THEMATIC REVIEW

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

Emma J Hamilton[1] and **Stephen M Twigg**[2]

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

This paper forms part of a special collection produced in collaboration with the Endocrine Society of Australia. The guest editors for this section were Timothy Cole and Bu Yeap.

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

Journal of Endocrinology (2023) **257**, **e220238**

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.* 2021*b*). 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 Commision on Safety and Quality in Healthcare and

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

National Health Performance Authority 2016). DFD is associated with high morbidity, mortality and healthcare costs (Lazzarini *et al.* 2018, Zhang *et al.* 2020, 2021*b*). 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.* 2021*a*), 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 Commision on Safety and Quality in Healthcare and National Health Performance Authority 2016, Zhang *et al.* 2021*a*, 2022, Tehan *et al.* 2022). New comprehensive Australian guidelines for DFD management, adapated 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.* 2021*b*, Perrin *et al.* 2021, Chen *et al.* 2022, Chuter *et al.* 2022, Commons *et al.* 2022, Fernando *et al.* 2022*b*, 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

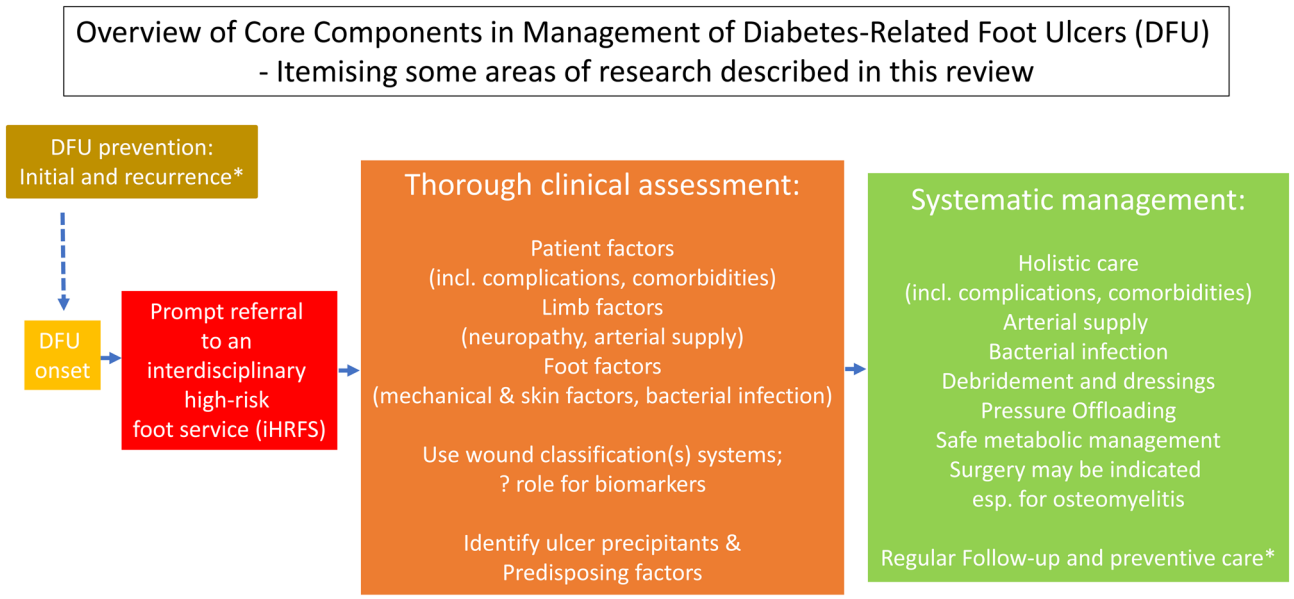

Figure 1
Overview of the core components in the management of diabetes-related foot ulcers.

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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.* 2021*a*,*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.* 2021*a*,*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

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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).

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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 (TNFα), interleukin-1β (IL-1β) and IL-6, which in turn leads to increased expression of the receptor activator of nuclear factor κβ ligand (RANKL) which binds to its receptor, receptor activator of nuclear factor κβ (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–NFKB 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

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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-modest 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 & DiPreta 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

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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.* 2021*a*). 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 growith 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 TNFα), genomic markers such as

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

HIF-1, Lox, neutrophil elastase, immune markers such as myeloid dendritis 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.* 2021*b*). 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.* 2021*b*). 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

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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.* 2017*a*, 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.* 2017*b*). 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 equinis 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

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

healing and can prevent ulcer recurrence, as well described in the recently published national clinical care guidelines in DFD (Fernando *et al.* 2022*b*), 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.* 2022*b*). 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.* 2022*a*, 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

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

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.

https://joe.bioscientifica.com
https://doi.org/10.1530/JOE-22-0238

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. Dr Emma Hamilton was supported by a Clinician Research Fellowship from the Raine Foundation and WA Health Department.

References

Australian Commision on Safety and Quality in Healthcare and National Health Performance Authority 2016 *Australian Atlas of Healthcare Variation* (ACSQHC Ed.). Sydney, Australia.

Alahakoon C, Fernando M, Galappaththy C, Matthews EO, Lazzarini P, Moxon JV & Golledge J 2020 Meta-analyses of randomized controlled trials reporting the effect of home foot temperature monitoring, patient education or offloading footwear on the incidence of diabetes-related foot ulcers. *Diabetic Medicine* **37** 1266–1279. (https://doi.org/10.1111/dme.14323)

Alam U, Jeziorska M, Petropoulos IN, Asghar O, Fadavi H, Ponirakis G, Marshall A, Tavakoli M, Boulton AJM, Efron N, *et al.* 2017 Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy. *PLoS One* **12** e0180175. (https://doi.org/10.1371/journal.pone.0180175)

Arnold R, Pianta TJ, Issar T, Kirby A, Scales CMK, Kwai NCG, Endre Z & Krishnan AV 2022 Peripheral neuropathy: an important contributor to physical limitation and morbidity in stages 3 and 4 chronic kidney disease. *Nephrology, Dialysis, Transplantation* **37** 713–719. (https://doi.org/10.1093/ndt/gfab043)

Arnott C, Huang Y, Neuen BL, Di Tanna GL, Cannon CP, Oh R, Edwards R, Kavalam M, Rosenthal N, Perkovic V, *et al.* 2020 The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial. *Diabetes, Obesity and Metabolism* **22** 1753–1766. (https://doi.org/10.1111/dom.14091)

Azmi S, Ferdousi M, Kalteniece A, Petropoulos IN, Ponirakis G, Alam U, Asghar O, Marshall A, Sankar A, Boulton AJM, *et al.* 2021 Protection from neuropathy in extreme duration type 1 diabetes. *Journal of the Peripheral Nervous System* **26** 49–54. (https://doi.org/10.1111/jns.12423)

Bagher AM 2022 The endocannabinoid system as a therapeutic target in diabetic peripheral neuropathic pain: a review. *Journal of Microscopy and Ultrastructure* **10** 47–54. (https://doi.org/10.4103/jmau.jmau_97_20)

Bechara N, Gunton JE, Flood V, Hng TM & Mcgloin C 2021 Associations between nutrients and foot ulceration in diabetes: a systematic review. *Nutrients* **13** 2576. (https://doi.org/10.3390/nu13082576)

Bergin SM, Gurr JM, Allard BP, Holland EL, Horsley MW, Kamp MC, Lazzarini PA, Nube VL, Sinha AK, Warnock JT, *et al.* 2012 Australian Diabetes Foot Network: management of diabetes-related foot ulceration – a clinical update. *Medical Journal of Australia* **197** 226–229. (https://doi.org/10.5694/mja11.10347)

Berhane T, Jeyaraman K, Hamilton M & Falhammar H 2022 Pressure relieving interventions for the management of diabetes-related foot ulcers: a study from the Northern Territory of Australia. *ANZ Journal of Surgery* **92** 723–729. (https://doi.org/10.1111/ans.17431)

Boyko EJ, Ahroni JH, Smith DG & Davignon D 1996 Increased mortality associated with diabetic foot ulcer. *Diabetic Medicine* **13** 967–972. (https://doi.org/10.1002/(SICI)1096-9136(199611)13:11<967::AID-DIA266>3.0.CO;2-K)

Brownlee M 2005 The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* **54** 1615–1625. (https://doi.org/10.2337/diabetes.54.6.1615)

Bruce DG, Davis TME & Davis WA 2019 Dementia complicating type 2 diabetes and the influence of premature mortality: the Fremantle Diabetes Study. *Acta Diabetologica* **56** 767–776. (https://doi.org/10.1007/s00592-019-01322-9)

Bruhn-Olszewska B, Korzon-Burakowska A, Wegrzyn G & Jakobkiewicz-Banecka J 2017 Prevalence of polymorphisms in OPG, RANKL and RANK as potential markers for Charcot arthropathy development. *Scientific Reports* **7** 501. (https://doi.org/10.1038/s41598-017-00563-4)

Bus SA, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, Lazzarini PA & International Working Group on the Diabetic Foot (IWGDF) 2020 Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes/Metabolism Research and Reviews* **36**(Supplement 1) e3274. (https://doi.org/10.1002/dmrr.3274)

Busch-Westbroek TE, Delpeut K, Balm R, Bus SA, Schepers T, Peters EJ, Smithuis FF, Maas M & Nieuwdorp M 2018 Effect of single dose of RANKL antibody treatment on acute charcot neuro-osteoarthropathy of the foot. *Diabetes Care* **41** e21–e22. (https://doi.org/10.2337/dc17-1517)

Carves S, Bourgeon-Ghittori M, Henry J, Belkhir R, Besson FL, Levante S, Mariette X & Seror R 2021 Denosumab in active Charcot neuro-osteoarthropathy of the foot. *Joint Bone Spine* **88** 105241. (https://doi.org/10.1016/j.jbspin.2021.105241)

Chammas NK, Hill RL & Edmonds ME 2016 Increased mortality in diabetic foot ulcer patients: the significance of ulcer type. *Journal of Diabetes Research* **2016** 2879809. (https://doi.org/10.1155/2016/2879809)

Chen P, Carville K, Swanson T, Lazzarini PA, Charles J, Cheney J, Prentice J & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2022 Australian guideline on wound healing interventions to enhance healing of foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **15** 40. (https://doi.org/10.1186/s13047-022-00544-5)

Cheng Q, Hu J, Yang P, Cao X, Deng X, Yang Q, Liu Z, Yang S, Goswami R, Wang Y, *et al.* 2017 Sarcopenia is independently associated with diabetic foot disease. *Scientific Reports* **7** 8372. (https://doi.org/10.1038/s41598-017-08972-1)

Cho YR, Lim JH, Kim MY, Kim TW, Hong BY, Kim YS, Chang YS, Kim HW & Park CW 2014 Therapeutic effects of fenofibrate on diabetic peripheral neuropathy by improving endothelial and neural survival in db/db mice. *PLoS One* **9** e83204. (https://doi.org/10.1371/journal.pone.0083204)

Chuter VH, Spink MJ, David M, Lanting S & Searle A 2021 Clinical foot measurements as a proxy for plantar pressure testing in people with diabetes. *Journal of Foot and Ankle Research* **14** 56. (https://doi.org/10.1186/s13047-021-00494-4)

Chuter V, Quigley F, Tosenovsky P, Ritter JC, Charles J, Cheney J, Fitridge R & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2022 Australian guideline on diagnosis and management of peripheral artery disease: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **15** 51. (https://doi.org/10.1186/s13047-022-00550-7)

Commons RJ, Robinson CH, Gawler D, Davis JS & Price RN 2015 High burden of diabetic foot infections in the top end of Australia: an emerging health crisis (DEFINE study). *Diabetes Research and Clinical Practice* **110** 147–157. (https://doi.org/10.1016/j.diabres.2015.09.016)

Commons RJ, Raby E, Athan E, Bhally H, Chen S, Guy S, Ingram PR, Lai K, Lemoh C, Lim LL, *et al.* 2018 Managing diabetic foot infections: a survey of Australasian infectious diseases clinicians. *Journal of Foot and Ankle Research* **11** 13. (https://doi.org/10.1186/s13047-018-0256-3)

Commons RJ, Charles J, Cheney J, Lynar SA, Malone M, Raby E & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2022 Australian guideline on management of diabetes-related foot infection: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **15** 47. (https://doi.org/10.1186/s13047-022-00545-4)

Corbett C, Jolley J, Barson E, Wraight P, Perrin B & Fisher C 2019 Cognition and understanding of neuropathy of inpatients admitted to a specialized tertiary diabetic foot unit with diabetes-related foot ulcers. *International Journal of Lower Extremity Wounds* **18** 294–300. (https://doi.org/10.1177/1534734619862085)

Dardari D 2020 An overview of Charcot's neuroarthropathy. *Journal of Clinical and Translational Endocrinology* **22** 100239. (https://doi.org/10.1016/j.jcte.2020.100239)

Diacogiorgis D, Perrin BM & Kingsley MIC 2021 Factors impacting the evidence-based assessment, diagnosis and management of Acute Charcot Neuroarthropathy: a systematic review. *Journal of Foot and Ankle Research* **14** 26. (https://doi.org/10.1186/s13047-021-00469-5)

D'Onofrio L, Ferdousi M, Kalteniece A, Iqbal Z, Petropoulos IN, Ponirakis G, Buzzetti R, Malik RA & Soran H 2022 Corneal confocal microscopy identifies small nerve fibre damage in patients with hypertriglyceridemia. *Journal of Clinical Lipidology* **16** 463–471. (https://doi.org/10.1016/j.jacl.2022.04.006)

Drovandi A, Wong S, Seng L, Crowley B, Alahakoon C, Banwait J, Fernando ME & Golledge J 2023 Remotely delivered monitoring and management of diabetes-related foot disease: an overview of systematic reviews. *Journal of Diabetes Science and Technology* **17** 59–69. (https://doi.org/10.1177/19322968211012456)

Eid S, Sas KM, Abcouwer SF, Feldman EL, Gardner TW, Pennathur S & Fort PE 2019 New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* **62** 1539–1549. (https://doi.org/10.1007/s00125-019-4959-1)

Esparza J, Gudimetla P, De Silva S & Unsworth CA 2021 An early warning system for diabetic automobile drivers with peripheral neuropathy. *Disability and Rehabilitation. Assistive Technology* **16** 624–631. (https://doi.org/10.1080/17483107.2019.1686076)

Ferdousi M, Azmi S, Kalteniece A, Petropoulos IN, Ponirakis G, Asghar O, Alam U, Marshall A, Boulton AJM, Efron N, *et al.* 2021 Greater small nerve fibre damage in the skin and cornea of type 1 diabetic patients with painful compared to painless diabetic neuropathy. *European Journal of Neurology* **28** 1745–1751. (https://doi.org/10.1111/ene.14757)

Fernando ME, Crowther RG, Lazzarini PA, Sangla KS, Wearing S, Buttner P & Golledge J 2019 Gait in people with nonhealing diabetes-related plantar ulcers. *Physical Therapy* **99** 1602–1615. (https://doi.org/10.1093/ptj/pzz119)

Fernando ME, Woelfel SL, Perry D, Najafi B, Khan T, Dubourdieu C, Shin L & Armstrong DG 2021 Dosing activity and return to Preulcer function in diabetes-related foot ulcer remission. *Journal of the American Podiatric Medical Association* **111**. (https://doi.org/10.7547/20-166)

Fernando ME, Blanchette V, Mishra R, Zulbaran-Rojas A, Rowe V, Mills JL, Armstrong DG & Najafi B 2022*a* Frailty in people with chronic limb threatening ischemia and diabetes-related foot ulcers: a systematic review. *Annals of Vascular Surgery* **89** 322–337. (https://doi.org/10.1016/j.avsg.2022.09.057)

Fernando ME, Horsley M, Jones S, Martin B, Nube VL, Charles J, Cheney J, Lazzarini PA & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2022*b* Australian guideline on offloading treatment for foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **15** 31. (https://doi.org/10.1186/s13047-022-00538-3)

Fleischer M, Lee I, Erdlenbruch F, Hinrichs L, Petropoulos IN, Malik RA, Hartung HP, Kieseier BC, Kleinschnitz C & Stettner M 2021 Corneal confocal microscopy differentiates inflammatory from diabetic neuropathy. *Journal of Neuroinflammation* **18** 89. (https://doi.org/10.1186/s12974-021-02130-1)

Fortrie G, De Geus HRH & Betjes MGH 2019 The aftermath of acute kidney injury: a narrative review of long-term mortality and renal function. *Critical Care* **23** 24. (https://doi.org/10.1186/s13054-019-2314-z)

Game FL, Catlow R, Jones GR, Edmonds ME, Jude EB, Rayman G & Jeffcoate WJ 2012 Audit of acute Charcot's disease in the UK: the CDUK study. *Diabetologia* **55** 32–35. (https://doi.org/10.1007/s00125-011-2354-7)

Gethin G, O'connor GM, Abedin J, Newell J, Flynn L, Watterson D & O'loughlin A 2018 Monitoring of pH and temperature of neuropathic diabetic and nondiabetic foot ulcers for 12 weeks: an observational study. *Wound Repair and Regeneration* **26** 251–256. (https://doi.org/10.1111/wrr.12628)

Golledge J 2022 Update on the pathophysiology and medical treatment of peripheral artery disease. *Nature Reviews. Cardiology* **19** 456–474. (https://doi.org/10.1038/s41569-021-00663-9)

Golledge J & Thanigaimani S 2021 Novel therapeutic targets for diabetes-related wounds or ulcers: an update on preclinical and clinical research. *Expert Opinion on Therapeutic Targets* **25** 1061–1075. (https://doi.org/10.1080/14728222.2021.2014816)

Gooday C, Gray K, Game F, Woodburn J, Poland F & Hardeman W 2020 Systematic review of techniques to monitor remission of acute Charcot neuroarthropathy in people with diabetes. *Diabetes/Metabolism Research and Reviews* e3328. (https://doi.org/10.1002/dmrr.3328)

Gooday C, Hardeman W, Game F, Woodburn J & Poland F 2022 A qualitative study to understand people's experiences of living with Charcot neuroarthropathy. *Diabetic Medicine* **39** e14784. (https://doi.org/10.1111/dme.14784)

Griffiths DA & Kaminski MR 2021 Duration of total contact casting for resolution of acute Charcot foot: a retrospective cohort study. *Journal of Foot and Ankle Research* **14** 44. (https://doi.org/10.1186/s13047-021-00477-5)

Gunton JE, Girgis CM, Lau T, Vicaretti M, Begg L & Flood V 2020 Vitamin C improves healing of foot ulcers: a randomised, double-blind, placebo-controlled trial. *British Journal of Nutrition* **126** 1451–1458. (https://doi.org/10.1017/s0007114520003815)

Gupta G, Maiya GA, Bhat SN, Hande MH, Dillon L & Keay L 2022 Fear of falling and functional mobility in elders with diabetic peripheral neuropathy in coastal Karnataka, India: a hospital-based study. *Current Aging Science* **15** 252–258. (https://doi.org/10.2174/1874609815666220324153104)

Hamilton EJ, Davis WA, Siru R, Baba M, Norman PE & Davis TME 2021*a* Temporal trends in incident hospitalization for diabetes-related foot ulcer in Type 2 diabetes: the Fremantle diabetes study. *Diabetes Care* **44** 722–730. (https://doi.org/10.2337/dc20-1743)

Hamilton EJ, Scheepers J, Ryan H, Perrin BM, Charles J, Cheney J, Twigg SM & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2021*b* Australian guideline on wound classification of diabetes-related foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **14** 60. (https://doi.org/10.1186/s13047-021-00503-6)

Hand R, Manning L, Ritter JC, Norman P, Lamb L, Makepeace A, Sankhesara D, Hamilton E & Ingram P 2019 Antimicrobial stewardship opportunities among inpatients with diabetic foot infections: microbiology results from a tertiary hospital multidisciplinary unit. *Internal Medicine Journal* **49** 533–536. (https://doi.org/10.1111/imj.14251)

Hussain N, Said ASA, Javaid FA, Al Haddad AHI, Anwar M, Khan Z & Abu-Mellal A 2021 The efficacy and safety profile of capsaicin 8% patch versus 5% lidocaine patch in patients with diabetic peripheral neuropathic pain: a randomized, placebo-controlled study of South Asian male patients. *Journal of Diabetes and Metabolic Disorders* **20** 271–278. (https://doi.org/10.1007/s40200-021-00741-2)

Ismail K, Winkley K, Stahl D, Chalder T & Edmonds M 2007 A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. *Diabetes Care* **30** 1473–1479. (https://doi.org/10.2337/dc06-2313)

Issar T, Kwai NCG, Poynten AM, Arnold R, Milner KL & Krishnan AV 2021*a* Effect of exenatide on peripheral nerve excitability in type 2 diabetes. *Clinical Neurophysiology* **132** 2532–2539. (https://doi.org/10.1016/j.clinph.2021.05.033)

Issar T, Tummanapalli S, Borire A, Kwai N, Poynten A, Arnold R, Markoulli M & Krishnan A 2021*b* Impact of the metabolic syndrome on peripheral nerve structure and function in type 2 diabetes. *European Journal of Neurology* **28** 2074–2082.

Jaiswal M, Martin CL, Brown MB, Callaghan B, Albers JW, Feldman EL & Pop-Busui R 2015 Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. *Journal of Diabetes and its Complications* **29** 1287–1294. (https://doi.org/10.1016/j.jdiacomp.2015.07.013)

Jansen RB & Svendsen OL 2018 A review of bone metabolism and developments in medical treatment of the diabetic Charcot foot.

Journal of Diabetes and its Complications **32** 708–712. (https://doi.org/10.1016/j.jdiacomp.2018.04.010)

Jeffcoate WJ 2015 Charcot foot syndrome. *Diabetic Medicine* **32** 760–770. (https://doi.org/10.1111/dme.12754)

Jeffcoate WJ, Game F & Cavanagh PR 2005 The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes. *Lancet* **366** 2058–2061. (https://doi.org/10.1016/S0140-6736(05)67029-8)

Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC, International Working Group on the Diabetic Foot and the European Wound Management Association & The European Wound Management 2016 Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinology* **4** 781–788. (https://doi.org/10.1016/S2213-8587(16)30012-2)

Jeffrey S, Samraj PI & Raj BS 2021 The role of alpha-lipoic acid supplementation in the prevention of diabetes complications: a comprehensive review of clinical trials. *Current Diabetes Reviews* **17** e011821190404. (https://doi.org/10.2174/1573399817666210118145550)

Jia L, Parker CN, Parker TJ, Kinnear EM, Derhy PH, Alvarado AM, Huygens F, Lazzarini PA & Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network (Australia) 2017 Incidence and risk factors for developing infection in patients presenting with uninfected diabetic foot ulcers. *PLoS One* **12** e0177916. (https://doi.org/10.1371/journal.pone.0177916)

Kaminski MR, Golledge J, Lasschuit JWJ, Schott KH, Charles J, Cheney J, Raspovic A & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2022 Australian guideline on prevention of foot ulceration: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **15** 53. (https://doi.org/10.1186/s13047-022-00534-7)

Khursheed R, Singh SK, Wadhwa S, Gulati M, Kapoor B, Awasthi A, Kr A, Kumar R, Pottoo FH, Kumar V, *et al.* 2021 Opening eyes to therapeutic perspectives of bioactive polyphenols and their nanoformulations against diabetic neuropathy and related complications. *Expert Opinion on Drug Delivery* **18** 427–448. (https://doi.org/10.1080/17425247.2021.1846517)

Klisser J, Tummanapalli SS, Kim J, Chiang JCB, Khou V, Issar T, Naduvilath T, Poynten AM, Markoulli M & Krishnan AV 2022 Automated analysis of corneal nerve tortuosity in diabetes: implications for neuropathy detection. *Clinical and Experimental Optometry* **105** 487–493. (https://doi.org/10.1080/08164622.2021.1940875)

Kloska A, Korzon-Burakowska A, Malinowska M, Bruhn-Olszewska B, Gabig-Ciminska M & Jakobkiewicz-Banecka J 2020 The role of genetic factors and monocyte-to-osteoclast differentiation in the pathogenesis of Charcot neuroarthropathy. *Diabetes Research and Clinical Practice* **166** 108337. (https://doi.org/10.1016/j.diabres.2020.108337)

Korzon-Burakowska A, Jakobkiewicz-Banecka J, Fiedosiuk A, Petrova N, Koblik T, Gabig-Ciminska M, Edmonds M, Malecki MT & Wegrzyn G 2012 Osteoprotegerin gene polymorphism in diabetic Charcot neuroarthropathy. *Diabetic Medicine* **29** 771–775. (https://doi.org/10.1111/j.1464-5491.2011.03442.x)

Lasschuit JWJ, Greenfield JR & Tonks KTT 2022 Contribution of peripheral neuropathy to poor bone health in the feet of people with type 2 diabetes mellitus. *Acta Diabetologica* **59** 217–224. (https://doi.org/10.1007/s00592-021-01803-w)

Lau NS, Malone M, Schwarzer S, France A, Rajarethanam G, Staunton E & Dickson HG 2019 Denosumab, compared to standard care alone, reduces disease activity of acute diabetes related Charcot neuropathy. EASD Annual Meeting 2019 ePoster 957. (available at: https://www.easd.org/media-centre/home.html%20#!resources/denosumab-compared-to-standard-care-alone-reduces-disease-activity-of-acute-diabetes-related-charcot-neuropathy)

Lazzarini PA, O'rourke SR, Russell AW, Derhy PH & Kamp MC 2015 Reduced Incidence of Foot-Related Hospitalisation and Amputation amongst Persons with Diabetes in Queensland, Australia. *PLoS One* **10** e0130609. (https://doi.org/10.1371/journal.pone.0130609)

Lazzarini PA, van Netten JJ, Fitridge RA, Griffiths I, Kinnear EM, Malone M, Perrin BM, Prentice J & Wraight PR 2018 Pathway to ending avoidable diabetes-related amputations in Australia. *Medical Journal of Australia* **209** 288–290. (https://doi.org/10.5694/mja17.01198)

Lazzarini PA, Crews RT, van Netten JJ, Bus SA, Fernando ME, Chadwick PJ & Najafi B 2019 Measuring plantar tissue stress in people with diabetic peripheral neuropathy: a critical concept in diabetic foot management. *Journal of Diabetes Science and Technology* **13** 869–880. (https://doi.org/10.1177/1932296819849092)

Lazzarini PA, Jarl G, Gooday C, Viswanathan V, Caravaggi CF, Armstrong DG & Bus SA 2020 Effectiveness of offloading interventions to heal foot ulcers in persons with diabetes: a systematic review. *Diabetes/Metabolism Research and Reviews* **36**(Supplement 1) e3275. (https://doi.org/10.1002/dmrr.3275)

Lazzarini PA, Raspovic A, Prentice J, Commons RJ, Fitridge RA, Charles J, Cheney J, Purcell N, Twigg SM & Australian Diabetes-related Foot Disease Guidelines & Pathways Project 2022 Guidelines development protocol and findings: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *Journal of Foot and Ankle Research* **15** 28. (https://doi.org/10.1186/s13047-022-00533-8)

Lee AS, Twigg SM & Flack JR 2021 Metabolic syndrome in type 1 diabetes and its association with diabetes complications. *Diabetic Medicine* **38** e14376. (https://doi.org/10.1111/dme.14376)

Liu Y, Min D, Bolton T, Nube V, Twigg SM, Yue DK & Mclennan SV 2009 Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers: response to Muller et al. *Diabetes Care* **32** e137. (https://doi.org/10.2337/dc09-1394)

Liu C, Ponsero AJ, Armstrong DG, Lipsky BA & Hurwitz BL 2020 The dynamic wound microbiome. *BMC Medicine* **18** 358. (https://doi.org/10.1186/s12916-020-01820-6)

Londahl M, Katzman P, Fredholm O, Nilsson A & Apelqvist J 2008 Is chronic diabetic foot ulcer an indicator of cardiac disease? *Journal of Wound Care* **17** 12–16. (https://doi.org/10.12968/jowc.2008.17.1.27915)

Longfield M, Nube V, White JM, Mclennan SV, Boughton P, MIN, D & Twigg SM 2022 Exploring MMP-9 as a prognostic marker in post-debridement wound fluid of diabetes-related foot ulcers, and the possibility of a point-of-care test. *EASD Proceedings* **2022** A22–1271.

Lowy DB, Makker PGS & Moalem-Taylor G 2021 Cutaneous neuroimmune interactions in peripheral neuropathic pain states. *Frontiers in Immunology* **12** 660203. (https://doi.org/10.3389/fimmu.2021.660203)

Ly DHM, Vangaveti VN, Urkude R, Biros E & Malabu UH 2021 Metabolic and anthropometric influences on nerve conduction parameters in patients with peripheral neuropathy: a retrospective chart analysis. *Neurology International* **13** 166–174. (https://doi.org/10.3390/neurolint13020016)

Lynar SA, Robinson CH, Boutlis CS & Commons RJ 2019 Risk factors for mortality in patients with diabetic foot infections: a prospective cohort study. *Internal Medicine Journal* **49** 867–873. (https://doi.org/10.1111/imj.14184)

Macdonald EM, Perrin BM, Cleeland L & Kingsley MIC 2021 Podiatrist-delivered health coaching to facilitate the use of a smart insole to support foot health monitoring in people with diabetes-related peripheral neuropathy. *Sensors (Basel)* **21** 3984. (https://doi.org/10.3390/s21123984)

Malone M, Fritz BG, Vickery K, Schwarzer S, Sharma V, Biggs N, Radzieta M, Jeffries TT, Dickson HG, Jensen SO, *et al.* 2019 Analysis of proximal bone margins in diabetic foot osteomyelitis by conventional culture, DNA sequencing and microscopy. *APMIS* **127** 660–670. (https://doi.org/10.1111/apm.12986)

Malone M, Gosbell IB, Dickson HG, Vickery K, Espedido BA & Jensen SO 2017*a* Can molecular DNA-based techniques unravel the truth about diabetic foot infections? *Diabetes/Metabolism Research and Reviews* **33**. (https://doi.org/10.1002/dmrr.2834)

Malone M, Johani K, Jensen SO, Gosbell IB, Dickson HG, Hu H & Vickery K 2017*b* Next generation DNA sequencing of tissues from infected diabetic foot ulcers. *EBiomedicine* **21** 142–149. (https://doi.org/10.1016/j.ebiom.2017.06.026)

Malone M, Radzieta M, Peters TJ, Dickson HG, Schwarzer S, Jensen SO & Lavery LA 2022 Host-microbe metatranscriptome reveals differences between acute and chronic infections in diabetes-related foot ulcers. *APMIS* **130** 751–762. (https://doi.org/10.1111/apm.13200)

Maltese G, Basile G, Meehan H, Fuller M, Cesari M, Fountoulakis N & Karalliedde J 2022 Frailty is associated with impaired diabetic foot ulcer healing and all-cause re-hospitalization. *Journal of Nutrition, Health and Aging* **26** 169–173. (https://doi.org/10.1007/s12603-022-1726-7)

McIllhatton A, Lanting S, Lambkin D, Leigh L, Casey S & Chuter V 2021 Reliability of recommended non-invasive chairside screening tests for diabetes-related peripheral neuropathy: a systematic review with meta-analyses. *BMJ Open Diabetes Research and Care* **9** e002528. (https://doi.org/10.1136/bmjdrc-2021-002528)

Mills SJ, Ahangar P, Thomas HM, Hofma BR, Murray RZ & Cowin AJ 2022 Flightless I negatively regulates macrophage surface TLR4, delays early inflammation, and impedes wound healing. *Cells* **11** 2192. (https://doi.org/10.3390/cells11142192)

Min D, Nube V, Tao A, Yuan X, Williams PF, Brooks BA, Wong J, Twigg SM & Mclennan SV 2021 Monocyte phenotype as a predictive marker for wound healing in diabetes-related foot ulcers. *Journal of Diabetes and its Complications* **35** 107889. (https://doi.org/10.1016/j.jdiacomp.2021.107889)

Mishra RK, Bara RO, Zulbaran-Rojas A, Park C, Fernando ME, Ross J, Lepow B & Najafi B 2022 The application of digital frailty screening to triage nonhealing and complex wounds. *Journal of Diabetes Science and Technology* **2022** 19322968221111194. (https://doi.org/10.1177/19322968221111194)

Mohammedi K, Harrap S, Mancia G, Marre M, Poulter N, Chalmers J & Woodward M 2021 History of lower-limb complications and risk of cancer death in people with type 2 diabetes. *Cardiovascular Diabetology* **20** 3. (https://doi.org/10.1186/s12933-020-01198-y)

Monami M, Longo R, Desideri CM, Masotti G, Marchionni N & Mannucci E 2008 The diabetic person beyond a foot ulcer: healing, recurrence, and depressive symptoms. *Journal of the American Podiatric Medical Association* **98** 130–136. (https://doi.org/10.7547/0980130)

Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S & Dinis-Ribeiro M 2014 Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews* **30** 610–622. (https://doi.org/10.1002/dmrr.2535)

Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, Game F & International Working Group on the Diabetic Foot (IWGDF) 2020 Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). *Diabetes/Metabolism Research and Reviews* **36**(Supplement 1) e3273. (https://doi.org/10.1002/dmrr.3273)

Natovich R, Kushnir T, Harman-Boehm I, Margalit D, Siev-Ner I, Tsalichin D, Volkov I, Giveon S, Rubin-Asher D & Cukierman-Yaffe T 2016 Cognitive dysfunction: part and parcel of the diabetic foot. *Diabetes Care* **39** 1202–1207. (https://doi.org/10.2337/dc15-2838)

Nejatian MM, Sobhi S, Sanchez BN, Linn K, Manning L, Soh SC, Hiew J, Ritter JC, Yeap BB & Hamilton EJ 2021 Reduction in femoral neck and total hip bone mineral density following hospitalisation for diabetes-related foot ulceration. *Scientific Reports* **11** 22742. (https://doi.org/10.1038/s41598-021-02233-y)

Nelson A, Wright-Hughes A, Backhouse MR, Lipsky BA, Nixon J, Bhogal MS, Reynolds C, Brown S & CODIFI Collaborators 2018 CODIFI (Concordance in Diabetic Foot Ulcer Infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England. *BMJ Open* **8** e019437. (https://doi.org/10.1136/bmjopen-2017-019437)

Nesto RW, Watson FS, Kowalchuk GJ, Zarich SW, Hill T, Lewis SM & Lane SE 1990 Silent myocardial ischemia and infarction in diabetics with peripheral vascular disease: assessment by dipyridamole thallium-201 scintigraphy. *American Heart Journal* **120** 1073–1077. (https://doi.org/10.1016/0002-8703(90)90118-h)

Nguyen ATM, Akhter R, Garde S, Scott C, Twigg SM, Colagiuri S, Ajwani S & Eberhard J 2020 The association of periodontal disease with the complications of diabetes mellitus. A systematic review. *Diabetes Research and Clinical Practice* **165** 108244. (https://doi.org/10.1016/j.diabres.2020.108244)

Nube VL, White JM, Brewer K, Veldhoen D, Meler C, Frank G, Carroll K, Featherston J, Batchelor J, Gebski V, *et al.* 2021 A randomized trial comparing weekly with every second week sharp debridement in people with diabetes-related foot ulcers shows similar healing outcomes: potential benefit to resource utilization. *Diabetes Care* **44** e203–e205. (https://doi.org/10.2337/dc21-1454)

O'Brien H, Scarlett S, O'hare C, Ni Bhriain S & Kenny RA 2018 Hospitalisation and surgery: is exposure associated with increased subsequent depressive symptoms? Evidence from the Irish longitudinal study on ageing (TILDA). *International Journal of Geriatric Psychiatry* **33** 1105–1113. (https://doi.org/10.1002/gps.4899)

O'Brien JA, Mcguire HM, Shinko D, Fazekas De St Groth B, Russo MA, Bailey D, Santarelli DM, Wynne K & Austin PJ 2021 T lymphocyte and monocyte subsets are dysregulated in type 1 diabetes patients with peripheral neuropathic pain. *Brain, Behavior, and Immunity – Health* **15** 100283. (https://doi.org/10.1016/j.bbih.2021.100283)

Ochoa-Precoma R, Pacheco-Soto BT, Porchia LM, Torres-Rasgado E, Perez-Fuentes R & Gonzalez-Mejia ME 2021 Association between osteoprotegerin and Charcot Neuroarthropathy: a systematic review. *Acta Diabetologica* **58** 475–484. (https://doi.org/10.1007/s00592-020-01638-x)

Pasquier J, Thomas B, Hoarau-Vechot J, Odeh T, Robay A, Chidiac O, Dargham SR, Turjoman R, Halama A, Fakhro K, *et al.* 2017 Circulating microparticles in acute diabetic Charcot foot exhibit a high content of inflammatory cytokines, and support monocyte-to-osteoclast cell induction. *Scientific Reports* **7** 16450. (https://doi.org/10.1038/s41598-017-16365-7)

Pasquier J, Ramachandran V, Abu-Qaoud MR, Thomas B, Benurwar MJ, Chidiac O, Hoarau-Vechot J, Robay A, Fakhro K, Menzies RA, *et al.* 2018 Differentially expressed circulating microRNAs in the development of acute diabetic Charcot foot. *Epigenomics* **10** 1267–1278. (https://doi.org/10.2217/epi-2018-0052)

Pasquier J, Spurgeon M, Bradic M, Thomas B, Robay A, Chidiac O, Dib MJ, Turjoman R, Liberska A, Staudt M, *et al.* 2019 Whole-methylome analysis of circulating monocytes in acute diabetic Charcot foot reveals differentially methylated genes involved in the formation of osteoclasts. *Epigenomics* **11** 281–296. (https://doi.org/10.2217/epi-2018-0144)

Pearson S, Nash T & Ireland V 2014 Depression symptoms in people with diabetes attending outpatient podiatry clinics for the treatment of foot ulcers. *Journal of Foot and Ankle Research* **7** 47. (https://doi.org/10.1186/s13047-014-0047-4)

Pedras S, Carvalho R & Pereira MG 2018 Predictors of quality of life in patients with diabetic foot ulcer: the role of anxiety, depression, and functionality. *Journal of Health Psychology* **23** 1488–1498. (https://doi.org/10.1177/1359105316656769)

Pena G, Kuang B, Cowled P, Howell S, Dawson J, Philpot R & Fitridge R 2020 Micronutrient status in diabetic patients with foot ulcers. *Advances in Wound Care (New Rochelle)* **9** 9–15. (https://doi.org/10.1089/wound.2019.0973)

Perrin BM, Raspovic A, Williams CM, Twigg SM, Golledge J, Hamilton EJ, Crawford A, Hargreaves C, van Netten JJ, Purcell N, *et al.* 2021 Establishing the national top 10 priority research questions to improve diabetes-related foot health and disease: a Delphi study of Australian stakeholders. *BMJ Open Diabetes Research and Care* **9**. (https://doi.org/10.1136/bmjdrc-2021-002570)

Petersen EA, Stauss TG, Scowcroft JA, Brooks ES, White JL, Sills SM, Amirdelfan K, Guirguis MN, Xu J, Yu C, *et al.* 2021 Effect of high-frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: a randomized clinical trial. *JAMA Neurology* **78** 687–698. (https://doi.org/10.1001/jamaneurol.2021.0538)

Petersen EA, Stauss TG, Scowcroft JA, Brooks ES, White JL, Sills SM, Amirdelfan K, Guirguis MN, Xu J, Yu C, *et al.* 2022 High-frequency

10-kHz spinal cord stimulation improves health-related quality of life in patients with refractory painful diabetic neuropathy: 12-month results from a randomized controlled trial. *Mayo Clinic Proceedings. Innovations, Quality and Outcomes* **6** 347–360. (https://doi.org/10.1016/j.mayocpiqo.2022.05.003)

Petrova NL, Donaldson NK, Bates M, Tang W, Jemmott T, Morris V, Dew T, Meacock L, Elias DA, Moniz CF, *et al.* 2021 Effect of recombinant human parathyroid hormone (1–84) on resolution of active charcot neuro-osteoarthropathy in diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Care* **44** 1613–1621. (https://doi.org/10.2337/dc21-0008)

Pichu S, Patel BM, Apparsundaram S & Goyal RK 2017 Role of biomarkers in predicting diabetes complications with special reference to diabetic foot ulcers. *Biomarkers in Medicine* **11** 377–388. (https://doi.org/10.2217/bmm-2016-0205)

Pitocco D, Zelano G, Gioffre G, Di Stasio E, Zaccardi F, Martini F, Musella T, Scavone G, Galli M, Caputo S, *et al.* 2009 Association between osteoprotegerin G1181C and T245G polymorphisms and diabetic charcot neuroarthropathy: a case-control study. *Diabetes Care* **32** 1694–1697. (https://doi.org/10.2337/dc09-0243)

Preston FG, Meng Y, Burgess J, Ferdousi M, Azmi S, Petropoulos IN, Kaye S, Malik RA, Zheng Y & Alam U 2022 Artificial intelligence utilising corneal confocal microscopy for the diagnosis of peripheral neuropathy in diabetes mellitus and prediabetes. *Diabetologia* **65** 457–466. (https://doi.org/10.1007/s00125-021-05617-x)

Rajamani K, Colman PG, Li LP, Best JD, Voysey M, D'emden MC, Laakso M, Baker JR, Keech AC & INVESTIGATORS FS 2009 Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* **373** 1780–1788. (https://doi.org/10.1016/S0140-6736(09)60698-X)

Rastogi A, Bhansali A & Jude EB 2021 Efficacy of medical treatment for Charcot neuroarthropathy: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetologica* **58** 687–696. (https://doi.org/10.1007/s00592-020-01664-9)

Rhou YJ, Henshaw FR, Mcgill MJ & Twigg SM 2015 Congestive heart failure presence predicts delayed healing of foot ulcers in diabetes: an audit from a multidisciplinary high-risk foot clinic. *Journal of Diabetes and its Complications* **29** 556–562. (https://doi.org/10.1016/j.jdiacomp.2015.02.009)

Richard JL, Almasri M & Schuldiner S 2012 Treatment of acute Charcot foot with bisphosphonates: a systematic review of the literature. *Diabetologia* **55** 1258–1264. (https://doi.org/10.1007/s00125-012-2507-3)

Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, Van GH, Hartemann A, Game F, Jeffcoate W, Jirkovska A, *et al.* 2011 The Charcot foot in diabetes. *Diabetes Care* **34** 2123–2129. (https://doi.org/10.2337/dc11-0844)

Rosenbaum AJ & DiPreta JA 2015 Classifications in brief: Eichenholtz classification of Charcot arthropathy. *Clinical Orthopaedics and Related Research* **473** 1168–1171. (https://doi.org/10.1007/s11999-014-4059-y)

Ruzehaji N, Grose R, Krumbiegel D, Zola H, Dasari P, Wallace H, Stacey M, Fitridge R & Cowin AJ 2012 Cytoskeletal protein Flightless (Flii) is elevated in chronic and acute human wounds and wound fluid: neutralizing its activity in chronic but not acute wound fluid improves cellular proliferation. *European Journal of Dermatology* **22** 740–750. (https://doi.org/10.1684/ejd.2012.1878)

Ryan E, Crisologo PA, Oz O, La Fontaine J, Wukich DK, Malone M & Lavery LA 2020 Incidence and recovery of acute kidney injury in diabetic and non-diabetic patients with foot infections. *Journal of the American Podiatric Medical Association* **112** 20-167. (https://doi.org/10.7547/20-167)

Ryan E, Ahn J, Wukich DK, Fontaine J, Crisologo PA, Malone M, Oz OK & Lavery LA 2022 Effect of sensory neuropathy on the predictive value of inflammatory biomarkers for osteomyelitis in diabetic and nondiabetic patients with foot infections. *Journal of the American Podiatric Medical Association* **112** 20-168. (https://doi.org/10.7547/20-168)

Saiprathiba A, Senthil G, Juttada U, Selvaraj B, Kumpatla S & Viswanathan V 2019 RANKL gene polymorphism as a potential biomarker to identify acute charcot foot among Indian population with Type 2 diabetes: a preliminary report. *International Journal of Lower Extremity Wounds* **18** 287–293. (https://doi.org/10.1177/1534734619859730)

Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA & IWGDF Editorial Board 2020 Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update) *Diabetes/Metabolism Research and Reviews* **36**(Supplement 1) e3266. (https://doi.org/10.1002/dmrr.3266)

Searle A, Spink MJ & Chuter VH 2018 Prevalence of ankle equinus and correlation with foot plantar pressures in people with diabetes. *Clinical Biomechanics* **60** 39–44. (https://doi.org/10.1016/j.clinbiomech.2018.10.006)

Seng L, Drovandi A, Fernando ME & Golledge J 2022 Opinions about the most appropriate surgical management of diabetes-related foot infection: a cross-sectional survey. *Journal of Foot and Ankle Research* **15** 18. (https://doi.org/10.1186/s13047-022-00523-w)

Sheehan P, Jones P, Caselli A, Giurini JM & Veves A 2003 Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* **26** 1879–1882. (https://doi.org/10.2337/diacare.26.6.1879)

Shofler D, Hamedani E, Seun J, Sathananthan A, Katsaros E, Liggan L, Kang S & Pham C 2021 Investigating the use of denosumab in the treatment of acute charcot neuroarthropathy. *Journal of Foot and Ankle Surgery* **60** 354–357. (https://doi.org/10.1053/j.jfas.2020.09.018)

Siru R, Burkhardt MS, Davis WA, Hiew J, Manning L, Ritter JC, Norman PE, Makepeace A, Fegan PG, Bruce DG, *et al.* 2021 Cognitive impairment in people with diabetes-related foot ulceration. *Journal of Clinical Medicine* **10** 2808. (https://doi.org/10.3390/jcm10132808)

The Royal Australian College of General Practitioners 2020. Management of type 2 diabetes: A handbook for general practice. *Handbook*. East Melbourne, Victoria: (available at: https://www.racgp.org.au/getattachment/41fee8dc-7f97-4f87-9d90-b7af337af778/Management-of-type-2-diabetes-A-handbook-for-general-practice.aspx)

Tehan PE, Hawes MB, Hurst J, Sebastian M, Peterson BJ & Chuter VH 2022 Factors influencing lower extremity amputation outcomes in people with active foot ulceration in regional Australia: a retrospective cohort study. *Wound Repair and Regeneration* **30** 24–33. (https://doi.org/10.1111/wrr.12978)

Tsai SHL, Lin CR, Shao SC, Fang CH, Fu TS, Lin TY & Hung YC 2022 Cannabinoid use for pain reduction in spinal cord injuries: a meta-analysis of randomized controlled trials. *Frontiers in Pharmacology* **13** 866235. (https://doi.org/10.3389/fphar.2022.866235)

Tsujimoto T, Kajio H, Takahashi Y, Kishimoto M, Noto H, Yamamoto-Honda R, Kamimura M, Morooka M, Kubota K, Shimbo T, *et al.* 2011 Asymptomatic coronary heart disease in patients with type 2 diabetes with vascular complications: a cross-sectional study. *BMJ Open* **1** e000139. (https://doi.org/10.1136/bmjopen-2011-000139)

Tuttolomondo A, Casuccio A, Guercio G, Maida C, Del Cuore A, Di Raimondo D, Simonetta I, Di Bona D, Pecoraro R, Della Corte V, *et al.* 2017 Arterial stiffness, endothelial and cognitive function in subjects with type 2 diabetes in accordance with absence or presence of diabetic foot syndrome. *Cardiovascular Diabetology* **16** 2. (https://doi.org/10.1186/s12933-016-0483-5)

van Asten SAV, Mithani M, Peters EJG, La Fontaine J, Kim PJ & Lavery LA 2018 Complications during the treatment of diabetic foot osteomyelitis. *Diabetes Research and Clinical Practice* **135** 58–64. (https://doi.org/10.1016/j.diabres.2017.06.002)

van Netten JJ, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F, Rayman G, Lazzarini PA, Forsythe RO, Peters EJG, *et al.* 2020 Definitions and criteria for diabetic foot disease. *Diabetes/Metabolism Research and Reviews* **36**(Supplement 1) e3268. (https://doi.org/10.1002/dmrr.3268)

Vangaveti VN, Heyes O, Jhamb S, Haleagrahara N & Malabu UH 2021 Usefulness of procalcitonin in diagnosing diabetic foot osteomyelitis: a

pilot study. *Wounds: A Compendium of Clinical Research and Practice* **33** 192–196. (https://doi.org/10.25270/wnds/2021.192196)

Velayutham V, Benitez-Aguirre PZ, Liew G, Wong TY, Jenkins AJ, Craig ME & Donaghue KC 2021 Baseline extended zone retinal vascular calibres associate with sensory nerve abnormalities in adolescents with type 1 diabetes: a prospective longitudinal study. *Diabetic Medicine* **38** e14662. (https://doi.org/10.1111/dme.14662)

Vileikyte L 2008 Psychosocial and behavioral aspects of diabetic foot lesions. *Current Diabetes Reports* **8** 119–125. (https://doi.org/10.1007/s11892-008-0022-1)

Vo UG, Gilfillan M, Hamilton EJ, Manning L, Munshi B, Hiew J, Norman PE & Ritter JC 2021 Availability and service provision of multidisciplinary diabetes foot units in Australia: a cross-sectional survey. *Journal of Foot and Ankle Research* **14** 27. (https://doi.org/10.1186/s13047-021-00471-x)

Wang Y, Shao T, Wang J, Huang X, Deng X, Cao Y, Zhou M & Zhao C 2021 An update on potential biomarkers for diagnosing diabetic foot ulcer at early stage. *Biomedicine and Pharmacotherapy* **133** 110991. (https://doi.org/10.1016/j.biopha.2020.110991)

West M, Chuter V, Munteanu S & Hawke F 2017 Defining the gap: a systematic review of the difference in rates of diabetes-related foot complications in Aboriginal and Torres Strait Islander Australians and non-indigenous Australians. *Journal of Foot and Ankle Research* **10** 48. (https://doi.org/10.1186/s13047-017-0230-5)

West M, Sadler S, Charles J, Hawke F, Lanting S, Munteanu SE & Chuter V 2022 Yarning about foot care: evaluation of a foot care service for Aboriginal and Torres Strait Islander Peoples. *Journal of Foot and Ankle Research* **15** 25. (https://doi.org/10.1186/s13047-022-00524-9)

Williams KH, Burns K, Constantino M, Shackel NA, Prakoso E, Wong J, Wu T, George J, Mccaughan GW & Twigg SM 2015 An association of large-fibre peripheral nerve dysfunction with non-invasive measures of liver fibrosis secondary to non-alcoholic fatty liver disease in diabetes. *Journal of Diabetes and its Complications* **29** 1240–1247. (https://doi.org/10.1016/j.jdiacomp.2015.06.015)

Williams KH, Burns K & Twigg SM 2018 Differing clinical phenotype for higher alanine-aminotransferase (ALT) compared with high-risk NAFLD fibrosis score in type 2 diabetes mellitus. *Journal of Diabetes and its Complications* **32** 321–324. (https://doi.org/10.1016/j.jdiacomp.2017.12.010)

Xu L, Qian H, Gu J, Shi J, Gu X & Tang Z 2013 Heart failure in hospitalized patients with diabetic foot ulcers: clinical characteristics and their relationship with prognosis. *Journal of Diabetes* **5** 429–438. (https://doi.org/10.1111/1753-0407.12062)

Yates TH, Cooperman SR, Shofler D & Agrawal DK 2020 Current concepts underlying the pathophysiology of acute Charcot neuroarthropathy in the diabetic foot and ankle. *Expert Review of Clinical Immunology* **16** 839–845. (https://doi.org/10.1080/1744666X.2020.1804869)

Ye D, Fairchild TJ, Vo L & Drummond PD 2022 Painful diabetic peripheral neuropathy: role of oxidative stress and central sensitisation. *Diabetic Medicine* **39** e14729. (https://doi.org/10.1111/dme.14729)

Zhang Y, Lazzarini PA, Mcphail SM, van Netten JJ, Armstrong DG & Pacella RE 2020 Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. *Diabetes Care* **43** 964–974. (https://doi.org/10.2337/dc19-1614)

Zhang Y, Cramb S, Mcphail SM, Pacella R, van Netten JJ, Cheng Q, Derhy PH, Kinnear EM, Lazzarini PA & Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network, Australia 2021*a* Factors associated with healing of diabetes-related foot ulcers: observations from a large prospective real-world cohort. *Diabetes Care* **44** e143–e145. (https://doi.org/10.2337/dc20-3120)

Zhang Y, van Netten JJ, Baba M, Cheng Q, Pacella R, Mcphail SM, Cramb S & Lazzarini PA 2021*b* Diabetes-related foot disease in Australia: a systematic review of the prevalence and incidence of risk factors, disease and amputation in Australian populations. *Journal of Foot and Ankle Research* **14** 8. (https://doi.org/10.1186/s13047-021-00447-x)

Zhang Y, Cramb S, Mcphail SM, Pacella R, van Netten JJ, Cheng Q, Derhy PH, Kinnear EM, Lazzarini PA & Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network, Australia 2022 Multiple factors predict longer and shorter time-to-ulcer-free in people with diabetes-related foot ulcers: survival analyses of a large prospective cohort followed-up for 24-months. *Diabetes Research and Clinical Practice* **185** 109239. (https://doi.org/10.1016/j.diabres.2022.109239)

Received 5 February 2023
Accepted 16 March 2023
Available online 20 March 2023
Version of Record published 2 May 2023