

Original article

Identifying at-risk foot among hospitalized patients with type 2 diabetes: A cross-sectional study in one Chinese tertiary hospital

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Abstract

Objective: To investigate the prevalence of diabetic at-risk foot and its associated factors.

Methods: A total of 838 hospitalized patients with type 2 diabetes were screened for at-risk foot. Neural and vascular disorders were evaluated by assessing vibration perception thresholds and ankle brachial indexes (ABIs). After excluding 12 patients with abnormally high ABIs, remaining individuals with neural and/or vascular disorder were identified as at-risk patients and further classified into three subtypes: isolated neural disorder, isolated vascular disorder and mixed disorder. Potential associated factors were examined using Logistic regression models.

Results: In the final sample of 826 individuals, the prevalence of diabetic at-risk foot was 30.6%. Among all at-risk patients, isolated neural disorders (69.6%) were more common than mixed (16.2%) or isolated vascular disorders (14.2%). Isolated neural and vascular disorders shared specific risk factors, including age per 20-year increment (odds ratio [95% CI], 3.73 [2.59–5.37] and 4.01 [1.98–8.11]), diabetic duration ≥ 10 years (1.69 [1.13–2.54] and 3.29 [1.49–7.24]) and systolic blood pressure ≥ 140 mmHg (1.96 [1.31–2.93] and 2.90 [1.38–6.10]) respectively. In addition, isolated neural disorders were associated with a heavy smoking history (95% CI 2.69 [1.15–6.31]), increased high-sensitivity C-reactive protein levels (95% CI 1.30 [1.04–1.62]) and mild obesity (95% CI 0.49 [0.20–1.24]). Isolated vascular disorders were linked with decreased high density lipoprotein (HDL) cholesterol levels (95% CI 3.42 [1.31–8.96]) and increased triglycerides levels (95% CI 2.74 [1.26–5.97]).

Conclusions: Diabetic at-risk foot is epidemic among hospitalized patients with type 2 diabetes. Aging, long-term diabetes, hypertension, smoking, inflammatory response and dyslipidemia may be associated with the prevalence of diabetic at-risk foot.

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Keywords: Ankle brachial index; Diabetic at-risk foot; Vibration perception threshold

Introduction

Diabetic foot disease is one of the most common and severe chronic complications of diabetes mellitus. About 15–25% of patients with diabetes will develop a foot ulcer during their lifetime.¹ The most feared consequence of a foot ulcer is lower-extremity amputation, which occurs about 23 times more often in patients with diabetes than in the population without diabetes.² Diabetic foot lesions are difficult to be cured but easily be prevented, which suggests the importance of early identification of patients at risk.

Diabetic foot disease develops as a result of a mixture of intrinsic conditions, such as neuropathy, vascular disease and foot deformity, along with extrinsic risks, such as unexpected trauma and infection, among which diabetic peripheral neuropathy (DPN) and peripheral artery disease (PAD) are believed to be the major initiating factors.^{2–4} PAD is reported to be presented in 49% of foot ulcers in Europe⁵ and up to 90% of diabetic foot lesions are related to neuropathy, alone or with ischemia, and the incidence of neuro-ischemic problems has increased in recent years.⁶ Therefore, screening tests focused on the presence of DPN and PAD can predict the risk of diabetic foot disease. Patients with diabetes and evidence of peripheral neuropathy and/or ischemia should be identified as individuals with at-risk foot. It is estimated that early recognition and appropriate protection of at-risk foot can prevent 50% of diabetic ulcerations and amputations.³

In order to investigate the prevalence and clinical characteristics of diabetic at-risk foot as well as to explore potential associated factors, we conducted this cross-sectional study on a population of hospitalized adult patients diagnosed with type 2 diabetes in a Chinese tertiary hospital from March 2013 to February 2014.

Materials and Methods

Study participants

The sample consisted of 899 consecutive hospitalized patients who underwent a diabetic foot screening from March 1, 2013 to February 28, 2014 and were diagnosed with diabetes at the Department of Endocrinology and Metabolic Disease of the First Affiliated Hospital of Soochow University in China. Informed

consents were received from all participants. We excluded patients who were; 1. not diagnosed with type 2 diabetes, 2. pregnant at the time of diabetic foot screening, 3. aged <20 years at the time of diabetic foot screening.

Screening criteria for diabetic at-risk foot

Every participant underwent a screening for diabetic at-risk foot on the first or second day after admission. The screening process, as recommended by the American Diabetes Association,⁷ was mainly comprised of taking a history focused on neuropathic and ischemic symptoms and a previous history of foot ulcerations and amputations, a careful inspection to detect foot deformities and inappropriate footwear, and tests targeting the presence of DPN and PAD. The vibration perception threshold (VPT) values of both feet were measured using a sensimeter as a semi-quantitative neurological assessment. A VPT over 25 volts has been associated with a high cumulative risk of neuropathic ulcerations.⁸ Therefore, we defined patients with a VPT >25 volts in at least one foot as individuals with neural disorder. Plus, we tested ankle brachial index (ABI) values of both sides using a standard Doppler ultrasonic probe to evaluate the peripheral artery condition. The ABI value was obtained by dividing the ankle systolic pressure by the higher of the two brachial systolic pressures. An ABI ≤ 0.9 is strongly linked with a 7-year risk of amputation in people with diabetes.⁹ In this study, we considered patients with an ABI ≤ 0.9 in either foot as individuals with vascular disorder. Additionally, we excluded patients with an abnormally high ABI >1.3 ¹⁰ on either side: no patient presented with an ABI ≤ 0.9 in one limb and an ABI >1.3 in the other. Patients with neural and/or vascular disorders were identified as individuals with at-risk foot. Otherwise, they were considered risk-free subjects.

Data collection

Each patient's gender, age, duration of diabetes and smoking history were collected on admission. Duration of diabetes was categorized as either short (<10 years) or long (≥ 10 years). The smoking history of each patient was evaluated by the level of pack-years of cigarette smoking (the total number of years smoked times the average number of packs of cigarettes

smoked per day). Each patient was then classified as a never-smoker, a light-smoker (<20 pack-years), a median-smoker (20–39 pack-years) or a heavy-smoker (≥ 40 pack-years). Height and weight were measured without shoes and heavy clothes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Systolic blood pressure (SBP) was measured on admission. The most recent laboratory results of hemoglobin A1c (HbA1c), triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and high-sensitivity C-reactive protein (hs-CRP) were ascertained.

Statistical analyses

Individuals with at-risk foot were further classified into three subtypes: isolated neural disorder (neural disorder +, vascular disorder –), isolated vascular disorder (neural disorder –, vascular disorder +) and mixed disorder (neural disorder +, vascular disorder +). Categorical variables were presented as counts (percentages), and continuous data that were not normally distributed were presented as median [interquartile range]. The prevalence rates of at-risk foot across age and duration of diabetes were calculated. Stepwise multivariate Logistic regression models (sle = 0.20, sls = 0.20) were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of isolated neural or isolated vascular disorder in relation to sex, age, duration of diabetes, smoking history, BMI, SBP, HbA1c, triglycerides, LDL-C, HDL-C and hs-CRP. All analyses were performed using the SAS software, version 8.1 (SAS Institute, Inc., Cary, NC, USA). Associations were considered statistically significant at the $P < 0.05$ level.

Results

By applying the initial exclusion criteria, we excluded 35 patients with type 1 diabetes, 15 with special types of diabetes, 5 with pregnancy and 6 with type 2 diabetes but younger than 20 years old. Additionally, we removed 12 subjects with abnormally high ABI (>1.3) to arrive at the final study sample of 826 patients (all Han Chinese). As displayed in Table 1, there were 435 (52.7%) males and 391 (47.3%) females in the study. The age ranged from 20 to 91 years old with a median [interquartile range] of 61 [20] years old. Almost half (43.5%) of patients had a duration of diabetes of 10 years or longer. Never-smokers and heavy-smokers represented 82.9% and 3.8% of the sample, respectively. According to the BMI measurement,

Table 1

Characteristics of the study participants.

Characteristics	Study participants
Gender (Male)	435 (52.7)
Age, years	61 (20)
Duration of diabetes ≥ 10 years	359 (43.5)
Smoking history ^a , pack-years	
Never-smoker	685 (82.9)
Light-smoker (<20)	26 (3.1)
Median-smoker (20–39)	42 (5.1)
Heavy-smoker (≥ 40)	31 (3.8)
BMI ^a , kg/m ²	23.8 (4.6)
Underweight (<18.5)	42 (5.1)
Normal-weight (18.5–23.9)	368 (44.6)
Overweight (24.0–27.9)	291 (35.2)
Mild obesity (28.0–29.9)	63 (7.6)
Severe obesity (≥ 30.0)	40 (4.8)
SBP ≥ 140 mmHg	293 (35.5)
HbA1c ^a <7.0% (53 mmol/mol)	107 (13.0)
Higher triglyceride level ^a (>1.7 mmol/l)	246 (29.8)
Lower HDL-C level ^a (<1.0 mmol/l for male or <1.3 mmol/l for female)	482 (58.4)
Higher LDL-C level ^a (>2.6 mmol/l)	384 (46.5)
Higher hs-CRP level ^a (>3.0 mg/l)	303 (36.7)

Data are n (%) or median [interquartile range]. $n = 826$. BMI: body mass index; SBP: systolic blood pressure; HbA1c: haemoglobinA1c; HDL-C: high density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein;

^a Numbers of subjects with missing values were 42 for smoking history, 22 for BMI, 128 for HbA1c, 24 for triglyceride, 29 for HDL-C, 21 for LDL-C and 30 for hs-CRP.

normal-weight (44.6%) and overweight (35.2%) patients were more common than obese (12.4%) and underweight (5.1%) patients among hospitalized patients with type 2 diabetes. Moreover, 35.5% of patients had elevated systolic blood pressure levels (≥ 140 mmHg) and only 13.0% had recently reached HbA1c levels <53 mmol/mol (7.0%). As for the lipid-metabolism related parameters, more patients (58.4%) had lower levels of HDL-C while fewer had higher levels of triglycerides (29.8%) and LDL-C (46.5%). Plus, 36.7% of patients had elevated hs-CRP levels (>3.0 mg/L).

We reviewed neuropathic and ischemic symptoms reported in the patient history and found that only 11 patients, all of them had an ABI ≤ 0.9 , complained about experiencing typical claudication or rest pain, and 139 (126 of them had a VPT >25 V) mentioned symptoms possibly related to neural disorder (e.g. numbness in the extremities, long-term itching without skin lesions).

Prevalence of diabetic at-risk foot

Table 2 shows that the prevalence of at-risk foot was 30.6% among hospitalized adult patients with type 2

Table 2
Prevalence of diabetic at-risk foot across age and duration of diabetes.^a

Foot screening	Age 20–39 years		Age 40–59 years		Age 60–79 years		Age ≥80 years		Total (n = 826)
	Duration <10 years	Duration ≥10 years	Duration <10 years	Duration ≥10 years	Duration <10 years	Duration ≥10 years	Duration <10 years	Duration ≥10 years	
	(n = 72)	(n = 7)	(n = 204)	(n = 103)	(n = 176)	(n = 224)	(n = 15)	(n = 25)	
Isolated neural disorder	1 (1.4)	0 (0)	18 (8.8)	20 (19.4)	44 (25.0)	76 (33.9)	7 (46.7)	10 (40.0)	176 (21.3)
Isolated vascular disorder	0 (0)	0 (0)	4 (2.0)	3 (2.9)	5 (2.8)	21 (9.4)	3 (20.0)	0 (0)	36 (4.4)
Mixed disorder	0 (0)	0 (0)	1 (0.5)	1 (1.0)	5 (2.8)	20 (8.9)	4 (26.7)	10 (40.0)	41 (5.0)
Total (at-risk foot)	1 (1.4)	0 (0)	23 (11.3)	24 (23.3)	54 (30.7)	117 (52.2)	14 (93.3)	20 (80.0)	253 (30.6)

Data are n (%) unless otherwise indicated.

^a Both age per 20-year increment and duration of diabetes ≥10 years were significantly associated with isolated neural and vascular disorders.

diabetes. For individuals who were 80 years or older, the prevalence could reach up to 85.0% (34/40). On the contrary, the prevalence rate was relatively low (1/79, 1.3%) in subjects younger than 40 years old. The prevalence of at-risk foot increased with age dramatically. Furthermore, in the age groups of 40–59 years and 60–79 years, the prevalence in patients with a longer duration of diabetes was approximately twice as high as in patients with a shorter duration. Among all patients with at-risk foot, isolated neural disorder, isolated vascular disorder and mixed disorder accounted for 69.6% (176/253), 14.2% (36/253) and 16.2% (41/253) respectively.

The prevalence rates of the three subtypes of diabetic at-risk foot were 21.3% for isolated neural disorder, 4.4% for isolated vascular disorder and 5.0% for mixed disorder, respectively. All of them shared an upward trend with age and duration of diabetes. Isolated neural disorder was infrequent (1.3%, 1/79) in patients aged 20–39 years but common (42.5%, 17/40) in patients ≥80 years. Isolated vascular disorder and mixed disorder were absent in 20–39 year-old subjects but highly prevalent in those aged ≥80 years, 7.5% and 35.0%, respectively. Among at-risk patients, younger individuals with a shorter duration of diabetes were more likely to suffer from neural disorder, and in comparison, older individuals with longer duration are more likely to present with both neural and vascular disorders.

Associated factors of diabetic at-risk foot

Potential associated factors of two subtypes of diabetic at-risk foot, isolated neural disorder and isolated vascular disorder, were examined separately using stepwise multivariate logistic regression models. In the model of isolated neural disorder (Table 3), age per 20-year increment (*OR* [95% *CI*], 3.73 [2.59–5.37]) posed as the strongest risk factor,

followed by heavy smoking history ≥40 pack-years (2.69 [1.15–6.31]), systolic blood pressure ≥140 mmHg (1.96 [1.31–2.93]), duration of diabetes ≥10 years (1.69 [1.13–2.54]) and hs-CRP level per 5 mg/L increment (1.30 [1.04–1.62]). Although it seemed that the effects of the male sex (1.39 [0.92–2.10]) and BMI values of 28.0–29.9 (0.49 [0.20–1.24]) were involved in the final model, the relationships did not reach statistical significance. The

Table 3
Associated factors of prevalent isolated neural disorder.^a

Factors	Isolated neural disorder (n = 157)		
	n	<i>OR</i> (95% <i>CI</i>)	<i>P</i>
Age per 20-year increment	157	3.73 (2.59–5.37)	<0.01
Smoking history, pack-years			
Never-smoker	133	1.00 (ref.)	–
Light-smoker (<20)	6	–	–
Median-smoker (20–39)	6	–	–
Heavy-smoker (≥40)	12	2.69 (1.15–6.31)	0.02
SBP ≥140 mmHg	78	1.96 (1.31–2.93)	<0.01
Duration of diabetes			
Shorter (<10 years)	64	1.00 (ref.)	–
Longer (≥10 years)	93	1.69 (1.13–2.54)	0.01
Hs-CRP per 5 mg/L increment	157	1.30 (1.04–1.62)	0.02
Male sex	86	1.39 (0.92–2.10)	0.11
BMI, kg/m ²			
Underweight (<18.5)	6	–	–
Normal-weight (18.5–23.9)	83	1.00 (ref.)	–
Overweight (24.0–27.9)	57	–	–
Mild obesity (28.0–29.9)	6	0.49 (0.20–1.24)	0.13
Severe obesity (≥30.0)	5	–	–

^a *ORs* and 95% *CI*s were calculated using stepwise multivariate logistic regression models (*sle* = 0.20, *sls* = 0.20). This model included patients with isolated neural disorder (n = 157, 19 observations deleted due to missing values) vs. risk-free subjects (n = 511, 62 observations deleted due to missing values). All factors listed entered into and stayed in the model during stepwise selection procedure. Effects of the most recent laboratory results of HbA1c, triglyceride, LDL-C and HDL-C did not meet the 0.20 significance level for entry into the model. SBP: systolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index.

Table 4
Associated factors of prevalent isolated vascular disorder.^a

Factors	Isolated vascular disorder (n = 36)		
	n	OR (95% CI)	P
Age per 20-year increment	36	4.01 (1.98–8.11)	<0.01
Lower HDL-C (<1.0 mmol/L for male or <1.3 mmol/L for female)	30	3.42 (1.31–8.96)	0.01
Duration of diabetes			
Shorter (<10 years)	12	1.00 (ref.)	–
Longer (≥10 years)	24	3.29 (1.49–7.24)	<0.01
SBP ≥140 mmHg	22	2.90 (1.38–6.10)	<0.01
Higher triglyceride (>1.7 mmol/L)	17	2.74 (1.26–5.97)	0.01
Higher LDL-C (>2.6 mmol/L)	19	1.70 (0.79–3.66)	0.17

^a ORs and 95% CIs were calculated using stepwise multivariate logistic regression models (sle = 0.20 sls = 0.20). This model included patients with isolated vascular disorder (n = 36) vs. risk-free subjects (n = 548, 25 observations deleted due to missing values). All factors listed entered into and stayed in the model during stepwise selection procedure. Effects of the male sex, smoking history, BMI, the most recent laboratory results of HbA1c and hs-CRP did not meet the 0.20 significance level for entry into the model. SBP: systolic blood pressure.

effects of the most recent laboratory results of HbA1c, triglycerides, LDL-C and HDL-C were not significantly associated with isolated neural disorder and failed to enter into the model.

On the other hand, among all the risk factors in the model of isolated vascular disorder (Table 4), age per 20-year increment had the highest OR [95% CI] of 4.01 [1.98–8.11], followed by the decreased HDL-C level (<1.0mmol/L for males or <1.3mmol/L for females) at 3.42 [1.31–8.96], duration of diabetes ≥10 years at 3.29 [1.49–7.24], systolic blood pressure ≥140mmHg at 2.90 [1.38–6.10] and the increased triglycerides level (>1.7mmol/L) at 2.74 [1.26–5.97]. The factor of an elevated LDL-C level (>2.6mmol/L) with an OR [95% CI] of 1.70 [0.79–3.66] also entered into and stayed in the model, but the association failed to meet the significance level. The effects of the male sex, smoking history, BMI and the most recent laboratory results of HbA1c and hs-CRP failed to enter into the model.

Discussion

The results from this cross-sectional study indicate that diabetic at-risk foot is common (30.6%) among hospitalized adult patients with type 2 diabetes. It is highly prevalent (85.0%) in individuals ≥80 years old and relatively rare (1.3%) in those <40 years old. The prevalence steeply increases with advancing age and duration of diabetes. Among patients with at-risk foot, those with isolated neural disorder are the most common, followed by those with mixed disorder and isolated vascular disorder. These findings provide an estimate of the future burden of diabetic foot disease in hospitalized patients with type 2 diabetes.

Importantly, we excluded patients with abnormally high ABI, which is related to calcification of the arterial wall. Vascular calcification and occlusive lesions frequently coexist, and when calcification is present, stenotic disease cannot be detected by the ABI measurement.⁹ Plus, the coexistence of mild medial arterial calcification in the lower extremities, which causes abnormally high ABI,¹¹ and clinically significant PAD, which causes low ABI, may result in a normal ABI.⁴ Moreover, the ABI test itself, whilst highly sensitive in the general population, may be less effective in individuals with diabetes, especially in cases complicated by peripheral and autonomic neuropathy.² Therefore, it is likely that the prevalence of isolated vascular and mixed disorders were underestimated in the study.

At present, numerous stratification systems using different methods have been proposed to identify the degree of risk for foot ulceration among patients with diabetes. In spite of the differences with regard to the development of prediction models, diagnostic accuracy measures and validation and generalizability, five variables were included in almost all the systems, namely: diabetic neuropathy, peripheral vascular disease (PVD), foot deformity, and previous foot ulcer and amputation.¹² In our study, we focused on the diabetic neuropathy assessed by VPT >25V and PVD determined by ABI <0.9. According to the International Working Group on the Diabetic Foot (IWGDF) guidelines,^{1,13} patients with isolated neural disorder in the present investigation might be assigned to risk stratification category 1 in need of foot examination every six months, while patients with mixed disorder are risk stratification category 2 which requires foot examination every three months.

Determining risk factors for diabetic at-risk foot may contribute to better protective strategies. Previous investigations have shown that the incidence of neuropathy was related to smoking, hypertension and higher levels of triglycerides and BMI in patients with type 1 diabetes.¹⁴ And Herder et al¹⁵ found the association between subclinical inflammation and diabetic polyneuropathy in type 2 diabetes. Joosten et al¹⁶ reported that hypertension, smoking, diabetes mellitus and hypercholesterolemia accounted for most of the risk associated with the development of clinically significant PAD in males. In the present study, we discovered that among hospitalized adult patients with type 2 diabetes, prevalent isolated neural and vascular disorders might share the role of main risk factors of aging, long-term diabetes and hypertension. We also found that the prevalence rates of both conditions were strongly linked with the duration of diabetes rather than the most recent HbA1c level, suggesting that diabetic neural and vascular diseases are chronic disorders that cannot be predicted by a single recent HbA1c result. Various studies have shown that glycaemic control is the critical factor in the development of diabetes and its complications. Therefore, more studies are needed to investigate whether other indexes, such as HbA1c variability or continuous glucose variability, are suitable to represent glycaemic control with respect to such long-term complications.

In addition, cumulative smoking exposure and higher hs-CRP level have a significant impact on the prevalence of isolated neural disorder, indicating a vital role of an inflammatory response in prevalent DPN. A heavy smoking history, in particular, stands out to be the second greatest risk factor for developing peripheral neuropathy among hospitalized patients with type 2 diabetes. Another interesting finding is the negative relationship between mild obesity and isolated neural disorder, although it did not reach statistical significance. This kind of obesity paradox was also found in foot ulceration risk¹⁷ and lower-extremity amputation risk¹⁸ but lacked a valid explanation.

On the other hand, dyslipidemia, which is characterized by a decreased HDL-C level but not an increased LDL-C level, appears to play a crucial role in the prevalence of isolated vascular disorder. The PAD is not a specific complication of diabetes but one of the most common manifestations of atherosclerosis in the lower extremities. It is well-established that smoking has a major influence on the initiation and progression of atherosclerosis. Additionally, Conen et al¹⁹ confirmed that smoking was a potent risk factor for the occurrence of symptomatic PAD among women

and smoking cessation was associated with a substantial reduction in the risk. We assume the reason why the effect of the smoking history failed to meet associative significance in this study would be the small proportion of smokers and small number of patients with isolated vascular disorder, which resulted in limited statistical power.

The strengths of this study are the relatively large sample population and the screening criteria of diabetic at-risk foot based on semi-quantitative or quantitative tests. However, several limitations do exist. First, neural and vascular disorders of diabetic foot are both integrated conditions with multiple assessments. A single examination might be inaccurate. However, the tests we used have been proven to possess relatively high sensitivity and specificity as well as predictive power,^{8,9} and we examined both feet of every participant to reduce the rate of misdiagnosis. Second, information on medication and comorbid diseases were not included. Third, the temporality of the presented associations is unclear due to the cross-sectional design of this study.

In summary, the prevalence of diabetic at-risk foot is about 30% among hospitalized adult patients diagnosed with type 2 diabetes. However, it is estimated²⁰ that only 10–20% of the patients with PAD present a typical claudication and 30–40% of the patients with neuropathy are asymptomatic in China. The discrepancy between the high prevalence and the low rate of awareness of at-risk foot puts patients with diabetes in a dangerous zone for progression to foot ulceration and even amputation. Therefore, frequent foot screening and appropriate control of risk factors should be taken to identify at-risk patients and to reduce the occurrence and potential consequences of diabetic foot disease.

Conflicts of interest

No potential conflicts of interest relevant to this article were declared.

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