Q J Med 2007; **100**:65–86
doi:10.1093/qjmed/hcl140

Review

QJM

Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis

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Summary

Clinical guidelines recommend that all patients with diabetes should be screened annually to establish their risk of foot ulceration. The aim of this systematic review was to quantify the predictive value of diagnostic tests, physical signs and elements from the patient's history in relation to diabetic foot ulcers. Observational studies were identified from: electronic databases (MEDLINE, EMBASE and CINAHL); bibliographies of studies meeting the inclusion criteria; review articles and clinical guidelines; direct contact with authors. Published reports of cohort and case-control studies were considered for inclusion. Pooled estimates were calculated from absolute numbers as weighted mean differences, standard mean differences or odds ratios. Adjusted odds ratios from published reports were also extracted. We identified five case-control and 11 cohort studies. The incidence of foot ulcers ranged from 8% to 17% in the cohort studies, with varying lengths of follow-up. Diagnostic tests and physical signs that detect peripheral neuropathy (biothesiometry, monofilaments and absent ankle reflexes), and those that detect excessive plantar pressure (peak plantar pressure and joint deformity) were all significantly associated with future diabetic foot ulceration. However, there was a paucity of evidence concerning the predictive value of symptoms and signs. Further research is needed to establish the independent factors associated with diabetic foot ulceration, particularly elements from a patient's history and physical examination.

Introduction

The prevalence of foot ulceration among patients with diabetes mellitus ranges from 1.3% to 4.8% in the community, to as high as 12% in hospital.[1] This represents considerable patient morbidity, and is associated with substantial health-care costs. The pathophysiology of diabetic foot ulceration is multifactorial, but peripheral neuropathy is thought to be responsible for most cases.

To prevent foot ulceration and amputation, clinical guidelines recommend early identification of risk, based on annual foot screening of all diabetic patients, with targeting of preventive and treatment interventions to 'high risk' individuals.[2–4] Key to this preventive strategy is a structured clinical assessment that incorporates diagnostic tests alongside a thorough history and examination.

Current guidelines have not integrated data from primary studies that relate to the prognostic importance of diagnostic tests, physical signs and patient history (alone or in combination), the indicators that underlie any structured approach to preventive risk stratification in diabetic patients. We therefore

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undertook a systematic review to determine the predictive values of such features in estimating the risk of diabetic foot ulceration.

Methods

We followed recommended guidance concerning the conduct of systematic reviews.[5]

Search strategy

Electronic search strategies were used to identify studies which assessed the predictive value of diagnostic tests, signs and symptoms using MEDLINE (1966–February 2005), EMBASE (1980–March 2005), CINAHL1982–February 2005. The electronic search strategy was developed from clinical MeSH headings and text words. The search strategy is available from authors. We searched the bibliographies of included studies, review articles and national clinical guidelines.

Inclusion criteria

(i) Published reports of cohort or case-control studies that evaluated the factors used to predict diabetic foot ulceration. (ii) All study participants free of active foot ulceration at the time of study entry. (iii) All study participants in either study design had a diagnosis of diabetes (either type I or type II). The outcome (reference standard) was foot ulceration.

Definitions and explanations for the predictive factors assessed in the review are presented in Box 1.

Quality assessment

Assessment of methodological quality was used items adapted from the QUADAS tool, recommendations for methodological standards for clinical prediction rules and a checklist for assessment of the methodological quality both of randomized and non-randomized studies of health-care interventions.[6–8] Quality assessment was done independently by two reviewers (FC, MI), and the results were used for descriptive purposes to provide an overall evaluation of the included studies. Disagreements were resolved by discussion, and information not available in the reports was sought from the corresponding authors of the primary study.

Data extraction

Data were extracted from the studies as absolute numbers and as means with SDs to permit the re-calculation of data as weighted or standardized mean differences and 95%CIs. Where data were available, they were re-calculated as pooled estimates of the effect of the predictive factors. All odds ratios and risk ratios presented in the included studies were also extracted from the published reports.

Statistical analyses

Data from the two different study designs are presented separately. We only present estimates of effectiveness where there were two or more reports for individual predictive factors. A complete list of estimates of all predictive factors is available from the authors.

As the review focused on a single outcome (diabetic foot ulceration) groups of patients were categorized into those who ulcerated and those who did not. Continuous outcomes, expressed as means and SDs, were pooled as weighted mean differences (WMD). Peak plantar pressure was measured using different dynamic platform-based equipment systems, and consequently a standardized mean difference (SMD) was used to pool data. Tests for heterogeneity were performed, and where heterogeneity was evident, a random effects model was used.[9]

Findings are presented using the following structure for potential predictive factors; diagnostic tests, physical signs and patient history.

Results

Characteristics of included studies

After independent assessment by two reviewers, 16 studies were judged to have met all inclusion criteria (Figure 1), with disagreements being resolved by discussion. Details of the study population and aspects of diagnostic tests, physical signs and patient history are presented in Tables 1 and 2. Five studies used a case-control design,[10–14] and eleven a cohort design,[15–25] (Tables 1 and 2). A conference abstract of unpublished data was also identified by the search.[26]

Data from nine studies were available to calculate pooled estimates.[10–14,16–18,22] The incidence of foot ulceration developed by patients in cohort studies ranged from 8% to 17%, but with lengths of follow-up varying from 12 weeks to 4 years (Table 2).

Quality assessment (Tables 3 and 4)

Case-control studies

All five studies used statistical methods to adjust for confounding factors in the analysis (Table 1).[10–14]

Box 1 Descriptions of the index tests used to predict those at risk of diabetic foot ulceration

Peak plantar pressures

Plantar pressure measurements are used to identify specific areas of high pressure under the foot. Several pieces of equipment exist to measure high plantar pressure, producing static or measurements from in-shoe or force plate systems, with outputs manifest as simple or highly sophisticated quantitative measures.[33]

Vibration perception threshold

Vibration perception threshold can be measured using a biothesiometer or a neurothesiometer. These are hand-held mains or battery operated units with a rubber tractor that vibrates at 100Hz. A linear scale or digital display shows the applied voltage. Subjects are tested by gradually increasing the amplitude from zero and indicating when they feel vibration. Scale readings of >25 V are considered to be a positive test result (i.e. an absence of sensation).[34]

Transcutaneous oxygen tension ($TcPO_2$)

$TcPO_2$ measures the amount of oxygen delivered to the skin. An electrode is attached to the dorsum of the foot, e.g. at the base of the second metatarsal. It has been suggested that a $TcPO_2$ level >30 mmHg is indicative of good blood flow in the lower limb.[35]

HbA_{1c} (glycosylated haemoglobin)

HbA_{1c} is the most widely used measure of long term glycaemic control in diabetes, being produced by the non-enzymatic glycosylation of haemoglobin at a rate proportional to prevailing glucose concentration and the life span of the erythrocyte. Target HbA_{1c} is set at between 6.5% and 7.5%.[36]

Fasting blood glucose

Diabetes mellitus is diagnosed on >7.0 mmol/l fasting blood glucose. If random blood glucose is >7.8 mmol/l, then FBG should be checked.[36]

Ankle brachial index

Ankle-brachial pressure index (or ABI, ankle-arm index, AAI) is used to diagnose lower limb ischemia. It is calculated by dividing the recorded the systolic pressure taken at a pedal artery by the value taken at the brachial artery, and is expressed as a ratio. Average values are 0.98 to 1.31, <0.8 is indicative of ischaemia and <0.5 indicative of a pre-gangrenous state. The position of the patient will influence the pressure in the artery at the ankle; when standing the pressure in the ankle will be >1, if supine the reading should be 1.[27]

Serum creatinine

Levels of serum creatinine >350 μmol/l (4.0 mg/dl) are indicative of chronic renal insufficiency.[36]

Cutaneous sensation (Monofilaments)

Monofilaments are used to detect presence or absence of cutaneous pressure sensation The filament is applied at 90° to the foot, with enough pressure to cause the filament to buckle. It should be held in place for 2 s. The 1st, 3rd and 5th metatarsal heads, the plantar aspect of great toe and the apex of third toe, in both feet should all be tested. The test result is positive (i.e. there is an absence of sensation) if the patient is able to feel fewer than eight sites with a monofilament (fewer than four sites if one foot has been amputated).[36]

Tuning fork

The tuning fork assesses vibration perception threshold (VPT). Although tuning forks permit the detection of vibration, traditional tuning forks do not allow the measurement of the amplitude threshold at which vibration becomes perceptible. Some tuning forks can be calibrated to vibrate at a given frequency (Hz), and can be interpreted by a score on a scale of 0–8.[38]

Visual acuity

Good eye sight is important for effective self foot care and the avoidance of harm. Visual acuity is usually measured by the Snellen test chart, and is defined as poor if worse than 20/40.[36]

Lower limb oedema

Distension of the affected tissues can be caused by a disruption to the normal mechanism of fluid exchange.[27]

Tendon reflexes

Tendon hammers are used to elicit tendon reflexes (jerks). The ankle reflex tests the integrity of the spinal reflex pathway (S1, S2). When the foot is held in a slightly dorsi-flexed position and the Achilles tendon tapped, the fore foot will gently plantar flex. The ankle reflex is recorded as present, or absent.[39]

Limited ST joint motion

At the subtalar joint, two-thirds inversion to one third eversion is considered normal.[33]

Limited 1st metatarsal motion

The expected range of motion (ROM) at the 1st metatarsal phalangeal joint is 70°.[33]

In two studies, insufficient detail was given about the index tests to permit the presentation of data.[12,13]

Cohort studies

Seven studies reported adjusted estimates for potential confounding factors (Table 2).[15–17,19,21,22,25] Patients received treatment between the index tests and the outcome (assessment of foot ulceration) in all except one study.[23]

Quantitative estimates concerning the predictive value of diagnostic tests, patient history, symptoms and signs

Unadjusted and adjusted estimates of effect of all predictive factors—diagnostic tests, physical signs and patient history—are summarized in Table 5. Pooled estimates (weighted and standardized mean differences) concerning the predictive value of diagnostic tests (peak plantar pressures, vibration perception threshold and HbA_{1c}) and the duration of diabetes are presented in Figure 2.

Diagnostic tests

Peak plantar pressures (Figure 2a, Table 5)

Two case-control studies and four cohort studies measured peak plantar pressure, using four different dynamic measuring systems (Musgrave,[10] F-scan,[22] EMED[12,18,21] and a pedobarograph[20,24]). High plantar pressures constitute a risk of ulceration: SMD 0.98 N/cm^2 (95%CI 0.63–1.33)[10,12] for case-control studies, and SMD 0.47 N/cm^2 (95%CI 0.24–0.70) for cohort studies.[18,22]

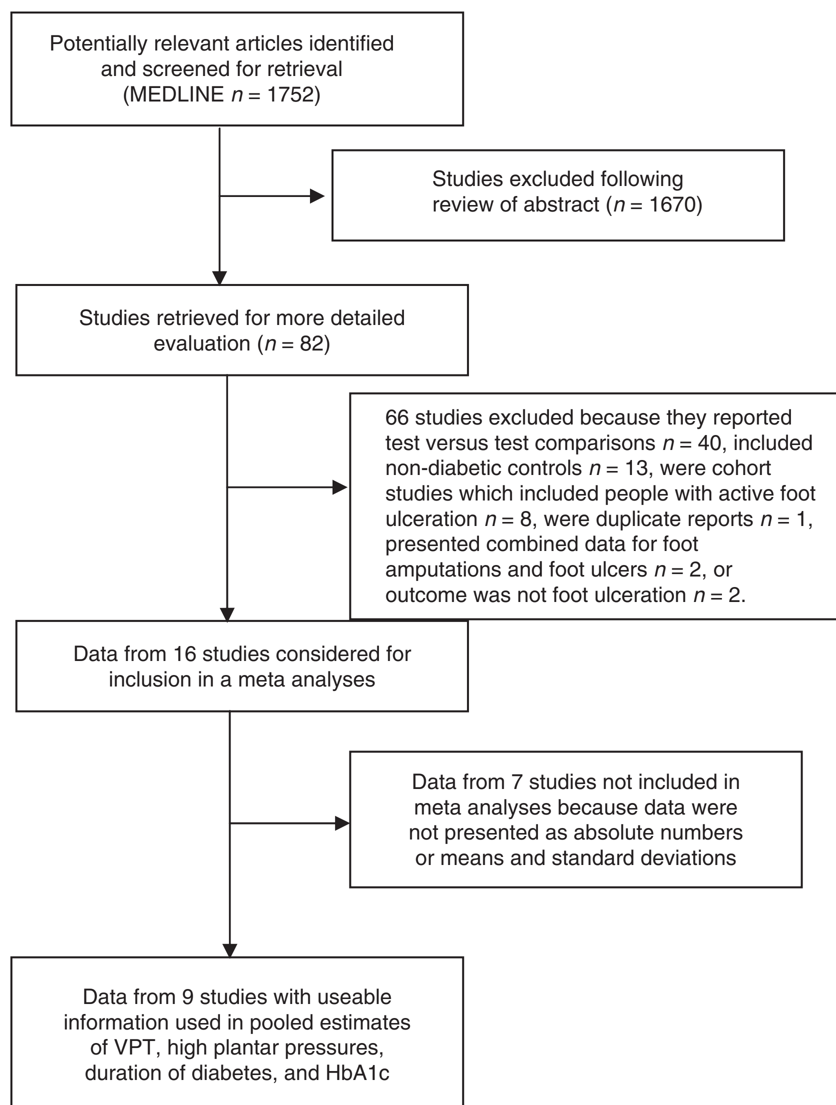


Figure 1. Flow diagram of studies in the review.

Table 1 Study interventions and outcomes: case-control studies

Author, year Study design, setting, and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)
Bennett, 1996[10] Secondary care; diabetic units, Brisbane, Australia 27 cases, 50 controls	Peripheral nerve function assessed using two tests: biothesiometer; and Semmes-Weinstein monofilaments. Peripheral joint flexibility. Ankle joint dorsiflexion range of motion, measured with goniometer. Pressure of plantar aspect of foot, measured using a Musgrave Footprint system. Dynamic pressure recordings made of six foot prints with highest and lowest pressure prints discarded and average foot pressure obtained from the remaining four prints.	Age Sex Duration of diabetes Type of diabetes BMI HbA_{1c}	Not stated.
Boulton 1986[11] Secondary care diabetic foot clinic or emergency room, Miami Florida. 86 cases, 49 controls	VPT measured with a biothesiometer (three readings on each side). API was defined as ratio of posterior tibial artery systolic pressure to the brachial systolic pressures and values <0.8 were considered abnormal. Limited joint mobility	Age Duration of diabetes BMI HbA_{1c}	Foot ulcer was defined as an open lesion that was present below the level of the malleolus.
Lavery 1998[12] Texas diabetes institute, USA 76 cases, 149 controls	Peripheral sensory neuropathy assessed using vibration perception threshold testing at the distal great toe with a biothesiometer. Peripheral vascular disease of lower extremities evaluated using the Rose Intermittent Claudication Scale, the absence of palpable dorsalis pedis and posterior tibial pulses in the foot, transcutaneous oxygen tension on the dorsal aspect of the first intermetatarsal space (<30 mmHg), and the ankle-brachial systolic blood pressure index (<0.8). Three measurements of the first metatarsophalangeal joint, the subtalar joint, and ankle joint range of motion were averaged to assess limited joint mobility of the forefoot, rearfoot, and ankle.	Age Sex Duration of diabetes Diabetes type Education HbA1c BMI Neuropathy Previous amputation Lower extremity bypass Tobacco use	Not stated.

Continued

Table 1 Continued

Author, year Study design, setting, and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)
	Evaluation of foot for presence of hallux valgus, toe contractures, subluxation or dislocation of the metatarsophalangeal joints, and prominent metatarsal heads on the sole of the foot. EMED pressure platform system used to evaluate dynamic barefoot pressures on the sole of the foot. An average of pressures from three midgait steps was used for the purposes of analysis.	Alcohol abuse Intermittent claudication Retinopathy	
McNeely 1995[13] Veterans affairs medical centre USA 46 cases, 322 controls	Distal vibratory sensation by vibrating 128 Hz tuning fork. If unable to perceive vibration at any of three sites on either foot, then vibratory sensation was considered absent. Aesthesiometry by Semmes-Weinstein monofilament on eight standardized plantar sites and one mid-dorsal site of each foot. Inability to perceive the 5.07 monofilament at any of the nine sites on either foot was classified as insensate. Achilles tendon reflexes were graded as present or absent for each ankle. Ankle-arm BP index computed as the highest ankle (dorsalis pedis or posterior tibial) BP divided by the highest brachial BP (right or left) for each side. Cutaneous circulation by measuring transcutaneous oxygen tension on mid-dorsum of each foot. For all variables measured bilaterally, the lower of the two readings (right or left) was used in the analysis.	% Men Age Caucasian BMI Married Education Cigarette use Alcohol use Diabetes type Current diabetes treatment Duration of diabetes Any formal diabetes education Random serum glucose Medical history	Foot ulcer graded as Seattle Wound Class 2.0 through 6.0.

Continued

Table 1 Continued

Author, year Study design, setting, and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)
Sriussadaporn 1997[14] 55 cases, 110 controls	Ratio of ankle to brachial systolic BP of same side was calculated as ankle-brachial systolic index (ABI). Peripheral vascular insufficiency was diagnosed when ABI was <0.9. ABI of >1.2 suggested the presence of medial arterial calcification. Peripheral nerve disorders were diagnosed on basis of short-latency somatosensory evoked potentials (SSEPs) following stimulation of the tibial nerve, recorded by Neuromatic 2000°C. Two questionnaires used to evaluate patients' knowledge of diabetes and foot-care behaviour.	Sex Marital status Religion Living area Occupations Education Economic status Smoking Alcohol consumption Diabetes duration BMI BP Visual acuity Diabetic knowledge score Foot-care score	Foot ulcers defined as full-thickness disruption of skin below mid-calf level with one or more of themore of the following features: duration of the ulcer >14 days, presence of severe infection, necrosis or gangrene. Diabetic patients in either group who had a past history of foot ulcer as defined by above criteria, lower limb amputation, chronic venous ulcer, cerebrovascular disease, or spinal cord disease were not included in this study.

Vibration perception threshold (VPT) (Figure 2b, Table 5)

Four case-control[10–13] and six cohort studies[16,17,20–22,25] found patients with foot ulcerations to have significantly higher VPT than those who did not: WMD 20.00 V (95%CI 11.81–28.20)[10,12] for case-control studies and WMD 17.07 V (95%CI 13.89–20.26)[17,22] for cohort studies.

Transcutaneous oxygen tension (Table 5)

Two case-control studies and one cohort study categorized patient measurements into groups ($\leqslant$30 mmHg and 31–60 mmHg). Transcutaneous $pO_2 \leqslant 30$ mmHg was more strongly associated with the development of a foot ulcer, compared with pO_2 31–60 mmHg.[12,13,16]

HbA_{1c} (Figure 2c, Table 5)

In pooled results from four case-control studies, patients who developed foot ulcers had higher levels of HbA_{1c} than those who did not, but the effect did not reach statistical significance: WMD 0.95% (95%CI −0.33 to 2.23).[10–12,14] Data from one cohort study did demonstrate a statistically significant effect: WMD 1.1% (95%CI 0.57–1.61).[16]

Table 2 Study interventions and outcomes: cohort studies

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Armstrong 2004[15] Texas, USA Duration = mean follow-up 37.1 (12.3) weeks $n = 100$	Daily activity accelerometer/pedometer (measures the number of steps taken over a period of time, and records the time of day each step taken). VPT meter threshold >25 V defined as neuropathy	Age 68.5 (10) Sex 95.0 Duration of diabetes 13.7 (9.3) Foot risk category 68/32 BMI 30.0 (3.0)	Not stated	8/100 (8%).
Boyko 1999[16] Ambulatory general internal medicine clinic patients at a veterans affairs medical centre Seattle, USA Duration not reported $n = 900$	Sensory testing performed at nine locations on each foot using Semmes-Weinstein monofilament. Inability to detect 10 g monofilament. Vibration sensation measured using a 128 Hz tuning fork. VPT graded present/absent. Cardiovascular autonomic neuropathy: mean heart rate variability on a continuous electrocardiogram, and immediate systolic BP response to standing from a supine position. Lower-limb transcutaneous O_2 tension with TCM-3 monitors. TC PO_2 flow measure in perfusion units Laser Doppler flowmetry on dorsal foot. Standard Doppler techniques for brachial and lower-limb arterial BP. BP measured in mmHg. Hallux BP measured using a penile cuff and hand-held Doppler. Random blood sample for plasma glucose (glucose oxidase method), serum creatinine and erythrocyte sedimentation rate.	Weight Height Diabetes duration Type 2 diabetes Insulin use Random glucose HbA_{1c} Erythrocyte sedimentation rate Serum creatinine $TcPO_2$ dorsal foot Claudication <1 block Peripheral vascular disease. History of laser photocoagulation treatment Vision <20/40 History of ulceration Previous amputation Foot numbness and pain	Foot ulcer was defined as a full-thickness skin defect that required >14 days to heal. Outcome was defined as the first ulcer occurrence on the foot. Follow-up on both limbs was terminated when the first ulcer occurred on either during the follow-up period.	162 ulcers developed over 5442.6 cumulative person-years (3.0/100 person-years).

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Kastenbauer 2001[17] Diabetes centre at the third medical department, Hospital Lainz, Vienna, Austria Duration = 4 years $n = 187$	X-ray taken of both feet to assess bone deformities and calcification of the media. Questionnaire for evaluating symptoms of peripheral neuropathy. Peripheral nerve conduction velocity, cardiorespiratory reflexes and orthostatic drop of systolic BP measured. PVD determined using palpability of foot pulses and ankle-arm index. VPT measured using a biothesiometer three times at the pulp of both great toes. Perception of 10 g monofilament tested at eight plantar sites on each foot: insensate to 2/8 regarded as abnormal.	Sex Age Diabetes duration Insulin use HbA_{1c} Serum creatinine Body weight BMI History of MI History of angiography Smoking Daily alcohol intake	Foot ulcers defined as full-thickness neuropathic plantar or lateral forefoot ulcerations penetrating the cutis and subcutis.	18 forefoot ulcerations in 10 patients out of a total of 187 patients.
Lavery 2003[18] In-patient and out-patient clinics in Texas, USA Duration = 2 years $n = 1666$	Lower extremity sensory examination using 10 g Semmes-Weinstein monofilament. Abnormality defined as inability to detect 10 sites evaluated with monofilament on each foot VPT using biothesiometer, abnormal reading >25 V. Lower-extremity vascular status assessed by palpitating dorsalis pedis and posterior tibial pulses. Peak foot pressures assessed using Novel EMED force-plate gait analysis system.	Age %Male Weight Duration of diabetes	Not stated.	263 patients (15.8%) developed an ulcer during 24 months follow-up.

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Litzelman 1997[19] Primary care, Indiana USA. Duration = 1 year *n* = 352	Lower-extremity oedema assessed by pressing thumb over pretibial area for 5 s. Sensortek Thermal Sensitivity Testing apparatus and Semmes-Weinstein monofilament used as objective measures of neuropathy. Thermal sensation was defined as abnormal if detection of temperature change from a reference of 25°C was >2 SDs from the mean sensitivity threshold for a group of healthy people without diabetes. Touch pressure sensation tested with a single 10 g Semmes-Weinstein monofilament. Abnormal pressure anaesthesiometry, defined as the absence of sensation at one or more of three sites tested on the plantar surface of each foot.	Race %Women Age Annual income <$10 000 Education level (years) BMI Duration of diabetes Taking insulin Taking oral hypoglycaemic agents.	Response variable was the existence of any foot wound at time of follow-up assessment. Rated using the Seattle Wound Classification System, which ranges from a grade 1.1, signifying absence of lesions, to grade 10, where the entire foot or leg is gangrenous. Outcome was then dichotomized and separately analysed at two thresholds of severity.	63/704 (8.9%)
Murray 1996[20] Secondary care diabetes centre and Manchester Foot Hospital, UK Duration = not reported *n* = 63	Neuropathy deficit score: sensations of pain, light touch, vibration and cold tested in both lower limbs and scored to the level up to which sensation was impaired. VPT measured at both great toes by biothesiometer and compared with age-matched 'normal' measurements. Mean of three measurements used for each great toe. Foot pressures measured using a dynamic optical pedobarograph.	Male Age Type 1 DM Duration of diabetes History of intrinsic ulcers	Ulcers were classed as intrinsic if they occurred on the plantar surface of the foot and were not associated with external trauma, extrinsic if they occurred as a result of shoe pressure or trauma (typically dorsal). Only intrinsic ulcers were considered in the analysis.	Seven intrinsic plantar ulcers documented in six patients. Total of 63 patients in study.

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Peters 2001[21] Texas Health Science Center, San Antonio, USA Duration = 3.5 years $n = 213$	Plantar peak pressures measured with Novel EMED-SF platform system (average of three steps used for analysis). Elevated plantar pressures defined as a peak plantar pressure of >70 N/cm^2. Several vascular parameters evaluated: TcPO$_2$ <40 mmHg, probe temp. of 45°C; ABI of <0.8; absence of dorsal pedal and posterior tibial artery pulsations; incompressibility of pedal arteries (ABI >1.2). PVD defined as ABI <0.8 or any non-palpable pedal pulsation. VPT measured with biothesiometer, voltage of >25 V defined as loss of protective sensation. 10 g SWM applied to 10 areas of foot, impaired sensation defined as one or more unnoticed pinpricks with SWM or VPT of >25 V. Joint mobility assessed by averaging three measurements from first metatarsal phalangeal joint, subtalar joint and ankle. CAGE questionnaire	Age Diabetes duration Follow-up BMI HbA$_{1c}$ Female Type 2 diabetes Previous or present drinker Present or previous tobacco use Nephropathy Retinopathy HbA$_{1c}$ > 9% Amputation history	Ulcers were defined as skin lesions distal to the ankle. Subjects who received an amputation as a direct result of their initial ulceration were disqualified from further analysis.	54 follow-up ulcers. Unclear from paper if this was in 213 patients or if analysis was based on the number of feet.
Pham 2000[22] Multi centre study. Primary foot care clinic, Israel. Primary foot care clinic Massachusetts, USA. University of Texas Health Science Center, San Antonio, Texas. California College of podiatric Medicine, San Francisco, USA. Duration = follow-up 30 months	Neuropathy symptom score NSS assessed by: patient questioned about nocturnal cramps, numbness, abnormal temperature sensation, burning, aching pain, irritation from bed clothes. Neuropathic disability score based on examination of tendon reflexes and sensory modalities (pin prick, light touch, temperature perception) all at different levels in the lower limb (toes, midfoot, heel and lower leg).	Age Sex BMI Duration of diabetes	Not stated	95 feet (19%). 73 patients (29%). 22 (9%) developed bilateral ulcers.

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
n = 248	Vibration perception threshold measured using a biothesiometer. 8 SWF monofilaments (1g to 100 g) used at the plantar aspect of the hallux. Maximal plantar foot pressure. F scan mat system, measuring dynamic pressure. Peripheral vascular disease (PVD) based on absent foot pulses.	History of foot amputation Type of diabetes		
Rith-Najarian 1992[23] Primary care, Minnesota, USA Duration = 3 years *n* = 358	Sensation status determined by applying the 5.07 monofilament to eight points on the plantar surface of each foot at time A or time B when the patient was blinded. Patients who failed to perceive the monofilament on one or more areas of either foot were retested twice before they were classified as insensate. Subset of patients had AAI calculated from measurements of right brachial artery and both posterior tibial arteries, obtained with a mercury manometer and a 2 MHz portable Doppler.	Age Duration of diabetes Sex	Ulcerations were defined as any full thickness penetration of the dermis on the plantar aspect of the foot.	41 ulcers from 358 patients (11.5%)
Veves 1992[24] Secondary care; clinics at diabetes centre, Manchester, UK.	Neuropathy deficit score (NDS) used to diagnose neuropathy, based on reduced or absent ankle reflexes and reduced or absent sensation to pain, touch and vibration.	Age Gender Diabetes type	Ulcers were classified as plantar when they occurred on plantar surface of foot and as dorsal if they occurred anywhere else on the foot.	15/86 with plantar ulceration and high pressures at baseline (17.4%)
Duration = 30 months *n* = 86	Foot pressures measured by optical pedobarography. Peak pressures >12.3 kg/cm^2 considered abnormal. VPT measured at the great toe by biothesiometry. Upper threshold of normality was taken from established data based on measurements of a large number of healthy subjects.	Duration of diabetes		

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Young 1994[25] Secondary care, diabetes centre and foot clinic Manchester, UK Duration = 4 years $n = 469$	VPT was assessed by biothesiometry. Mean of three readings used to derive the value for each foot.	Sex Age Diabetes type Duration of diabetes HbA_{1c} Creatinine	Not stated.	First ulcers = 8/469 patients (10.2%)

Ankle brachial indices (ABI) (Table 5)

Four cohort[16,17,21,23] and four case control studies[11–14] measured blood pressure at the ankle and arm. Only one cohort study found an effect which remained evident after an adjustment for confounding.[16]

Fasting blood glucose and serum creatinine (Table 5)

There was inconsistent evidence that increasing levels of blood sugar (mmol/l)[14,19] and creatinine (µmol/l) were associated with increased risk of ulceration.[16,19]

Physical signs

Cutaneous sensation (monofilaments) (Table 5)

One case-control study and five cohort studies all found statistically significant differences in the rate of foot ulceration between people whose feet were insensate to $\leqslant 5.07$ monofilaments ($\leqslant 10$ g pressure) and those who were not, with ORs ranging from 2 to 10.[13,16,19,21–23]

Absent ankle reflexes (Table 5)

Absent ankle reflexes were predictive of a higher risk of foot ulceration in one case-control[13] and one cohort study,[16] with unadjusted ORs of 4.9 and 1.4, respectively.

Visual acuity (Table 5)

Patients with lower mean visual acuity were at greater risk of foot ulceration in one case-control and one cohort study (adjusted RR 1.9).[14,16]

Patient history

Duration of diabetes (Figure 2d, Table 5)

In five case-control studies, patients who developed foot ulcers had diabetes for longer than those who did not, but this effect was not statistically significant: WMD 2.62 (95%CI −0.75 to 5.99).[10–14] Combined data from two cohort studies did find a statistically significant effect: WMD 1.88 (95%CI 0.48–3.28).[16,22]

History of foot ulceration, amputation and history of lower limb bypass (Table 5)

In four cohort studies investigating the risk associated with a history of foot ulceration,[16,20–22] patients who had previous ulceration were more likely to develop diabetic foot ulcers (adjusted ORs ranging from 1.6 to 4.2). One case-control study and one cohort study found a history of amputation to be a risk factor for foot ulceration.[12,16] These two studies also found that a history of lower limb bypass operation predicted future foot ulceration.

Discussion

Summary of findings

We found evidence to support the use of diagnostic tests and physical signs that detect peripheral neuropathy, the principal cause of diabetic foot ulceration. High vibration perception thresholds (VPTs) using a biothesiometer or a tuning fork, high plantar pressure and 10 g monofilaments appear reliable methods to identify

Table 3 Case-control studies: quality assessment

Authors . . .	Bennett 1996[10]	Boulton 1986[11]	Lavery 1998[12]	McNeeley 1995[13]	Sriussadaporn 1997[14]
Hypothesis clearly defined?	Y	Y	Y	Y	Y
Patient characteristics clearly described?	Y	Y	Y	Y	Y
Predictive factors clearly described?	Y	Y	Y	Y	Y
Main outcome measure defined?	Y	Y	Y	Y	Y
Patients selected consecutively?	NC	NC	Y	Y	NC
Patients representative of those who receive the test in practice?	Y	Y	Y	Y	Y
Context representative of the treatment majority of patients receive?	Y	Y	Y	Y	Y
Index tests (PF) reproducible?	Y	N	N	N	Y
Adjustment made for confounders?	Y	Y	Y	Y	Y
Same clinical data available when test results (PF) interpreted?	Y	Y	Y	Y	Y
Assessment of outcome blind to the results of the index test (PF)?	NA	NA	Y	NA	NA
Uninterpretable/intermediate test results (PF) reported?	N	N	NA	N	N
Sample size adequate for number of outcome events?	Y	Y	Y	Y	Y
Statistical tests for main outcomes adequate?	Y	Y	Y	Y	Y
Study sought to measure and report adverse events?	N	N	N	N	N

those at risk of future ulceration. Absent ankle reflexes, and limited joint motion at both the first metatarsal-phalangeal joint and the subtalar joint were also found to increase the risk of foot ulceration. These findings were evident across different study designs, pooled, unadjusted and adjusted estimates of effect. Established vascular disease, in the form of a history of previous amputation, ulceration or lower limb bypass procedures, was also consistently associated with risk of future ulceration.

None of the published studies reported on the predictive value of signs associated with foot trauma, such as inappropriate footwear and improperly cut toenails.

Evidence concerning the predictive value of 'contributory' factors in diabetic foot ulceration, such as some physical signs and elements from the patient's history, was less clear. For example, HbA_{1c} and ankle brachial indices (ABI, ABPI, or AAI) produced inconsistent and contradictory findings (Table 5). The length of time that a person had diabetes was marginally predictive in two cohort studies,[16,22] although in five methodologically weaker case-control studies, the association was not statistically significant.[10–14]

Shortcomings of this review

Synthesized evidence from this review does support the predictive value of most conventional diagnostic tests used to assess the risk of foot ulceration in people with diabetes. However, only a minority of primary studies assessed the independent predictive value of diagnostic tests in addition to physical signs and elements from a patient's history. Furthermore, different cut-points have been used for many of the diagnostic tests, making comparisons between studies difficult. Some diagnostic tests require a standardized procedure when being carried out. For example, ankle brachial index studies (ABI, ABPI, or AAI) were difficult to interpret because of the lack of detail disclosed as to the position of the patient when blood pressure was measured. Ankle systolic pressure is affected by posture; 1 mmHg higher for each inch the ankle is below the heart.[27] This detail was missing from three case-control and four cohort studies, and prevented us from pooling data. Only one cohort study found <0.8 ABI to be predictive of future ulcer risk.[16] The value of this procedure in that ulceration risk assessment is yet to be established.

Table 4 Cohort studies: quality assessment

Authors . . .	Armstrong 2004[15]	Boyko 1999[16]	Kastenbauer 2001[17]	Lavery 2003[18]	Litzelman 1997[19]	Murray 1996[20]	Peters 2001[21]	Pham 2000[22]	Rith-Najarian 1992[23]	Veves 1992[24]	Young 1994[25]
Hypothesis clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Patient characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Predictive factors clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Main outcome measure defined?	Y	Y	Y	N	Y	Y	Y	N	Y	N	N
Patients selected consecutively?	Y	Y	Y	Y	NA	NC	Y	Y	Y	N	Y
Patients representative of those who receive the test in practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Whole sample or random selection of the sample's outcome verified?	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
Characteristics of the patients lost to follow-up described?	NA	N	N	NA	N	NC	N	N	N	Y	NA
Context representative of the treatment majority of patients receive?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Index tests (PF) reproducible?	Y	N	N	Y	Y	Y	N	Y	N	Y	Y
Treatment given between index tests and outcome?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Adjustment made for confounders?	N	Y	N	NC	Y	N	N	Y	N	N	Y
Length of follow-up the same for all participants?	Y	N	N	Y	Y	N	N	N	N	N	NC
Same clinical data available when test results (PF) interpreted?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assessment of outcome blind to the results of the index test (PF)?	NC	NA	Y	NA	NC	N	N	Y	N	N	NC
Uninterpretable/intermediate test results (PF) reported?	N	N	N	N	N	N	NC	N	N	N	NC
Withdrawals for the study explained?	NA	N	Y	NA	N	NA	NC	Y	N	Y	NA
Sample size adequate for number of outcome events?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statistical tests for main outcomes adequate?	N	Y	Y	Y	Y	N	N	Y	N	N	Y
Study sought to measure and report adverse events?	N	N	N	N	N	N	N	N	N	N	N

Table 5 Summary of pooled estimates for predictive value of diagnostic tests, physical signs and patient history in relation to diabetic foot ulceration

	Pooled estimates WMD/SMD (95%CI)		Unadjusted risk/OR (95%CI)		Adjusted risk/OR (95%CI)	
	Case-control	Cohort	Case-control	Cohort**	Case-control	Cohort**
Diagnostic tests						
Peak plantar pressure[10,12,17,18,20,22] (kg/cm^2 or N/cm^2)	SMD 0.98 (0.63–1.33)[10,12]	SMD 0.47 (0.24–0.70)[18,20]	3.6 ($p < 0.001$)[12]	3.2 (2.0–5.1)[22]	4.8 kg/cm^2 (1.44–16.3)[10]	6.3 (1.2–32.7)*[17]
				4.7 (1.2–18.9)*[20]	5.9 ($p < 0.001$)[12]	2 (1.4–2.9)[18] 2.0 kg/cm^2 (1.2–3.3)[22]
Vibration perception threshold[10–13,16,17,22,25]	WMD 20.00 (11.81–28.20)[10,12]	WMD 17.07 (13.89–20.26)[17,22]	10.77 (4.59–25.73)[11]	8.2 (7.4–18.4)[22]	4.9 (1.0–24.0)[10]	25.4 (3.1–205)*[17]
			32.5 ($p < 0.001$)[12]	7.99 (3.65–17.5)[25]	15.2 ($p < 0.001$)[12]	3.4 (1.7–6.8)[22]
			7.38 (2.52–21.66)[13]	2.33 (1.66–3.28)[16]	18.42 (3.83–88.47)[13]	6.82 (2.75–16.92)[25]
Transcutaneous oxygen tension <30 mmHg[12,13,18]	–	–	1.1 ($p = 0.85$)[12]	1.35 (1.18–1.56)*[16]	57.87 (5.08–658.9)[13]	1.25 (1.08–1.45)*[16]
			26.9 (3.03–218.99)[13]			
HbA_{1c}[10–12,14–16,19]	0.95 (−0.33 to 2.23)[10,11,12,14],	1 (0.46–1.5)[16]	3.0 ($p < 0.001$)[12]	1.26 (1.11–1.43)*[16]	1.69 (0.96 to 2.99)[10]	–
			2.99 (0.49–8.99)[14]	1.08 (0.94–1.24)[19]	3.2 ($p < 0.03$)[12]	
Fasting blood glucose[14,19] (mmol increase)	–	–	–	1.00 (1.00 to1.00)[19]	1.01 (1.00–1.02)[14]	–
Ankle brachial index[11,13,16]	–	–	1.16 (0.40–3.33)[13]	1.25 (1.05–1.47)*[16]	–	1.20 (1.04–1.37)*[16]
			2.84 ($p = 0.08$)[11]			

Serum creatinine[16,19]	–	–		1.16 (1.04–1.29)*[16]	–	–
Physical signs						
Monofilament (SWF)[13,16,19,21–23]	–	–	9.99 (3.50–28.49)[13]	3.37 (2.45–4.63)*[16] 5.46 (2.39–12.45)[19] 5.4 (2.6–11.6)[22] 9.9 (4.8–21.0)[24]	–	2.17 (52–3.08)*[17] 5.23 (2.26–12.13)[19] 33.2 (5.6–181.6)[21] 2.4 (1.1–5.3)[22]
Visual acuity <20/20[14] (<20/40)[16]	–	–	–	2.31 (1.72–3.09)*[16]	0.223 per unit decrease in decimal visual acuity (0.005–0.39)[14]	1.93 (1.42–2.63)*[16]
Lower limb oedema[16,19]	–	–	–	1.52 (1.12–2.06)*[16] 0.88 (0.37–2.10)[19]	–	–
Absent reflexes[13,16]	–	–	4.58 (2.11–9.94)[13]	1.40 (1.03–1.90)*[16]	6.48 (2.37–18.06)[13]	–
Limited subtalar joint motion[12,22]	–	–	2.1 ($p<0.009$)[12]	1.03 (1.00–1.05)[22]	–	–
(ROM degrees)						
Limited 1st metatarsal-phalangeal motion[11,12,16,22]	–	–	3.57 (1.71–7.46)[11]	1.30 (1.11–1.54)*[16]	–	
(ROM degrees)			4.6 ($p<0.001$)[12]	1.05 (1.01–1.03)[22]		
Patient history						
Gender[12,22]	–	–	5.7 ($p<0.001$)[12]	2.27 (1.43–3.70)[22]	2.7 ($p<0.05$)[12]	–
Duration of diabetes[10–14,16,22]	2.62 (−0.75 to 5.99)[10–14]	1.0 (0.57–1.62)[16]	–	1.18 (1.05–1.32)*[16] 1.03 (1.00–1.05)[22]	1.0 (0.97–1.06)[10] 3.0 (<0.04)[12]	–

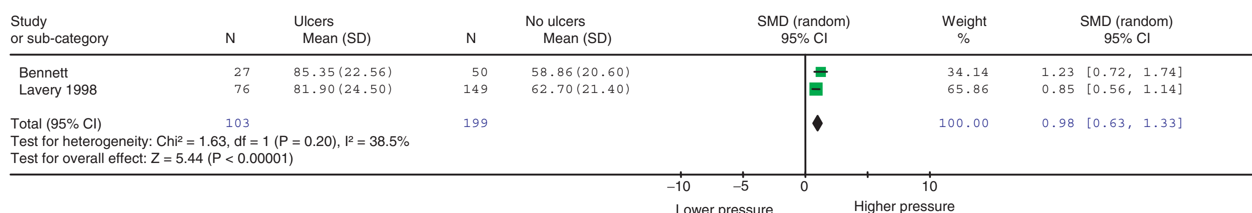
Continued

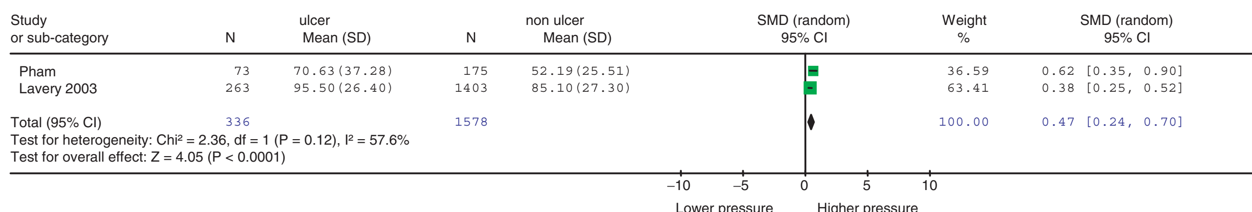
Table 5 Continued

	Pooled estimates WMD/SMD (95%CI)		Unadjusted risk/OR (95%CI)		Adjusted risk/OR (95%CI)	
	Case-control	Cohort	Case-control	Cohort**	Case-control	Cohort**
Alcohol use[12,17]	–	–	1.8 ($p = 0.19$)[12]	–	–	5.1 (1.1–24.0)*[17]
Previous ulceration[16,20–22]	–	–	–	2.46 (1.84–3.29)*[16] 5.11 (3.17–8.24)[22] 56.8 (13.4–241.2)*[20]	–	1.63 (1.17–2.26)*[16] 4.2 (1.1–16.7)[21]
Previous amputation[12,16]	–	–	40.5 ($p < 0.001$)[12]	3.99 (2.71–5.87)*[16]	10.0 ($p < 0.02$)[12]	2.81(1.84–4.29)*[16]
Lower limb bypass[12,16]	–	–	3.0 ($p < 0.04$)[12]	2.51 (1.53–4.10)*[16]		–

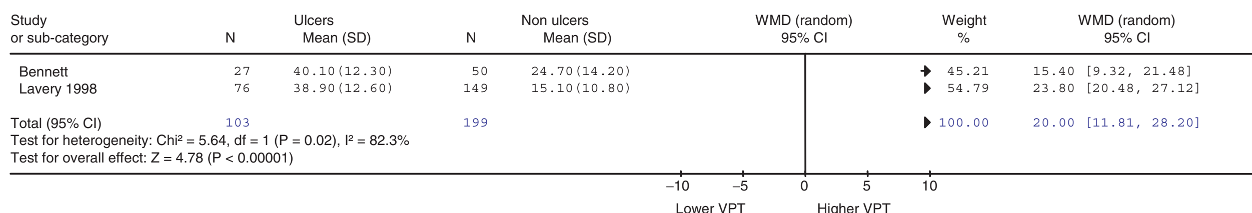
*Data reported as relative risk rather than odds ratio in these cohort studies. **Reciprocal of relative risk reported in some cohort studies, so that reference category remained consistent for all comparisons. WMD, weighted mean differences; SMD, standardized mean differences; –, pooled estimate not calculated.

a





b



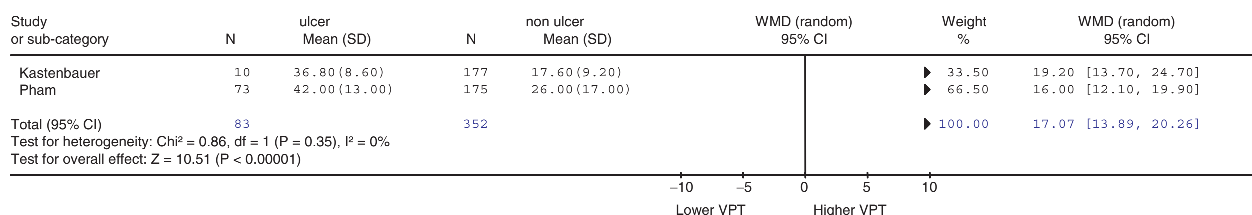


Figure 2. Forest plots of pooled data for the predictive value of **a** peak plantar pressure, **b** vibration perception threshold, **c** HbA_{1c} and **d** duration of diabetes, for foot ulceration in diabetes. Continues overleaf.

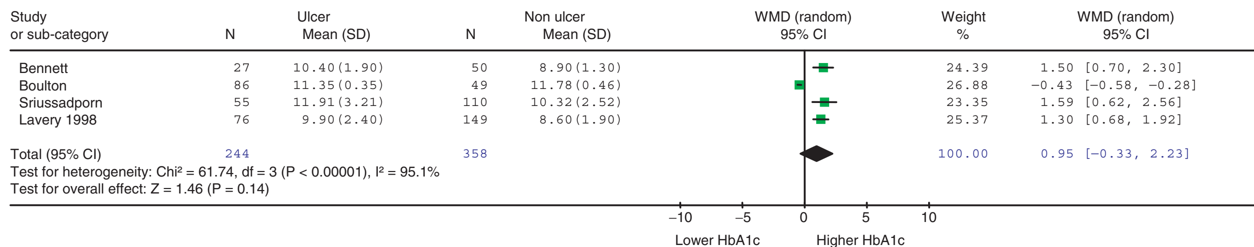
The review included studies that assessed multiple potential predictive factors, and there is a risk of false positive findings in the estimates reported from the primary studies.[28] The pooled estimates of nearly all predictive factors showed evidence of significant heterogeneity. This is a consequence of the different and varied definitions for some of the predictive factors, that different cut-points were used, different methods with ascertaining diabetic ulceration and different lengths of follow-up (Tables 1 and 2). Standardizing diagnostic tests and the cut-offs used would be helpful for both research and practice.

Context of other studies

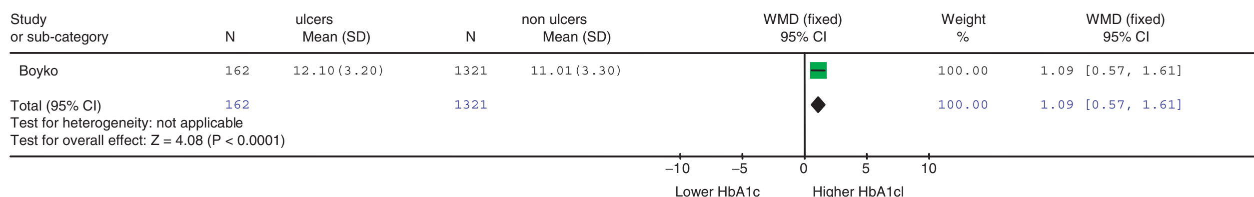
A previous systematic review assessing some of the methods advocated for preventing diabetic foot ulceration suggested that monofilaments, biothesiometer, tuning fork and peak plantar pressure were useful screening tests.[29] Our results are

c

Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
Comparison: 03 HbA1c (%)
Outcome: 01 Case control studies

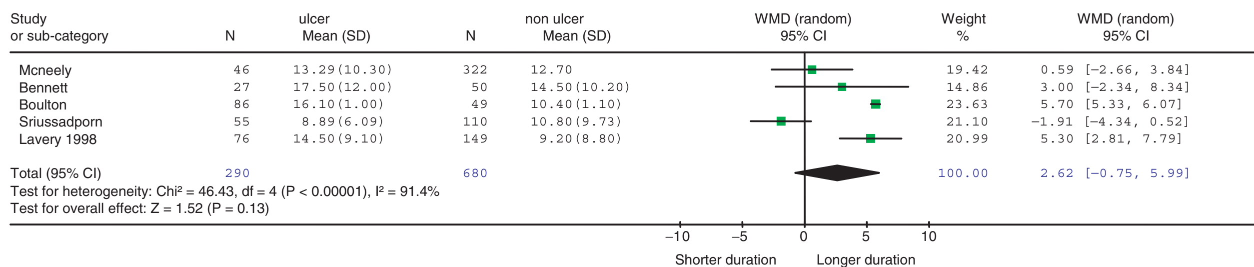


Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
Comparison: 03 HbA1c (%)
Outcome: 02 Cohort studies



d

Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
Comparison: 04 Duration of diabetes (years)
Outcome: 01 Case control



Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
Comparison: 04 Duration of diabetes (years)
Outcome: 02 Cohort

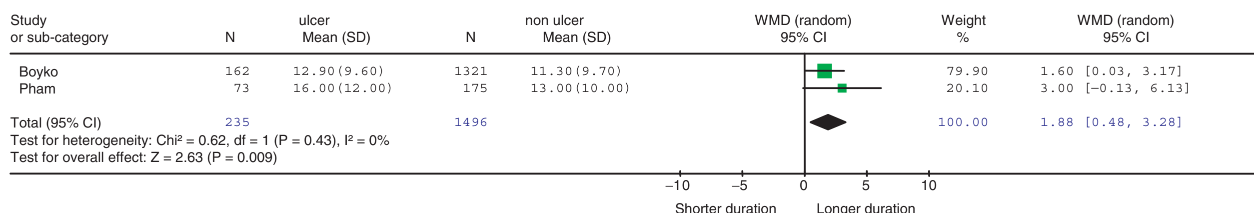


Figure 2. Continued.

consistent with these findings. We also identified eight additional studies that have provided more evidence of the predictive value of tests, and a more integrated approach has permitted data to be pooled.

National and international clinical guidelines also suggest that previous foot amputation and foot ulceration are useful criteria for the identification of patients at 'high risk' of foot ulceration.[2–4] These guidelines are supported by the findings from this systematic review. However, some recommendations in clinical guidelines do not appear to be based on any firm evidence. For example, we could find no convincing data to support that 'absent leg or pedal pulses' is a risk factor for diabetic foot ulceration, despite the suggestion that this clinical sign is a key indicator of risk.[3,4] Few studies adopted a comprehensive approach to the evaluation of predictive factors, and some variables that could predispose to foot ulceration, such as levels of exercise, the presence of callus, Charcot deformity or adequate footwear,

have not been subject to extensive evaluation. There is a clear need for further research to address these clinical uncertainties.

Generalizability of findings

The incidence of foot ulcerations in the cohort studies varied from 8% to 17% (Table 2). These are much higher levels of ulceration than those cited in UK national clinical guidelines (5–7%), diabetes text books (7%) and in a national survey (5%).[3,4,30,31] This observed difference in incidence may imply that patients included in the studies had more severe disease than those in the general diabetic population. Most of these patients were recruited from hospital diabetes clinics and dedicated foot clinics.

Future studies

Future observational studies need to include the characteristics of patients who were lost to follow-up, and should also attempt to explain the reasons for patients' withdrawal from studies. None of the sixteen studies included in the review measured adverse events from any of the diagnostic tests evaluated.

The predictive value of relatively simple clinical signs such as the presence or absence of leg and pedal pulses, skin colour, skin texture, hairlessness of the lower legs and condition of the toenails are not known. Clinical signs are potentially more cost-effective than more complex diagnostic tests, and are more feasible in community settings. Given that there are quite marked differences in cost between different tests, any new evidence about cost-effectiveness would deserve consideration. A diagnostic rule, based on elements of the clinical history, examination and available diagnostic tests needs to be developed, validated and tested to establish the effectiveness and cost-effectiveness of using such an approach when assessing the risk of diabetic foot ulceration in community settings.[32]

Conclusions

Diagnostic tests and clinical signs are helpful in predicting the risk of diabetic foot ulceration. Evidence concerning the predictive value of simpler elements from the clinical history and examination is less clear. Future studies should assess the independent predictive value of all elements of patient history, physical signs and diagnostic tests when assessing the risk of diabetic foot ulceration.

Acknowledgements

The authors thank Ms Julie Glanville, the Centre for Reviews and Dissemination at the University of York and Mr Donald Orrock, Ninewells Hospital Library at the University of Dundee, for their help with the development of the electronic search strategies. Also Professors Armstrong, Boyko, Boulton, Kastenbauer, Rith Najarian and Veves, who provided additional information about the primary studies. Fay Crawford and Melanie Inkster are funded by the Chief Scientist Office, The Scottish Executive, Edinburgh.

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