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The early diagnostic value of ankle-brachial index combined with feet electrochemical skin conductance for peripheral artery disease in type 2 diabetes

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ABSTRACT

Aims/Introduction: In this paper, we focused on exploring the diagnostic and predictive clinical utility of ankle-brachial index (ABI) in combination with feet electrochemical skin conductance (FESC) for peripheral artery disease (PAD) in Chinese patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: Overall, 183 Chinese T2DM patients were enrolled in this study. The patients were classified into three groups: Group 1 comprised of uncomplicated type 2 diabetics (n = 36), Group 2 consisted of patients with diabetic peripheral neuropathy (n = 103) whereas Group 3 patients displayed peripheral artery disease (n = 44). All patients underwent Sudoscan test using a Sudoscan (Paris, France) and ABI assessment.

Results: Multivariate logistic regression models revealed that FESC was an independent risk factor of developing PAD in patients with type 2 diabetes. The AUC for diagnostic, positive predictive and negative predictive value of ABI in combination with FESC for PAD were 0.907, 0.733 and 0.920, respectively. The specificity and sensitivity of ABI in combination with FESC for PAD were 0.914 and 0.750, respectively.

Conclusions: Ankle-brachial index in combination with FESC can accurately be used in early diagnosis of PAD.

INTRODUCTION

The global cases of obesity parallel the incidences of diabetes, with the latter cases reaching 463 million in 2019. Intriguingly, the number of diabetics is expected to increase by 25% in 2030 and by 51% in 2045 [1]. Diabetes-related complications, particularly PAD, have imposed a huge public health burden on numerous countries. Most PAD patients undergo amputation and are likely to suffer premature death[2]. The incidence of cardiovascular events is as high as 21.14% in individuals with PAD, just one year after the onset of the disease[3].

Peripheral artery disease in diabetic patients manifests with stenosis or occlusion of arteries in the lower extremities. PAD is the main pathological process underlying atherosclerosis. In particular, PAD induces inflammation, endothelial dysfunction, oxidative stress, coagulation and fibrinolysis disorders[4]. Early PAD is often accompanied by distal symmetric neuropathy. Diabetic peripheral neuropathy (DPN) impairs pain transmission, and as a result, T2DM patients may not notice injuries on the lower limbs in time. Unfortunately, a combination of neuropathy and ischemia accelerates foot ulcers and is associated with a poor prognosis of T2DM.

Diabetic autonomic neuropathy (DAN) is one of the common types of DPN. DAN disrupts perfusion of skin nutrients by increasing the flow of arteriovenous shunts, which contributes to the occurrence of PAD or even foot ulceration[5]. Therefore, the majority of disabilities and refractories rate in diabetic peripheral neuropathy results from DAN. In addition to cardiovascular, gastrointestinal and genitourinary systems, diabetic autonomic neuropathy usually affects sudomotor function (SMF). SMF is mainly innervated by unmyelinated sympathetic small nerve C fibers. In diabetics, damage to these nerve fibers is more common and serious than those of large fiber

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nerves. Even though Sudomotor dysfunction (SMD) may occur before large fiber neuropathy, it has also been observed in prediabetes. Therefore, SMD can reflect early diabetic autonomic neuropathy[6]. SUDOSCAN has been used in clinical diagnosis of diabetes mellitus (DM), DPN and metabolic syndrome among other complications, all shown to be risk factors for PAD.

Ankle-brachial index is widely used in the diagnosis of PAD, and the process is closely related to the degree of atherosclerosis. However, the sensitivity of ABI for PAD is substantially low, especially in the elderly and diabetics[7,8]. Distal diabetic neuropathy has been implicated in medial arterial calcification, leading to incompressible arteries. It weakens the reliability of the ABI test[9].

Accordingly, we aimed to assess the performance of ABI in combination with FESC in discriminating PAD in Chinese patients with T2DM.

MATERIALS AND METHODS

Study population

All T2DM participants were selected from 1057 individuals attending the Jiangsu Provincial Hospital of Traditional Chinese Medicine between May 2020 and November 2020. Only subjects who underwent Sudoscan test and ABI measurement and had complete clinical data were enrolled in this study. Based on clinical diagnosis, the patients were divided into three groups: Group 1 – T2DM patients without diabetes-related complications; Group 2 – DPN patients without other diabetes-related complications; Group 3 – PAD patients with or without other diabetes-related complications. T2DM diagnosis was performed according to the 1999 World Health Organization diagnosis criteria. DPN diagnosis was as follows: (i) the presence of clinical symptoms or signs of peripheral neuropathy such as limb pain, numbness and sensory disturbances; (ii) electrodiagnostic criteria of electromyography: Abnormality of the sensory and motor nerve conduction velocity and amplitude of two or more nerves except the median nerve of the upper limbs; (iii) exclude other causes of peripheral neuropathy. PAD was diagnosed based on the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) guidelines[10]: (i) Patients with resting ABI≤0.90, regardless of whether the patient experiences lower limb discomfort; (ii) Patients with lower limb discomfort when exercising and resting ABI ≥ 0.90, but the ABI decreases by 15–20% after the treadmill plate test; (iii) Patients with severe limb ischemia and resting ABI<0.40 or ankle arterial pressure <50 mmHg or toe arterial pressure <30 mmHg.

Patients (i) under age of 18; (ii) with type I, Gestational and other types of diabetes; (iii) on medications such as beta blockers, antineoplastic agents, steroids tricyclic antidepressants that can affect the sympathetic system; (iv) not legible for Sudoscan test such as those with electrical implants, pregnant and without limbs; (v) with history of epilepsy; (vi) with lumbar sciatic nerve lesion and varicose veins of the lower limbs; (vii) with thyroid disease or vitamin B12 deficiency; (viii) with active foot ulcer; (ix) with severe hepatic and renal dysfunction; (x) anemic, alcoholic, diabetic ketosis, ketoacidosis, hyperosmolar hyperglycaemic state, serious infection and with recent cardiovascular and cerebrovascular events; (xi) with ABI≥1.4 were all excluded from the study. The protocol for this study was approved by the ethical review committee of the Jiangsu Provincial Center for Disease Control and Prevention (JSJK2016-B003-03) and was conducted in accordance with the Helsinki Declaration. Each participant consented to participate in this study.

Baseline clinical and laboratory parameters

Patient characteristics captured at baseline included age, sex, duration of T2DM, height, weight as well as history of smoking, drinking and other underlying diseases, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body mass index (BMI) was calculated as weight divided by the square of the height. Blood samples were collected for measuring fasting blood glucose (FBG), 2-h postprandial blood glucose (PBG), hemoglobin A1c (HbA1c), C-Reactive Protein (CRP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and total bilirubin (TBIL).

Assessment of sudomotor function

Sudomotor function was assessed using a SUDOSCAN 2 (Paris, France). A SUDOSCAN is a non-invasive device that rapidly measures electrochemical skin conductivity (ESC) of sweat glands based on reverse ion electroosmosis technique induced by a low dc voltage[11,12]. It is currently the most sensitive device for the detection of sudomotor function. Damage to sympathetic C fibers impairs the secretion of chloride ions in the sweat glands, which substantially reduces the ESC output. A SUDOSCAN is the objective device for early detection of diabetes[13] and associated complications[14,15].

Hands mean electrochemical skin conductance (HESC, uS), Feet mean electrochemical skin conductance (FESC, uS), Hands asymmetry (HASYM,%), Feet asymmetry (FASYM,%) and cardiovascular autonomic neuropathy risk (CAN-RS,%) were measured using a SUDOSCAN 2.

ABI measurement

The ABI was measured using the color Doppler blood flow device (Chioy Medical, Beijing) by an experienced physician. The tests were performed after 5 minutes of supine rest. Four cuffs were also placed on both ankles and upper arms of the patient as the time of assessing different parameters. The ankle-brachial index was expressed as the ratio of the highest ankle pressure of one limb to the highest brachial artery pressure. Normal ABI is 0.9–1.3, but ≤0.9 for PAD and >1.3 for extensive atherosclerosis of lower limb arteries. The lower ABI of each patient was recorded.

Table 1 | Baseline characteristics of the three groups

Characteristics	Group 1 T2DM	Group 2 DPN	Group 3 PAD	*P*-value
N	36	103	44	
Age (years)	49.3 ± 9.6	59.7 ± 12.1	62.7 ± 13.7	<0.001***
Duration of T2DM (years)	2.0 (0.6–6.2)	10.0 (2.0–16.0)	15.0 (6.0–20.0)	<0.001***
BMI (kg/m^2)	25.7 ± 3.6	24.8 ± 3.8	24.7 ± 4.0	0.440
SBP (mmHg)	126.4 ± 13.7	133.6 ± 19.6	134.3 ± 19.7	0.102
DBP (mmHg)	79.3 ± 10.1	73.8 ± 10.5	75.8 ± 10.7	0.025*
FBG (mmol/L)	7.6 ± 2.6	7.1 ± 2.6	7.7 ± 3.0	0.417
PBG (mmol/L)	14.3 ± 4.3	13.6 ± 4.6	14.7 ± 4.2	0.404
HbA1c (%)	9.8 ± 2.6	9.0 ± 2.3	9.2 ± 2.0	0.271
CRP (mg/L)	3.3 (2.2–4.4)	2.2 (1.6–3.6)	2.6 (1.7–6.2)	0.033*
TC (mmol/L)	4.9 ± 1.0	4.7 ± 1.2	4.7 ± 1.4	0.734
TG (mmol/L)	1.5 (1.2–2.4)	1.3 (0.9–2.0)	1.3 (1.1–2.5)	0.057
HDL-C (mmol/L)	1.1 ± 0.2	1.2 ± 0.3	1.1 ± 0.4	0.352
LDL-C (mmol/L)	3.3 ± 1.0	3.1 ± 1.2	3.0 ± 1.1	0.365
TBIL (μmol/L)	9.3 (7.8–13.8)	10.77 ± 4.96	8.2 (7.1–12.6)	0.279
Hands mean ESC (uS)	66.0 ± 15.2	60.9 ± 16.4	56.0 ± 20.3	0.070
Hands asymmetry (%)	5.0 (1.0–10.0)	6.0 (2.0–11.0)	5.5 (1.0–15.5)	0.053
Feet mean ESC (uS)	69.5 ± 14.8	67.7 ± 15.4	56.0 ± 20.2	<0.001***
Feet asymmetry (%)	3.0 (1.0–6.0)	3.0 (2.0–6.5)	3.5 (2.0–7.0)	0.369
CAN-RS (%)	22.0 ± 9.4	27.6 ± 9.5	29.6 ± 8.9	0.001**
ABI	1.1 ± 0.1	1.1 ± 0.1	0.9 ± 0.2	<0.001***
Sex				
Male	24 (66.67%)	57 (55.34%)	22 (50.00%)	0.313
Female	12 (33.33%)	46 (44.66%)	22 (50.00%)	
Smoking (%)				
No	28 (77.78%)	87 (85.29%)	36 (81.82%)	0.572
Yes	8 (22.22%)	15 (14.71%)	8 (18.18%)	
Drinking (%)				
No	31 (86.11%)	89 (86.41%)	42 (95.45%)	0.254
Yes	5 (13.89%)	14 (13.59%)	2 (4.55%)	

Continuous data are Mean ± SD/median (Q1–Q3), and categorical data are *N* (%). **P*-value <0.05; ***P*-value <0.01; ****P*-value <0.001. ABI, Ankle-brachial index; BMI, body mass index; CAN-RS, cardiovascular autonomic neuropathy risk; CRP, C-Reactive Protein; DBP, diastolic blood pressure; DPN, diabetic peripheral neuropathy; ESC, electrochemical skin conductance; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; PBG, postprandial blood glucose; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TBIL, Total bilirubin; TC, total cholesterol; TG, triglyceride.

Statistical analysis

Continuous data were expressed as mean ± standard deviation or median (Q1–Q3). Categorical variables were expressed as percentages. Differences between means of continuous variables were analyzed using Analysis of variance (ANOVA) or Kruskal–Wallis test, whereas chi-square test or Fisher's exact test was used for categorical variables. The relationship between PAD and associated risk factors was assessed using univariate logistic regression analysis. The association between FESC and PAD events was evaluated using multivariate logistic regression analysis. The diagnostic performance of ABI, FESC, ABI+FESC model for PAD was assessed using receiver operating characteristic (ROC). Statistical differences between ROC curves were evaluated using DeLong's test for 2 correlated ROC curves. All analyses were performed using R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com) (Boston, MA, USA).

RESULTS

Baseline characteristics of participants

The clinical, physical and chemical characteristics of patients in the three diabetes groups are listed in Table 1. The average age of the patients enrolled in this study was 58.38 ± 12.89 years. Also, 56.28% of study participants were men. The prevalence of PAD among T2DM patients was approximately 4.16%. There was no significant difference in BMI, SBP, FBG, PBG, HbA1c, TC, TG, HDL-C, LDL-C, TBIL, sex, smoking, drinking among the three groups. However, there were significant differences in age, duration of T2DM, DBP, CRP and ABI among the three diabetes groups. HESC and FESC decreased along group 1 to

Table 2 | Risk factors associated with PAD in univariable regression analysis

Characteristics	OR	95% CI	*P*-value
Age (years)	1.038	1.008–1.068	0.01189*
Sex			
Male	1.0		
Female	1.397	0.707–2.758	0.33595
Duration of T2DM (years)	1.087	1.039–1.137	0.00026***
Smoking			
No	1.0		
Yes	1.111	0.458–2.698	0.81597
Drinking			
No	1.0		
Yes	0.301	0.067–1.346	0.11610
BMI (kg/m^2)	0.976	0.892–1.068	0.59484
SBP (mmHg)	1.007	0.989–1.026	0.42863
DBP (mmHg)	1.006	0.974–1.038	0.73320
FBG (mmol/L)	1.058	0.935–1.196	0.37128
PBG (mmol/L)	1.045	0.966–1.131	0.26925
HbA1c (%)	0.996	0.859–1.153	0.95286
CRP (mg/L)	1.006	0.969–1.044	0.77067
TC (mmol/L)	1.011	0.756–1.353	0.94075
TG (mmol/L)	1.148	1.003–1.313	0.04495*
HDL-C (mmol/L)	0.911	0.284–2.918	0.87470
LDL-C (mmol/L)	0.841	0.612–1.157	0.28767
TBIL (μmol/L)	0.975	0.915–1.038	0.42104
Hands mean ESC (uS)	0.980	0.961–0.999	0.04109*
Hands asymmetry (%)	1.050	1.007–1.095	0.02198*
Feet mean ESC (uS)	0.962	0.943–0.981	0.00012***
Feet asymmetry (%)	1.079	1.011–1.152	0.02164*
CAN-RS (%)	1.041	1.001–1.082	0.04342*
ABI	0.000	0.000–0.000	<0.00001***

**P*-value <0.05; ***P*-value <0.01; ****P*-value <0.001. ABI, Ankle-brachial index; BMI, body mass index; CAN-RS, cardiovascular autonomic neuropathy risk; CRP, C-Reactive Protein; DBP, diastolic blood pressure; DPN, diabetic peripheral neuropathy; ESC, electrochemical skin conductance; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; PBG, postprandial blood glucose; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TBIL, Total bilirubin; TC, total cholesterol; TG, triglyceride.

group 3, whereas HASYM, FASYM and CAN-RS displayed a reverse trend. Only FESC and CAN-RS had statistically significant differences among all the Sudoscan parameters.

The relationship between patient as well as clinical factors and PAD

Univariate analysis revealed that age, duration, TG, HESC, HASYM, FESC, FASYM and CAN-RS were related to PAD events (Table 2). Multivariate regression analysis for the relationship between FESC and PAD is shown in Table 3. Both continuous and categorical FESC was associated with PAD events. Based on the crude model (adjusted for none), continuous FESC levels negatively correlated PAD development (OR = 0.962, 95% CI: 0.943–0.981). After adjusting for age, disease duration, TG, HESC, HASYM, FASYM and CAN-RS, FESC was still strongly associated with the development of PAD in diabetic patients (OR = 0.948, 95%CI: 0.916–0.981). For sensitivity analysis, FESC was first converted into quartile categorical variable. In the fully adjusted model, the ORs of PAD decreased progressively across FESC quartiles. Compared with reference Q1 group, the incidence of subjects in Q4 was significantly different, and the *P*-value for the trend was 0.02911.

The diagnostic utility of ABI, FESC and ABI + FESC model

The diagnostic utility of ABI, FESC and ABI + FESC for PAD is shown in Figures 1 and 2. The cut-off value for ABI in predicting PAD was 0.945. The specificity and sensitivity of ABI in predicting the development of PAD were 0.942 and 0.705, respectively. The optimal cut-off value of FESC for PAD diagnosis was 66.5uS, whereas its specificity and sensitivity for PAD were 0.633 and 0.659, respectively. The diagnostic efficacies of ABI, FESC, ABI + FESC for PAD are shown in Table 4. The AUC of ABI in combination with FESC was significantly greater than that of ABI method alone (0.907, 95% CI: 0.8545–0.9586, $P = 0.0373$).

DISCUSSION

Peripheral artery disease is a serious complication associated with T2DM. It is the main cause of foot ulcers, amputations

Table 3 | Relationship between FESC and PAD events in different models

Characteristics	Crude model†		Fully adjusted model‡	
	OR 95% CI	*P*-value	OR 95% CI	*P*-value
Feet mean ESC (uS)	0.962 (0.943, 0.981)	0.00012***	0.948 (0.916, 0.981)	0.00237**
Feet mean ESC (uS)				
Q1	Ref		Ref	
Q2	0.622 (0.255, 1.521)	0.29812	0.528 (0.171, 1.633)	0.26758
Q3	0.319 (0.122, 0.837)	0.02021*	0.310 (0.083, 1.152)	0.08037
Q4	0.222 (0.079, 0.629)	0.00460**	0.175 (0.034, 0.913)	0.03865*
P for trend	0.593 (0.429, 0.818)	0.00149**	0.559 (0.332, 0.943)	0.02911*

**P*-value <0.05; ***P*-value <0.01; ****P*-value <0.001. †Crude model adjust for: None. ‡Fully adjusted model adjust for: Age; Duration of T2DM; TG; Hands mean ESC; Hands asymmetry; Feet asymmetry; CAN-RS.

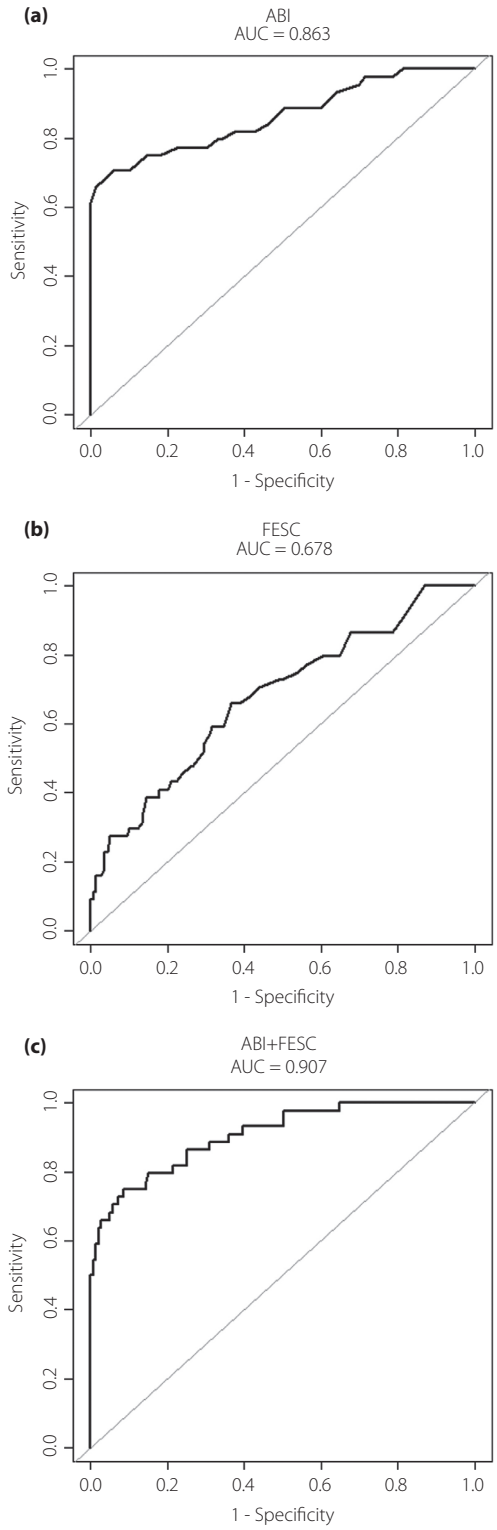

Figure 1 | The Receiver operating characteristic curves for the diagnostic utility of (a) ABI, (b) FESC and (c) a combination of ABI + FESC in PAD diagnosis in patients with type 2 diabetes. ABI, Ankle-brachial index; AUC, area under the curve; FESC, Feet mean electrochemical skin conductance.

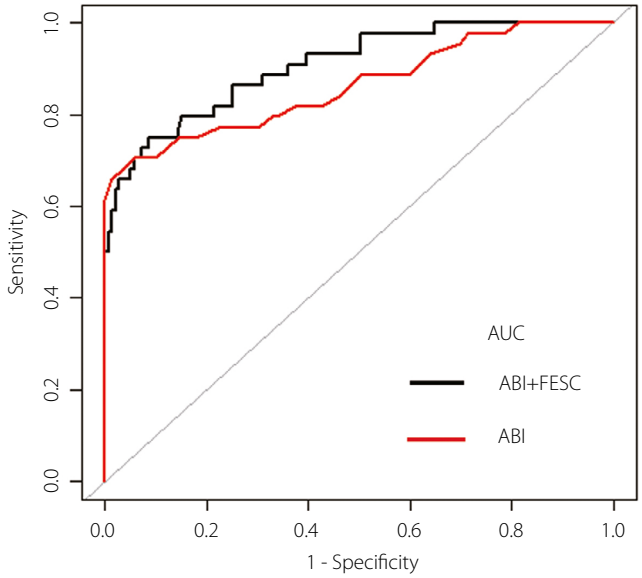

Figure 2 | The Receiver operating characteristic curves for the comparative accuracy of ABI alone and ABI + FESC model in PAD diagnosis among T2DM patients.

and even death in diabetic patients[16]. PAD is more serious in diabetics, relative to non-diabetic individuals because in diabetics, the internal iliac artery, deep femoral artery and anterior tibial artery are more likely to be involved. PAD is insidious, and thus unnoticeable in some patients, even those with stenosis and occlusion of blood vessels. Currently, scientific and objective evaluation of vascular disease often depends on instrumental examination.

Ankle-brachial index is widely used for PAD screening in clinical practice. Unfortunately, a recent meta-analysis revealed that the sensitivity and specificity of ABI is only 61 and 92%, respectively, for spinal stenosis equal to or >50%[17]. In the study, the sensitivity and specificity of ABI were slightly higher than those reported in the meta-analysis. ABI can be grouped into three categories: Normal ABI (1.00–1.30); borderline ABI (0.91-0.99); ABI > 1.30 (vascular calcification and arterial elasticity impairment) and abnormal (PAD) ABI ≤ 0.90. ABI test suffers several limitations in PAD diagnosis in diabetics[18,19]. In particular, diabetic patients present with underlying arterial calcification, which often leads to a false negative PAD diagnosis. Wukich *et al.*[20] found that 42.7% of DM patients with diagnosed PAD were classified as normal ABI. Several diseases such as arteriosclerosis obliterans and arterial calcification in the lower limb interfere with accurate PAD diagnosis using ABI[8]. However, increasing the cut-off value of normal ABI decreases the specificity of the test[21]. However, combining ABI with other parameters can improve the diagnostic accuracy for PAD[22]. Color Doppler ultrasound examination and vascular imaging are also used in PAD screening. However, in diabetics, PAD

Table 4 | ROC analysis for diagnosis in ABI, FESC and ABI+FESC

Test	AUC	Best threshold	Specificity	Sensitivity	Accuracy	PLR	NLR	PPV	NPV
ABI	0.863	0.945	0.942	0.705	0.885	12.242	0.314	0.795	0.910
FESC	0.678	66.500	0.633	0.659	0.639	1.796	0.539	0.363	0.854
ABI+FESC	0.907	-0.428	0.914	0.750	0.874	8.688	0.274	0.733	0.920

AUC, area under the curve; NLR, negative likelihood ratios; NPV, negative predictive value; PLR, positive likelihood ratios; PPV, positive predictive value.

often occurs in small and medium arteries. Limited by the professional level, some primary care practitioners can not assess small and medium arteries by ultrasound examination. Given that vascular imaging does not offer cost, operational risk and rapidity benefits. There is a need to explore better PAD diagnosis techniques.

In this study, FESC displayed the strongest correlation with PAD, second to ABI. Vascular injury and neuropathy of the lower extremities are the most prominent complications associated with diabetes, particularly type 2 diabetes. In most cases, vascular injury and neuropathy usually coexist in diabetic patients. In a study involving 125,674 veterans, Beckman *et al.*[23] found that microvascular disease increases the risk of PAD, and is an independent risk factor for amputation. Peripheral neuropathy is one of the main causes of severe ischemic injury and foot ulcers in patients with peripheral arterial occlusive disease (PAOD)[24]. DPN affects sensory, motor and autonomic (especially sudomotor function) nerves[6]. Sudomotor function is mainly mediated by unmyelinated sympathetic C fibers. Sudomotor dysfunction is the earliest manifestation of distal small fiber neuropathy in T2DM. SUDOSCAN is a simple, non-invasive, and reliable device with a rapid assessment of small nerve fiber neuropathy[25]. The diagnostic accuracy of Sudoscan for DPN, foot ulceration and diabetic foot has been previously evaluated[14,15, 26–28].

Previous related studies have shown[29] that the diagnostic accuracy of ABI in combination with the percentage mean arterial pressure (% MAP) and the upstroke time (UT) for PAD is superior to ABI alone. However, the specificity of the above combination approach is significantly lower than that of ABI alone (60.0 vs 84.4%). A similar limitation was reported in a separate study. The sensitivity and specificity for PAD diagnosis based on an ABI $\leq$ 0.90 and a %MAP $\geq$ 42.5% is 76.9 and 75.9%, respectively, whereas when ABI $\leq$ 0.90, the sensitivity and specificity of the test for PAD diagnosis reach 56.5 and 86.2%, respectively. It was demonstrated that a combination of ABI and FESC in predicting PAD in diabetics was superior to ABI alone (DeLong's test: $P = 0.0373$). The ROC analysis revealed relatively stable sensitivity and specificity of our combination approach for PAD diagnosis. The incidence of atherosclerosis is substantially higher in young patients, relative to older counterparts. The risk of adverse cardiovascular events is greater in young patients with type 2 diabetes[30]. However, young patients pay little attention to their conditions. As such, it is imperative to prevent the occurrence of PAD in individuals at risk of false negative outcomes, especially young patients. Compared with other evaluation methods, our model is more targeted and convenient. Overall, our model can be used in PAD prediction and diagnosis in T2DM patients, which can prevent the occurrence of adverse outcomes and cardiovascular events.

Regarding limitations, first, the sample size was relatively small. Second, in PAD diagnosis process, errors from artificial subjectivity could not be avoided. Third, some comorbidities not assessed at baseline may have interfered with the outcome of some results.

In conclusion, early diagnosis of PAD among people with diabetes remains a formidable challenge. The combination method with ABI and FESC is a promising approach for early PAD diagnosis.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of the Jiangsu Provincial Center for Disease Control and Prevention, Approval No. JSJK2016-B003-03. All informed consent was obtained from the subject(s) and/or guardian(s). All participants preserved patient anonymity.

Approval date of Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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