REVIEW

Evidence-based Management of PAD & the Diabetic Foot CME

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WHAT THIS PAPER ADDS

Despite their widespread use, the evidence to support many interventions in the diabetic foot derives from studies of poor quality. We highlight the need for separate reporting of outcomes in patients with diabetes undergoing revascularisation for critical limb ischaemia and challenge current classification systems for peripheral arterial disease in this cohort. The review focuses on evidence-based strategies for diabetic foot ulceration (DFU) to promote healing and preserve life and limb. We emphasize the importance of referring all patients presenting with DFU to a multidisciplinary team involving vascular surgeons and interventional radiologists.

Diabetic foot ulceration (DFU) is associated with high morbidity and mortality, and represents the leading cause of hospitalization in patients with diabetes. Peripheral arterial disease (PAD), present in half of patients with DFU, is an independent predictor of limb loss and can be difficult to diagnose in a diabetic population. This review focuses on the evidence for therapeutic strategies in the management of patients with DFU. We highlight the importance of timely referral of patients presenting with a new foot ulcer to a multidisciplinary team, which includes vascular surgeons and interventional radiologists.

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INTRODUCTION/EPIDEMIOLOGY

The dramatic increase in the worldwide prevalence of diabetes mellitus (DM) has resulted in an inevitable rise in diabetes-related complications. In 2011, there were an estimated 366 million adults with diabetes worldwide and projections indicate this figure will rise to 552 million by 2030.[1] Amputation is a largely preventable complication of diabetes and >85% of major amputations in patients with diabetes are preceded by foot ulceration.[2] Despite evidence to suggest that targeted interventions resulting from multidisciplinary care can reduce limb loss, progress to date has been slow.[3] Whilst the number and incidence of amputations have fallen in an ageing population without diabetes, those in patients with type 2 diabetes have risen in some countries.[4] Twenty years on from the St Vincent's Declaration,[5] attempts to achieve 5-year targets to halve the number of lower limb amputations in patients with diabetes have failed. It is therefore timely to review the evidence for the management of peripheral arterial disease (PAD) and the diabetic foot, highlighting recent guidelines produced by the International Working Group on the Diabetic Foot (IWGDF) and the European Society of Vascular Surgery (ESVS).[6,7]

Foot lesions carry high morbidity and mortality and represent the most common cause of hospitalization in patients with diabetes. The lifetime risk of foot ulceration in patients with diabetes lies between 15% and 25%,[8,9] with an annual incidence of around 2%.[10] The risk of a person with diabetes undergoing a lower extremity amputation is estimated to be 23 times that of a person without diabetes,[11] and the National Diabetes Audit estimates that every 7 out of 10 000 people with diabetes in England and Wales underwent a major amputation in 2008–2009. In 2010–2011 there were 72 459 hospital admissions for diabetes-related foot complications,[12] at an estimated cost of between £639 million and £662 million to the National Health Service in England and Wales.[13]

PAD is an independent risk factor for subsequent ulceration and limb loss in diabetes. It is present in 50% of patients with diabetic foot ulceration (DFU), a proportion which may be increasing.[14,15] Those with DFU and PAD are less likely to heal and more likely to require amputation

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compared to patients without PAD. It is therefore essential that PAD is identified in all patients with diabetes.

PATHOLOGY IN DFU

The aetiology of DFU is multifactorial and involves a complex interplay between distal polyneuropathy (motor, sensory and autonomic), abnormal foot anatomy, functional changes in the microcirculation and PAD. The pathway to ulceration typically follows abnormal loading or trauma of the painless neuropathic foot, which may be poorly perfused due to PAD, rendering it less able to heal. Both ulceration and infection in the foot will increase the demand for oxygen and, as such, vascular intervention may be required to achieve healing in cases where objective measures of perfusion suggest that PAD is only of mild severity. The wound repair process may be further impaired by virtue of various biological factors inherent to diabetes, including impaired humoral immunity and abnormal inflammatory responses.[16,17]

Early descriptions of diabetes as an occlusive small vessel disease were disproven by histological staining of amputated limbs,[18] and subsequently by arterial casting studies. This led to the identification of several functional abnormalities of the microvasculature including an increase in arterio-venous shunting and impaired vasoreactivity.[19] In patients with type 2 diabetes these changes lead to capillary hypoperfusion, probably further impairing wound healing.[20] Furthermore, the development of collateral vessels is impaired in patients with diabetes.[21] Consequently arterial occlusions may result in more severe perfusion deficits in those with diabetes compared to those without diabetes. The distribution of PAD in patients with diabetes is characteristically distal and diffuse, with a greater prevalence of crural disease and long arterial occlusions.[22–24] The distribution of PAD in diabetes may relate to the presence of somatic neuropathy, which has been implicated in the development of medial arterial calcification.[25]

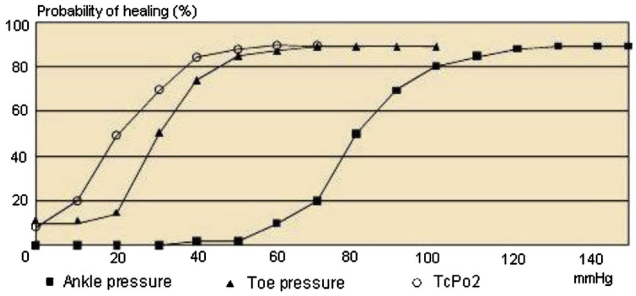

Figure 1. Schematic estimate of the probability of healing of foot ulcers and minor amputations in relation to ankle blood pressure, toe blood pressure, and transcutaneous oxygen pressure (TcPo2) based on selected reports. From Bakker K, Apelqvist J, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev, 2012;28 Suppl 1:225–31.

DIAGNOSIS OF PAD

Identification of PAD in patients with diabetes may be difficult because symptoms and signs are frequently masked by co-existing distal symmetrical polyneuropathy. Furthermore, most patients with DFU present to primary care, podiatry or internal medicine clinicians who are not experts in the diagnosis of PAD. IWGDF guidelines suggest that, in addition to a thorough history for symptoms of arterial insufficiency, all patients with a diabetic foot ulcer should undergo hand-held Doppler evaluation of both pedal pulses, measurement of ABI and, in cases of diagnostic uncertainty, measurement of toe-brachial index (TBI) or transcutaneous pressure of oxygen ($TcPO_2$).[6] Importantly these screening tools, whilst highly sensitive in the non-diabetic population, may be less efficacious in diabetes, especially in the presence of peripheral and autonomic neuropathy.[26,27] Those patients with signs and symptoms of PAD, including claudication, rest pain, absent foot pulses, monophasic Doppler signals, ABI <0.9 or TBI <0.7 should be referred to a vascular surgeon for imaging of the vascular tree and to consider revascularisation options as part of an interdisciplinary approach. However, vascular specialists might wish to be involved in the diagnosis and management of any new patient presenting with DFU given that the majority will have PAD.

Once a diagnosis of PAD is established, it is important to assess the severity of the perfusion deficit and what impact this may have on ulcer healing. With respect to ankle pressures, an ABI of <0.6 corresponds to a significant impairment in wound healing (Fig. 1).[28] A low probability of wound healing due to poor perfusion should prompt further investigations to establish the distribution of PAD.

Guidelines published by the National Institute for Clinical Excellence (NICE) in the UK recommend offering duplex ultrasound as first-line imaging to all people with PAD where revascularisation is being considered.[29] Evaluation of the below-knee vessels is particularly important in patients with diabetes and the sensitivity of DUS for detecting a high-grade stenosis ($\geq$50%) are 90% for the anterior and posterior tibial arteries and 82% for the peroneal artery.[30] Although DUS is non-invasive and relatively inexpensive compared with other imaging modalities, its reliability is dependent on operator expertise. The evaluation of below-knee vessels with haemodynamic parameters alone does not provide adequate information for preoperative planning, but may serve as a useful and intermediate adjunct to other, more invasive modalities.[31]

Digital subtraction angiography (DSA) remains the gold standard imaging modality for evaluating the distribution of PAD when revascularisation is planned and has the advantage of allowing simultaneous endovascular intervention. Its main drawback in patients with diabetes and a high prevalence of renal insufficiency is the risk of contrast-induced nephropathy. As a precaution, patients with renal impairment should receive peri-procedural intravenous volume expansion and metformin should be stopped prior to DSA as it may cause a lactic acidosis.[32] The visualization of pedal

vessels with DSA may be limited in patients with severe occlusive disease, where the concentration of contrast falls short of the sensitivity threshold. In such instances, a hand-held Doppler probe can be useful in unmasking pedal target arteries not visible on DSA.

Contrast-enhanced magnetic resonance angiography (CE-MRA) is a low-invasive modality capable of imaging calcified vessels without artifact and avoids the need for nephrotoxic iodinated contrast. Temporally resolved hybrid CE-MRA using an aortoiliac and femoral bolus-chase achieves the best diagnostic performance. In a study of patients with diabetes, the sensitivity and specificity for time-resolved CE-MRA of crural vessels was 79% and 90% respectively.[33] Disadvantages of MRA include limited spatial resolution and a relative contraindication for the use of gadolinium in patients with severe renal insufficiency (creatinine clearance $<$30 ml/min), which has been linked to the development of nephrogenic systemic fibrosis.[34] In addition, the occurrence of stent artefacts in MRA limit its use for the detection of in-stent stenosis.

Computed tomography angiography (CTA) should be offered where MRA is contraindicated,[29] and has several advantages over MRA with respect to the speed of examination and spatial resolution. It is limited by image interference from calcified arteries, which can make interpretation difficult. A systematic review comparing sensitivity and specificity of DUS, contrast enhanced MRA and multidetector-row CTA reported similar accuracies across these modalities for detecting high-grade stenoses above and below the knee.[35]

REVASCULARISATION

Data from the EURODIALE Study (a prospective study of newly presenting patients with DFU to 14 experienced European diabetic foot centres) would seem to suggest that many patients are not having vascular imaging nor being considered for revascularisation.[36] Of those patients with severe ischaemia (ABPI $<$0.5) appropriate vascular imaging was performed in just 56%, and only 43% of those imaged were revascularised. It is quite possible that the picture is even bleaker for patients outside specialist centres. Retrospective review of the Eurodiale data suggests there are various reasons why revascularisation was not performed, including spontaneous wound healing, poor clinical condition of the patient or surgeon preference.

The decision to revascularise the ulcerated foot is complex. Multiple factors influence wound healing in diabetes in addition to PAD. Patients with mild PAD and adequate perfusion measurements (ABI $\geq$0.6, $TcPO_2$ $>$50 mmHg) should be initially managed with optimal wound care (debridement, treatment of infection and off-loading) and a 6-week period of observation. There is level II evidence to suggest the healing response to 'best medical therapy' during this period gives a good indication as to the adequacy of perfusion.[37] In large ulcers and in those with the combination of PAD and infection, the expected outcome of conservative treatment is poor (level I evidence) and earlier vascular intervention may be required. If it is felt that PAD is contributing towards impaired wound healing then patients, if ambulatory, should be considered for revascularisation with the exception of the severely frail or functionally impaired and those with an unsalvageable foot. Importantly, where PAD is likely to compromise healing of a major amputation wound, interventions to optimize inflow should be considered.

Revascularisation in patients with diabetes can be technically difficult by virtue of the distal distribution of disease, impaired collateral formation and vessel calcification. Data pooled by the IWGDF from 19 studies of patients with DFU and PAD showed a median limb salvage rate of 85% at 1-year.[38] Half of patients with DFU and PAD can expect to be alive at 5-years and mortality rises to 50% in 2-years following a major amputation.[39] Patients with co-existing chronic kidney disease (CKD) fare worse and the severity of CKD has been shown to correspond with poor outcomes and mortality following revascularisation.[40]

There are no randomized trial data comparing surgical bypass and endovascular interventions in selected patients with diabetes or infrageniculate disease, however, in patients with diabetes and an ischaemic foot ulcer, these techniques appear to offer equivalent outcomes where revascularisation is successful.[41,42] The BASIL trial,[43] which randomized patients with severe limb ischaemia (rest pain or tissue loss for $>$2 weeks) to bypass or balloon-angioplasty, demonstrated similar outcomes in terms of health-related quality of life and amputation-free survival, although less than half of randomized patients had diabetes and no sub-group analyses were performed. Endovascular techniques performed under local anaesthesia are lower-risk than bypass surgery and cost considerably less; however, an increased re-intervention rate following angioplasty in the BASIL trial reduced any overall cost difference.[44] Data from the BASIL trial suggest they are also associated with lower short-term morbidity and, as such, endovascular therapy is probably justified as the initial approach to restoring perfusion. Surgical bypass has the advantage of increased durability when autologous vein is used but patients with multiple comorbidities and a short life expectancy (6—12 months) are unlikely to realize this benefit.

The distal distribution of PAD in diabetes has brought about innovation and development in both endovascular techniques and open bypass surgery. Distal endovascular interventions and distal origin bypass grafts arising from the SFA, popliteal or crural vessels show good outcomes in selected patients. Identifying the optimal artery for angioplasty or run-off vessel for bypass requires careful scrutiny of anatomic and haemodynamic factors and some authors advocate revascularisation based on the angiosome model of perfusion, where the target artery corresponds to the area of tissue loss.[45] It is important to note that angiosomes are a representation of normal anatomy and changes to the collateral circulation that result from PAD mean the success of this technique in reconstructive surgery will not necessarily extrapolate to revascularization in cases of DFU. The available evidence for the angiosome concept is limited, but it does seem a logical step to achieve healing in diabetic

foot ulcers. In a series of patients with DFU treated by angiosome-guided endovascular techniques, rates of limb salvage and healing at 1-year were encouraging, at 91% and 85% respectively.[46] Interestingly, a meta-analysis of 31 studies reporting results of popliteal to distal vein bypasses has demonstrated greater limb salvage rates than corresponding patency data.[41] Primary patency at 1 and 5-years was 82% and 63% respectively with corresponding foot salvage rates of 89% and 78%. This observation suggests that long-term graft patency is not always necessary for a successful outcome in patients with diabetes, providing that wound healing precedes graft failure.

A meta-analysis of crural angioplasty performed by the same group reported comparable limb salvage rates of 93% and 82% at 1 and 36 months respectively.[42] As with surgical bypass, long term patency is less relevant, providing wound healing is achieved following an intervention. The development of drug-eluting stents and balloons offers the potential to reduce rates of re-stenosis following endovascular therapy, however, there is currently insufficient evidence to support the use of these devices in patients with DFU. Some contemporary series report a combined surgical and endovascular approach to the problem of inflow disease[47] which may be most useful in patients with concomitant SFA and distal arterial occlusive disease. A hybrid approach is particularly attractive in patients with limited availability of vein conduit, which may otherwise necessitate the use of prosthetic grafts. We expect that both endovascular and bypass techniques will remain widely used and complementary in the foreseeable future.

PREVENTION OF ULCERATION/SCREENING

Foot examination focussing on the presence of peripheral neuropathy, PAD and abnormal foot anatomy can predict risk of developing a diabetic foot ulcer.[10,48] Diverse risk stratification systems exist incorporating these and additional risk factors, although none has been universally adopted (Table 1). In a Scottish study which stratified foot ulcer risk in 3526 patients with diabetes, foot ulceration was 83 times more common in high-risk patients, compared with low-risk patients.[49] During a mean follow-up duration of 1.7 years, the risk of foot ulceration was 0.36% in low-risk patients (64% of the population), 2.3% in moderate-risk patients and 29.4% in high-risk patients. The negative predictive value of a low-risk score may be useful in directing the resources of specialized foot clinics towards the minority of patients at medium- or high-risk.

Primary care physicians in the UK undertake annual foot checks and stratify patients with diabetes according to their risk of ulceration, however, the effectiveness of screening programmes and complex interventions (education, podiatry, orthoses) in reducing both the risk of foot ulceration and mortality is difficult to confirm.[50,51] While the evidence for specific interventions is sparse, it is clear that patients with an established diabetic foot ulcer benefit from prompt recognition and early referral to a limb salvage team. Following the introduction of a multidisciplinary foot team at Ipswich hospital, UK, Krishnan et al. observed a 62% reduction in major amputations in a catchment general population.[3] Larger ulcers are more difficult to manage hence the need for early identification and intervention; data from another established foot clinic demonstrated a direct relationship between cross-sectional area (and ulcer duration) at first assessment and time to healing.[52]

Despite the prognostic performance of neuropathy and PAD in predicting ulceration, a risk stratification tool that uses routinely available demographic and clinical data would be more practical on a population level. The training required for accurate clinical assessment of PAD and neuropathy may not be feasible outside well-resourced settings. Reallocating resources towards evidence based multidisciplinary foot clinics may offer a better alternative to primary care-led screening.

MEDICAL OPTIMIZATION

DM is recognized as a key risk factor for the development of cardiovascular disease (CVD) and mortality from CVD causes is ≈2-fold higher compared with individuals without DM.[53] Recent evidence suggests that a history of foot ulceration may increase this risk further still, showing excess all-cause mortality in patients with DFU, compared with patients with diabetes without a history of DFU.[54] Accordingly, the benefits of CVD risk modification in reducing morbidity and mortality have been shown in populations with diabetes and DFU.

The Steno-2 study randomized patients with type 2 diabetes and persistent microalbuminaemia to intensive CV risk management, which corresponded to an absolute risk reduction for all-cause mortality of 20% after a mean follow up of 13.3 years (7.8 years of multifactorial intervention and

Table 1. Variables included in the diverse stratification systems.

Stratification	Variables					
	DN	PAD	Foot deformity	Previous ulcer	Previous amputation	Visual impairment
UTFRS[90]	✓		✓	✓	✓	
IWGDF[15]	✓	✓	✓	✓	✓	
SIGN[10]	✓	✓	✓	✓	✓	✓
ADA[91]	✓	✓	✓	✓	✓	
Boyko et al.[92]	✓			✓	✓	✓

UTFRS: University of Texas Foot Risk Stratification; IWGDF: International Working Group on the Diabetic Foot; SIGN: Scottish Intercollegiate Guideline Network; ADA: American Diabetes Association; DN: diabetic neuropathy; PAD: peripheral arterial disease.

Adapted from Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia 2011;54:1190–1199.

an additional 5.5 years of follow-up).[55] Participants were selected for the presence of microalbuminuria which is associated with microvascular disease and therefore neuropathy and ulceration, and is itself a strong predictor of CV events.[56,57] In the setting of patients with DFU, Young et al. reported improved survival of patients treated with intensive CV risk modification.[58] In a foot clinic population, 5-year mortality fell from 48% to 27% following introduction of a protocol incorporating CV risk screening and administration of an antiplatelet agent, statin and antihypertensive where indicated (level II evidence).

No direct evidence supports a role for tight glycaemic control in preventing ulceration, although epidemiological data suggests that optimizing blood glucose levels can prevent peripheral neuropathy and PAD in patients with diabetes. In the UK Prospective Diabetes Study, a reduction in $HbA1_C$ of 1% was associated with a reduction in risk of 43% for amputation or death from PAD.[59] Similarly, there are no data to support aggressive glycaemic control to aid healing in active ulceration; however this is also likely to be important, not least because raised blood glucose encourages infection. Strict glycaemic control will increase the risk of hypoglycaemic attacks and weight gain in some patients. In the majority of frail and elderly patients with DFU, less intensive glycaemic goals are probably indicated, with target blood glucose levels between 6 and 10 mmol/l.

ULCER/WOUND MANAGEMENT AND DRESSINGS

The quality of published reports supporting the use of local interventions in DFU is poor but some principles guiding foot care can be derived from the available literature.[60,61] The cornerstone of early management in neuropathic ulcers is offloading pressure with appropriate footwear, removable devices or total contact casts (TCCs). The efficacy of prescribed footwear and removable devices is dependent on patient compliance and, probably for this reason, the TCC has demonstrated superior results in randomized trials,[62] and is recommended by the IWGDF as first-choice treatment.[63] A perception of increased risk of falls with TCCs appears to be unfounded.[64,65] Despite all this, only 18% of approximately 600 patients with a plantar foot ulcer in the Eurodiale study were treated with TCCs.[36] Callus formation contributes to abnormal loading and failure to heal, and debridement should be routinely provided by trained podiatrists. Evidence suggests that removal of calluses is beneficial for reducing plantar pressures,[66,67] although this has yet to be confirmed in randomized trials.

Despite their widespread use there is a paucity of evidence to support the use of topical therapies for diabetic foot ulcers. In agreement with the conclusions of an earlier Cochrane review,[68] the IWGDF identified no good quality randomized controlled trials (RCTs) reporting healing rate or infection outcomes from which to produce clinical guidelines.[60] The application of factors which aim to promote healing by altering cell biology have failed to demonstrate consistent efficacy and there is insufficient evidence to justify the use of these expensive agents in routine practice. Bioengineered skin grafts have demonstrated favourable results in a prospective RCT involving more than 300 patients receiving a dermal fibroblast culture[69] A greater proportion of patients receiving the bioengineered skin achieved complete healing at 12 weeks (30% vs 18%) compared with conventional therapy (dressings, offloading footwear and debridements), however the healing rates in the control group were lower than expected. Although negative pressure wound therapy (NPWT) is widely used in the treatment of chronic wounds, much of the supporting evidence is based on industry funded trials and unpublished data are largely inaccessible.[70] One well-designed, industry supported RCT of 342 patients with an ulcer >2 cm^2 reported promising outcomes.[71] NPWT was associated with reduced time to wound closure, increased incidence of healing by 16 weeks and reduced incidence of minor amputation. Further study is, however, needed to justify the use of NPWT in routine clinical practice. The evidence to support the use of a particular dressing or topical therapy for the ulcer bed is thin. Providing a comprehensive environment to improve healing with antibiotics, debridement and offloading is superior to the use of a novel, and often expensive, dressing. It is what you take off the wound and not what you put on it that counts.

INFECTION/ANTIBIOTICS

The risk of infection in the diabetic foot increases with the presence of PAD, recurrent or chronic wounds and those penetrating to bone.[72] The majority of infections are contained within the soft tissue, but around a fifth involve underlying bone (osteomyelitis) which is associated with a worse outcome. The diagnosis of diabetic foot infection is based on clinical findings; superficial wound cultures are not useful and should not be treated, as bacterial colonization appears to be ubiquitous in diabetic foot ulcers. Bone biopsy for histopathology and culture remains the “gold standard” for diagnosing osteomyelitis, yet unfortunately this procedure is not routinely performed in clinical practice.[73]

Infection of a foot ulcer can be a major threat to limb and life and should be treated promptly. The IWGDF has produced guidelines for the treatment of diabetic foot infections based on the severity of infection,[28] which predicts amputation. Ulcers with superficial infection should be treated with debridement and oral antibiotics aimed at *Staphylococcus aureus* and streptococci. Targeted therapy against gram positive cocci has been shown to be equally effective as broader spectrum regimens (level I evidence),[74] even in the presence of osteomyelitis which will respond to antimicrobial therapy in most cases. Deep infection, characterized by purulent discharge or fullness in the plantar space,[75] necessitates urgent debridement of necrotic tissue including infected bone, and revascularisation if indicated. Intravenous broad-spectrum antibiotics should target Gram-positive and negative micro-organisms, including anaerobes. Signs of life and limb threatening infection include bullae, ecchymoses, soft tissue crepitus and rapid spread of infection.[76]

In the Eurodiale cohort, investigators observed a markedly negative impact of infection on ulcer healing that was confined to patients with PAD. These findings emphasize the need for studies comparing different antibiotic regimens in PAD and for those investigating the effects of early revascularisation on control of infection.[77]

CLASSIFICATION AND OUTCOMES (REPORTING)

In studies of outcome following lower limb revascularisation for critical limb ischaemia (CLI), patients with and without diabetes are typically reported as one group. The unique characteristics of PAD in diabetes, in its distribution and presentation, make it difficult to extrapolate clinical significance from data on unselected patients. Additionally, CLI remains a problematic definition in patients with diabetes as symptoms of ischaemic pain (claudication, rest pain) may be masked by the presence of distal symmetric polyneuropathy, and ulceration may develop with very mild PAD of little haemodynamic significance. In contrast, patients without diabetes are unlikely to develop tissue loss in the absence of a severe perfusion deficit. A haemodynamic classification of PAD using ankle brachial index (ABI), toe pressures or transcutaneous oxygen tension is more useful in patients with diabetes with the caveat that ABIs may be falsely elevated due to arterial calcification and have a poor predictive value. Patients with diabetes need to be identified as an important subgroup in the PAD literature to allow pooling of results for systematic review and meta-analysis.

Several angiographic classification schemes exist to describe the anatomical distribution of disease in patients with PAD. The limitations of the currently available schemes may, in part, explain the poor reporting of PAD distribution in the literature. The Trans-Atlantic Inter-Society Consensus (TASC) guidelines classify femoral popliteal lesions based on their anatomical distribution,[78] however, the classification of infrapopliteal lesions is not specifically addressed. This is significant given that the patency of the outflow artery is critical in determining the success of arterial bypass, and this is especially true in diabetes where run-off is more likely to be poor. The Bollinger score,[79,80] albeit more cumbersome clinically, describes the infrapopliteal arterial segments in some detail and is advantageous in this respect. In the BASIL trial, below knee Bollinger scores were significantly greater in patients presenting with tissue loss; however the same difference in above knee scores was not significant. Interestingly there was a negative correlation between mean above and below knee Bollinger scores, suggesting that the TASC score, in its current form, may underestimate disease severity in a cohort of patients with diabetes and relative sparing of the above knee arterial segments.

Several validated scoring systems have been developed for use in diabetic foot ulcers. These include the University of Texas Wound Classification system and the Size (Area and Depth), Sepsis, Arteriopathy, and Denervation (S(AD)SAD) score,[81,82] the latter of which has been prospectively validated in different ethnic groups and is a reliable predictor of healing.[83] The PEDIS score of the International Working Group on the Diabetic Foot (IWDGF) was developed for research purposes,[84] but the grading of infection in this system according to its severity is also advocated for clinical use as it predicts outcome.[85] A universal classification system of diabetic foot ulcers would enable consistent reporting among studies in DFU to guide the development of novel therapies while increasing the external validity of research in this field and allowing fair comparison between centres.[86] To this end the European Wound Management Association (EMWA) has produced a set of recommendations for standardized reporting of outcomes in studies of wound management.[87] Clearly there will be some overlap with the Society for Vascular Surgery standard reporting criteria for the lower limb ischaemia,[88] although some important outcomes may be distinct. Ulcer healing has been shown to be of particular importance to patients with diabetes and is associated with improvements in health-related quality of life (HRQOL).[89] One study demonstrated improvements in QOL in both the patient and caregiver following ulcer healing.[90]

In a study of 449 patients with an index diabetic foot ulcer, Jeffcoate et al. demonstrated how the use of ulcer-related endpoints may underestimate morbidity and mortality in this cohort.[15] At 12 months, ulcer healing without amputation was achieved in 65.7% whereas only 45% of patients were alive, without amputation and ulcer free. The authors suggest that ulceration free survival may merit further exploration as an outcome measure in diabetic foot disease. The balance of risk and benefit for interventions in diabetic foot disease is probably best assessed through a combination of defined clinical endpoints including mortality, amputation-free survival, healing and re-ulceration with patient-reported outcome measures.

FUTURE PERSPECTIVES

Better selection of patients for revascularisation procedures will rely on improvements in the reporting of outcome in diabetic foot disease. Whilst new data on the impact of revascularisation are awaited, there are encouraging developments in other treatment modalities, including stem cell and progenitor cell therapy. As discussed previously, PAD is present in around half of patients with DFU. The impact of PAD on wound healing is compounded by impaired formation of new capillaries (angiogenesis) and proliferation of pre-existing micro-vessels into collateral arteries (arteriogenesis) in patients with diabetes. Stimulation of angiogenesis and arteriogenesis represent attractive approaches in DFU and there is accumulating evidence to confirm their efficacy in the treatment of critical limb ischaemia.[91] Pooled data from studies of autologous bone marrow mononuclear cell (BMMNC) therapy in patients with PAD show increases in ABI values between 0.1 and 0.2 points, $TcPO_2$ increases between 10 and 20 mmHg O_2 and improvements in walking distances. Although data in selected populations with DFU are limited, one study in China demonstrated improved ulcer healing rates with BMMNCs and bone marrow mesenchymal stem cells

compared with controls.[92] Further research should clarify the role of cell therapies in DFU.

CONCLUSIONS

The present review underlines the difficulty in diagnosing PAD in patients with diabetes and the importance of referring those presenting with a new foot ulcer to a multidisciplinary team, which includes vascular surgeons and interventional radiologists. Interventions should aim not only to preserve limb, but also attenuate the excess mortality observed in patients with diabetic foot disease; there is likely an unmet potential for CVD prevention in this cohort.

The role of population based screening to identify those at risk of developing ulceration remains unclear and the evidence for interventions in this high risk population derives from studies of poor methodological quality. The development of future clinical guidelines will rely on selective reporting of relevant outcomes in patients with diabetes following lower limb revascularisation. Patients with diabetes represent a distinct and important sub-group because they behave differently to non-diabetics in almost all respects.

CONFLICT OF INTEREST/FUNDING

None.

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