gait Parameters Among Different Groups

Spatiotemporal analysis was conducted for cadence, step time, stride length, walking speed, walk ratio and duty-factor\_double stance (Fig. 1). When compared with NGT, IGT, and DM ones, increased step time, decreased cadence and walking speed were detected in individuals with lower extremity complications (all  $p < 0.05$ , Fig. [1](#)). As illustrated, no notable differences of stride length was exhibited ( $p > 0.05$ , Fig. [1](#)) among all these groups. And, increased walk ratio was recorded among participants with DPN or LEAD (6.07 and 6.04 mm/(steps/min),  $p < 0.05$ , Fig. [1-2](#)), yet no similar alteration was shown in DPN + LEAD group. While participants burdened with LEAD alone, not complicated with DPN, duty-factor\_double stance elevated sharply (32.51%,  $p < 0.05$ , Fig. [1-2](#)). Furthermore, DPN individuals were subdivided into symptomatic DPN ( $n = 77$ ) and non-symptomatic DPN ones ( $n = 67$ ), no difference was detected between the two groups (544.6 ms vs. 551.8 ms,  $p > 0.05$ ).

Phase plot analysis was performed for  $SD_A$ ,  $SD_B$ , A ratio and  $\Delta$ angle  $\beta$  (Fig. [1-3](#)). The results displayed lower  $SD_A$  (1.32 vs. an average of 1.57 in NGT, IGT and DM,  $p < 0.01$ ) and lower  $SD_B$  (0.38 vs. an average of 0.51 in NGT, IGT and DM,  $p < 0.01$ ) in subjects with both DPN and LEAD. Besides, trend analysis revealed that gradually decreased  $SD_A$  and  $SD_B$  in the four DM groups ( $p < 0.05$ ). No significant difference was found for A ratio and  $\Delta$ angle  $\beta$  ( $p > 0.05$ ).

## Factors associated with altered gait parameters

Stepwise multivariate regression models to predict gait characteristics are shown in Table 2. For gait parameters, the significant independent variables were sex and/or age ( $p < 0.01$ ). Leg length turned out to be another important index that could influence stride length, walking speed, walk ratio,  $SD_A$  and  $SD_B$  ( $p < 0.01$ ). VPT was listed as significant independent predictor of cadence ( $B = -0.203$ ,  $p = 0.000$ ), step time ( $B = 1.146$ ,  $p = 0.000$ ),  $SD_A$  ( $B = -0.007$ ,  $p = 0.005$ ) and  $SD_B$  ( $B = -0.002$ ,  $p = 0.000$ ). And ABI was documented as

significant independent predictor of stride length ( $B = 0.088$ ,  $p = 0.002$ ), duty-factor\_Double stance ( $B = -4.135$ ,  $p = 0.010$ ),  $SD_A$  ( $B = 0.204$ ,  $p = 0.015$ ) and  $SD_B$  ( $B = 0.059$ ,  $p = 0.002$ ).

Table 2

Regression coefficient summary for independent variables included in multivariate regression models for gait characteristic dependent variables—spatiotemporal analysis.

Dependent variables	Predictors	Regression coefficient (B)	95% confidence interval	Adjusted R <sup>2</sup>	p value
<b>Cadence</b> (strides/min)	Age	-0.267	-0.374 ~ -0.161	0.022	0.000
	Sex	3.598	0.112 ~ 3.806	0.037	0.000
	VPT	-0.203	-0.332 ~ -0.074	0.044	0.000
	Constant	130.802	122.685 ~ 136.320		
<b>Step time</b> (ms)	Sex	-19.681	-25.057 ~ -14.305	0.038	0.000
	VPT	1.146	0.290 ~ 6.650	0.054	0.000
	Age	0.418	0.132 ~ 0.703	0.058	0.000
	Constant	524.993	507.707 ~ 542.280		
<b>Stride length</b> (m)	Leg length	0.009	0.008 ~ 0.011	0.199	0.000
	Sex	-0.074	-0.092 ~ -0.057	0.242	0.000
	ABI	0.088	0.002 ~ 0.142	0.247	0.002
	Constant	0.460	0.282 ~ 0.639		
<b>Walking speed</b> (m/s)	Age	-0.004	-0.005 ~ -0.003	0.041	0.000
	Leg length	0.009	0.007 ~ 0.011	0.066	0.000
	Constant	0.706	0.478 ~ 0.926		
<b>Walk ratio</b> (mm/steps/min)	Sex	-0.655	-0.739 ~ -0.571	0.175	0.000
	Leg length	0.038	0.030 ~ 0.046	0.206	0.000
	Constant	3.114	2.297 ~ 3.932		
<b>Duty factor</b> -Double Stance	Sex	-1.945	-2.824 ~ -1.066	0.015	0.000
	ABI	-4.135	-7.296 ~ -1.066	0.020	0.010
	Constant	36.794	33.039 ~ 40.548		

VPT: vibration perception threshold. ABI, ankle-brachial index.

## Comparison of gait parameters when sex and age were matched

Based on the results above, the impact of sex and age on gait parameters needed to be clarified further, which was provided in Fig. 2. We selected 1420 individuals, and divided them into four groups according to their sex and age. Group 1 was defined as male, age < 65 years ( $56.1 \pm 5.2$  years),  $n = 372$ ; Group 2, male, age  $\geq 65$  years ( $69.7 \pm 3.2$  years),  $n = 190$ ; Group 3, female, age < 65 years ( $56.5 \pm 5.8$  years),  $n = 571$ ; Group 4, female, age  $\geq 65$  years ( $69.7 \pm 3.3$  years),  $n = 287$ . As shown in these figures (Fig. 3), male participants performed less steps per min (113.38 vs. 119.07 steps/min,  $p < 0.01$ ), took remarkably longer stride length (1.36 vs. 1.24 m,  $p < 0.01$ ), walked more quickly (1.30 vs. 1.24 m/s,  $p < 0.05$ ), spent more time per walk (546.54 vs. 522.19 ms,  $p < 0.01$ ), and showed greater  $SD_A$  (1.68 vs. 1.42,  $p < 0.01$ ) and  $SD_B$  (0.47 vs. 0.41,  $p < 0.01$ ). Besides, male individuals had an increased walk ratio (6.11 vs. 5.29 mm/(steps/min),  $p < 0.01$ ) and duty-factor\_double stance (30.41 vs. 28.33%,  $p < 0.01$ ). Elder participants walked remarkably more slowly (1.23 vs. 1.29 m/s,  $p < 0.01$ ) and have smaller  $SD_A$  (1.49 vs. 1.61,  $p < 0.01$ ). A larger part of distinction was observed only in female subjects, such as less steps per min (116.68 vs. 122.26 steps/min,  $p < 0.01$ ), shorter stride length (1.23 vs. 1.25 m,  $p < 0.05$ ), more time spent per walk (526.13 vs. 516.34 ms,  $p < 0.01$ ), and smaller  $SD_A$  (1.38 vs. 1.47,  $p < 0.01$ ),  $SD_B$  (0.40 vs. 0.42,  $p < 0.05$ ) and A ratio (3.55 vs. 3.68,  $p < 0.05$ ).

## Discriminatory power of step time for the occurrence of DPN

Since step time was an independent correlative factor for DPN, ROC analysis was explored to find any discriminatory power and sensitivity and specificity of step time for the occurrence of DPN (Fig. 3). The AUC value was 0.752 (95% CI: 0.721–0.782,  $p < 0.01$ ). In total, the cut-off point of step time was 526.13 ms for indicating DPN. The Youden index at this level was 0.387; its sensitivity reached to 82.22% and the specificity was relatively low 56.56%.

## The Risk Of Different Abi On Decreased Stride Length

We chose a group of individuals who received the examination of ABI, 1165 cases were enrolled totally. All these subjects were divided into four groups according to the ABI value,  $ABI > 1.30$  ( $n = 46$ ),  $0.90 \sim 1.30$  ( $n = 1068$ ),  $0.60 \sim 0.89$  ( $n = 34$ ),  $ABI < 0.60$  ( $n = 17$ ), and  $ABI$  ranged from 0.90 to 1.30 was defined as normal and was chosen as the control group. We calculated the relative risk of altered ABI on stride length by binary logistic regression analysis. Finally, a significant risk between  $ABI < 0.60$  and decreased stride length was observed (OR = 51.37,  $p < 0.05$ ). Further, the analysis in other three adjusted models was performed (Table 3). After adjusted for leg length, sex and age, this prominent risk still existed (OR = 112.19, 95% CI: 3.11- 4040.13,  $p = 0.01$ ).

Table 3  
Odds ratio analysis of ABI with decreased stride length.

	Model 1		Model 2		Model 3		Model 4	
ABI	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
>1.30	2.58 (0.36-18.00)	0.340	3.64 (0.41-32.11)	0.554	4.93 (0.55-44.34)	0.154	3.92 (0.44-35.12)	0.223
0.90 ~ 1.30	1	/	1	/	1	/	1	/
0.60 ~ 0.89	1.88 (0.19-18.23)	0.588	4.11 (0.35-48.69)	0.262	6.00 (0.49-72.25)	0.158	4.50 (0.38-53.49)	0.233
< 0.60	51.37* (1.67-1576.85)	0.024	136.02* (3.79-4881.29)	0.007	171.42* (4.74-6194.81)	0.005	112.19* (3.11-4040.13)	0.010
*, <i>p</i> < 0.05.								
Model 1, odds ratio analysis of different ABI with stride length.								
Model 2, leg length adjusted.								
Model 3, leg length and sex adjusted.								
Model 4, leg length, sex and age adjusted.								

## Discussions

Most recently, several researches have focused on the measurement of gait parameters to illustrate the role of diabetes, diabetic peripheral neuropathy, or other diabetes related complications [2-6]. Whist, results differ due to different population, various devices and methods of examination, diverse analysis and so on. For the purpose of verifying the effect of different conditions of diabetes on gait alterations during shod walking. The present study investigated the changes during walking among different diabetic individuals with controls for the first time, and provided a first step of the whole diabetic population towards substantiating the impact of diabetes and diabetic lower extremity complications on gait.

Our results demonstrated that only the incidence of elevated blood glucose or diabetes was not adequate to imply any evident alterations of gait, during both spatiotemporal or phase plot analysis, which is contradicted with other data on the association between impaired blood glucose and abnormal gait. In a study by Almurthi et al [5], subjects with impaired glucose tolerance displayed a significantly higher

dynamic mediolateral sway during walking, suggesting alterations in gait may occur very early, even in the pre-diabetes phase, indicating the impairment of gait could be observed as early as the emergence of IGT. And as documented in other studies [5,6], diabetes alone could induce gait alterations, such as slower gait speed, shorter stride length, increased cadence and high gait variability. Contradicted to these results, we did not detect similar abnormalities. But there are no previous studies examining the alteration of phase plot, within such extended range of diabetes subjects. The trend analysis during phase plot assessment revealed that the decline of variability and symmetry appears as long as diabetes occurred. Many other investigations had offered explanations why abnormality in diabetes. For instance, a significant reduction in proximal and distal leg muscle strength and a proximal reduction in muscle volume [15] played a role in gait abnormalities among diabetes with a further contribution of brain atrophy and cognitive impairments that were related with dysregulation of glycemic control [16]. With the purpose of early detection of gait pathology to discriminate subjects with impaired blood glucose or diabetes, maybe a 10m level walking with self-selected speed is inadequate to minor remarkable disparity, and stimulation tests, such as long-distance walking or climbing stairs, are needed.

It is widely recognized that, DPN affects peripheral sensory and motor nerves [2] and in the wake of the sensory-motor system is gradually affected, reduced sensation towards pain, tissue damage, loss of muscle strength, altered foot structure and ultimately abnormal gait [17]. Lowered cadence, modified stride length and decreased gait speed were reckoned as characteristics of impaired gait performance among DPN groups [2]. Menz et al. [8] observed shorter step length of DPN patients when walking on irregular surfaces, and other evidence suggested that irregular terrain accentuates differences in step time variability between older women with and without peripheral neuropathy [18]. Walking speeds (average 4.5km/h-4.8 km/h) in the present study were within the range of values recorded in previous studies on comparable surfaces (3.4km/h-5.1 km/h) [19]. Consistent with these results, decreased cadence, increased step time and decreased walking speed were confirmed again. In this investigation, ROC analysis was employed to seek the predictive value of step time in indicating the presence of DPN, and our research maybe the first effort to find an optimal cut-off point of step time for predicting DPN (526.13ms). And stepwise regression analysis showed VPT was an independent risk factor for decreased  $SD_A$  and  $SD_B$ , Which means a poor gait variability and symmetry when lower extremity neural function deteriorates. All these findings in our research revealed that DPN participants manifested a moderate modification of gait while walking to adapt sensory-motor system abnormality. Although the findings from previous studies were seemingly consistent [8,20,21], the simple size were strikingly small (around 50~100 cases), and usually the healthy individuals were picked as controls. We enhanced the influence of DPN on gait further. Therefore, this non-invasive and non-irritating gait examination, may be an alternative adoption in the near future that could help distinguish diabetic neuropathy conveniently.

Though a plenty of previous studies recruited DPN participants, only few studies excluded patients with LEAD particularly. LEAD is a common co-morbidity of diabetes, and has been reported to have significant effects on walking patterns. Data from the Women' Health and Aging Study showed that peripheral artery disease, peripheral nerve dysfunction and depression were the major contributors to the impairment in

mobility observed in women with diabetes [22]. Furthermore, earlier findings showed that symptomatic PAD (peripheral artery disease) patients with hypertension displayed a slower cadence and shorter stride length during a constant-load, sub-maximal treadmill test [4]. Patients with symptomatic PAD are at particularly high risk for slow gait as a result of the development of leg pain during walking, Gardner et al even found a slower gait speed in PAD patients than in controls during pain-free ambulation [23]. Both symptomatic and asymptomatic patients with LEAD were included, thus the results of our research may be generalized to the population with LEAD. Our data displayed some similar difference. Reduced cadence, increased step time and decreased walking speed and increased duty factor\_double stance were recorded. And stepwise regression analysis showed that ABI was an independent risk factor for decreased stride length, elevated  $SD_A$  and  $SD_B$ . An ABI less than 0.6 means a manifestly lowered stride length. All these means patients with LEAD needed more stand\_phase with two legs to sustain the posture and walking balance, and performed a much more conservative walking style. There are potential mechanisms underlying the association of PAD and mobility impairment, including inflammation, mitochondria dysfunction and reduced muscle perfusion [10]. And PAD patients have impaired exercise performance, as measured by slow oxygen kinetics during a constant-load, sub-maximal treadmill test [4]. As consequence, it is unsurprising that individuals with LEAD commonly have impaired gait performance, indicating the important role of LEAD in gait alterations.

In this large-sample and wide-range trial of elder individuals, we were able to examine potential explanatory factors (sex, age, BMI, height, leg length, complications, DM duration, diabetic co-morbidities, smoking, VPT and ABI) of the altered gait parameters. And the key observation was that stepwise multivariate analyses identified sex, age, leg length were more significant independent predictors of gait parameters, in addition to VPT and ABI. In the present investigation, age-deteriorated changes existed almost in every gait feature. The elderly walked slower with lower cadence, shorter stride length as age increased. Slow walking speed is highly prevalent in men and women above age 65 [24]. Reduced walking speed appears to be a compensatory strategy adopted by the elders to maintain trunk stability, and it is associated with increased risk of all-cause-mortality, impaired gait efficiency and increased risk of disability [25]. As Tine et al illustrated [9], older participants with diabetes walked slower, took shorter strides during simple, counting backward by 3 from 40, reciting animal names conditions when compared with controls, and showed more gait variability during dual-task conditions. Declined nervous system and musculoskeletal system because of aging may affect gait control [26]. Age-deteriorated changes in the production of sex steroids and cortisol, and in the secretion of the growth hormone and insulin-like growth factor-1 have also been identified in the pathogenesis of weakness during gait [27, 28]. Sex-related changes in our investigation were popular too, which is consistent to other conclusions. As one South Korea trial described, females have shorter stride length and walked slower than males mostly due to their shorter height, and the researchers assume that the difference is due to gender features of the gait-related anatomy and habits [29]. The rapid reduction of estrogen in postmenopausal female and the gradual decline of testosterone in male lead to decrease in muscle mass and strength [27]. Besides, we illustrated the influence of leg length on gait indexes, which should not be ignored during gait analysis. Decades ago, the locomotor advantages of longer lower limbs has been documented [30]. And

recently eighteen male healthy subjects were enrolled in a walking gait analysis [31], Fazreena et al maintained the mean contact forces for all joints (ankle, knee, hip and pelvis) in the short leg were increased. Researchers also claimed gait impairments are associated with age, sex, diabetes, hypertension and history of cerebrovascular accidents, of which greater age and female sex were listed to be associated with slower gait speed and shorter stride length [25].

There are some limitations of the present study, which should be identified. These data came from a multiple-center, large-sample randomized and controlled trial, but this manuscript only performed the cross-sectional analysis of outpatients with type 2 diabetes. Additional prospective outcomes are further required to demonstrate the role of all diabetic conditions on the alterations of gait.

Gait parameters was collected during the 10-m walk on the flat land among different conditions of diabetes. It is meaningful to observe differences in various gait parameters while walking on challenging surfaces. Evidences suggested that irregular terrain accentuates differences in step time variability [18,32]. With respect to the impact of walking style demanded, the results differ apparently. It has also been reported that both initiation and termination of gait were more complex procedures than steady-state walking [33]. Therefore, challenging surfaces or different walking style may explain more. Besides, this was a study of relatively older adults. Thus, the findings may not be suitable to assess younger samples or to individuals. Although these limitations exist, we believe that the novel findings of the present research are generalizable to the large number of elder diabetic outpatients in clinic.

## Conclusions

To date, current literature supports the role of DPN in altering gait parameters. The present investigation extended the participants to varies diabetic individuals, accompanied with or without lower extremity complications. And we identifies some significant differences in gait among diabetes complicated with lower extremity complications, such as lowered cadence, increased step time and decreased walking speed. LEAD subjects also showed increased duty factor\_double stance. Besides, lower  $SD_A$  and  $SD_B$  was documented in subjects with both DPN and LEAD. And, we revealed a close correlation between sex, age, leg length and the gait indexes, and verified a relationship between VPT, ABI and gait alterations among elder Chinese individuals. Further, ROC analysis substantiate that step time might be adopted as an index for early detection of patients at risk for diabetic peripheral neuropathy. OR analysis revealed the relative risk of lowered ABI ( $< 0.6$ ) on decreased stride length.

Generally, our study provides instructive significance of the measurement of gait, the screening for gait as early as possible could help to distinguish diabetes complicated with lower extremity complications. Maybe, this non-invasive and non-irritating gait examination could be an alternative measurement that could help distinguish diabetic neuropathy conveniently.

## Abbreviations

T2DM: type 2 diabetes mellitus; NGT: normal glucose tolerance; IGT: impaired glucose tolerance; DPN: diabetic peripheral neuropathy; LEAD: lower extremity artery disease; PAD: peripheral artery disease; VPT: vibration peiception threshold; ABI: ankle-brachial index; CHD: chronic heart disease; CI: cerebral infarction; HP: hypertension; BMI: body mass index; HbA1c: glycosylated hemoglobin; FPG: fasting plasma glucose; PPG: 2-h postprandial blood glucose; ROC: reveiver operating characteristic; AUC: area under the curve; OR: odds ratio; CI: confidence interval

## **Declarations**

### **Authors' contributions**

All authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript and have participated in drafting and reviewing the manuscript. All authors read and approved the fnal manuscript.

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### **Competing interests**

No competing financial interests exist.

### **Availability of data and materials**

Not applicable. No new datasets were generated for this review article.

### **Consent for publication**

All authors gave their consent for publication of this manuscript.

### **Ethics approval and consent to participate**

Not applicable for this article as no new studies were conducted or data generated.

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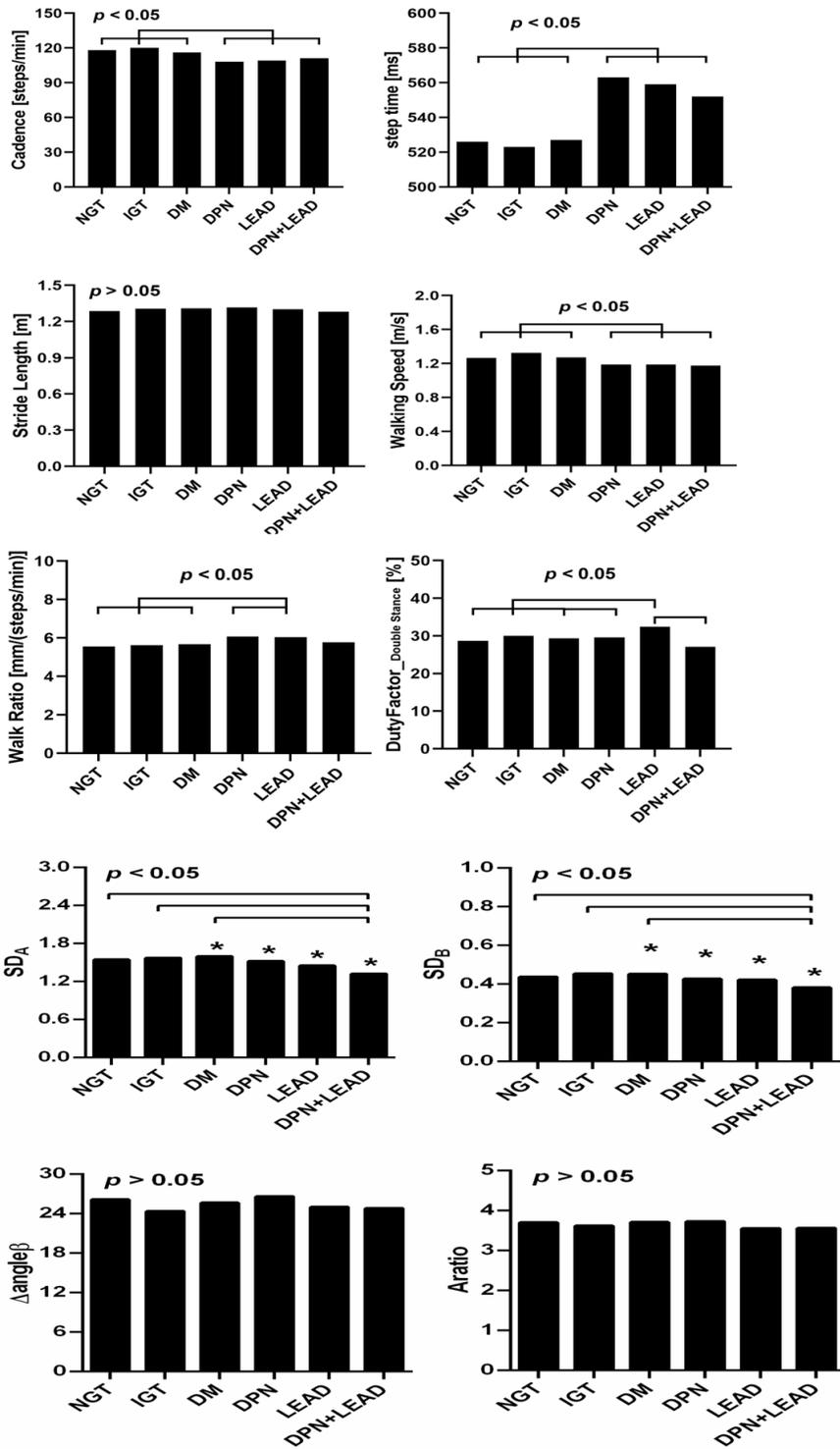
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## Figures



**Figure 1**

The comparison of gait spatiotemporal and phase plot variables among different groups. Spatiotemporal analysis: variables were cadence, step time, stride length, walking speed and walk ratio, duty-factor\_double stance. Difference of all gait variables between groups was significant ( $p < 0.05$ ). Lowered cadence, increased step time and decreased walking speed were detected in diabetes with lower extremity neural and/or vascular complications (all  $p < 0.05$ ). Increased duty factor\_double stance was displayed in

participants with LEAD alone (32.51%,  $p < 0.05$ ). Phase plot analysis: variables were SDA, SDB, Aratio and  $\Delta\text{angle}\beta$ . Difference of all gait variables between groups was significant ( $p < 0.05$ ). \*  $p < 0.05$ , trend analysis. The results displayed lower SDA (1.32 vs. 1.57,  $p < 0.01$ ) and SDB (0.38 vs. 0.51,  $p < 0.01$ ) of subjects with both DPN and LEAD. Besides, trend analysis revealed that gradually decreased SDA and SDB in the four DM groups ( $p < 0.05$ ).

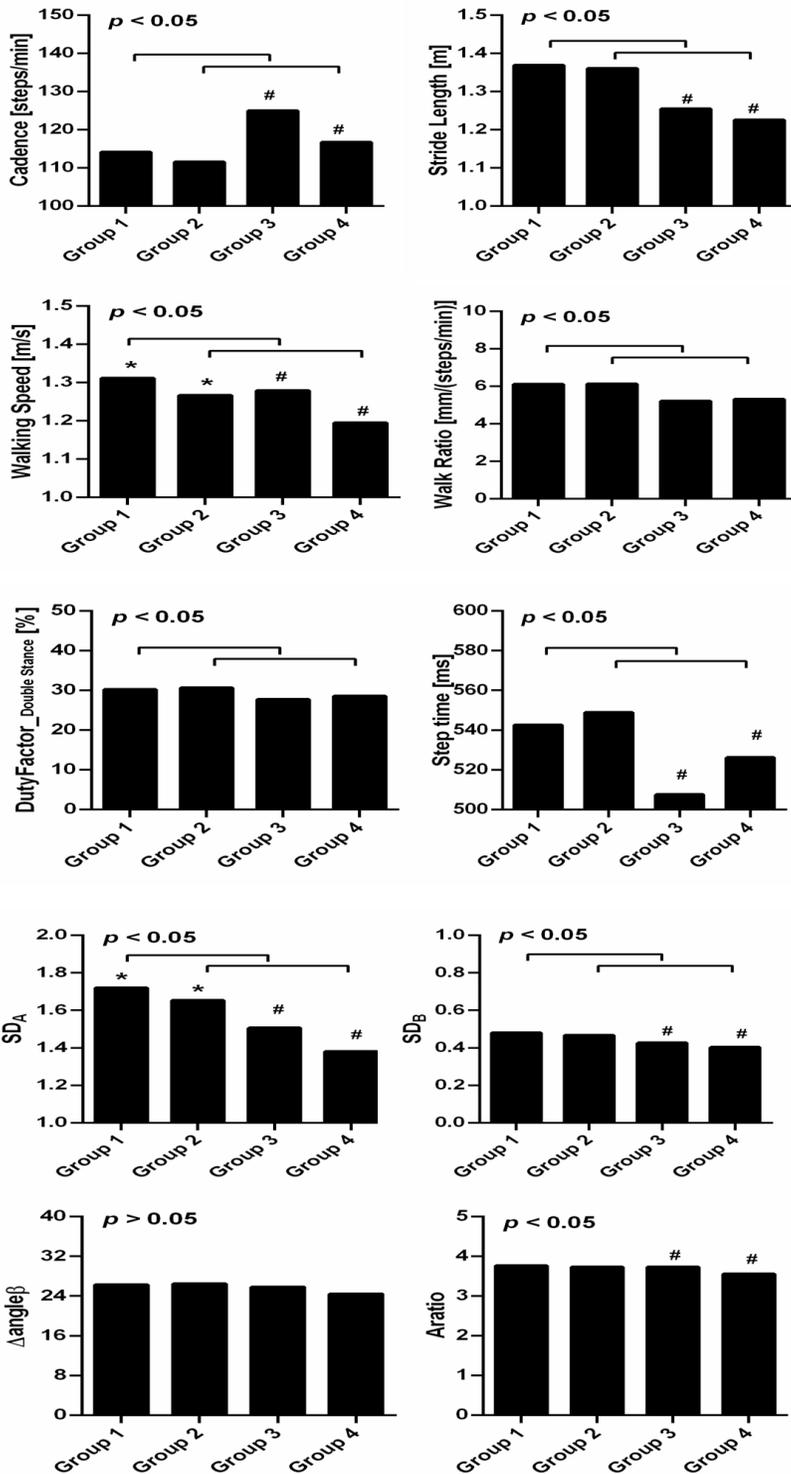
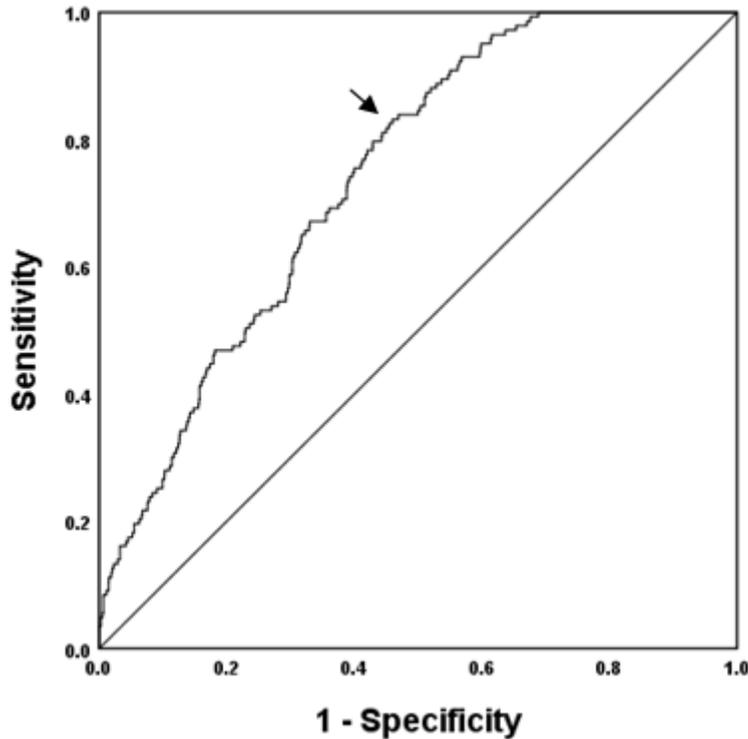


Figure 2

The comparison of gait variables among sex and age matched groups. Totally, 1420 individuals were selected, and divided into four groups according to their sex and age. Group 1 was defined as male, age<65 years (56.1±5.2 years), n=372; Group 2, male, age≥65 years (69.7±3.2 years), n=190; Group 3, female, age<65 years (56.5±5.8 years), n=571; Group 4, female, age≥65 years (69.7±3.3 years), n=287.



**Figure 3**

ROC analysis. ROC analysis was explored to find any discriminatory power of step time for the occurrence of DPN. The AUC value was 0.752 (95% CI: 0.721-0.782,  $p < 0.01$ ). Cut-off point was 526.13ms. The Youden index at this level was 0.387; its sensitivity was 82.22% and the specificity was 56.56%.

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