Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention

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Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and 2 diabetes. It is a leading cause of lower-limb amputation and disabling neuropathic pain. Amputations in patients with diabetes have a devastating effect on quality of life and are associated with an alarmingly low life expectancy (on average only 2 years from the amputation). Amputation also places a substantial financial burden on health-care systems and society in general. With the introduction of national diabetes eye screening programmes, the prevalence of blindness in working-age adults is falling. This is not the case, however, with diabetes related amputations. In this Review, we appraise innovative point-of-care devices that enable the early diagnosis of DPN and assess the evidence for early risk factor-based management strategies to reduce the incidence and slow the progression of DPN. We also propose a framework for screening and early multifactorial interventions as the best prospect for preventing or halting DPN and its devastating sequelae.

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Introduction

Diabetic peripheral neuropathy (DPN) is the most common complication of both type 1 and 2 diabetes and occurs in more than half of affected individuals.[1,2] It is a predominantly sensory neuropathy with autonomic nervous system involvement, although there are often motor features with advancing disease. DPN is the key initiating factor for the development of diabetic foot ulceration[3] and the most common cause of non-traumatic lower-limb amputations in most high-income countries.[4] It can also cause impaired balance and gait[5] and distressing neuropathic pain, which is often unresponsive to therapy.[6] The neuropathy is symmetrical and length-dependent, affecting the longest nerves, hence involving the feet first.[7] Unfortunately, the early manifestations of this insidious disease are often missed until the disease is well established, at which point it seems to be irreversible.

For more than a decade now, it has been recognised that a lower limb is lost to diabetes every 30 s worldwide.[8,9] According to WHO, lower-limb amputations are ten-times more common in people with diabetes than in people without diabetes.[10] Each week in England there are about 169 amputations in people with diabetes and almost all of these individuals have DPN.[11] Amputation is not only devastating in its impact on the individual and their family, but also leads to loss of independence and livelihood. In low-income countries, the financial costs can be equivalent to 5·7 years of annual income, potentially resulting in financial ruin for individuals and their families.[12] DPN also places a substantial financial burden on health-care systems and society in general. In the USA, the total annual cost of managing symptomatic DPN (painful) and its complications (foot ulcerations and lower-limb amputations) was estimated to be between US$4·6 billion and $13·7 billion, with up to 27% of the direct medical costs of diabetes attributed to DPN.[13] In Brazil, the annual direct medical costs of diabetic foot disease (foot ulcerations and amputations) was estimated to be $361 million.[14] In Europe, the direct cost of amputation per patient ranged from $13 842 in 2001 to $83 728 between 2005 and 2009.[15] Many studies have shown substantially increased mortality in people with diabetes who have undergone a major amputation, with 5-year mortality ranging from 44% to 68%.[16–19] Urgent action is needed to address this growing global health problem.

Importantly, most DPN-related amputations are preventable. 80% of these amputations could be prevented through good multidisciplinary care, which not only reduces amputation risk, but also substantially reduces the rates of hospitalisation and re-ulceration.[3] Notably, the relative likelihood of death within 5 years following a lower-limb amputation secondary to a diabetic foot ulcer is greater than for prostate and breast cancer (figure 1).[16] Although there are inherent limitations to this comparison (with data from different time periods and geographical locations), this finding nevertheless serves to emphasise the poor prognosis of patients with major amputations due to diabetic foot disease. Furthermore, a history of foot ulceration has been shown to be associated with more than doubling of risk (hazard ratio 2·29, 95% CI 1·82–2·88) for mortality compared with a population without diabetes.[20]

Data published in 2018 from the Scottish Diabetes Register of 17 353 patients with diabetes and high-risk feet showed that those with healed ulcers had a 23% mortality within 2 years.[21] These data show that patients with DPN with or without ulceration have a high mortality.

Here, we review innovative point-of-care devices (POCDs) that enable the early diagnosis of DPN and assess the evidence for early management strategies based on targeting of multiple risk factors to reduce the incidence and slow the progression of DPN. We also propose a framework for screening and early multifactorial intervention as the best prospect for preventing or halting DPN and its devastating sequelae.

Diagnosis of DPN: current status

DPN is the strongest initiating risk factor for foot ulceration and amputations. Nerve conduction studies are the current gold standard for the diagnosis of DPN.[22]

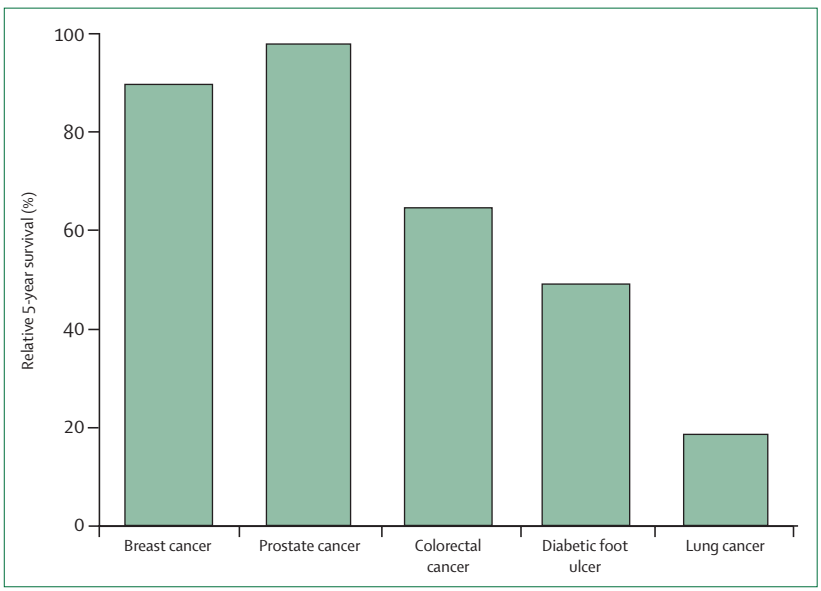

Figure 1: **Relative 5-year survival after diabetic foot ulcer following lower-limb amputation and the most common cancers**

Data for 5-year survival after diabetic foot ulcer following lower-limb amputation are from a cohort in Germany (2005–09).[16] Cancer survival data from the USA are for 2008–14 and are from the Surveillance, Epidemiology and End Results Program Cancer Statistics Review.

For the **Surveillance, Epidemiology and End Results Program Cancer Statistics Review** see https://seer.cancer.gov/statfacts/html

This robust measure also predicts foot ulceration and mortality.[23] However, nerve conduction studies are labour intensive, time consuming, costly, and impractical to implement in routine clinical care. Currently, there are no simple markers for early detection of DPN in routine clinical practice. The measures we use are crude and detect the disease very late in its natural history. Even the benefits gained by standardising clinical assessment with scored clinical assessments such as the Michigan Neuropathy Screening Instrument,[24] the Toronto Clinical Neuropathy Score,[25] and the United Kingdom Screening Test[26] remain subjective, heavily reliant on the examiners' interpretations.[27]

Bedside tests used to aid diagnosis of DPN—including the 10 g monofilament,[28] the Ipswich Touch Test,[29] and vibration perception threshold testing with the Vibratip,[30] a tuning fork,[31] or automated devices (eg, the Vibration Sensory Analyser VSA-3000,[32] the Neurometer,[33,34] and the biothesiometer[35])—are not only reliant on patients' subjective response, but are also mainly used to identify the loss of protective foot sensation and risk of ulceration.[36] As such, these tests tend to diagnose DPN when it is already well established.[37] Late diagnosis hampers the potential benefits of intensified multifactorial intervention at an early stage of the disease, which could prevent the sequelae of DPN. Unfortunately, by the time DPN is detected with the crude tests currently used, it is often very well established and consequently impossible to reverse or even to halt the inexorable neuropathic process. The situation with respect to diagnosis of neuropathy contrasts with developments in the detection of diabetic retinopathy with digital camera-based retinal photography and diabetic kidney disease with blood and urine tests. These developments led to the establishment of robust annual screening programmes in many countries, leading to a substantial reduction in blindness,[38] such that diabetic retinopathy is no longer the most common cause of blindness in working-age adults in the UK,[39] as well as reductions in end-stage kidney failure.[40]

Recent developments in early diagnosis of DPN with POCDs

Some progress has been made in the development of POCDs that are capable of diagnosing DPN early, before overt clinical signs are apparent. These devices are still predominantly at an experimental stage, although specialist centres are beginning to explore their use in clinical practice.[41,42] We have briefly outlined the devices that are most advanced in terms of their development and hold the most promise for adoption in clinical practice (table): DPNCheck,[49–51] Neuropad,[43] and Sudoscan.[47,52]

DPNCheck

DPNCheck is a handheld POCD that does a sural nerve conduction study in 3 min. It is an acceptable proxy for standard nerve conduction studies, which are time consuming, expensive, and often require patients to be seen in specialist clinics. DPNCheck has been shown to have very good reliability (inter-observer 0·83 and intra-observer 0·97 intraclass correlation coefficients) for sural nerve action potentials.[43] It also has good validity, with 95% sensitivity and 71% specificity when compared against a reference standard nerve conduction study for the diagnosis of DPN.[43,49]

Nerve conduction studies, however, are only an assessment of large nerve fibre function. DPN usually involves both small and large nerve fibres, with some evidence suggesting small nerve fibre involvement occurs early in its natural history.[53,54] Small nerve fibres constitute 80–91% of peripheral nerve fibres and control pain perception and autonomic and sudomotor function. Although intra-epidermal nerve fibre density measurement from lower-limb skin biopsy is considered the gold standard for the diagnosis of small fibre neuropathy,[55,56] it is invasive and therefore not suitable for routine screening.

Neuropad

Neuropad is a 10-min test that measures sweat production on the plantar surface of the foot. It is based on a colour change in a cobalt compound from blue to pink, which produces a categorical output with a modest diagnostic performance for DPN compared with electrophysiological assessments. Several clinical validation studies[51,57–59] have been done, which show low sensitivity for large fibre neuropathy (50–64%), but much higher sensitivity for small fibre neuropathy (80%).[60] When compared with other bedside tests for detection of DPN, the sensitivity of Neuropad was

	Function	Fibres assessed	Validated against	Sensitivity (%)	Specificity (%)	Intra-observer intraclass correlation coefficient	Inter-observer intraclass correlation coefficient
DPNCheck[43,44]	Sural sensory nerve function	Large Aα Aβ fibres	Nerve conduction studies, standardised clinical examination, and laser Doppler flare imaging	84·3–90·5%	68·3–86·1%	0·94–0·97	0·79–0·83
Neuropad[45,46]	Sudomotor function	Small C fibres	Nerve conduction studies, standardised clinical examination, vibration perception threshold, and skin biopsy intraepidermal nerve fibre density	65·1–100·0%	32·0–78·5%	4·1	5·1
Sudoscan[47,48]	Sudomotor function	Small C fibres	Nerve conduction studies, standardised clinical examination, and thermal perception threshold	87·5%	76·2%	0·88	0·95

Adapted from Papanas and colleagues,[42] by permission of Springer Nature. All devices and approaches listed in this table enable early diagnosis. NA=not available.

Table: **Clinical utility of devices used for the diagnosis of diabetic peripheral neuropathy**

higher than that of the 10 g monofilament (95%) and the biothesiometer (73%).[61] Neuropad has also shown good reproducibility with intra-observer (4·1%) and inter-observer (5·1%) coefficients of variation.[45] No training is needed to administer Neuropad, nor does it require responses from the patient. Hence, some researchers argue that this method of assessment might be more suitable than others for screening in community settings and for individuals with cognitive or communication difficulties who are unable to comply with other methods of assessment. However, there is insufficient evidence to support the use of Neuropad in patients for whom 10 g monofilament testing for DPN is not possible.[46]

Sudoscan

Sudomotor function has been proposed as a surrogate marker for small fibre involvement in DPN.[47,52,62] Sudoscan, provides a quantitative measurement of sudomotor function within 3 min. Its measurement is based on an electrochemical reaction between electrodes and chloride ions after stimulation of sweat glands by a low-voltage current (<4 volts).[63] A measurement of electrochemical skin conductance for the hands and feet, which are rich in sweat glands, is generated from the derivative current associated with the applied voltage.[63] Foot electrochemical skin conductance for classifying DPN has a sensitivity of 87·5% and a specificity of 76·2%.[52] The area under the receiver operating characteristic curve was 0·85, which is better than the other devices discussed in this Review.[52] The reproducibility was also tested in type 2 diabetes, showing a mean intraclass correlation coefficient for feet of 0·95 (95% CI 0·89–0·98) and for hands of 0·88 (0·74–0·96).[48]

Summary

In summary, the sensitivity of POCDs are acceptable and a combination of devices assessing both small fibre and large fibre function should be used for detection of DPN. However, there is high heterogeneity and participant selection bias in most of the studies, which have relatively small sample sizes. Other devices such as NeuroQuick, which despite showing some early potential, have not shown further evidence of clinical utility to back widespread adoption. Further studies are needed to assess the performance of each POCD based on Wilson and Jungner criteria for screening of undiagnosed DPN at the population level.[64] Prospective studies with hard clinical endpoints (eg, foot ulceration and lower-limb amputation) are also necessary to ensure that screening with these devices leads to improvements in the outcomes that are important for patients. The cost-effectiveness of implementing screening with these devices also needs to be carefully appraised. POCDs provide rapid, non-invasive tests that could be used as an objective screening test for DPN in busy diabetes clinics, ensuring adherence to current recommendations of annual assessment for all people with diabetes,[1,65] which remains unfulfilled.[66]

Modifiable risk factors for DPN incidence and progression

Early detection of DPN can only be advocated if there is robust evidence that early treatment or intervention results in better outcomes than intervention at a later stage. DPN is a culmination of a complex interaction of several causatively linked pathophysiological processes, many of which are not fully understood. Although hyperglycaemia and duration of diabetes have an important role in DPN, other risk factors have also been identified.[67] The EURODIAB Prospective Complications study[68] in type 1 diabetes showed that the incidence of DPN is associated with other potentially modifiable cardiovascular risk factors, including a raised triglyceride level, hypertension, obesity, and smoking (figure 2). More recently, data from the ADDITION study[69] also implicated similar cardiovascular risk factors in the pathogenesis of DPN in type 2 diabetes.

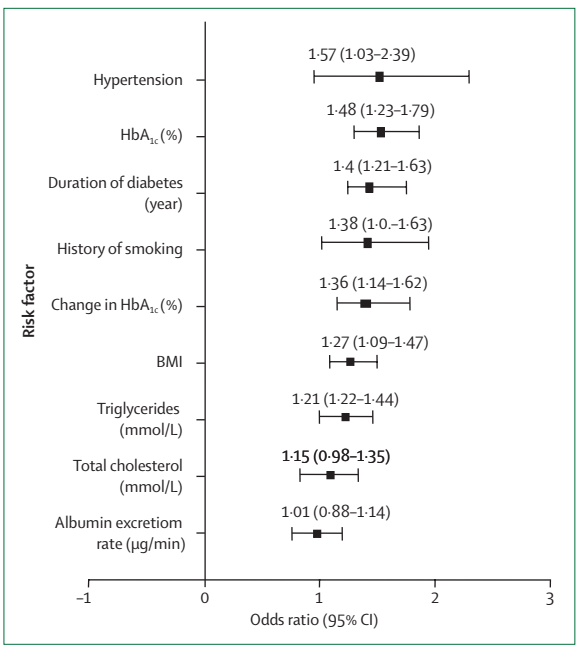

Figure 2: **Odds ratios (95% CI) for associations between key risk factors and the incidence of diabetic peripheral neuropathy**
Neuropathy was diagnosed in patients with two or more of the following four measures: the presence of one or more neuropathic symptoms, the absence of two or more reflexes of the ankle or knee tendons, a vibration-perception threshold that was abnormal for the patient's age, and abnormal autonomic function. Figure created from data from the EURODIAB Prospective Complications Study[68] in patients with type 1 diabetes. Odds ratios for dichotomous variables express the risk of neuropathy for patients with the risk factors as compared with those without the risk factors. Odds ratios for continuous risk factors were standardised, thus expressing the risk associated with a 1-SD increase in the continuous risk factors. Change in HbA_{1c} per patient per year of follow-up was calculated from a linear regression of all available HbA_{1c} values at each study visit.

Hyperglycaemia

Chronic hyperglycaemia has a key role in the pathogenesis of DPN.[70,71] Through several disturbances in metabolic pathways, hyperglycaemia leads to abnormalities in nerve polyol, hexosamine, and protein kinase C pathways.[72] These abnormalities trigger the release of proinflammatory cytokines, accumulation of advanced glycation end products, and generation of reactive oxygen species.[72] Simultaneously, microangiopathic changes of the vasa nervorum result in neuroischaemia.[73] These changes are further exacerbated by impaired endothelial nitric-oxide-mediated vasodilatory mechanisms (nitrosative stress).[74] Separately and in concert, these glucotoxic metabolic and ischaemic changes lead to DPN by producing nervous system oxidative stress and apoptosis of both neurons and supporting glia.

In the Diabetes Control and Complications Trial (DCCT),[75] intensive insulin treatment in type 1 diabetes reduced the relative risk of DPN by 78% compared with conventional therapy. In the Epidemiology of Diabetic Complications study,[76] which was an observational follow-up of DCCT participants, although DPN progressed substantially in both treatment groups, its prevalence and incidence remained significantly lower in the previously intensively treated group 14 years after the end of the original trial. According to a Cochrane review, however, the evidence for the benefit of intensive glucose control in type 1 diabetes is mainly derived from studies in younger patients at early stages of the disease, and the effects of tight blood glucose control seem to become weaker once complications are established.[77] Notably, in type 2 diabetes, improving glycaemic control alone does not have the same degree of effect on the incidence of DPN (5–9% relative risk reduction).[77] Even when trials have shown that tighter glucose control might have a beneficial effect in preventing progression of DPN in type 2 diabetes, such as in the ACCORD study,[78] confusion has arisen when it was reported that a self-reported history of DPN at baseline was associated with an increased risk of mortality with intensive glycaemic treatment.[79] However, in this study, neither Michigan Neuropathy Screening Instrument-documented DPN nor history of amputation was associated with a differential effect on mortality between the two treatment groups. This discrepancy suggests the different methods of detecting DPN might identify different populations and merits further investigation. Similar discordance among various indices of DPN in their strength for predicting outcomes was also apparent in the DIAD study.[80] In several other long-term studies in participants with type 2 diabetes[81–83] or prediabetes,[84] multifactorial cardiovascular risk interventions have not slowed the progression or reduced the incidence of DPN. It should be emphasised that DPN was not a primary outcome in these trials and its inclusion seems to have been an afterthought, since inconsistent and insensitive measures to detect and monitor DPN were used.

By contrast, when appropriate DPN clinical endpoints are used, results seem to be more promising. The first randomised controlled trial that showed the benefit of intensive management on the incidence of DPN in type 2 diabetes was the Kumamoto trial.[85] This study showed significant improvement in nerve conduction parameters, albeit of the median nerve, in the group assigned to intensive insulin treatment (multiple injections three or more times a day with rapid acting insulin at meal times and intermediate acting insulin at bedtime) compared with those assigned to conventional insulin treatment (1–2 daily injections of intermediate acting insulin), showing the importance of choosing the most appropriate surrogate marker of DPN. Nearly 50 years ago, a smaller study also using nerve conduction tests showed that DPN is reversible in patients with newly diagnosed type 2 diabetes, with appropriate treatment.[86] Moreover, in type 2 diabetes, the choice of therapies used to achieve targets might also be as important as the glucose targets themselves. In the BARI 2D trial,[87] the cumulative incidence of DPN was significantly lower when insulin-sensitising drugs (metformin, thiazolidinediones) were used compared with an insulin-providing (sulfonylureas, insulin) strategy.

Dyslipidaemia

Cross-sectional and longitudinal observational studies have shown, to varying degrees, an association between dyslipidaemia and DPN.[88] The strongest evidence, however, is for the association of increased concentrations of triglycerides and DPN.[89] In type 2 diabetes, a graded association between triglyceride concentrations and the risk of lower-limb amputations has been reported.[89] Another study showed that hypertriglyceridaemia was an independent risk factor for loss of sural (myelinated) nerve fibre density, supporting the concept that hyperlipidaemia is instrumental in the progression of DPN.[90] In addition to hypertriglyceridemia, low concentrations of HDL cholesterol have been reported as an independent risk factor for DPN.[69,88,91] However, clinical studies investigating the effects of statins on the development of DPN are far from conclusive. This discrepancy is partly because several large statin studies that included participants with diabetes did not report data for the development of microvascular disease,[92–94] let alone DPN. Data from the Freemantle Diabetes Study,[95] an observational study with cross-sectional and longitudinal analyses, suggested that use of statin or fibrate therapy might be associated with a reduced risk of DPN in type 2 diabetes. Two subsequent, relatively small, randomised clinical studies have shown improvements in nerve conduction parameters of DPN following 6–12 weeks of statin treatment.[96,97] In the FIELD study[98] of fenofibrate in patients with type 2 diabetes, fibrate treatment was shown to be beneficial in preventing microvascular complications (retinopathy and nephropathy) and non-traumatic lower-limb amputations, but DPN outcomes have not been reported. In a patient registry study from Denmark,[99] the use of statins before diagnosis of incident diabetes was shown to be protective against the development of DPN. Finally, in a recent large study from Taiwan of more than 18 000 people with type 2 diabetes who were using statins and a similar number of age-matched and sex-matched controls not using statins,[100] statin use was shown to significantly reduce the risk of new-onset diabetic neuropathy and foot ulcers.

In summary, whether lipid lowering treatment reduces the risk of DPN—a possibility raised by these data—will need to be addressed in future studies, and preferably in randomised controlled trials.

Hypertension

An association between hypertension and DPN has been shown in several observational studies in both type 2 diabetes[101,102] and type 1 diabetes.[103] Some preliminary evidence from relatively small randomised controlled trials has shown improvements in DPN based on clinical and nerve conduction parameters following antihypertensive treatment with angiotensin-converting enzyme inhibitors[104] and calcium-channel blockers.[105] However, more recent longitudinal studies have not shown an association between hypertension and incident neuropathy.[69,91] A possible explanation for this finding could be the strengthening of guidelines for diabetes care and the more widespread routine use antihypertensive treatment.

Lifestyle

Several studies have revealed an association between obesity and DPN even in the presence of normoglycaemia.[106–108] Unsurprisingly, DPN prevalence increases in patients who are obese with prediabetes (29%) and diabetes (35%) compared with patients who are obese with normoglycaemia (11%).[109] These finding been replicated in studies of populations from the USA,[91] China,[110] the Netherlands,[111] Germany,[112] and Denmark.[69] Subsequent studies seem to show that adopting a healthy lifestyle, incorporating a balanced diet and regular aerobic and weight-resistance physical activities, might reverse the process, particularly if these activities are undertaken at an early stage of DPN.[113–115] A non-randomised study of 2·5-h, once per week, supervised treadmill exercise and dietary intervention programme aimed at normalising BMI or losing 7% baseline bodyweight in 55 patients with the metabolic syndrome (including 19 patients with type 2 diabetes) showed significant improvement in markers of DPN (intraepithelial nerve fibre density and regenerative capacity).[116] However, once DPN is established, restoration of normal weight did not result in significant improvement.[116] Various dietary interventions have been examined, including a low-fat, low-calorie diet in the Diabetes Prevention Program study[84] and a Mediterranean diet,[117] but there is no consensus on a specific regimen. However, overall, the existing evidence suggests that if the disease is identified early and the appropriate surrogate marker is used, DPN can be reversed by lifestyle interventions.

Multiple risk factor-lowering interventions

Based on the studies discussed, some evidence suggests that targeting lifestyle and individual risk factors can reduce the risk of DPN. Disappointingly, however, several large intervention studies targeting multiple risk factors (UKPDS,[118] STENO-2,[119] and ADDITION[120]) did not show a reduction in DPN despite clear benefits in kidney and retinal complications. The best possible explanation for these findings is that the methods used to diagnose or quantify DPN lacked the necessary sensitivity or reliability to diagnose or quantify the condition, let alone examine differences between study groups. The heterogeneity in effect size estimates for DPN in these studies supports this view. Furthermore, in the ADDITION study[120] there were only minor differences in cardiovascular disease risk between the standard and intensive treatment groups throughout the trial. Nevertheless, the STENO-2 study[119] did show that 4 years of intensive multifactorial treatment slowed the progression of autonomic neuropathy (odds ratio 0·32, 95% CI 0·12–0·78) compared with conventional therapy, an effect that remained apparent in the 21-year follow-up analysis of the study with a 41%

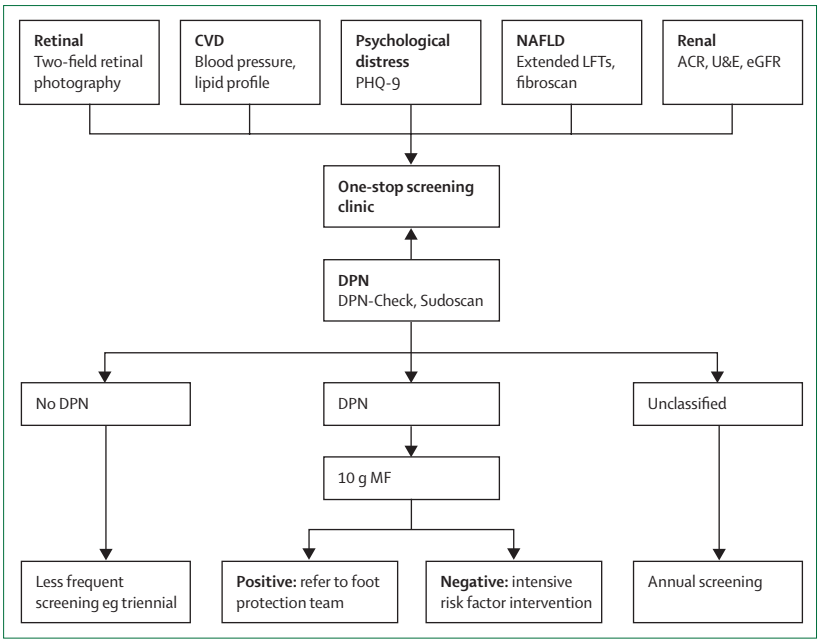

Figure 3: **Proposed assessments for a one-stop screening clinic for diabetes complications, including use of point-of-care devices for DPN**

Adapted from Binns-Hall and colleagues,[66] by permission of the authors. DPN=diabetic peripheral neuropathy. PHQ-9=Patient Health Questionnaire-9. NAFLD=non-alcoholic fatty liver disease. LFTs=liver function tests. ACR=urine albumin-to-creatinine ratio. U&E=urea and electrolytes. eGFR=estimated glomerular filtration rate.

(hazard ratio 0·59, 95% CI 0·40–0·89) reduction in the progression of autonomic neuropathy.[121] These data suggest a long-term benefit of early multifactorial intervention—ie, a legacy effect. Further research is needed to re-examine the effect of multifactorial interventions on DPN using more reliable, reproducible, and sensitive measures of DPN. Improvements in risk factors in clinical practice could be reflected in standard treatment groups of trials, as seen in the ADDITION study,[120] which could hamper further efficacy studies of multiple risk factor-lowering interventions. However, outside the context of a clinical trial, the standard of general diabetes care remains poor and these targets are not being achieved in the majority of patients in most countries.[122,123] In this context, a prospective study comparing standard multifactorial treatment with a more intensive, target-driven approach, with sensitive measures to detect differences in DPN, could be worthwhile.

Summary

In summary, although the risk factors for DPN are well recognised, to date only small-scale intervention studies targeting these risk factors, with appropriate measures of DPN, have been done. These studies suggest that such interventions can delay the onset and slow the progression of DPN. However, once DPN has reached a stage at which it is detectable by conventional bedside tools, it might be too advanced for any intervention to reverse or halt the process. Unfortunately, despite several clinical trials,[124] there has been little progress in the development of disease-modifying treatments,[125,126] although there have been some advances in the management of symptoms in painful DPN.[127] Most of the current evidence points to multifactorial risk reduction strategies—including structured exercise and education on lifestyle, a healthy diet, smoking cessation, and obesity management—as the best way to prevent the development and progression of DPN, particularly early in the course of diabetes (and in prediabetes).[113,114,128]

Conclusions and future directions

Ultimately, the prevention of DPN will have the greatest effect on reducing amputations in patients with diabetes, given that 90% of patients attending the diabetic foot clinic and almost all patients who are amputees with diabetes have DPN.[11] Clearly, in individuals with established DPN, careful foot ulcer risk assessment (including peripheral vascular status and foot deformity),[129] appropriate management (eg, education, footwear, and podiatry),[129] and risk factor intervention are warranted.

Currently, a robust system of an annual foot screening—let alone multifactorial risk factor interventions—for all people with diabetes in most countries, as advocated by Diabetes UK and the American Diabetes Association, has not been implemented systematically. Most foot screening in the UK is done by practice nurses who do not have specialist training in this task. This finding was confirmed by the National Diabetes Audit in England (2017–18),[130] and the US National Health and Nutrition Examination Surveys.[123] In the UK, the attainment of any recommended vascular risk management targets (HbA_{1c}, blood pressure, or cholesterol) was alarmingly low at 29·9–76·6%. Moreover, attainment of all three vascular risk factor targets was only 40·1%. More worryingly, less than 30% of adults aged 50 years or younger achieved these targets.[122] Between 60 671 and 75 838 people with diabetes in England are thought to have foot ulcers at any given time.[131] The system is not robust enough as evidenced by the increasing prevalence of foot ulcers and amputations. As most screening occurs in primary care and is done by untrained staff, foot surveillance screening did not identify a third of individuals who subsequently developed diabetic foot ulcers.[132] This finding suggests that the current process of care—which involves multiple visits to different members of the clinical team—is inadequate. Health-care providers involved in the existing care pathway do not have specialist training to assess the level of risk and provide advice or education to ensure that patients to receive appropriate interventions or treatment.[133] Additionally, these data confirm that the methods used to screen for DPN are insensitive or lack reliability to accurately measure risk of developing foot ulceration.

To improve clinical outcomes in DPN, as has been done for retinopathy and nephropathy, there is an urgent need to diagnose DPN early before overt clinical signs are apparent; assess disease progression accurately to effectively reduce morbidity; and reliably inform

Search strategy and selection criteria

For this Review, we searched MEDLINE and PubMed (from Jan 1, 1946, to Aug 29, 2019), Embase (from Jan 1, 1974, to Aug 29, 2019), CINAHL (from Jan 1, 1937, to Aug 29, 2019), and Google Scholar (from Nov 20, 2004, to Aug 29, 2019) for articles published in English, using the search terms "diabetes mellitus", "type 1 diabetes mellitus", "type 2 diabetes mellitus", "IDDM", "NIDDM", "insulin-treated type 2 diabetes", "T1DM", and "T2DM", and the Boolean operator "OR". The term "diabetes insipidus" was excluded by use of the operator "NOT". Subsequent keywords used were "diabetic peripheral neuropathy", "DPN", "screening", and "multifactorial intervention"; these keywords were initially used as a single search term, then combined using the Boolean operator "AND". We also searched the references of relevant articles and conference abstracts. Finally, we searched the Cochrane Library and Cochrane Database (from Jan 1, 2000, to Aug 29, 2019) for systematic reviews and meta-analyses on screening and intervention for diabetic peripheral neuropathy. Articles were selected on the basis of relevance to the topic of Review.

patients of their underlying risk of foot ulceration. A one-stop service would be useful to screen for various diabetes complications in a single visit (figure 3). In this context, foot screening could be done by a specialist podiatrist to assess the level of foot ulcer risk and manage patients appropriately, to prevent foot ulceration and amputation. Additionally, DPN screening can be done with POCDs in patients with normal physical examination (eg, 10 g monofilament, 128 hz tuning fork, Ipswich touch test, Vibratip) to identify early subclinical disease. One potentially useful method is corneal confocal microscopy. This technique is a non-invasive ophthalmic application that measures various structural parameters (eg, branch density and length) of small corneal nerve fibres.[134,135] Currently, corneal confocal microscopy is not a POCD and is mainly used in specialist centres. Nevertheless, it would suit widespread application given its easy application for patient follow-up. There have been a number of clinical validation studies,[136] including one 4-year prospective study in type 1 diabetes that showed modest to high sensitivity (82%) and specificity (69%) of corneal confocal microscopy for incipient DPN.[137] It has good reproducibility for corneal nerve fibre length measurements with intra-observer intraclass correlation coefficients of 0·66–0·97 and inter-observer intraclass correlation coefficients of 0·54–0·95.[138,139] The reproducibility improves with the automated algorithm (intraclass correlation coefficient 1·0).[140] Large, multicentre, prospective studies are now required to confirm that corneal nerve changes unequivocally reflect the complex pathological processes in the peripheral nerve.[141]

A one-stop service for screening of complications was recently piloted in retinal screening clinics in a hospital and community setting in the UK.[66] A trained podiatrist did detailed assessments of foot ulcer risk and used combined small and large nerve fibre assessments (DPNCheck and Sudoscan) for the diagnosis of subclinical DPN. This pilot study also examined the feasibility and acceptability of a one-stop clinic for combined screening for all diabetes microvascular complications. Combined eye, kidney, DPN, and foot ulcer risk screening had a high uptake, reduced clinic visits, led to an early diagnosis of DPN (93·2% sensitivity for the diagnosis of DPN), and identified new painful DPN. This model is effective for the early diagnosis of DPN and management of foot complications. Future studies should examine if intensive cardiometabolic risk factor management targeted at patients with incipient or subclinical DPN identified with POCDs can prevent clinical DPN or halt disease progression.

Contributors

DS and DK are joint first authors and contributed equally to the search of the scientific literature and the conception, writing, and revision of the Review. KK, MJD, ARS, and JW contributed to the interpretation and evaluation of the manuscript, interpretation of the scientific literature, and the writing and revision of the Review. ST developed the interpretation and evaluation of the manuscript, supervised the work, and contributed to the interpretation of the scientific literature and the writing and revision of the Review.

Declaration of interests

DS has received a research grant from Impeto Medical and non-financial support (equipment donation) from NeuroMetrix. He was a member (unpaid) of a scientific advisory panel for Impeto Medical. KK has been a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme. He has received grants in support of investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, and Merck Sharp & Dohme. MJD has been a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen and has been a speaker for Mitsubishi Tanabe Pharma. She has received grants in support of investigated-initiated trials from Novo Nordisk, Boeringher Ingelheim, and Janssen. ST has received a research grant from Impeto Medical and honoraria for advisory board membership or speaker fees from NeuroMetrix, Pfizer, Novo Nordisk, Miro, Wörwag Pharma, Mundipharma, and Merck. He has also received support to attend a diabetes conference from Novo Nordisk and honoraria for serving as the chair of a data safety and monitoring board for a clinical trial from Mitsubishi Tanabe Pharma. All other authors declare no competing interests.

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