

Screening Techniques to Identify People at High Risk for Diabetic Foot Ulceration

A prospective multicenter trial

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OBJECTIVE — Diabetic foot ulceration is a preventable long-term complication of diabetes. A multicenter prospective follow-up study was conducted to determine which risk factors in foot screening have a high association with the development of foot ulceration.

RESEARCH DESIGN AND METHODS — A total of 248 patients from 3 large diabetic foot centers were enrolled in a prospective study. Neuropathy symptom score, neuropathy disability score (NDS), vibration perception threshold (VPT), Semmes-Weinstein monofilaments (SWFs), joint mobility, peak plantar foot pressures, and vascular status were evaluated in all patients at the beginning of the study. Patients were followed-up every 6 months for a mean period of 30 months (range 6–40), and all new foot ulcers were recorded. The sensitivity, specificity, and positive predictive value of each risk factor were evaluated.

RESULTS — Foot ulcers developed in 95 feet (19%) or 73 patients (29%) during the study. Patients who developed foot ulcers were more frequently men, had diabetes for a longer duration, had nonpalpable pedal pulses, had reduced joint mobility, had a high NDS, had a high VPT, and had an inability to feel a 5.07 SWE. NDS alone had the best sensitivity, whereas the combination of the NDS and the inability to feel a 5.07 SWF reached a sensitivity of 99%. On the other hand, the best specificity for a single factor was offered by foot pressures, and the best combination was that of NDS and foot pressures. Univariate logistical regression analysis yielded a statistically significant odds ratio (OR) for sex, race, duration of diabetes, palpable pulses, history of foot ulceration, high NDSs, high VPTs, high SWFs, and high foot pressures. In addition, 94 (99%) of the 95 ulcerated feet had a high NDS and/or SWE, which resulted in the highest OR of 26.2 (95% CI 3.6–190). Furthermore, in multivariate logistical regression analysis, the only significant factors were high NDSs, VPTs, SWFs, and foot pressures.

CONCLUSIONS — Clinical examination and a 5.07 SWF test are the two most sensitive tests in identifying patients at risk for foot ulceration, especially when the tests are used in conjunction with each other. VPT measurements are also helpful and can be used as an alternative. Finally, foot pressure measurements offer a substantially higher specificity and can be used as a postscreening test in conjunction with providing appropriate footwear.

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Abbreviations: MTPJ, metatarsophalangeal joint; NDS, neuropathy disability score; NSS, neuropathy symptom score; OR, odds ratio; STJ, subtalar joint; SWE, Semmes-Weinstein monofilament; VPT, vibration perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Foot ulceration is a major complication of diabetes and consumes a major portion of the resources allocated for the treatment of diabetes (1). Estimates show that foot ulceration may occur in up to 15% of diabetic patients during their lifetime (2). Diabetic foot ulceration is a significant cause of morbidity and can lead to prolonged hospital stays, which is evidenced by the fact that ~20% of hospitalizations related to diabetes involve diabetic foot ulceration (3). Furthermore, ~60,000 major lower-extremity amputations are performed annually on patients with diabetes (4). The mortality rate in patients with diabetic foot ulceration is also high and is approximately twice that of patients without ulceration (5).

Neuropathy and peripheral vascular disease have been identified as major risk factors for diabetic foot ulceration and amputation (6,7). Autonomic neuropathy can cause increased blood pooling and swelling in the foot. Motor neuropathy leads to atrophic changes in the foot musculature that cause foot deformity and decreased joint mobility. These problems subsequently lead to an area of increased plantar foot pressure. The lack of protective sensation from sensory neuropathy leads to repetitive trauma from an area of high pressure that results in ulceration. Peripheral vascular disease has been observed to affect vessels below the knee in patients with diabetes. Even in the face of nonobstructed vessels, impaired microvascular reactivity diminishes blood supply to the ulcerated areas (8).

Although the end results of diabetic foot ulceration may be devastating, the development of ulceration is preventable. Patient education regarding foot hygiene, skin care, nail care, proper footwear, and appropriate foot care administered by qualified professionals can reduce injuries that may lead to foot ulceration. Therefore, identifying the at-risk patient is probably the most important step in reducing the rate of foot ulceration. To this end, various screening techniques have been proposed and are currently in use. These include the evaluation of vibration perception threshold (VPT) (7,9), plantar foot pressure measurements (10), joint mobility (11), and 5.07 Semmes-

Table 1—Characteristics of the entire study population

Total subjects	248
Caucasian	119
Black	36
Hispanic	93
Age (years)	58 ± 12 (20–83)
Sex (M/F)	126/125
BMI	30.1 ± 6.4 (15.4–57.1)
Diabetes type (1/2)	49/199
Diabetes duration (years)	14 ± 11 (1–54)
History of foot ulceration	87
NSS	3.9 ± 4.1 (0–16)
NDS	10 ± 8 (0–28)
VPT (V)	29 ± 17 (1–51)
SWF	5.4 ± 1.4 (1.85–7.00)
Maximal plantar pressure (kg/cm ²)	5.71 ± 2.91 (1.50–28.0)

Data are *n* or means ± SD (ranges).

Weinstein monofilament (SWF) testing (12). In addition, a history of previous foot ulceration, a TcPO₂ level of <30 mmHg (13), and the existence of foot deformities (14) have also been shown to be risk factors for the development of diabetic foot ulceration. However, no available clinical studies have compared all the above risk factors in a prospective longitudinal mode.

The objective of the present study was to compare the specificity, sensitivity, and positive predictive value of the most commonly used screening techniques for the identification of the patient at high risk for foot ulceration in a prospective multicenter fashion. Furthermore, this study aimed to identify as many risk factors as possible and to develop a screening strategy that, by combining the detection of 2 or more risk factors, would provide the best tool for identifying the at-risk patient.

RESEARCH DESIGN AND METHODS

Patients

A total of 248 patients with diabetes were included in the study. These patients were recruited from the Joslin-Beth Israel Deaconess Foot Center and a primary foot care clinic in Boston, Massachusetts; the University of Texas Health Science Center in San Antonio, Texas; and the California College of Podiatric Medicine in San Francisco, California. Patients were enrolled consecutively in their respective clinics. The diagnosis of diabetes had been made before enrollment and was confirmed by either communication with primary care providers or by

reviewing medical records. Patients attended the above clinics for various reasons, including regular foot care and foot care related to previous foot problems such as ulceration and peripheral vascular disease.

Data collection

All investigators met before the start of the study to discuss and review methods for data collection. The testing modalities and examination methods were demonstrated to all investigators to ensure uniformity.

All patients underwent a complete history and physical examination in addition to other modalities to assess abnormalities associated with neuropathy, peripheral vascular disease, and foot deformity. For the purposes of data analysis, each foot was examined and scored separately.

Neuropathy symptom score

The neuropathic symptoms were assessed by using a modified neuropathy symptom score (NSS) that was simplified from a version developed by Boulton (14). Patients were questioned about the presence or absence and possible nocturnal exacerbation of muscular cramps, numbness, abnormal hot or cold sensations, tingling sensations, burning pain, aching pain, and irritation from bed clothes in the lower legs and feet.

If the patient did not have a given symptom, then a score of 0 was given. A score of 1 was given if the patient reported the symptom, and a score of 2 was given if the patient described nocturnal exacerbation. The summation of all symptom scores gave the NSS. An NSS of ≥3 was considered to be abnormal.

Neuropathy disability score

The neuropathy disability score (NDS) was used to quantify the severity of diabetic neuropathy obtained from physical examination and was based on the examination of tendon reflexes and sensory modalities as previously described (15). The patella and Achilles tendon reflexes were examined. A score of 0 was given if the reflex was normal. A score of 1 was given if the reflex could be elicited with reinforcement. A score of 2 was given if the reflex was absent. The total sum represented the reflex score.

Sensory tests included a pinprick with a pointed metal or wooden pin, light touch with a strip of cotton ball, vibration with a tuning fork, and temperature perception with a test tube filled with cold water. A score was given according to the anatomical location in which the patient could not identify the stimuli introduced. If the patient perceived the stimulus at all levels, then a score of 0 was given. A score of 1 was given if the patient failed to perceive the stimulus at the base of the toe, a score of 2 was given if the patient failed to perceive the sensory at the midfoot, a score of 3 was given if the patient failed to perceive the stimulus at the heel, a score of 4 was given if the patient failed to perceive the stimulus at the lower leg, and a score of 5 was given if the patient failed to perceive the stimulus at the knee. The average score of both feet was entered as the sensory score. The summation of reflex and sensory scores for each modality was entered as the NDS. An NDS of ≥5 was indicative of the existence of moderate or severe neuropathy (16).

VPT

We used a biothesiometer (Biomedical, Newbury, OH) to test the VPT. This is a hand-held device with a rubber tractor that vibrates at 100 Hz. The hand-held unit is connected by an electrical cord to a base unit. This unit contains a linear scale that displays the applied voltage, which ranges from 0 to 50 V. The method of testing was standardized. The device was held with the tractor balanced vertically on the pulp of the toe. At this time, the voltage was increased on the base unit until the patient could perceive the vibration (17).

If a patient could not detect vibration at the maximum voltage of 50 V, then a value of 51 V was used for statistical analysis. A mean of 3 readings in each foot was entered for final data analysis. A value of 25 V was considered to be indicative of a patient at risk for foot ulceration (9).

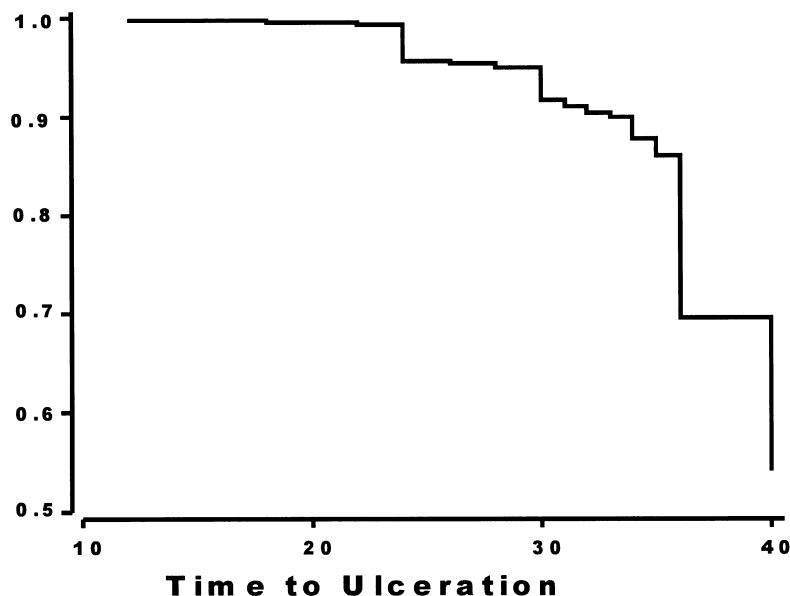


Figure 1—Kaplan-Meier plot of foot ulcer development in all participants during the study period.

SWF

We used a set of 8 SWFs that apply pressure from 1 to 100 g to evaluate the cutaneous perception threshold. The plantar aspect of the hallux was used for this testing. With the eyes closed, the patient related to the investigator when he or she could feel the filament. Inability to feel a 5.07 SWF (10 g of pressure) was considered to be indicative of being at high risk for foot ulceration (13).

Maximal plantar foot pressure

The F-Scan mat system (Tekscan, Boston, MA) was used to measure the dynamic plantar foot pressures (18). The mat was calibrated for each patient by using the patient's weight before each testing session. The patients walked without shoes over the mat, and the maximal plantar foot pressure for the entire foot was obtained. Several practice runs were made to familiarize the patient with the system and to ensure the recording of a natural gait. The mean reading of 3 midgait footsteps was entered for final data analysis. Foot pressures ≥ 6 kg/cm² were considered to be indicative of patients at high risk for foot ulceration according to previously published studies (11).

Joint mobility

The total range of motion at the first metatarsophalangeal joint (MTPJ) and the subtalar joint (STJ) was measured by using a goniometer (19). For the first MTPJ, the range of motion from maximal passive

plantar flexion to maximal passive dorsiflexion was measured. For the STJ, the range of motion from maximal passive inversion to maximal passive eversion was measured. The average of 3 readings in each foot was recorded.

Peripheral vascular disease

The diagnosis of peripheral vascular disease was based on the absence of foot pulses

and/or symptoms of claudication or a history of bypass operation.

Statistical analysis

The Minitab statistical package Version 12.0 (Minitab, State College, PA) for personal computers was used for statistical analysis. Comparisons between patients who developed and did not develop foot ulceration were made by using χ^2 tests for categorical variables. For individual continuous variables, comparisons were made by using the 2-tailed Student's *t* test if assumptions of normality were achieved or with Wilcoxon's rank-sum test if nonparametric hypothesis testing was required. Univariate and multivariate logistical regression was used in a stepwise fashion to assess variables that were independently significant predictors of ulceration. Significance levels of *P* = 0.05 were used throughout.

RESULTS — A total of 248 patients were included in the study and were followed for a mean period of 30 months (range 6–40). Information about the patient characteristics is given in Table 1. Details about the baseline measurements have been previously published elsewhere (20). Peripheral vascular disease was present in 78 patients, of whom 18 had a history of previous bypass operations. In the remaining 60 patients, at least 1 artery was palpable in 49 (82%) patients. Foot ulcers

Table 2—Comparison between nonulcerated and ulcerated patients

	Nonulcerated	Ulcerated	<i>P</i>
<i>n</i>	175	73	—
Age (years)	58 ± 13	59 ± 11	NS
Sex (M/F)	75/100	49/24	0.000
BMI	31.3 ± 7.0	29.6 ± 7.1	NS
Diabetes duration (years)	13 ± 10	16 ± 12	0.019
History of foot ulceration	55	32	0.062
Type of diabetes (1/2)	32/143	17/56	0.36
Nonpalpable pedal pulses (feet)	45 (11)	25 (26)	0.000
Maximal plantar pressure (kg/cm ²)	5.32 ± 2.6	7.2 ± 3.8	0.000
STJ mobility	24° ± 9°	22° ± 10°	0.026
First MTPJ mobility	76° ± 23°	62° ± 24°	0.000
NSS	4 ± 4	4 ± 4	NS
NDS	9 ± 7	16 ± 6	0.000
VPT (V)	26 ± 17	42 ± 13	0.000
SWF	5.18 ± 1.39	7.20 ± 3.83	0.000
Feet with high foot pressure (≥ 6.00 kg/cm ²)	119 (30)	54 (59)	0.000
Feet with high NDSs (≥ 5)	227 (57)	87 (92)	0.000
Feet with high VPTs (≥ 25 V)	173 (44)	82 (86)	0.000
Feet with high SWFs (≥ 5.07)	263 (66)	86 (91)	0.000

Data are *n*, means ± SD or *n* (%).

Table 3—Sensitivity, specificity, and positive predictive value of tested techniques

	Sensitivity	Specificity	Positive predictive value
High NDS	92	43	28
High VPT	86	56	32
High SWF	91	34	25
High foot pressure	59	69	31
High NDS and/or VPT	94	38	26
High NDS and/or SWF	99	22	23
High SWF and/or VPT	98	28	24
High NDS and/or foot pressure	58	78	38

Data are %.

developed in 95 (19%) feet or 73 (29%) patients during the study. Thus, 22 (9%) of the studied patients developed ulcers in both feet. The locations of the ulcers were as follows: 17 (18%) at the toe area, 76 (80%) at the plantar surface of the forefoot, 1 (1%) at the rear foot, and 1 (1%) at the dorsum of the foot. A Kaplan-Meier plot of ulcer development is shown in Fig. 1.

A comparison of baseline characteristics between patients who developed a foot ulcer and those who did not is shown in Table 2. Patients who developed foot ulcers were more frequently men, had diabetes for a longer duration, had nonpalpable pedal pulses, had reduced joint mobility, had a higher NDS, had a higher VPT, and had a higher SWF. Furthermore, the number of feet with high NDSs (≥ 5 U), VPTs (≥ 25 V), SWFs (≥ 10 g of pressure), and foot pressures (≥ 6 kg/cm²) was also significantly higher in the ulcerated group compared with nonulcerated patients. The sensitivity, specificity, and positive predictive value of each of the screening techniques are presented in Table 3. NDS had the best sensitivity as a single technique, whereas the combination of NDS and SWF further improved the sensitivity to 99%. On the other hand, the greatest specificity by a single technique was offered by foot pressures, and the best combination was that of NDS and foot pressures.

Univariate logistical regression analysis yielded a statistically significant odds ratio (OR) for sex, race, duration of diabetes, history of foot ulceration, palpable pulses, high NDSs, high VPTs, high SWFs, high joint mobility, and high foot pressures (Table 4). In addition, 94 (99%) of the 95 ulcerated feet had a high NDS and/or SWF, which resulted in the highest OR of 26.2 (95% CI 3.6–190). No significant OR was found for age, BMI, history of peripheral vascular disease, or NSS. However, in multivariate logis-

tical regression analysis, sex, race, duration of diabetes, history of previous foot ulceration, and palpable pulses were no longer significant, and the only significant factors were high NDSs, VPTs, SWFs, and foot pressures. The results of the multivariate analysis for these factors are shown in Table 3.

A total of 13 patients (3%) died during the study. In the ulcerated group, 7 (10%) patients died compared with 6 (3%) in the nonulcerated group ($P < 0.05$). Differences in the clinical characteristics between the patients who died during the study and those who survived are shown in Table 5.

CONCLUSIONS — In this study, we prospectively studied the association of sev-

eral risk factors for foot ulceration in a large sample of diabetic patients. Our results show that a high NDS obtained during a simple stratified clinical examination provides the best sensitivity in identifying patients at risk for foot ulceration, whereas high VPT, the inability to feel a 5.07 SWE, and high foot pressures were independent risk factors. Furthermore, the combination of NDS and a 5.07 (10-g) SWF could identify all but 1 of the 95 ulcerated feet. Therefore, use of these 2 simple methods in clinical practice can be useful in identifying the at-risk patient, which is the first step in the prevention of foot ulceration.

The assessment of the NDS involves only a simple stratified clinical examination that includes the ankle reflexes and the sensation to pain, touch, cold, and vibration. Because ankle reflexes can be absent in elderly patients, sensory deficit was also required to be present to classify NDS as high (>5 U). Thus, the existence of a high NDS could identify 92% of patients who developed foot ulceration, and this was further increased by combining clinical examination and SWF. Because the last technique is very simple, inexpensive, and can be easily performed by medical or paramedical staff members, this strategy can be used in almost any place in the world without any significant burden in terms of cost. The

Table 4—Logistic regression results for risk of ulceration

	ORs (95% CI)	P
Univariate results		
Sex*	0.44 (0.27–0.70)	0.000
Race†	0.71 (0.55–0.92)	0.01
Diabetes duration	1.03 (1.0012–1.0500)	0.01
History of foot ulceration	5.11 (3.17–8.24)	0.001
Palpable pulses	0.36 (0.21–0.62)	0.000
First MTPJ	0.98 (0.97–0.99)	0.000
STJ	0.97 (0.95–1.00)	0.026
High NDS (≥ 5)	8.1 (3.8–17.3)	0.000
High VPT (≥ 25 V)	8.2 (7.4–18.4)	0.000
High SWF (≥ 5.07)	5.4 (2.6–11.6)	0.000
High foot pressure (≥ 6 kg/cm ²)	3.2 (2.0–5.1)	0.000
High NDS and/or high VPT	9.0 (3.9–21.1)	0.000
High NDS and/or high SWF	26.2 (3.6–190.0)	0.000
High VPT and/or high SWF	17.7 (4.3–73.0)	0.000
Multivariate results‡		
High NDS	3.1 (1.3–7.6)	0.013
High VPT	3.4 (1.7–6.8)	0.001
High SWF	2.4 (1.1–5.3)	0.036
High foot pressure	2.0 (1.2–3.3)	0.007

*Reduced risk of ulceration in women compared with men; †reduced risk of ulceration in African-Americans and Hispanics compared with Caucasians; ‡controlling for sex, duration of diabetes, race, and palpable pulses.

Table 5—Clinical characteristics of patients who were alive and who died during the study

	Patients who were alive at the end of the study	Patients who died during study	P
n	175	73	
Age (years)	58 ± 12	59 ± 14	NS
Sex (M/F)	114/121	10/3	0.046
BMI	30.5 ± 6.5	32.4 ± 12.9	NS
Diabetes duration (years)	14 ± 11	18 ± 12	NS
Diabetes type (1/2)	44/191	5/8	NS
Nonpalpable pedal pulses (feet)	62 (13)	8 (31)	0.013
NDS	10 ± 7	15 ± 8	0.24
VPT (V)	29 ± 17	36 ± 18	0.035
SWF	5.40 ± 1.42	5.58 ± 1.66	NS

Data are n, means ± SD, or n (%).

time required for clinical examination and a 10-g SWF test does not exceed 5 min and can be part of the recommended annual review of the clinical examination (21).

Several previous studies have examined the contribution of various risk factors to foot ulceration, but none has examined in a prospective way the contribution of all significant risk factors. Thus, high VPT, inability to feel the 10-g SWF, autonomic neuropathy, and limited joint mobility have all been associated with foot ulceration (7,8,11–13). The main contribution of the present study is that it provides valuable information about which methods the busy clinician should use. Thus, VPT measurements are not as relatively accessible as SWF and can be easily substituted in clinical practice. Furthermore, the evaluation of joint mobility, although undoubtedly an important part of a comprehensive diabetic foot evaluation, was not as strong a predictive factor as neuropathy and may not be as critical to assess during a screening.

The high sensitivity levels achieved with the combination of NDS and SWFs were also accompanied by a relatively low specificity and positive predictive value. However, remember that these are screening tests in which a high sensitivity level is of paramount importance because the most important aspect of these tests is not to miss at-risk patients. One could argue that such methods may lead to overdiagnosis and overtreatment, but this is not a major problem for the at-risk diabetic patient, for whom foot care, education, and proper footwear are the cornerstones of prevention (22). This argument is further weakened when comparing the high cost of treating foot ulceration (\$27,987 in the U.S. for the first 2 years of a new foot

ulcer) with the relatively inexpensive methods of prevention (23).

High foot pressures have been shown in the past to be associated with an increased risk of developing foot ulceration, especially in the presence of neuropathy (7,10,20). Similar results were found in the present study when using a simple method that involves a portable mat and a computer to measure foot pressures. Although the sensitivity of foot pressure measurement was considerably lower compared with the other techniques, this method had a substantially higher specificity that makes it more suitable as a second-line test rather than as a screening testing. Use of foot pressure measurements can also be particularly helpful in providing patients with the proper footwear, including shoes, socks, and orthoses.

Patients who attended tertiary centers and/or primary care clinics in 3 different cities were included in the present study. This resulted in a population that included Caucasians, Hispanics, and African-Americans with and without neuropathy. One could argue that the prevalence of neuropathy was higher in our group. However, high NDSs were present in 57% of the nonulcerated feet, high VPTs were present in 44%, and high SWFs were present in 66%. Given the fact that clinical neuropathy can affect 35–45% of all diabetic patients, we believe that our sample was close enough to the general diabetic population. In any case, this was not an epidemiological study; rather, it was a cohort study that aimed to identify the best screening techniques. Therefore, the inclusion of patients with a slightly higher prevalence of diabetic neuropathy is quite acceptable.

Race was not found to be a factor associated with foot ulceration when severity of neuropathy, age, and sex were taken into account. One could also argue that socioeconomic status is the most important factor and that race acts as a simple marker of this factor. Although this may be the case, the design of the present study cannot answer such a challenging question. However, because race was not an important factor when other factors were considered, the conclusions of the present study (namely that the screening criteria in this study can be used in any population) are still valid despite the lack of information regarding socioeconomic status.

Foot ulcers developed in 95 feet (19%) or 73 patients (29%) during the present study, which translates to annual rates of 7.6 and 11.6%, respectively. In a recent multicenter prospective study, the first-time foot ulceration rate in diabetic patients with VPTs between 25 and 50 V was 7.2% (24). However, this incidence is higher than that reported in large epidemiological community-based studies (25–27). This difference is mainly related to the fact that the followed population was at higher risk for developing a foot ulcer, which was a deliberate strategy because the intention of this study was not to assess the incidence and prevalence of foot ulceration but rather was to identify the best screening techniques that predict foot ulceration. Nevertheless, this study also emphasizes the unacceptably high rate of foot ulceration in at-risk diabetic patients and the need for better preventive methods.

In summary, we have shown that the combination of clinical examination and SWF testing is the most sensitive method for identifying the patient at risk for foot ulceration. VPT measurements are also helpful and can be used as an alternative. Finally, foot pressure measurements offer a substantially higher specificity and can be used as a postscreening test in conjunction with providing appropriate footwear.

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