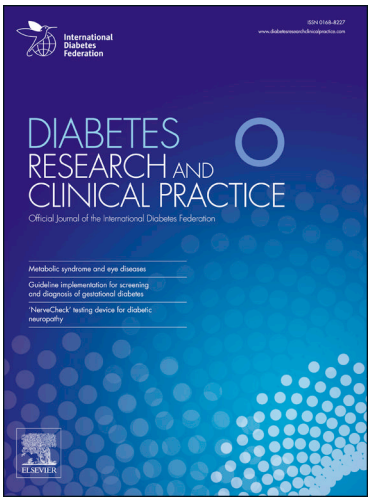

Advantages of early diagnosis of diabetic neuropathy in the prevention of diabetic foot ulcers

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TITTLE: ADVANTAGES OF EARLY DIAGNOSIS OF DIABETIC NEUROPATHY IN THE PREVENTION OF DIABETIC FOOT ULCERS

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Abstract:

Aims: to evaluate the utility of the sudomotor function test (SFT) as a clinical tool in the Risk Stratification System of diabetic patients and to demonstrate the earlier detection of the risk of developing diabetic foot ulcers (DFU) compared to the standard clinical tests.

Methods: prospective follow-up study on 263 patients enrolled consecutively over 3.5 years. Diabetic patients without active DFU were classified according to the International Working Group Risk Stratification System (RSS) and categorized according to the results of the Semmes-Wenstein Monofilament (SWM) and biothesiometer measurements or the SFT. The main outcome evaluated was the development of DFU.

Results: median follow-up was 42 [38–44] months. Sixty patients (22.8%) developed DFU after a median of 6.2 [3–17] months. Ten patients that were included in the no-risk group (group 0) based on the SWM and biothesiometer results developed DFU. Thus the sensitivity of this approach was 83.33% and the specificity was 50.47%. Based on the SFT results, all patients that developed DFU were included in the correct risk group. This approach had 100% sensitivity and 31.53% specificity. Regarding the diagnostic accuracy of the two Methods, the respective AUC values were 0.776 (95% CI 0.702–0.849) and 0.816 (95% CI 0.757–0.874).

Conclusions: SFT improved RSS in diabetic patients in a specialized diabetic foot unit. SFT categorized patients correctly according to the risk of developing DFU.

Key words: Diabetic foot, Diabetic symmetric polyneuropathy, Risk stratification system, Sudomotor function test.

1. INTRODUCTION

The diabetic foot ulcer is one of the major complications of diabetes mellitus (DM), with an estimated 10% to 25% of patients with diabetes developing a diabetic foot ulcer (DFU) in their lifetime [1]. A DFU precedes 85% of non-traumatic lower limb amputations [2].

Diabetic symmetric polyneuropathy (DSPN) is the most important cause of foot ulceration, drives amputation risk and is also a predictor of mortality. DSPN is the most common cause of ulceration in 90% of patients with DFU [3].

DSPN is a progressive manifestation of diabetes with length-dependent, symmetrical and distal damage of nerve fibres [4]. The involvement of large fibres may cause a loss of protective sensation and allow the patient to walk on an insensitive foot.

The most important clinical guidelines regarding the prevention of DFU define the main risk factors for the development DFU (besides peripheral neuropathy) as: painless, foot deformities, minor foot trauma, footwear and peripheral arterial disease (PAD) [5, 6].

Based on previously published guidelines, Diabetic Foot Risk Stratification Systems in the literature [7-9] place patients into the risk group 0 when none of the most important risk factors are present (diabetic neuropathy, limb ischaemia, foot deformities and history of ulceration and/or amputation). The risk is increased when DSPN is diagnosed, and can lead to patients moving from risk group 0 to groups 1 or 2.

Practical clinical guidelines recommend using clinical tests such as the vibration perception threshold (VPT) >25 V, 10-g monofilament or Neuropathy Disability Score (NDS) to assess risk, as these have been validated as first-line screening tools for identifying people with established DSPN [10, 11].

These tests are mainly used in primary care, because they are an easy and cheap way of identifying those patients “at risk” of developing DFU. Nevertheless, these clinical tools are mainly useful for detecting more advanced neuropathy and identifying patients at an increased risk of DFU and amputation [11, 12].

At a specialised diabetic foot unit where the prevalence of the diabetic population with diabetic neuropathy is high, the standard clinical tests used to evaluate DSPN do not show great reproducibility. One of the main focuses in a trained diabetic foot context is to design a programme for preventing diabetic foot complications and identifying persons with early DPSN, in order to predict progressive morbidity that may involve foot deformities, ulceration and amputation [11-14].

Furthermore, several reports have identified deficiencies in the accuracy and durability of the standard clinical tests [15, 16] and a systematic review of the foot ulcer prevention programme in diabetes showed the variable and low efficacy of these clinical examinations [17].

A 10-g monofilament has shown high sensitivity but low specificity for detecting the risk of developing DFU, with values ranging between 57% and 93% for sensitivity and 75% and 100% for specificity for the diagnosis of DSPN [18, 19]. Therefore, some patients with sensibility impairment are not being diagnosed by these tools. Responses are subjective and vary; age, cognitive capacity and attention of the patient may also lead to different interpretations of test results.

For this reason, the early detection of neuropathy in specialised diabetic foot clinics is important, and new diagnostic methods are needed to identify the disease as early as possible.

Recent diagnostic autonomic function tests have been described based on the evaluation of sudomotor function, applying an indicator patch on the plantar aspect to evaluate the integrity of skin sympathetic cholinergic innervation by autonomic small unmyelinated C-fibres [20-22].

Sudomotor dysfunction may manifest as dry skin and anhydrosis [23] and plays a significant role in the aetiopathogenesis of foot ulceration. It develops before sensory loss and has been accepted as one of the diagnostic tests for diabetic neuropathy by the Toronto Consensus Panel [24].

Several studies have examined the diagnostic validity of SFT for diagnosing DSPN and have shown a high sensitivity (85–97%), but lower specificity (45–67%) [25, 26]. Given that the specificity of a test indicates whether an individual is free from disease, and given that diabetic neuropathy affects small fibres before large fibres, the low specificity of SFT reflects the fact that the test diagnoses early neuropathy in patients which the large fibres' test cannot yet detect.

The main advantage of SFT is its ability to identify patients with subclinical neuropathy and its capacity to evaluate the risk of developing DFU at an early stage [20, 22, 24]. The aim of this study was thus to evaluate the utility of this test as a clinical tool in the risk stratification of patients with DM, and to demonstrate the ability of SFT to identify the risk of developing DFU earlier than the standard clinical test.

2. MATERIAL AND METHODS

We conducted a prospective observational follow-up study. Subjects were recruited from our Diabetic Foot Unit. Two hundred and sixty-three patients with DM were recruited consecutively over 12 months from July 2011, and were followed up to April 2015. The inclusion criteria were patients between 18 to 75 years with a previous diagnosis of DM and classified as type 1 or 2 according to the American Diabetes Association [27]. Patients were excluded if they had active DFU, if they were unable to walk, if they had another cause of neuropathy of non-diabetic origin, other causes of sudomotor dysfunction, or if they had Charcot´s foot. This study was approved by our Ethics Committee and all included participants signed the informed consent.

At the baseline visit, all patients underwent different evaluations, DPSN screening, foot deformity evaluations, and peripheral arterial disease examinations, and provided their previous history of ulceration and/or amputation.

DPSN examination was performed via three tests: 1) 10-g SWM (Novalab® Iberica, Madrid): the outcome of this test was considered abnormal when the patient did not feel the filament at more than four of the ten examined points [17]; 2) biothesiometer (Horwell® Scientific; Battery 50 V): vibratory sensitivity was considered to be affected when the patient did not feel the vibration of the instrument's head when a voltage greater than 25 V was applied in the hallux [28]; and 3) examination with SFT was performed as previously described [29, 30]. Patients were allowed a ten-minute acclimatisation period in constant room temperature (25°C) after they had removed their socks and shoes. Indicator tests were applied to both soles at the level of the 1st-2nd metatarsal heads. Time until complete colour change of the test from blue to pink was recorded in seconds with an exactitude of 10 s. Abnormal SFT diagnostic of sudomotor dysfunction was defined as time until the complete colour change exceeding 600 s [21].

We defined foot deformity as any contracture that could not be fully corrected manually, such as hallux valgus, hammer toes, claw toes, ankle equinus (when the ankle joint mobility was less than 0º degrees of dorsiflexion at the ankle), and hallux rigidus (when dorsiflexion of the first metatarsophalangeal joint (1st MPJ) was less than 30º degrees) [31].

Peripheral arterial disease (PAD) was defined as a nonpalpable dorsalis pedis or posterior tibial arterial pulse, ankle-brachial index less than 0.9, toe arterial systolic pressure less than 55 mmHg and toe-brachial index less than 0.7 [32].

Based on the above assessment, all patients were classified according to the IWGDF stratification system developed by Peters et al. [9]: group 0: without DPSN; group 1: with DPSN but without foot deformity or PAD; group 2: with DPSN and foot deformity or PAD; and group 3: history of ulcer or amputation.

In order to evaluate the outcomes of the study, the patients were classified into two groups: Method A: patients in whom the diagnosis of DSPN was made by SWM and/or biothesiometer; and Method B: patients in whom clinical diagnosis was made by SFT.

2.1 Follow-up data collection

Patients were evaluated by the same researcher (ISC) and were subjected to periodic assessment, as recommended by the IWGDF stratification system. Patients in group 0 were reviewed annually. Those in group 1 were reviewed every 6 months, those in group 2 every 3 months, and those in group 3 were reviewed monthly [9]. When a participant missed a follow-up session, they were contacted by phone to check for new ulcerations, and the date of ulceration or the last phone contact was noted.

2.2 Outcome measurement

The main outcome variable evaluated in the present study was ulceration. This outcome was considered as the first ulcer occurrence on either foot after the baseline examination. DFU was defined as a full thickness lesion of the skin, i.e., a wound penetrating through the dermis on the plantar side of the foot, without reference to time present [13]. The follow-up period ended after the first ulcer occurrence or on the closing date of the study.
Those patients that developed a DFU during the follow-up were treated by Good Wound Care for our Diabetic Foot Unit and were followed until the wounds were completely cared for.

2.3 Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 19.0 (SPSS, Inc., Chicago, IL, USA).

Student´s *t* test was performed for the independent samples to compare the means of quantitative variables. The X^2 test and McNemar test were used to identify differences in the qualitative variables. Odds ratios and their 95% confidence intervals were determined using a univariate analysis. A difference of less than 5% was assumed to be significant for a type I error ($p<0.05$).

Receiver operating characteristics (ROC) curve analysis was used to compare the diagnostic accuracy of the IWGDF Risk Stratification System when using the SWM/biothesiometer or SFT. ROC curve analysis established the area under the curve (AUC), which was used to determine the optimal

sensitivity and specificity of Method A and Method B. An AUC of 0.5 indicates that the classification does not have the ability to discriminate between persons who do and do not develop ulcers, whereas a value between 0.5 and the maximum value of 1 indicates that the classification can distinguish between those who do and do not develop foot ulcers.

The sensitivity, specificity, predictive value and likelihood ratio were calculated for Method A and Method B in relation to the risk of developing DFU.

Sensitivity was defined as the ratio of true positives/(true positives and false negatives).

True positive were patients in groups with a risk (1+2+3) that developed DFU. False negatives were those patients included in a group without a risk but who developed DFU during the follow-up (patients that develop DFU into the group of risk 0).

Specificity was defined as the ratio of true negatives/(true negatives and false positives).

True negatives were those patients included in the group without risk who did not develop DFU (patients into de risk 0 that did not develop DFU).

False positive: those patients included in the groups with risk but did not develop DFU (patients into the group of risk 1+2+3 who did not develop DFU).

The positive prognostic value (PPV) was defined as the ratio of true positives/(true positives and false positives). The negative prognostic value (NPV) was defined as the ratio of true negatives/(true negatives and false negatives).

3. RESULTS

We recruited 263 patients, 140 (53.2%) of which were male with a mean age of 68.37±9.9 years. Two hundred and thirty-seven patients (90.1%) were type 2 DM with a mean of 13.99±11.5 years since diagnosis. The patients had a mean body mass index of 29.01±7.9 Kg/cm^2 and the mean HbA1c was 7.30±1.2% (56.28±8.3 mmol/ml).

The 263 patients were followed-up for a median of 42 [38–44] months. Sixty patients (22.8%) developed DFU after a median of 6.2 [3–17] months following the first examination.

The general characteristics of the sample are shown in table 1.

Table 2 shows the distribution of patients according to risk group and the risk of developing DFU according to Methods A and B. We found significant differences between the groups of risk 0, 1 and 2 ($p<0.001$). The group of risk 3 does not show any statistical difference ($p=1$).

The sensitivity, specificity, predictive positive value (PPV), negative predictive value (PNV), and positive likelihood ratio (LR+) are shown in Table 3.

The results show that the sensitivity of Method B amounts to 100% with respect to 83.3% from Method A. Nevertheless, the specificity in the Method B decreased from 50.7% to 31.3% with respect to Method A.

Regarding the diagnostic accuracy of the two Methods, the respective AUC values were 0.776 (95% CI 0.702–0.849) for Method A and 0.816 (95% CI 0.757–0.874) for Method B.

The diagnostic accuracy by prediction model according to the ROC curve is shown in Figure 1.

4. DISCUSSION

This study showed that SFT improves the IWGDF risk stratification system in patients with diabetes for preventing DFU. When DPSN assessment was performed by SFT, the patients were categorised correctly according to the risk of developing DFU.

Underdiagnosis of neuropathic patients may occur when using standard neurological tests. Patients who are categorised into the lowest risk group will only receive a check-up once a year based on current recommendations. Under such circumstances, these patients will not be treated by preventative strategies, and there is inadequate follow-up, which would considerably increase the risk of developing a DFU.

Stratification systems are an essential tool for classifying patients according to a cumulative risk of foot ulcer development and consequently allowing the limited existing medical care resources to be distributed to those most in need [33]. The IWGDF Risk Stratification System for patients with diabetes includes diabetic neuropathy in the first level of risk [34]. Nevertheless, there is no consensus regarding which or how many neurological clinical tests are necessary to identify a neuropathic patient. In primary care, SWM and the biothesiometer are great for detecting DPSN widely, but in a DFU risk population, we need to determine which clinical tool will have the greatest diagnostic accuracy for diabetic neuropathy.

In this study, 60 patients developed DFU (22.8%) during the follow-up period, although 10 of them had been placed in risk category 0. Similar results were reported by Peters et al. [9]: 54 (25.35%) patients developed DFU during the follow-up period and four subjects had been placed in risk group 0. Lavery et al. [7] modified the classification and found that 12% of their sample developed DFU, among which four patients were classified as risk group 0.

Risk group 0 should include patients without neuropathy and without risk factors for the development of DFU. However, almost 2% of ulcerated patients in the study by Peters et al. [9] and 5% of patients in our sample who were classified as non-neuropathic and were included in risk group 0 subsequently developed an ulcer during follow-up.

When classifying patients based on the SFT results, no patients with an ulcer were classified in risk group 0. All patients that developed DFU during the follow-up period were correctly classified into a higher risk group (1 or 2).

The same patients were placed in risk group 3 using the SWM/biothesiometer and SFT results, because this group has a previous history of amputation and ulceration and classification is not dependent on DPSN status.

In this study, Method A had a sensitivity of 83.3%, a specificity of 50.7%, a PPV of 33.3% and PNV of 91.1%. In the study by Peters et al. [9], the classification system had a sensitivity of 74%, specificity of 86% and PPV of 64%. Method B had a sensitivity of 100%, specificity of 31.5%, PPV of 30.15% and PNV of 100%.

The sensitivity and PPV were significantly higher in Method B than Method A. Method B stratified all patients with DFU as patients with risk of foot ulceration and included them in one of the higher

risk categories (group 1 or 2). However, the specificity and PNV of Method B were lower than those of Method A. It is possible that most of the patients placed in the higher risk groups at baseline did not develop an ulcer during follow-up.

The moderate specificity of SFT is because the validation of diagnostic accuracy is based on the risk of developing DFU. The majority of validation studies of SFT have been based on the diagnosis of neuropathy [20, 24]. If the follow-up was longer the outcomes of DFU might be different.

Miranda-Palma et al. [35] showed that SWM has low sensitivity and high specificity for detecting the risk of developing DFU. Their study suggested that this method is not the most optimal way to identify patients at risk of developing DFU. Also, the low detection of at-risk patients by these diagnostic tools is correlated with the variability of the data regarding the sensitivity and specificity of the DPSN diagnosis [19].

The diagnostic accuracy of Method A was 0.7 and the Method B ascended to 0.81. Our results suggest that the inclusion of a SFT for diagnosis the DPSN could improve the stratification, mainly in the group of risk 0. Monteiro Soares et al. [36] show that the inclusion of a footwear variable improve the model (AUC 0.88). In another study by prediction model, Boyko et al. [37] displayed good short and medium-term classification accuracy regarding the development of foot ulcer over 1 and 5 years of follow-up, with areas under the ROC curves of 0.81 and 0.76, respectively.

The SWM and biothesiometer are clinical tests for identifying patients when neuropathy is established and the degeneration of the nerve fibres is underway. The DSPN diagnosis by these methods is useful in a broader context where a general screening for neuropathy is required [11].

Small-fibre impairment is an early manifestation of diabetic neuropathy and plays a crucial role in the aetiopathogenesis of DFU. The detection of subclinical diabetic neuropathy by SFT allows the implementation of preventative treatment strategies to avoid further progression of impairment [38]. This test should be implemented in specialised diabetic foot clinics where the prevalence of DPSN is high and the risk of developing DFU is increased.

SFT is not only performed to detect early DPSN, but should also be included in the DPSN screening to predict DFU in patients with diabetes. In a study of 379 patients with diabetes, 121 of them developed DFU and, in the multivariate analysis, the risk increased when the SFT was abnormal. The authors found that SFT identified the risk of developing DFU more accurately than other DPSN screening methods [38].

The limitations of this study relate to the type of sample. The prevalence of DPSN in our sample was elevated. The diagnostic validation of the test was affected because all patients were recruited from the diabetic foot unit and had a greater probability of being neuropathic.

The main strength of this study is the long-term follow-up period (3.5 years). Furthermore, this is the first study to include SFT as a clinical tool for identifying the risk of developing DFU in patients with diabetes.

In conclusion, we consider that SFT is a simple, objective, inexpensive and early diagnostic tool for the diagnosis of diabetic neuropathy that could be added in a care setting where the categorisation of risk is required. The results of the test are independent from the response of the patient and highly qualified professionals are not required to perform the test.

In a secondary or tertiary care setting, SFT enables the greater accuracy of identification of patients with a risk of developing DFU; their inclusion in a higher risk group means that they will be enrolled in a prevention programme and that clinical review will take place every 6 or 3 months. Patients placed into the lowest risk group only undergo annual review, with the consequent risk of developing DFU during the intervening period.

All patients with abnormal SFT results and with small-fibre impairment could be considered at risk of developing DFU and must be included in appropriate follow-up protocols.

The authors declare that there is no conflict of interest regarding the publication of this article.

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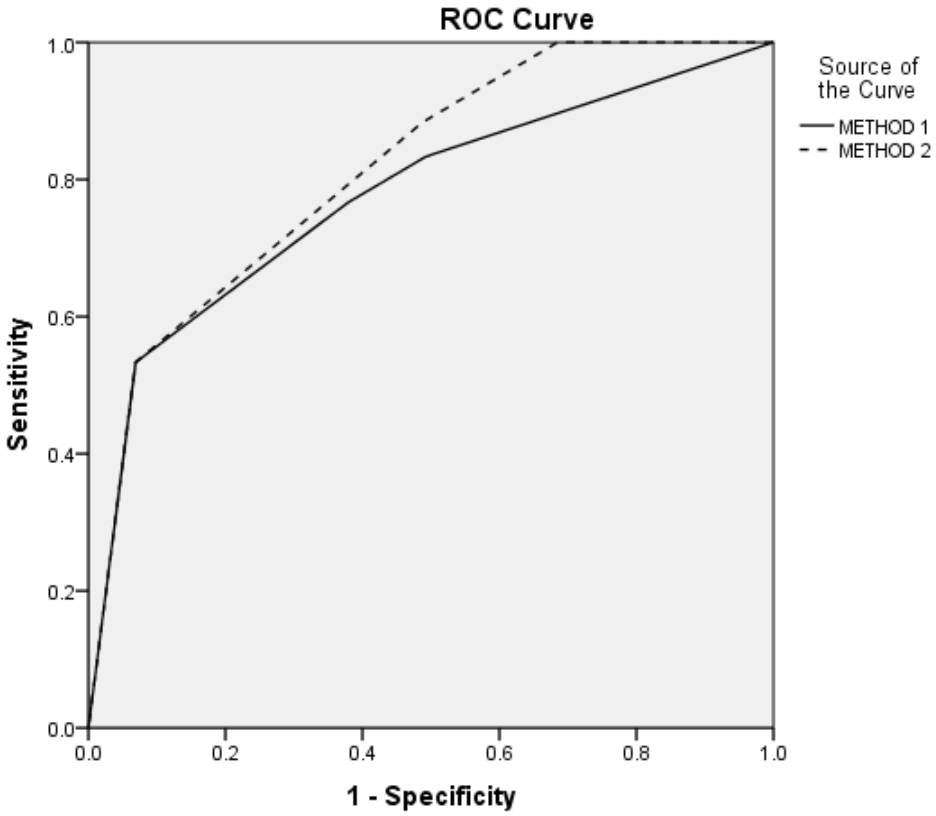

Figure 1. Diagnostic accuracy by prediction model according to ROC curve. Dotted line = Method A. Straight line = Method B. Abbreviation: ROC, receiver operating curve.

N=263	FREQUENCY (%)		MEAN ±SD
MALE	140 (53.2%)	AGE (years)	68.37±9.9
TYPE 2 OF DM	237 (90.1%)	DM DURATION (years)	13.99±11.5
RETINOPATHY	53 (20.2%)	BODY MASS INDEX (Kg/cm^2)	of 29.01±7.9
NEPROPATHY	22 (8.4%)	HbA1c (%)	7.30±1.2
		mmol/ml	56.28±8.3
CARDIOVASCULAR DISEASE	72 (27.4%)		
HYPERTENSION	267 (63.5%)		
HYPERCHOLESTEROLEMIA	176 (66.9%)		
SEDENTARISM	44 (16.7%)		
TABAQUISM	32 (12.2%)		
ENOLISM	4 (1.5%)		
PAD	39 (14.8%)		
FOOT DEFORMITIES	162 (61.6%)		
SWM AFFECTED	42 (16%)		
BIOTHESIOMETER AFFECTED	131 (49.8%)		
SFT AFFECTED	167 (63.4%)		
HISTORY OF ULCER	46 (17.5%)		
HITORY OF AMPUTATION	17 (6.5%)		

Table 1. General characteristics of the sample. Abbreviation: PAD; peripheral arterial disease, SWM; Semmes Weinstein Monofilament, SFT; sudomotor function test.

	METHOD A		METHOD B		
	PATIENTS (n=263)	**ULCER (n=60)**	**SUBJECTS (n=263)**	**ULCER (n=60)**	**P value**
RISK 0	113 (43%)	10 (8.8%)	64 (24.3%)	0	<0.001[a]
RISK 1	27 (10.3%)	4 (14.8%)	47 (17.1%)	7 (14.8%)	<0.001[a]
RISK 2	77 (29.3%)	14 (18.1%)	106 (40.3%)	21 (19.8%)	<0.001[a]
RISK 3	46 (17.5%)	32 (69.5%)	46 (17.5%)	32 (69.5%)	1

Table 2. Distribution of patients according to risk group and the risk of developing DFU according to Method A and B. Method A: IWGDF classification using SWM and biothesiometer. Method B: IWGDF classification using SFT.
Data are N (%) unless otherwise indicated.
[a] p value < 0.001 (McNemar test)

	METHOD A	METHOD B
SENSITIVITY	83.33% (73.07–93.60)	100% (99.17–100)
SPECIFICITY	50.47% (43.62–57.86)	31.53% (24.89–38.16)
PPV	33.33% (25.46–41.21)	30.15% (23.52–36.78)
PNV	91.15% (85.47–96.83)	100% (99.22–100)
LR+	1.69 (1.41–2.02)	1.46 (1.33–1.60)

Table 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (PNV), and positive likelihood ratio (LR+) for Method A and B.
Data are in % (Confidence interval 95%)

Research highlights

To evaluate sudomotor test as a clinical tool in risk stratification system

To demonstrate that sudomotor test identify the risk of develop foot ulcer

Risk stratification by sudomotor test has more accuracy than standard clinical test

Sudomotor test improves risk stratification in diabetic patients to prevent foot ulcer