

THEMATIC REVIEW

Diabetes-related foot disease: new insights with an antipodean focus

Emma J Hamilton¹ and Stephen M Twigg²

¹Medical School, University of Western Australia, Fiona Stanley Hospital, Murdoch and Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

²Central Clinical School, Sydney Medical School, the Faculty of Medicine and Health, University of Sydney and Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

Correspondence should be addressed to E Hamilton: emma.hamilton@uwa.edu.au

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Abstract

Diabetes-related foot disease (DFD), defined as ulceration, infection or destruction of tissues of the foot in a person with current or previously diagnosed diabetes mellitus, is associated with a heavy burden for both patients and the healthcare system with high morbidity, mortality and costs. Improved outcomes for people with DFD are achieved with an interdisciplinary approach and adherence to best practice clinical guidelines; however, in the Australian context, the vastness of the country presents unique challenges in achieving optimal outcomes for all people with DFD, with variation in service delivery, availability and accessibility between metropolitan, rural and remote areas. Aboriginal and Torres Strait Islander Australians and people with diabetes living in rural and remote areas experience higher rates of lower-extremity amputation, and further efforts and resources are required to improve outcomes for these high-risk groups. In recent years, there have been advances in knowledge, including the understanding of the pathogenesis of diabetes-related peripheral neuropathy, genetic polymorphisms and mechanisms of disease associated with acute Charcot neuroarthropathy, biomarkers and potential mediators of diabetes-related foot ulcer (DFU) healing, the microbiology and microbiome profile of DFUs, pressure assessment and management as well as an expanded understanding of DFU sequelae and comorbidities. In this review, we describe new insights into pathophysiology, sequelae and comorbidities of DFD with a focus on basic and translational aspects and contributions to the field from Australian and New Zealand DFD researchers.

Key Words

- ▶ diabetes-related foot disease
- ▶ peripheral neuropathy
- ▶ Charcot foot
- ▶ diabetes-related foot ulcer
- ▶ diabetes complications

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Introduction

Diabetes-related foot disease (DFD) is defined as ulceration, infection or destruction of tissues of the foot in a person with current or previously diagnosed diabetes mellitus, usually associated with the risk factors of peripheral neuropathy and/or peripheral arterial disease (PAD) in the

lower limbs ([van Netten *et al.* 2020](#), [Zhang *et al.* 2021b](#)). The impacts of foot disease for people with diabetes are significant – one Australian loses a limb, or part thereof, every 2 h as a consequence of DFD ([Australian Commission on Safety and Quality in Healthcare and](#)

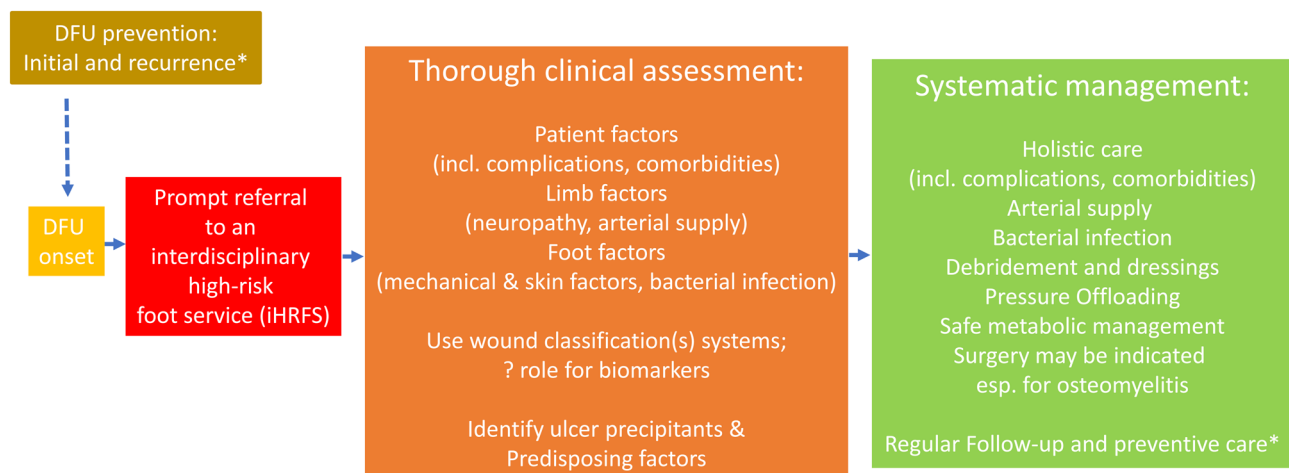
National Health Performance Authority 2016). DFD is associated with high morbidity, mortality and healthcare costs (Lazzarini *et al.* 2018, Zhang *et al.* 2020, 2021b). The introduction of a multidisciplinary team approach to the management of DFD has been associated with improved outcomes in an Australian context, including reductions in lower-extremity amputation (LEA) (Lazzarini *et al.* 2015); however, an increase in incident hospitalisation for diabetes-related foot ulcer (DFU) has recently been reported in a Western Australian cohort of people with type 2 diabetes mellitus (T2DM), particularly amongst younger patients (Hamilton *et al.* 2021a), and heterogeneity in composition and function of interdisciplinary diabetes high-risk foot services (iHRFS) around Australia has been described (Vo *et al.* 2021). Aboriginal and Torres Strait Islander Australians experience a three- to six-fold increase in DFD compared with non-Indigenous Australians (West *et al.* 2017). Access to evidence-based, culturally appropriate foot care screening and intervention services for Aboriginal and Torres Strait Islander Australians is required to reduce this gap in outcomes (West *et al.* 2017, 2022). Patients with diabetes living in rural and remote regions of Australia also experience higher rates of LEAs, and distance from specialist services has been identified as a risk factor for poorer DFU healing outcomes (Australian Commission on Safety and Quality in Healthcare and National Health Performance Authority 2016,

Zhang *et al.* 2021a, 2022, Tehan *et al.* 2022). New comprehensive Australian guidelines for DFD management, adapted from the International Working Group for the Diabetic Foot (IWGDF) guidelines, were recently launched as well as Australian research priorities for diabetes-related foot health and disease, national standards for iHRFS (<https://nadc.net.au/hrfs-accreditation/>) and national DFD screening and active foot disease pathways (<https://www.footforward.org.au/>), which will hopefully drive further improvements in clinical care delivery and inspire new Australian DFD research into the future (Schaper *et al.* 2020, Hamilton *et al.* 2021b, Perrin *et al.* 2021, Chen *et al.* 2022, Chuter *et al.* 2022, Commons *et al.* 2022, Fernando *et al.* 2022b, Kaminski *et al.* 2022, Lazzarini *et al.* 2022). The focus of this narrative review is to describe and highlight new insights into pathophysiology, sequelae and comorbidities of DFD with a focus on basic and translational aspects and contributions to the field from Australian and New Zealand DFD researchers (Fig. 1).

New insights in diabetes-related peripheral neuropathy

Peripheral nerves are highly susceptible to the adverse metabolic environment of diabetes, given their greater length with cell bodies in the dorsal root ganglia and high

Overview of Core Components in Management of Diabetes-Related Foot Ulcers (DFU) - Itemising some areas of research described in this review



Also described in this review, the condition Charcot neuroarthropathy is much less common than DFU, has its own pathogenesis, it requires timely careful clinical assessment by a iHRFS, and specific care and clinical followup.

Figure 1

Overview of the core components in the management of diabetes-related foot ulcers.

metabolism with metabolic glucose dependence. In recent years, the pathogenesis of DPN has been explored by epidemiological as well as correlative structure–function studies. Issar and colleagues found that amongst those with T2DM who had metabolic syndrome compared with those with T2DM but no metabolic syndrome, larger median nerves, increased nerve excitability measures, greater neuropathy clinical scores and lesser related regional corneal nerve whorl measures were present (Issar *et al.* 2021a,b). They concluded that dysregulation of the peripheral nerve sodium and potassium pump may underlie the greater alterations in the peripheral nerve structure and function in T2DM with metabolic syndrome than in T2DM with no metabolic syndrome, suggesting some factors in metabolic syndrome, such as dyslipidaemia, may be causing such changes. Thus, in addition to the established evidence from the Diabetes Control and Complications Trial that hyperglycaemia mediates neuropathy by multiple potential mechanisms (Brownlee 2005), lipid dysregulation, with triglycerides (TGs) as a marker and potentially reflecting diacylglycerol or sphingolipid pathways, has been implicated as contributors to DPN (Eid *et al.* 2019). Also across recent years, in T2DM cohorts, non-alcoholic steatohepatitis fibrosis has been associated with the presence and progression of DPN and DFU and amputation as described by Williams *et al.*, and lipid dysregulation has been proposed as a mediator (Williams *et al.* 2015, 2018). Furthermore, higher age, glycated haemoglobin (HbA1c) level and chronic kidney disease (CKD) markers have been associated with more severe DPN detected by nerve studies in a recent Queensland audit (Ly *et al.* 2021).

Continuing the theme linking lipids to peripheral nerve dysfunction, the Australian Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) double-blinded randomised controlled trial (RCT) of fenofibrate reported, as a predefined secondary study endpoint, that fenofibrate use was associated with reduced lesser (below ankle) amputations in those receiving fenofibrate (Rajamani *et al.* 2009). The mechanism of action of fenofibrate could be many fold as it has activity as an antioxidant, to improve microvascular function, as well as its metabolic syndrome lipid targeting (Cho *et al.* 2014). If the RCT studies could be confirmed in a primary endpoint study, then they could shift the paradigm for prevention of DPN and amputations, by enabling an additional option in the prevention of such DFD complications. Moreover, a recent Australian study of exenatide, compared with dipeptidyl dipeptidase inhibitors (DPP-IVi) or sodium/glucose co-transporter 2 inhibitors (SGLT2is), suggests that it may improve some

objective measures of peripheral nerve function, in a manner independent of HbA1c, and possibly linked to lipid regulation, offering hope that this class of drug might reverse some aspects of DPN (Issar *et al.* 2021a,b). In contrast, international studies did not show clinical benefits of exenatide in DPN (Jaiswal *et al.* 2015). Moreover, in terms of amputation risk in one study in T2DM, the SGLT2i, canagliflozin, was associated with increased risk of amputation (Arnott *et al.* 2020), whilst this has not been found in randomised trials using other SGLT2i.

Corneal confocal microscopy-related findings are becoming increasingly established as a non-invasive assessment method for neuropathy. Corneal nerve fibre reduced tortuosity in those with DPN, which was documented by Krishnan and colleagues using an automated system (Klisser *et al.* 2022). These reflect the findings by Malik *et al.* with Queensland collaborators that corneal confocal microscopy findings of density and length correlate with DPN and suggest that such measures, if routinely automated, may aid diabetes complication neuropathy screening (Alam *et al.* 2017, Fleischer *et al.* 2021, Preston *et al.* 2022). Interestingly, blood TG levels correlated with corneal nerve fibre loss (D'Onofrio *et al.* 2022). Moreover, this same group has found that those with extreme long duration of type 1 diabetes mellitus (T1DM) who do not have corneal neuropathy structural changes had more normal lipid parameters and less alcohol intake (Azmi *et al.* 2021). In a national Australian audit of T1DM, metabolic syndrome presence was found by Flack *et al.* to be associated with more DPN than in those without metabolic syndrome with T1DM, especially in younger age of onset patients (Lee *et al.* 2021).

In a systematic review of the reliability of non-invasive, chairside screening tests for DPN diagnosis, Chuter and colleagues reported that ankle reflexes, vibration perception threshold, and four site 10 g 5.07 gauge S-W monofilament testing, in combination reliably detect clinical DPN (McIllhatton *et al.* 2021), also reflecting recent national guidelines (Lazzarini *et al.* 2022). Studies by Perrin and Kingsley *et al.* from Victoria and New Zealand have shown that podiatrist-led health coaching can aid patient understanding and implementation of neuropathy foot care practices, including application of modern technology such as smart insole adoption (Macdonald *et al.* 2021). Practical studies in DPN and driving, developing new technology, have reported on an early warning system for drivers with insensate DPN (Esparza *et al.* 2021).

In comorbidities and complication linkages, DPN associates with an increasing spectrum of conditions. Impaired bone health has been associated with T2DM, and

a recent study by Lasschuit and colleagues demonstrated that people with type 2 diabetes with DPN had poorer bone health measured by quantitative calcaneal ultrasound, than people with T2DM without DPN (Lasschuit *et al.* 2022). In T1DM, retinal vascular calibre has been linked to DPN in adolescents, potentially helping to explain DPN pathogenesis (Velayutham *et al.* 2021). DPN was common in a study in CKD stages 4 and 5, and its presence was linked to reduced quality of life and higher physical limitation scores (Arnold *et al.* 2022). Fear of falling and reduced physical functioning were prominent in a study in India with Australian collaborators and linked DPN to functional loss (Gupta *et al.* 2022). DPN was strongly associated with periodontal disease in a Sydney-based systematic review (Nguyen *et al.* 2020). DPN presence in older age of diabetes onset was linked to greater dementia occurrence in the Fremantle Diabetes Study (Bruce *et al.* 2019). Furthermore, hypothesis-generating studies from the Australasian Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study cohort reported that DPN and PAD each associates not only with cardiovascular disease (CVD)-related death, but also with increased 5-year risk of cancer death, especially for epithelial derived cancers (Mohammedi *et al.* 2021).

Although painful DPN remains an enigma, research into its mysteries has been progressing in recent years. A review from Western Australia emphasises that oxidative stress may be a main peripheral pathogenic mediator, and central regulation with sensitisation of pain requires further examination (Ye *et al.* 2022). Another recent Australian review, by Lowy *et al.*, has highlighted the neuroimmune linkages in skin that may underlie painful neuropathies including in DPN (Lowy *et al.* 2021). Along those lines, Austin *et al.* in Sydney reported that T-lymphocyte and monocyte subsets are dysregulated in people with T1DM and painful DPN, implicating specific immune dysregulation in mediating painful DPN (O'Brien *et al.* 2021). Studies from the UK with Australian collaborators have confirmed that there is greater small nerve intraepidermal nerve fibre density reduction and damage, in skin biopsy samples in those with painful, rather than in painless, DPN (Ferdousi *et al.* 2021). The overall negative results of CBD oil studies in spinal cord pain to date (Tsai *et al.* 2022) have tempered enthusiasm for study of this intervention in painful DPN, and high-quality RCTs are awaited (Bagher 2022), including through dedicated funding models in Australia. In contrast, an Australian systematic review

has reported potential benefits of alpha lipoic acid supplementation in treating painful DPN symptoms (Jeffrey *et al.* 2021). Moreover, an 8% topical capsaicin patch added to lidocaine 5% patch was effective and well tolerated over 24 weeks in treating painful DPN in an RCT of $n=291$ (Hussain *et al.* 2021). Currently, combinations of centrally acting agents as specific classes of antidepressants, anticonvulsants, and opioids as second line can improve pain in most patients with painful DPN, with a typical number needed to treat of ~3–6. However, refractory, disabling pain persists in some, and the increasingly strong evidence base for use of high-frequency (10 kHz) spinal cord stimulation (Hi-10) in markedly improved pain control (Petersen *et al.* 2021, 2022) reflects that current Australian guidelines (Practitioners 2020) and referral systems need to be further refined to enable such therapy to be an option for people with medication-refractory painful DPN. Of note, those high-quality RCTs have also indicated that spinal cord stimulation with Hi-10 led to improved measures of neuropathy, such as light touch and vibration, with the hypothesis that spinal cord inhibitory interneuron regulation by Hi-10 may mediate this benefit (Petersen *et al.* 2021, 2022); such measures were subjective endpoints and studies objectively assessing nerve function for example, by peripheral nerve conduction and effects of Hi-10, are eagerly anticipated.

In summary, as there is no proven intervention to stabilise or reverse DPN other than glycaemic control, the exact pathogenesis of painful DPN, mixed, and painless types remains to be defined with both neural direct toxicity and injury to the vasa nervorum plus oxidant stress and inflammation and immunity, being implicated. Emphasising the ongoing import of this topic, a recent Delphi method identified that consumers in Australia prioritise research in diabetes that addresses mechanisms of DPN and methods to better manage painful DPN (Perrin *et al.* 2021). Certainly, in addition to targeting glucose, metabolic management of certain lipid moieties holds promise, and for painful DPN, mechanical methods with high-frequency spinal cord stimulation is increasingly evidence based requiring adjustment in interdisciplinary healthcare models of diabetes care. However, its financial cost, non-reimbursement in public health services in Australia and access to care for device insertion are currently limiting its usage. Nanoformulations including topical therapy delivery methods may aid DPN pharmacological treatments (Khursheed *et al.* 2021).

New insights in the Charcot foot in people with diabetes

Charcot foot, also known as Charcot neuropathic osteoarthropathy, is an uncommon but serious and potentially limb-threatening complication in people with diabetes (Rogers *et al.* 2011, Jeffcoate 2015). Charcot foot is an inflammatory condition involving the bones, joints and soft tissues of the foot and ankle which develops in people with peripheral neuropathy, with diabetes currently being the most common underlying aetiology (Rogers *et al.* 2011, Jeffcoate 2015). The acute localised inflammation of the foot and ankle results in varying degrees of destruction, subluxation, dislocation and foot deformity, including the classic 'rocker-bottom' deformity due to collapse of the mid-foot (Rogers *et al.* 2011). Swelling, warmth and erythema are typically present in the acute phase; pain may also be present but is often mild or moderate due to the presence of peripheral neuropathy (Rogers *et al.* 2011). A number of theories have been postulated regarding the pathogenesis including neuro-traumatic, neurovascular and neuro-bone-inflammatory mechanisms underlying the clinical features of acute Charcot neuroarthropathy; it is likely that these pathways are not exclusionary but are in fact occurring simultaneously (Jeffcoate 2015, Dardari 2020, Kloska *et al.* 2020). Although there remains uncertainty regarding the exact causes and mechanisms underlying the bone, joint and soft tissue damage observed in Charcot foot, there has been great progress in recent years in understanding the associated changes in bone metabolism, cytokines, monocyte to osteoclast differentiation as well as potential genetic polymorphisms, which may predispose to this condition (Jeffcoate 2015, Jansen & Svendsen 2018, Dardari 2020, Kloska *et al.* 2020, Yates *et al.* 2020).

Currently, it is widely believed that the clinical features observed in acute Charcot foot arise as a result of dysregulated inflammation in the foot that becomes prolonged in the context of peripheral neuropathy; this inflammatory process may be triggered by a number of factors including unrecognised injury or minor trauma and persists due to neuropathy and continued ambulation (Rogers *et al.* 2011, Jeffcoate 2015, Kloska *et al.* 2020, Dardari 2020). In 2005, Jeffcoate *et al.* first described the hypothesis that this inflammatory cascade was associated with increased expression of pro-inflammatory cytokines such as tumour necrosis factor α (TNF α), interleukin-1 β (IL-1 β) and IL-6, which in turn leads to increased expression of the receptor activator of nuclear factor κ B ligand (RANKL) which binds to its

receptor, receptor activator of nuclear factor κ B (RANK), leading to osteoclast maturation and osteolysis (Jeffcoate *et al.* 2005). Osteoprotegerin (OPG) is a soluble decoy receptor for RANKL, binding and neutralising RANKL and inhibiting differentiation and function of osteoclasts, limiting excessive osteolysis (Ochoa-Precoma *et al.* 2021). A balanced equilibrium between RANKL and OPG levels and activity is important for the maintenance of normal bone metabolism (Bruhn-Olszewska *et al.* 2017). Osteoclast activation is a normal response to injury and is usually short lived; however, in the presence of DPN and reduced pain sensation, continued ambulation on the injured foot may result in persistent inflammation and prolonged activation of the RANKL–NF κ B pathway, leading to the excessive osteolysis, bony destruction and fractures observed in acute Charcot foot (Jeffcoate *et al.* 2005). A number of clinical studies have subsequently described elevated levels of pro-inflammatory cytokines, increases in both serum RANKL and OPG levels, with increased RANKL/OPG ratios in some but not all studies, and the relationship between the pro-inflammatory state and increased bone remodelling in acute Charcot neuroarthropathy; however, it remains unclear if the observed changes are the cause or consequence of the acute Charcot foot; this work has been extensively reviewed previously (Jeffcoate 2015, Jansen & Svendsen 2018, Kloska *et al.* 2020, Dardari 2020, Yates *et al.* 2020).

A number of studies have reported an association between variants in OPG, RANKL and RANK genes and development of Charcot neuroarthropathy (Kloska *et al.* 2020), indicating there may be an underlying genetic predisposition. A relationship between genetic regulation of bone remodelling and development of Charcot foot was first described by Pitocco *et al.* in a case-control study which identified a significant association between two single-nucleotide polymorphisms (SNPs) of the OPG gene (G1181C and T245G) in people with diabetes and Charcot foot compared to those with diabetes and peripheral neuropathy and no Charcot foot (Pitocco *et al.* 2009). Subsequent studies have identified a number of SNPs in OPG, RANK and RANKL genes in patients with acute Charcot foot (Korzon-Burakowska *et al.* 2012, Bruhn-Olszewska *et al.* 2017, SaiPrathiba *et al.* 2019, Kloska *et al.* 2020). Other recent work has focused on the role of monocyte to osteoclast differentiation in the development of acute Charcot foot (Kloska *et al.* 2020), including the finding of increased cytokine levels in circulating microparticles in patients with acute Charcot foot, differential expression of circulating micro-RNAs in patients with diabetes and Charcot foot

compared to patients with diabetes and neuropathy and the differential methylation of genes in circulating monocytes, all of which may affect monocyte to osteoclast differentiation and have a role in the development of the excessive osteolysis which arises in acute Charcot neuroarthropathy (Pasquier *et al.* 2017, 2018, 2019). Whilst further studies are required, this work provides useful insights into potential pathophysiological mechanisms and possible genetic associations underlying the development of acute Charcot foot, which could be explored in future work to potentially assist with the prediction of risk for the development of acute Charcot foot in people with diabetes, development of novel therapeutic interventions as well as development of new diagnostic markers for rapid identification in the early stage of the disease (Kloska *et al.* 2020).

The initial clinical features of acute Charcot foot include erythema, warmth and swelling, with only mild-to-moderate discomfort (Rogers *et al.* 2011). These non-specific findings may occur in other common conditions such as cellulitis, gout and deep vein thrombosis, and as a result, misdiagnosis and diagnosis delays are common (Rogers *et al.* 2011). An Australian review has described a number of barriers to the timely diagnosis and management of acute Charcot foot, including lack of patient awareness of the condition, lack of health professional awareness and knowledge of the condition and variation in access to appropriately skilled specialist services for optimal management (Diacogiorgis *et al.* 2021). Once established, a number of clinical and radiographic stages have been described in the progression of the acute Charcot foot (the modified Eichenholtz classification) from prodromal (stage 0), development (stage I), coalescence (stage II) and reconstruction (stage III) (Rosenbaum & DiPrea 2015). Improving awareness of acute Charcot foot amongst both people with diabetes and healthcare professionals across the care spectrum is vital to achieving detection in the earlier stages of the condition, in order to achieve optimal outcomes and reduced foot deformity.

The recommended treatment of the acute Charcot foot is offloading and immobilisation, ideally with a total contact cast (TCC), if appropriate and acceptable to the patient, and a period of non-weight bearing with the aim of reducing inflammation and limiting further destruction and deformity (Rogers *et al.* 2011, Jeffcoate 2015). Offloading and immobilisation is ideally continued until resolution of the acute Charcot foot which is considered to have occurred when swelling settles, there is less than 2°C temperature difference between the affected and contralateral foot (except in the case of bilateral

Charcot foot) and x-rays indicate stabilisation and healing, at which point transition to appropriate footwear may occur (Rogers *et al.* 2011, Jeffcoate 2015). Duration of time to resolution of acute Charcot foot does differ between publications, likely due to variation in study design, local practices and use of different definitions and methods for determining resolution (Rogers *et al.* 2011, Game *et al.* 2012, Jeffcoate 2015). The largest published observational study of acute Charcot foot, the Audit of Acute Charcot's Disease in the UK (CDUK) study, reported a median resolution time of 9 months for patients managed initially with a non-removable offloading device vs 12 months for the remainder ($P=0.001$) (Game *et al.* 2012). This is longer than typically reported in single-centre studies, including a recent Australian publication which reported a median resolution time of 4.3 months in patients with acute Charcot foot managed with a TCC (Griffiths & Kaminski 2021). A recent systematic review identified that multiple techniques for determining remission of acute Charcot neuroarthropathy are utilised with considerable uncertainty regarding effectiveness; further work is required to determine the optimal monitoring method and a consensus definition for acute Charcot foot remission (Gooday *et al.* 2020).

A number of pharmacological agents have been studied for the management of acute Charcot foot; however, no medication is presently recommended for routine use (Rogers *et al.* 2011, Jeffcoate 2015); lack of demonstrated efficacy for improved outcomes in addition to the standard of care treatment with immobilisation has been confirmed in a recent meta-analysis (Rastogi *et al.* 2021). A number of small RCTs of bisphosphonates have been conducted, with some reporting improved symptom scores and reductions in temperature as well as the expected decrease in bone turnover markers compared to placebo; however, time to resolution was increased following intravenous zoledronic acid, and there is insufficient evidence to support widespread use for acute Charcot foot (Rogers *et al.* 2011, Richard *et al.* 2012, Jeffcoate 2015). More recently, as the prolonged activation of the RANKL–NFKB pathway has been described, there has been great interest in the potential for the treatment of acute Charcot foot with denosumab, a fully monoclonal anti-RANKL antibody which binds and inhibits RANKL, resulting in reduced bone resorption via inhibition of osteoclast recruitment, maturation and action. Recent observational studies have reported that denosumab may be an effective treatment for acute Charcot foot with reduced time to resolution; however, RCT data are lacking (Busch-Westbroek *et al.* 2018, Lau *et al.* 2019, Carves

et al. 2021, Shofler *et al.* 2021). A number of denosumab RCTs are underway, including the CRUSADES study (ACTRN12617000937314) from Australia. Recombinant human parathyroid hormone (1-84), an anabolic bone agent used for the treatment of severe osteoporosis, has also recently been investigated as a potential therapy for acute Charcot foot but was not found to decrease time to resolution or enhance fracture healing (Petrova *et al.* 2021). Surgical intervention may be recommended in certain circumstances but should be performed by surgeons with specialist expertise and is typically avoided, where possible, in the acute inflammatory stages (Rogers *et al.* 2011). Surgery may be required for bony resection in osteomyelitis and may also be considered for correcting deformities and removing bony prominences that cannot be accommodated by custom footwear or orthoses or a Charcot Restraint Orthotic Walker; however, the evidence for benefit is somewhat limited (Rogers *et al.* 2011).

Charcot foot is an uncommon and challenging condition associated with considerable disability, distress and reduced survival (Rogers *et al.* 2011, Jeffcoate 2015, Gooday *et al.* 2022). Despite new insights in pathophysiology and potential genetic susceptibility as well as recent studies investigating novel pharmacological interventions, there are many existing challenges to achieve timely diagnosis, delivery of effective evidence-based management and improved longer term outcomes for people with diabetes and Charcot foot (Diacogiorgis *et al.* 2021).

New insights in DFU

A DFU is defined as a break of the skin of the foot that involves as a minimum the epidermis and part of the dermis in a person with currently or previously diagnosed diabetes mellitus and is usually accompanied by neuropathy and/or PAD in the lower extremity (van Netten *et al.* 2020). DFUs present a complex clinical problem, typically taking weeks to months to heal, and are associated with an increased risk of infection, hospitalisation and amputation (Zhang *et al.* 2021a). Here, we review new insights in DFU biomarkers, potential mediators of DFU healing, the DFU microbiome profile as well as pressure assessment and management.

Biomarkers and potential mediators of DFU healing

A recent Australia review indicates that whilst in normal wound healing a coordinated remodeling process

orchestrated by fibroblasts, endothelial cells, phagocytes and platelets, controlled by an array of growth factors, occurs, dysfunction occurs in wounds in diabetes including persistent and prolonged inflammation and a lack of wound maturation (Golledge & Thanigaimani 2021). Identification and utilisation of factors that may reliably predict DFU healing has great potential clinical value as the minority of ulcers that do not heal well can be targeted for more intensive therapy. In DFU tissue and fluid, McLennan and colleagues from Sydney reported some years ago that the pro-inflammatory protease MMP-9 in post-debridement DFU wound fluid, when at higher levels including in neuropathic ulcers, predicts adverse healing outcome at 12 weeks (Liu *et al.* 2009). Recent research confirms these findings in an independent cohort with longer DFU healing times in a debridement study (Nube *et al.* 2021) and also suggests MMP-9 protein measures may be able to be developed into a point of care test in DFU, which is currently being examined by Longfield and colleagues (Longfield *et al.* 2022). In terms of growth factor dysregulation in DFU, the transforming growth factor beta-related actin-binding cytoskeletal protein, flightless, was earlier reported by Cowan and colleagues to have predictive ability for chronic ulcer, albeit non-DFU, healing (Ruzehaji *et al.* 2012). More recent publications in preclinical models indicate that reduction in flightless in wounds may potentiate a switch from inflammatory to reparative macrophages (Mills *et al.* 2022). In other Australian growth factor-related matrix studies, whilst Henshaw *et al.* found that connective tissue growth factor (CTGF also known as CCN2) increases in post-debridement wound fluid as DFUs heal, preclinical bioactivity studies support CCN2 in potentiating DFU healing (Rhou *et al.* 2015); however, readily accessible chairside assays are yet to be developed.

Reflecting that systemic factors may be dysregulated in people with DFU, Min and colleagues recently reported that levels of certain lineage-specific monocytes with strong CD-16 expression predict DFU healing (Min *et al.* 2021), whereas circulating MMP-9 did not. These intriguing findings in linking monocyte/macrophage profiling in the circulation to DFU healing require replication in larger cohorts with longer DFU outcome follow-up. Another group found in a pilot study that blood measures of procalcitonin differentiated well between DFU with clinically definite osteomyelitis compared with cellulitis (Vangaveti *et al.* 2021). Other potential biomarkers include: microRNA species profiling in tissue and blood samples, inflammatory proteins (pentraxin-3, various interleukins and TNF α), genomic markers such as

HIF-1, Lox, neutrophil elastase, immune markers such as myeloid dendritic cell (MDC) and thymus- and activation-regulated chemokine (TARC), and clusterin including using techniques such as single-cell transcriptome profiling which may aid biomarker analysis as prognostic factors in the future (Pichu *et al.* 2017, Wang *et al.* 2021).

Irrespective of whether markers are in DFU wound fluid or tissue, or analysed from the circulation, some key factors to resolve in future research will be standardisation of robust methods of analysis and determination of the clinical utility of such measures using appropriate study cohorts with well-defined endpoints for healing such as at 6 months or the need for amputation (Jeffcoate *et al.* 2016). It has not yet been determined whether biomarker measures complement well-characterised clinical prognostic factors such as the presence of clinical PAD, bacterial infection, the ulcer depth and change in ulcer area across the first 4 weeks of multidisciplinary team-based DFU care, which has been verified recurrently to profile later DFU healing trajectory (Sheehan *et al.* 2003), as well as other simple measures such as temperature of the DFU site, ulcer pH (Gethin *et al.* 2018) and, as reaffirmed recently in a series by Lavery *et al.*, also blood CRP and erythrocyte sedimentation rate (ESR) to aid osteomyelitis detection (Ryan *et al.* 2022). Indeed, the wound microenvironment and systemic measures may be reflecting some of those established key clinical parameters just described. Even if such biomarkers are confirmed by multivariable analyses to have independent prediction for DFU healing, the issue of group compared with personalised prediction for DFU healing remains controversial. In the recent IWGDF guidelines, a recommendation was made to not provide individual prognosis to patients related to their DFU outcome, including healing and amputation, based on any wound classification system (Monteiro-Soares *et al.* 2020), whereas in the more recent Australian guidelines, a related recommendation was to be guarded in providing any personalised prognosis for DFU outcomes (Hamilton *et al.* 2021b). These recommendations reflect the available evidence, in which a number of classification systems, including wound ischaemia foot infection (WIFI) and site, ischaemia, neuropathy, bacterial infection, area and depth (SINBAD), have been externally validated for the prediction of DFU outcomes including LEA and ulcer healing within patient cohorts but not prognostication at an individual level (Monteiro-Soares *et al.* 2020). In addition the Australian guidelines wound classification chapter reinforces that documentation of the degree of any ischaemia present is of great import in enabling rational prognostication for healing outcomes; thus using granular

wound classification systems such as WIFI, rather than the simpler SINBAD system alone, is preferred (Hamilton *et al.* 2021b). With respect to DFU complexity (such as more ischaemic), general frailty, and DFU healing prognosis, in an international collaborative study, Fernando and colleagues found that digital assessment of human frailty associated with more complex DFU that had a worse prognosis (Mishra *et al.* 2022). This fascinating research may in time add prognostic value to DFU outcomes in particular patients.

In terms of interventions for DFU healing, the recently published Australian guidelines are a helpful contemporaneous reference to which the reader is referred, highlighting approved therapies, with five being recommended as part of MDT care: sucrose octasulfate-impregnated dressings, negative pressure wound therapy, systemic hyperbaric oxygen therapy, certain approved placental derived products and autologous combined leucocyte, platelet and fibrin dressing (Chen *et al.* 2022). Others in preclinical settings or in early phases such as EGF topical therapy are yet to be adequately tested clinically.

Diabetes-related foot infections: microbiology and microbiome

A recent Australian study found that approximately 40% of patients with a DFU experienced a diabetic foot infection (DFI) over a 12-month follow-up period (Jia *et al.* 2017). In a study from Darwin, Australia, hospitalisation with DFI was associated with a major amputation rate approaching 10% and an extended median hospital length of stay of 29 days (Commons *et al.* 2015). One-year mortality after hospitalisation with DFI was approximately 9% and substantially increased amongst patients on haemodialysis (Lynar *et al.* 2019). A survey of Australian Infectious Diseases (ID) physicians reported that management of patients with DFI accounted for approximately 19% of ID physician caseload, and there was marked heterogeneity in antimicrobial treatment regimen recommendations (Commons *et al.* 2018). A survey of Australian and New Zealand vascular and orthopaedic surgeons found they had relatively similar management practices, but few were guided by best practice clinical guidelines for DFI (Seng *et al.* 2022). An Australian study reported microbiology results from patients with DFI managed in a tertiary inpatient setting and revealed antimicrobial stewardship opportunities with overuse of antipseudomonal agents despite adherence to national antibiotic prescribing

guidelines (Hand *et al.* 2019). The utility of wound swab vs tissue sampling in patients with DFI has been investigated by the CODIFI study, which found that the most commonly reported pathogens were *Staphylococcus aureus* (43.8%), *Streptococcus* (16.7%) and other aerobic Gram-positive cocci (70.6%) and 86.1% of tissue samples reported at least one potential pathogen compared with 70.1% of wound swabs collected (Nelson *et al.* 2018). Microbiology results differed between sampling methods in 58% of patients, with more pathogens and fewer contaminants reported from tissue specimens than wound swabs (Nelson *et al.* 2018). Whilst more pathogens were identified on tissue samples compared with wound swabs, it is unclear whether providing more comprehensive microbiological information improves the efficacy of antibiotic prescribing and better infection treatment and/or DFU healing outcomes or alternatively results in the prescription of broader antibiotic regimens which may drive antibiotic resistance in the longer term.

In comparison with traditional wound swab and/or tissue culture-based methods, recent research has seen the utilisation of advanced sequencing technologies to provide a comprehensive DFU microbiome profile, with detailed taxonomic information and additional characteristics such as virulence and antibiotic resistance profiling (Malone *et al.* 2017a, Liu *et al.* 2020). Using next-generation DNA sequencing, Australian researchers have confirmed that infected DFUs of shorter duration have a simpler microbiome usually consisting of pyogenic cocci compared with chronic DFUs which have a highly polymicrobial microbiome (Malone *et al.* 2017b). Using multiple approaches including traditional culture, DNA sequencing and microscopy, Malone *et al.* have reported that half of seemingly 'clean' uninfected proximal bone specimens collected in the operating theatre from patients requiring bone resection for management of osteomyelitis have evidence of the presence of microorganisms (Malone *et al.* 2019). Further work from this group has also provided insights into the host-microbe function in acutely vs chronically infected DFUs, revealing that bacteria in acutely infected DFUs prioritise motility over biofilm formation and demonstrate greater pathogenicity (Malone *et al.* 2022). These promising new developments and advanced techniques provide a wealth of information regarding the microbiome profile of DFUs which may potentially be harnessed in future to provide personalised antibiotic prescribing and DFI management; however, the clinical application is uncertain at this stage, and at present these techniques remain predominantly research tools (Liu *et al.* 2020, Commons *et al.* 2022).

Pressure assessment and care

That minimisation of plantar pressure, at and around an ulcer, is critically important to aid DFU healing and to prevent recurrence has been reasserted by a group of researchers in Darwin, Northern Territory, who found in an observational audit across 15 years with routine clinic use in their high-risk foot service that application of the TCC led to higher overall healing and longer time in usage than those where removable non-TCC devices were used (Berhane *et al.* 2022). An Australian systematic review by Lazzarini *et al.* reinforced these findings, showing that knee-high irremovable casts provided best DFU healing outcomes in MDT care (Lazzarini *et al.* 2020). Measures of barefoot and in-shoe plantar pressures may be of clinical predictive value in people with DFD, reflecting abnormalities in foot biomechanics in a Newcastle, NSW series by Chuter *et al.* (Chuter *et al.* 2021). These abnormal foot biomechanics include equinus deformities, with reduced ankle dorsiflexion, which are common in people with diabetes (Searle *et al.* 2018). Plantar tissue stress (comprising a combination of factors including plantar pressure, shear stress, daily weight-bearing activity, and adherence to prescribed offloading interventions) is increasingly recognised as a critical modifiable factor in DFU development and healing (Lazzarini *et al.* 2019). It is anticipated that as technology for plantar tissue stress measurement becomes more widely available and accessible to patients with DFU, these advances will enable more personalised offloading management plans for patients in the future (Lazzarini *et al.* 2019). Remotely delivered monitoring in DFD including with telehealth has been reported in a recent Australian systematic review by Golledge and colleagues, and whilst it is well received by patients, its effectiveness is unclear, requiring more dedicated research (Drovandi *et al.* 2023). Each of home temperature monitoring and pressure offloading device use may help to prevent DFU recurrence as reported in another Golledge *et al.* review (Alahakoon *et al.* 2020). Once a DFU has healed, Fernando *et al.* have provided recommendations for safe resumption of activity, including monitoring of activity training, with carefully dosed activity increments and the use of daily skin temperature monitoring (Fernando *et al.* 2021). Golledge and colleagues also identified gait abnormalities in those with non-healing DFU with further research required to determine whether the observed gait abnormalities were the cause or consequence of a non-healing DFU (Fernando *et al.* 2019). Overall, these studies indicate that minimisation of plantar ulcer pressure optimises DFU

healing and can prevent ulcer recurrence, as well described in the recently published national clinical care guidelines in DFD (Fernando *et al.* 2022b), where for Australians with plantar DFU, a practical, targeted step-down offloading treatment approach based on patient contraindications and tolerance has been recommended.

Comorbidities and sequelae of DFU

Despite advances in care, many patients with a DFU experience poor outcomes, including non-healing, complex medical comorbidities and increased mortality. It is possible that the relationship between medical comorbidities and DFU may be bidirectional, with conditions such as heart failure and renal disease impairing wound healing whilst at the same time DFU-associated changes such as chronic inflammation promoting premature onset of cardiovascular, renal and musculoskeletal disease in this high-risk patient group. Moreover, as well described in a recent Australian impactful review article (Golledge 2022), chronic limb-threatening ischaemia, which is present in ischaemic and mixed neuroischaemic ulcers, occurs in some series in most of the DFU requiring hospitalisation, as well as commonly linking to major CVD events. Epidemiological data suggest that patients with diabetes who develop a DFU have a more than two-fold increase in mortality compared to patients with diabetes alone, after adjustment for age, diabetes type, duration and treatment, HbA1c, history of amputation and smoking (Boyko *et al.* 1996). CVD has been found to be the predominant cause of death in patients with DFU (Chammas *et al.* 2016). Mechanistic explanations for increased cardiovascular morbidity in patients with DFU are limited to small, cross-sectional nuclear cardiac imaging or echocardiographic studies. In these, rates of undetected cardiovascular abnormalities were between 50% and 76% (Nesto *et al.* 1990, Londahl *et al.* 2008, Tsujimoto *et al.* 2011). Conversely, CVD in patients with DFU may also have important impacts on wound healing, with at least two studies finding that impaired cardiac function was associated with slower DFU healing (Xu *et al.* 2013, Rhou *et al.* 2015).

Acute kidney injury (AKI) is associated with adverse outcomes, including increased mortality and progression of CKD (Fortrie *et al.* 2019). Recent retrospective studies have reported an incidence of AKI of 48.5% amongst patients hospitalised with DFI (Ryan *et al.* 2020) and 27% amongst patients with diabetes and osteomyelitis (van Asten *et al.* 2018). Although there is evidence that

patients requiring dialysis for end-stage renal disease have poorer DFU outcomes, including increased risk of LEA (Monteiro-Soares *et al.* 2014), there is a paucity of prospective data describing wound healing outcomes amongst patients with DFI complicated by AKI. AKI occurring during hospitalisation for acute DFI may be an important factor associated with DFU outcomes and an indicator of more rapid decline in renal function amongst patients with diabetes.

Pressure offloading is one of the cornerstones of DFU management and people with DFU are typically advised to limit physical activity to promote ulcer healing, particularly for plantar wounds (Bus *et al.* 2020, Fernando *et al.* 2022b). A recent study found the prevalence of low muscle mass in people with T2DM with DFU to be more than double that in people with T2DM without DFU, independent of age and diabetes duration (Cheng *et al.* 2017). It is possible that low muscle mass and increased fat mass may be a consequence of DFU and/or DFU treatment; however, prospective data are lacking. A recent Australian study has reported significant losses of total hip BMD of the ipsilateral limb (-1.7%, $P < 0.001$), total hip BMD of the contralateral limb (-1.4%, $P = 0.005$), femoral neck BMD of the ipsilateral limb (-2.8%, $P < 0.001$) and femoral neck BMD of the contralateral limb (-2.2%, $P = 0.008$) 12 weeks after hospitalisation for DFU (Nejatian *et al.* 2021). No changes to lean and fat mass were demonstrated (Nejatian *et al.* 2021). These findings need to be confirmed in a larger-scale study of longer duration and explore whether interventions such as an exercise programme designed specifically for patients with DFU or use of a pharmacological antiresorptive agent may reduce the observed decline in BMD. Whether patients with DFU are at increased risk of fracture compared to people with diabetes and no DFU and/or healthy controls is unknown. Additionally, frailty has recently been reported to be highly prevalent amongst patients hospitalised with DFU and associated with poorer outcomes including DFU non-healing and all-cause rehospitalisation (Fernando *et al.* 2022a, Maltese *et al.* 2022). Further efforts are required to understand and address the multi-morbidity and multi-system impairment experienced by patients with DFU, especially in acute care settings.

A number of studies have described nutritional deficiencies and/ or supplementation in people with DFU; however, conclusive data regarding the effects of nutritional or micronutrient supplementation on DFU healing outcomes are lacking (Bechara *et al.* 2021). A recent Australian cross-sectional study found a high prevalence of micronutrient deficiencies amongst patients with

DFU, with 51% of patients experiencing vitamin C (VitC) deficiency, 27% having zinc deficiency and 10.9% being deficient in vitamin A (VitA) (Pena *et al.* 2020). In addition, the presence of VitC deficiency was associated with more severe foot ulceration; however, as the study was cross-sectional, it is unclear if deficiencies of VitC, VitA and/ or zinc were associated with poorer DFU healing outcomes (Pena *et al.* 2020). A recent small RCT from Australia demonstrated a striking effect of VitC on wound healing trajectory (Gunton *et al.* 2020); although low participant numbers are a limitation, the results support further trials of micronutrient supplementation in patients with DFUs, and an Australian RCT has recently commenced to evaluate the effect of a combined VitC, VitA and zinc supplement (VITAFOOT ACTRN12621001493831) on DFU healing outcomes.

DFD increases the treatment burden and daily self-management tasks associated with diabetes (Vileikyte 2008). Optimal foot care and wound healing for patients with DFD requires significant cognitive resources to achieve adherence to a number of diabetes and foot self-care behaviours (Bergin *et al.* 2012). Cognitive impairment in people with DFU has been explored in a number of recent studies. The largest study of subjects with T2DM with and without DFU used a battery of neuropsychological tests designed for the detection of mild cognitive impairment and dementia, and greater deficits in multiple cognitive domains, including memory, attention and concentration, reaction time, executive function and psychomotor function, were identified in those with DFU (Natovich *et al.* 2016). There were also differences between the two groups in education level, chronic diabetes complications, and HbA1c; however, differences in cognition remained after adjustment for these potential confounders (Natovich *et al.* 2016). Another study designed to assess endothelial dysfunction and arterial stiffness in people with DFU reported lower MMSE scores in patients with DFU compared to those with diabetes without DFU; however, potential confounding risk factors were imbalanced between the groups with higher blood pressure, BMI, previous cardiovascular events and dyslipidemia amongst patients with DFU (Tuttolomondo *et al.* 2017). A recent Australian study found no difference in cognition, using readily available screening tools (MMSE and Montreal cognitive assessment (MOCA)), between patients with T2DM with and without DFU; however, it was notable that at least mild cognitive impairment was very common in both groups, with approximately half of the participants with T2DM with or without DFU

recruited from hospital complex diabetes and high-risk foot clinics scoring ≤ 25 on the MOCA test (Siru *et al.* 2021). Another Australian study of patients requiring hospitalisation for DFU management reported a low average MOCA score of 22 (Corbett *et al.* 2019); however, hospitalisation is itself associated with cognitive decline (O'Brien *et al.* 2018); longitudinal data would be useful to determine whether the cognitive impairment observed in this patient group persisted after recovery from the acute illness. Further research is required to determine whether cognitive deficits described amongst patients with DFU are associated with adverse outcomes such as impaired ulcer healing.

Depression is common amongst people with DFD and is frequently unrecognised and untreated (Ismail *et al.* 2007, Pearson *et al.* 2014). Depression has been linked to poorer outcomes for people with DFU, including impaired ulcer healing, increased ulcer recurrence, poorer quality of life and increased mortality (Ismail *et al.* 2007, Monami *et al.* 2008, Pedras *et al.* 2018). Australian researchers reported that depressive symptoms were associated with less optimal diabetes self-management and poorer health-related quality of life but not DFU healing outcomes at 6 months (Pearson *et al.* 2014). People living with DFD have complex medical and psychosocial needs which should be addressed with a holistic evidence based approach.

Conclusion

DFD is associated with increased morbidity, mortality and costs and a heavy burden for patients and the healthcare system. Collectively, researchers, scientists, clinicians, patients and policy makers can synergise to have a positive impact on outcomes and also in setting the agenda for future Australian DFD research. Here we have highlighted recent advances in DFD research with a focus on contributions from Australia and New Zealand, providing important insights into pathogenesis and mechanisms of disease as well as providing hope for the development of innovative therapeutic interventions in the future, in the process contributing substantially to global translational research progress in addressing this common and morbid diabetes-related complication.

Declaration of interest

Prof. Stephen Twigg is a member of the Australian Nevro Advisory Board, addressing spinal cord stimulation for painful DPN. Dr Emma Hamilton has no relevant conflicts of interest.

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