Vanessa L Nube

Sharp debridement in the management of diabetes-related foot ulcers: outcomes of a randomised study of debridement frequency, current practice of debridement and implications for frequency of treatment

University of Sydney

Faculty of Health and Medicine, Central Clinical School

A thesis submitted to fulfil requirements for the degree of

Doctor of Philosophy

2024

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Professor Stephen Twigg
Primary Supervisor

Preface and rationale for this thesis

This body of work has been undertaken from my perspective as clinician and manager within the NSW public health system and with an interest in providing what is of value to our patients with diabetes and foot ulceration, my colleagues and to myself.

Working within the Diabetes Centre at the Royal Prince Alfred Hospital, since early in my career has meant that caring for the patient, systematic documentation, research, and clinical outcomes have co-existed. While not all patients will heal, their experience regarding the care they receive and their overall quality of life, still matters greatly. Patients with foot complications already suffer a high disease burden with co-morbidities and other complications. Those impacted, are more often vulnerable and financially disadvantaged and with Aboriginal and Torres Strait Islander people disproportionately represented and often presenting at an earlier age. Where people with foot complications have family or people who help care for them as friends or neighbours, it is evident that they also experience the burden of the disease. For some people, a visit to the hospital for treatment is a weekly highlight. For others, it is physical struggle or another appointment to fit around work and family with parking costs and walking on an already compromised foot, posing real challenges.

The resources of the NSW Translational Research Grant for the randomised study assisted us to conduct the study with the rigor it needed and enabled additional treatment centres to be involved, without which the participant numbers would not have been achieved.

To provide further context, this research was undertaken during a time when there was state and national focus on how services should be organised and provided for people with diabetes-related foot complications, and I was engaged in this work. At a state level, NSW Health was implementing Standards for High Risk Foot Services and nationally within the National Association of Diabetes Centres, standards for High Risk Foot Services were also being developed with a National Accreditation process.

The rationale for this research is to contribute to the understanding optimal care and how this should be delivered. I hope this research provides useful evidence to support clinicians and patients in decisions regarding their care.

Acknowledgments

My sincerest thanks to my primary supervisor, Professor Stephen Twigg, and associate supervisor Professor Jennifer Alison. The remarkable achievements of both, are an inspiration to me and others. Their belief that I could complete this research was the tipping point for my decision to enrol in the PhD and their academic support, expertise, encouragement, and great kindness over the course of this endeavour has meant that I was able to complete this work. Their investment in me has been a great gift.

Undertaking a PhD at this stage in my life, has meant a constant internally prioritising and re-prioritising of commitments. I have sought to make this deserving of the time and effort I have devoted personally but also with respect to the clinicians and patients involved, the University, District, and my profession.

Thank you to my extraordinary daughters Lucinda and Annabel for being self-sufficient and learning to manage up, my husband Peter for knowing what this means to me and having a door built which allowed me an office. Thank you to my friends who enquired about progress and listened on long walks and corridor catch-ups even if you were not interested in feet. Of my colleagues, I would particularly like to acknowledge the generosity of Georgina Frank and Jessica White.

The following acknowledges the role of others in supporting this work.

Original concept for the randomised trial of debridement frequency described in this proposal was originally conceived by the candidate, Professor Stephen Twigg and Ms Danielle Veldhoen. The protocol was then further developed and awarded a Ministry of Health funded Translational Research Grant.

Site investigators for the randomised controlled study sites:

- Ms Cindy Meler and Mr Luke Taylor (Bankstown Hospital)
- Ms Kate Carroll and Ms Julie Zwarteveen (John Hunter Hospital)
- Ms Georgina Frank (Concord Hospital)
- Ms Jessica White and Ms Louise Pfrunder (Royal Prince Alfred Hospital)
- Mr Alan Kennedy (St George Hospital)
- Ms Jacqueline Batchelor and Catherine Stephens (Hornsby Hospital)
- Ms Jill Featherston (St Vincents Hospital)

Research Project Co-ordinator

Ms Jessica White: Assisted in operationalising the study activities and provided invaluable support to the CI and site investigators in the preparation of documents for ethics amendments, collation and maintenance of forms used in collection of data and data entry. Ms Purnima Rao (Royal Prince Alfred and Concord Hospitals) also assisted with data entry.

Independent assessor of digital images

- Jana Pinkova, Royal Prince Alfred Hospital Vascular CNC
- Michelle Baraket-Johnson, Sydney Local Health District Skin Integrity Lead

Podiatry clinicians across NSW Health who reviewed and provided feedback on the protocol, who participated in the survey and supported the completion of the patient survey

- Julie Zwarteveen
- Molly Cocks
- Purnima Rao
- Georgina Frank
- Chloe Katsanos
- Clare McDonogh
- Sarah Manewell

Organisations who supported the projects which make up this thesis:

- The Agency for Clinical Innovation, Endocrine Network Managers (Marina Davis) who facilitated engagement with NSW Health clinicians through the High Risk Foot Community of Practice, circulated newsletters, and survey links.
- The Podiatry Association (NSW&ACT) (Helen Conneally) for distributing information and survey links.
- Sydney Clinical Research Centre: Yelena Fridgant for REDCap support

Abbreviations

ABI	Ankle brachial index
BMI	Body Mass Index
CSWD	Conservative Sharp Wound Debridement
CVD	Cardiovascular Disease
DFU	Diabetes-related Foot Ulcer
DR	Diabetes-related Retinopathy
DSPN	Distal symmetrical sensorimotor polyneuropathy
EWMA	European Wound Management Association
HbA1c	Glycated haemoglobin
HRFS	High Risk Foot Service
IWGDF	International Working Group on the Diabetic Foot
LOPS	Loss of protective sensation
MAC	Medial arterial calcification
MGF	Medical Grade Footwear
NSW	New South Wales
PAD	Peripheral Arterial Disease
PWR	Percent wound reduction
RCW	Removable Cast Walker (knee-high prefabricated brace)
SLHD	Sydney Local Health District
TBI	Toe brachial index
TCC	Total contact cast
WIfI	Wound Infection Ischaemia (Wound Grading)

Publications

1. Nube, V. L., Alison, J. A., & Twigg, S. M. (2021). Frequency of sharp wound debridement in the management of diabetes-related foot ulcers: exploring current practice. Journal of Foot and Ankle Research, 14(1), 52–52.

2. Nube, V. L., White, J. M., Brewer, K., Veldhoen, D., Meler, C., Frank, G., Carroll, K., Featherston, J., Batchelor, J., Gebski, V., Alison, J. A., & Twigg, S. M. (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(12), e203–e205.

3. Nube, V. L., Alison, J. A., & Twigg, S. M. (2023). Diabetic foot ulcers: weekly versus second-weekly conservative sharp wound debridement. Journal of Wound Care, 32(6), 383–390.

4. Nube, V. L., Zwarteveen, J., Frank, G., Manewell, S. M., Cocks, M. L., Rao, P., Twigg, S. M., & Alison, J. A. (2023). Challenges faced by people with diabetes related foot ulcers in attending hospital based high risk foot services: results of a consumer survey. Wound Practice & Research, 31(3), 99-105.

Presentations and posters

The following presentations, related to this research were given during my candidature

2019	**Title**: Sharp wound debridement of diabetes-related foot ulcers: An investigation of current practice **Meeting**: **The Australian Diabetes Society National Conference.** Poster: Nube VL, Twigg SM and Alison, JA.
2019	**Title:** Debriding diabetes-related foot ulcers: Results of a clinician survey **Meeting**: **Australian Wound Management Association Conference.** Adelaide. Oral Presentation of accepted abstract presented by Vanessa Nube Co-authors: Twigg SM and Alison, JA.
2019	**Title:** Wound debridement frequency and healing outcomes in diabetes-related foot ulcers. Sydney. **Meeting**: **Sydney Health Partners Conference** Invited speaker: Presenter Vanessa Nube Co-authors: White, JM, Brewer, Veldhoen, D, Meler, C, Frank G, Carroll K, Featherston J, Batchelor J, Gebski V, Aliso, JA, & Twigg SM.
2020	**Title:** The Diabetes Debridement Study: Addressing the frequency effect of sharp wound debridement on healing outcomes in diabetes-related foot ulcers **Meeting: Australian Diabetes Congress.** Oral presentation of accepted abstract presented by Vanessa Nube Co-authors: White, JM, Brewer, Veldhoen, D, Meler, C, Frank G, Carroll K, Featherston J, Batchelor J, Gebski V, Aliso, JA, & Twigg SM.
2020, 2021, 2022	**Title**: Overview of PhD – Sharp Debridement **Meeting**: **The Greg Brown Endocrinology Laboratory Meeting. Sydney** Presenter: Vanessa Nube
2022	**Title**: Research Journey and Addressing the frequency effect of sharp debridement on healing outcomes of diabetes-related foot ulcers **Meeting**: **SLHD Allied Health Research Conference. Sydney.** Invited Speaker: Presenter Vanessa Nube
2022	**Title**: The Diabetes Debridement Study **Meeting**: **NSW Ministry of Health, Allied Health Research Showcase.** Invited Speaker: Presenter Vanessa Nube Co-authors: White, JM, Brewer, Veldhoen, D, Meler, C, Frank G, Carroll K, Featherston J, Batchelor J, Gebski V, Aliso, JA, & Twigg SM.
2022	**Title**: The Diabetes Debridement Study **Meeting**: **The Lower Extremity Amputation Prevention (National) Conference** (Advanced Practicing Podiatry Group Australia). Melbourne. Invited Speaker, Vanessa Nube Co-authors: Co-authors: White, JM, Brewer, Veldhoen, D, Meler, C, Frank G, Carroll K, Featherston J, Batchelor J, Gebski V, Aliso, JA, & Twigg SM.

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Abstract

Introduction Diabetes related foot ulcers (DFU) are a complication of diabetes, associated with loss of protective sensation, often complicated by peripheral arterial disease and a leading cause of hospital admission and lower extremity amputation. While some will heal readily, DFU can be complex and costly with high rates of co-morbid mental and physical health problems experienced by people with DFU. Management is optimally provided with the support of an interdisciplinary team with podiatrists in Australia and other countries, providing assessment, pressure offloading, local wound management and sharp wound debridement which aims to support healing by the removal of non-viable tissue. Frequent clinic attendance for treatment is supported by evidence-based practice guidelines which reference emerging evidence on the role of sharp debridement in preparing the wound bed for healing and studies showing that where more frequent sharp debridement is provided, healing rates improve. Despite being purported to aid in healing by reducing bacterial load, removing senescent cells, callus and creating a wound environment in which chronicity is reversed, there are no prospective studies on healing outcomes achieved with regular sharp debridement. Furthermore, translating of available evidence requires an understanding of the context and local practice which may differ from the patient populations and centres where research was undertaken. There is a need to understand how the current evidence relates to practice in Australia.

This thesis explored the available literature relating to sharp debridement including how frequently it was performed and the healing outcomes together with other potentially relevant, surrogate measures. The data informed a prospective randomised study to determine the optimal frequency of sharp debridement in the types of DFU managed in specialised interdisciplinary foot care services, High Risk Foot Services (HRFS).

To support the implementation of evidence into practice, it is important to understand the current models and standards of care, which differ according to the local healthcare system, workforce factors, and the patients for whom the treatment is intended. Therefore, this body of work also sought to understand the context of implementing frequent sharp debridement

into practice by exploring the current practice of those clinicians engaged in providing sharp debridement and the impact on patients attending services.

In chapter one, the available literature is described in a narrative review to understand the aetiology and management of DFU, what standard care is (as recommended in evidence-based practice guidelines) and available evidence, with particular focus on sharp debridement. The organisation of care is also explored to understand the context in which care is provided.

The aims of the research undertaken for this thesis are addressed in three separate studies in Chapters two, three and four.

Chapter two contains the report of study one, "Frequency of Sharp Wound Debridement in the Management of Diabetes-Related Foot Ulcers: an exploration of current practice" as published in the *Journal of Foot and Ankle Research*. The survey aimed to document what is the current practice amongst clinicians engaged in the management of people with DFU with regards to sharp debridement, how often they debride and what factors they use to decide this. An electronic survey was developed which was distributed to NSW Health employed podiatrists who were targeted through clinical networks and responded anonymously. Of the 100 respondents, 75 completed responses were included in the analyses. Clinicians reported that sharp debridement (conservative, non-surgical) was the main method of debridement used, and 92% of NSW Health employed respondents debrided patients' DFU at every visit suggesting that debridement and visit frequency were synonymous. Most respondents debrided a patients' DFU weekly or second weekly. Regional and rural podiatrists were more likely to debride less frequently with 68% debriding their patients' DFU every 2 weeks (or less often) compared to 35% ($z=2.35$, $p=0.02$) of those working in metropolitan areas. The main conclusions were that weekly and second weekly debridement regimens are the normal practice and that podiatrists in rural and regional areas debrided their patients' DFU less often than their metropolitan-based colleagues. Clinicians use the clinical features of DFU to inform debridement frequency with workforce availability and accessibility being a limiting factor in how frequently debridement is provided.

Chapter three contains the report of Study Two. A randomised controlled trial of sharp debridement by podiatrists managing DFU. This multi-site, prospective randomised study aimed to compare the healing rates of DFU receiving weekly or second weekly sharp debridement. Participants were randomised to receive sharp debridement weekly or every second week with factors such as local service provision, weekly attendance, and pressure offloading standardised between groups. Block randomisation by treatment centre was used with DFU stratified by size, greater or less than $3cm^2$. Blind assessment of the primary outcome, healing at 12 weeks, was used and secondary outcomes included the percent wound closure. Seven treatment centres recruited 122 participants. DFU were mainly small and chronic. Images of 78 DFU were available for assessment by wound experts blinded to treatment allocation showed that 53% of weekly and 52% of second weekly debrided DFU healed by 12 weeks (mean difference 1.8% 95% CI -16.3 to 20%) meaning there was no between-group difference in the proportion of participants' DFUs completely healed. Sensitivity analysis using the clinician reported healing and a completers analysis performed post-hoc, drew the same result of no statistically significant difference between groups for the proportion of DFU completely healed at week 12. Included in this Chapter are the following:

(a) Full version of the paper submitted for publication

(b) 750 word e'letter titled "A Randomised Trial Comparing Weekly with Every Second Week Sharp Debridement in People with Diabetes-Related Foot Ulcers Shows Similar Healing Outcomes: Potential Benefit to Service Utilisation" published in *Diabetes Care*

(c) the Commentary on the randomised study published in the *Journal of Wound Care.*

Chapter four contains the report of Study Three, "Challenges faced by people with diabetes-related foot ulcers in attending hospital-based High Risk Foot Services: Results of a consumer survey" published in *Wound Practice and Research*.

Given the data that weekly and second weekly debridement results in a similar likelihood of healing of DFU within 12 weeks, we hypothesised that patient preference would be for less frequent treatment visits to the HRFS .The objectives were to explore the experience of patients receiving sharp debridement for treatment of DFU at one of three HRFS. Participants were asked about (a) Barriers to attendance for treatment (b) Perception of the benefits and (c) Preferred frequency of treatment visits. The electronic survey was also developed to record patient preferences and ask about how they travelled to appointments, the duration of time and cost of parking. The study protocol permitted the survey to be completed online using a QR Code linking to the online survey and participants could also choose to complete the survey on paper, have the clinician read the questions and record their responses or have the survey conducted by phone at a later time. Participants expressed high levels of satisfaction with receiving debridement as part of the treatment. Half reported that mobility restricted their capacity to attend, and the majority used a private vehicle to travel to the appointments. Family was often relied on for travel. Clinicians and service providers should consider poor mobility and reliance on a private vehicle to access the hospital for treatment.

Chapter Five contains the discussion and conclusions arising from the literature review and the studies undertaken for this thesis. The chapter summarises the implications for clinical practice and service provision, as well as the limitations and suggested future research.

Discussion and conclusions. The aetiology of DFU is multifactorial and there are many factors impacting healing, including the severity and duration of the wound, efficacy of pressure offloading and adherence to treatment, adequacy of perfusion, care standards, patient behaviour, mental health, renal disease, and nutrition. Sharp debridement is most often performed weekly or every second week by clinicians surveyed who report clinical indications determine frequency while they also rank resources as a limiting factor. This may explain why regional and rural practising clinicians are more likely to debride less frequently. In this context, our randomised study demonstrated there was no difference in healing outcomes between weekly debridement and second weekly. Therefore, where good healing trajectories are observed, patients with DFU receiving weekly care, may do as well with less frequent treatment (every 2 weeks), in the absence of any indication for more frequent care. For services providing weekly treatment, a change in practice to debridement every second week, may equate to more resources being available for more urgent cases, quality improvement and ease the burden of family and carers. Services should be cognisant of potential barriers to access for people referred for treatment and help to link patients to available transport. Commissioners of services need to plan to deliver care in a way that facilitates timely access.

Direct or surrogate measures of bioburden and inflammation, factors which contribute to healing delay, may be useful to determine debridement frequency and measure the impact. Tests for biofilm, bioburden and metalloproteinases are currently being investigated and have this potential. With further research, evidence could lead to point of care testing to support decisions about the extent and frequency of sharp debridement which is indicated for specific patients. Knowing how much and how often to debride to optimise healing has benefits patients and their families and helps to ensure optimal use of health service resources.

Chapter One: Literature Review

The scope of this review includes a high-level summary of diabetes and its management to provide context for a deeper discussion regarding the complications relating to foot disease.

An overview of wound healing will be presented as a background to understanding the current research and expert opinion regarding the role of debridement, in particular sharp debridement, in managing DFU as a chronic wound type.

A critique and summary of the available studies reporting outcomes relating to sharp debridement of diabetes-related foot ulcer will be presented.

A discussion on the organisation and delivery of care for people with diabetes-related foot ulcers will be explored with reference to the Australian model of care and podiatrists' role as this is the setting in which the sharp debridement is performed and where the research in this thesis was implemented.

Where data are available and based on the knowledge and experience of the author, information will be presented from the perspective of the Australian population and the health care system.

1.1 Diabetes

Diabetes mellitus is a serious and prevalent chronic disease experienced by millions worldwide. Prevalence is increasing in Australia, with 1.3 million Australians, or 5.3% of our total population reporting they have been diagnosed with diabetes in the 2022 National Health Survey(1) The true prevalence of diabetes however may be around 20% higher based on the AusDiab study which shows that the inclusion of blood tests will detect previously undiagnosed cases (1, 2). While the data is over 20 years old, the Ausdiab study was a major longitudinal, study of the Australian population which included 11, 247 people from 42 locations nationally, providing important data relating to diabetes incidence and associated factors based on self-report and physical testing of participants (3). Other contemporary data is compiled by the Australian Institute of Health and Welfare which draws information on population health from datasets including the Australian National Diabetes Audit (ANDA), the National Diabetes Register (NDS), National Diabetes Services Scheme (NDSS), Medicare Benefits Scheme (MBS), National Health Survey (NHS) and Pharmaceutical Benefits Scheme

(PBS)(4) Diabetes is particularly prevalent in older Australians with one in five over 75 years of age diagnosed (1). This is similar to international trends (5, 6) which can be primarily attributed to changing patterns of obesity and overweight (7) but is also a consequence of population, and chronological ageing on the incidence of type 2 Diabetes (8) for which these two aspects are major risk factors. Diabetes is also more prevalent and impactful for people who live in more rural and remote areas and is linked to socioeconomic disadvantage(9). Indigenous people are also disproportionally affected both here and in other countries. Aboriginal and Torres Strait Islander people have 2.9 times the prevalence of diabetes, are more likely to be hospitalised or die for reasons related to diabetes; and have disability adjusted life year (DALY) estimates of 7966 years for endocrine disorders (predominantly diabetes), a figure several times that of their non-indigenous peers (9, 10).

Diabetes is defined as chronic high blood glucose, with hyperglycaemia in a defined abnormal range, which can result from metabolic and genetic factors impacting on ability of the pancreas to produce insulin, resistance to the actions of insulin or both (11, 12). Indeed, diabetes will only develop if the pancreatic beta cells fail to produce enough insulin to keep blood glucose in the normal range.

Insulin, the hormone responsible for cellular uptake and metabolism of glucose is secreted by islet cells within the pancreas in response to the presence of intestinal glucose following the ingestion of food. In addition to being regulated by the ambient blood glucose, insulin secretion is mediated by the hormone incretin, produced in the small intestine (13). Normal production and release of insulin from the pancreas, facilitates the uptake of glucose by cells for energy or storage(13). When this fails to occur, glucose accumulates in the blood stream causing both short and long-term complications.

Type 1 and Type 2 Diabetes, and (transient) gestational diabetes, are the predominant forms of the disease with steroid induced or monogenic types occurring as relatively rare conditions. Of these common types, Type 1 represents around 10% of cases and Type 2, 90%(6). Gestational diabetes, which as the name suggests presents during pregnancy, is by definition, transient and blood glucose levels stabilise shortly after delivery. While Gestational diabetes per se is not associated with long term complications in the pregnant mother, 60%

of those with gestational diabetes, later develop type 2 diabetes and there is also an increased risk of large birth weight at the time of delivery, complications during birth and also type 2 diabetes for the child in later life (14, 15).

Blood glucose concentrations of $\geq$7.0 mmol/L when fasting, $\geq$11.1 mmol/L as a random blood glucose test or $\geq$6.5% as a measure of glycated haemoglobin percentage (HbA1c) are the current diagnostic criteria for diabetes(16), with cut-offs determined by expert consensus. When blood glucose ranges are between normal and that defined as Diabetes, the condition of pre-diabetes exists (17). Pre-diabetes is defined by the presence of impaired fasting blood glucose or impaired glucose tolerance in response to the administration of 75 oral glucose (glucose tolerance test) or both. Pre-diabetes is highly prevalent, affecting ~1 in 6 Australian adults and like Type 2 diabetes, is associated with high blood pressure, dyslipidaemia, excess central adiposity, obesity, and pre-mature onset of cardiovascular disease (17, 18) .

Gestational and other rare forms of diabetes will not be further discussed here.

1.1.1 Type 1 Diabetes

Type 1 diabetes is an autoimmune disease with an onset typically occurring in the first two decades of life following destruction of beta cells by inflammation. Slow-onset autoimmune forms, such as Latent Onset Autoimmune Diabetes of Adulthood (LADA) are increasingly recognised. The cause of Type 1 diabetes is not known and there are no known modifiable risk factors, each triggering an autoimmune response in what are often found to be genetically susceptible individuals based on their immune genotyping (19). There is however epidemiological evidence that the incidence of Type 1 diabetes is increasing and may be related to factors such as Vitamin D deficiency, some viruses or other maternal, perinatal or lifestyle factors including dietary sugar (19, 20).

Type 1 diabetes is a condition of near or absolute insulin deficiency such that the only life-saving treatment is regular insulin injections, or more recently, continuous systemic insulin infusion, to replace endogenous insulin and sustain life. To mimic natural insulin function, the standard treatment is multiple daily subcutaneous injections of synthetic insulins, designed to provide a basal level of insulin, released slowly across the day, plus short acting (prandial) insulin doses used to manage meals(21).

1.1.2 Type 2 Diabetes

Type 2 diabetes is one of relative insulin deficiency and altered sensitivity of the tissues to respond to the available insulin. Reduced insulin sensitivity is associated with obesity, in particular increased visceral fat, or central (22).

Genetic predisposition for inadequate beta cell function which decreases over time plays a role in the development of type 2 diabetes. In genetically pre-disposed individuals, overweight and obesity place higher demand on the pancreatic beta cells to produce insulin with function decreasing over time. Type 2 diabetes typically presents in late adulthood, in the 50th decade or later. While relatively uncommon, there are growing numbers of young adults, below age 40, and even adolescents, presenting with Type 2 diabetes as a result of increasing rates of overweight and obesity in young people (23). The anticipated flow on effect of earlier diabetes onset will be the impact of diabetes organ complications during the productive years of life.

Significant public health investment has been made to address modifiable risk factors for type 2 diabetes, such as focusing on avoiding over consumption of food and physical inactivity forming part of public health campaigns (24). Such programs follow evidence from the pivotal Diabetes Prevention Study in which people with elevated fasting blood glucose in the pre-diabetic stage were enrolled (25, 26). Participants were randomised to one of three intervention groups; intensive behavioural intervention focused on weight loss through exercise and dietary changes had less, pharmacotherapy with Metformin, together with diet and exercise or a placebo, together with diet and exercise. Both the intensive behavioural group and those given Metformin had a reduction in the incidence of Type 2 Diabetes, at 58 and 31% respectively with an average follow-up period of 2.8 years (25). The large study showed that participants who had signs of elevated blood glucose or "pre-diabetes" could potentially reverse their diabetes risk (25). The benefit was prolonged. At 10 and 15 year follow-up studies after the groups were unblinded (and all participants offered the group lifestyle modification), the original, intensively treated group maintained a lower incidence of diabetes (34-27%), as did those treated with Metformin, but to a lesser degree (18%) (27, 28). The large, landmark study showed that treatment of people with signs of elevated blood glucose or "pre-diabetes" could potentially reverse their diabetes risk(25). Hence, with appropriate lifestyle interventions or targeted medicines, most people with pre-diabetes may be prevented or delayed from developing Type 2 diabetes (29, 30). The detection and management of hyperglycaemia in pre-diabetes is therefore also important for the prevention of long-term microvascular complications of Type 2 diabetes.

1.1.3 Management of Type 1 and Type 2 Diabetes

The main goals of therapy for the management of both main types of diabetes are to achieve close to normal blood glucose levels to prevent the short and long-term complications of diabetes. Type 2 diabetes is managed with lifestyle modification to control total caloric intake, dietary carbohydrate, together with increased physical activity. Type 2 diabetes in some cases can go into remission in overweight people if large weight loss (>15kg or more) is achieved and maintained however oral hypoglycaemic medication is the usually needed, at diagnosis or in later stages as beta cell function further declines. Insulin may also be needed to adequately lower and stabilise blood glucose levels (BGL) (13).

Management of diabetes also involves control of the risk factors for microvascular and macrovascular complications which includes hypertension, dyslipidaemia and particularly for people with Type 2 diabetes, overweight and obesity(31). If weight loss cannot be achieved with healthy diet and increased physical activity, then the prescription of low-energy, or very low-energy diets, pharmacotherapy and/or bariatric surgery (for people who are severely obese with BMI $\geq$ 40kg/m^2) may be required to achieve and maintain weight loss for management of diabetes (32).

While not all people with diabetes will have access to, or require intensive management, the complexity and demands of managing diabetes are ideally managed with a team approach, incorporating the patient and their general practitioner, practice nurse, endocrinologist, and relevant allied health such as podiatry, psychologist and/or optometrist. Other specialist care may be necessitated for specific diabetes complications including ophthalmology, cardiology and nephrology (33).

In addition to the aforementioned areas of management, pharmacotherapy is introduced according to patient age, blood glucose level (BGL) targets and specific health condition(s) and co-morbidities. While not all people with diabetes will develop complications, a key goal of treatment is to reduce the likelihood of long-term complications which are responsible for most morbidity and mortality associated with diabetes.

The relationship between poor diabetes control and microvascular complications, while observed prior to 1977, was confirmed in a large longitudinal study (n=4400) that year and reproduced in Diabetes Care in 1978 by Pirart (34). The study showed the close association between worse hyperglycaemia and prevalence of neuropathy, retinopathy and nephropathy(34). Publication of pivotal longitudinal, interventional studies followed. The Diabetes Control and Complications Trial (DCCT) and Stockholm Diabetes Intervention Studies of people with Type 1 and the United Kingdom Prospective Diabetes Study (UKPDS) of people with Type 2 diabetes have shown that intensified treatment of hyperglycaemia with targets of around 7.0% HbA1c, provides a level of protection from long term diabetes complications, mainly microvascular changes, whilst minimising risk of hypoglycaemia (35, 36). With the longer follow-up of the participants of both Type 1 patients from the DCCT became the EDIC study and UKPDS which became the post-study follow-up of the UKPDS, a reduction in risk of not only microvascular but also macrovascular complications has also been demonstrated (36-38). In addition to glycaemic control, management of hypertension, smoking cessation, and management of dyslipidaemia, is also critical for reducing risk of macrovascular complications; myocardial infarction, coronary artery disease and peripheral arterial disease (39-41).

Large studies have now confirmed the role of optimal blood glucose control for people with diabetes to reduce risk of long term microvascular complications; diabetic retinopathy, chronic kidney disease and peripheral neuropathy (42, 43). In the North American, Action to

Control Cardiovascular Risk in Diabetes (ACCORD) study, a large sample of 10, 251 people with Type 2 diabetes were randomised to receive intensive (Targeting a HbA1c level of < 6%) or standard management of their diabetes (targeting 7-7.9% HbA1c) with the primary outcome of interest, the rate of cardiovascular related events. The study was ceased early due to a higher than expected rate of deaths in the intensive group(44). Neuropathy as determined by the Michigan Neuropathy Screening Instrument, was less in the intensively treated group (42). In another landmark study, the Action in Diabetes and Vascular Disease (ADVANCE) trial aimed to measure the effect of intensive treatment of people with type 2 diabetes (to a target of 6.5% or less). This study across multiple countries, including Australia recruited 11, 140 participants and over a similar follow-up time also showed some reduction in microvascular events in the intensively treated group(43).

Therapeutic guidelines propose that three monthly testing of Hb1Ac be used to monitor people with diabetes and as a guide to therapy, although recommended targets differ depending on patients' and co-morbidities(45, 46). Additionally, self-monitoring of blood glucose provides allows them and treating teams to assess variability in blood glucose which can assist in titrating medication and insulin more concisely(46). Further to this, the use of new, continuous glucose monitoring technology can aid in the achievement of better glycaemic control and lowering of HbA1c% in people with Type 1 and Type 2 Diabetes when there is suboptimal control despite multiple insulin doses a day (47-49).

Achieving the targets for glycaemic control in people with Type 2 diabetes follows an individualised but stepwise approach of diet, with a focus on high fibre, low fat foods and reduction of saturated fats and calorie-dense sweet foods, and regular exercise. Initially, single pharmacotherapy with Metformin or Sulfonylurea and sometimes insulin injection is recommended for most patients. These antidiabetic agents aim to improve insulin secretion and/or insulin sensitivity. As shown in the UKPDS, there is evidence for maintaining a target of HbA_{1c} close to or below 7% to prevent long term microvascular complications however, tighter control may be safe and desirable for some patients while a higher target more safe in people who are older, have established complications, those who are more prone to severe hypoglycaemia (35, 36, 50).

Where monotherapy fails, additional agents are introduced with options selected on the basis of their additive benefits for protection against cardiovascular disease, renal disease and obesity and balanced against risk of hypoglycaemia. These include the oral SGLT2 or peptidase-4 inhibitor, or insulin, added in combinations according to risks, benefits, clinical guidelines and subsidised pharmaceutical benefits schedules (50-52).

The focus on therapy to manage Type 1 diabetes is more related to the need to replace endogenous insulin. The pivotal DCCT study and long term follow-up analyses have framed the importance of lowering blood glucose and maintaining tight glycaemic control to reduce the risk of microvascular complications of Type 1 (53). For people with Type 1 diabetes, glycaemic control is also the main modifiable risk factor for death from macrovascular complications (38).

Basal insulin is injected in some people with Type 2 diabetes and all people with Type 1 diabetes. Short acting insulin is also injected according to dietary intake of carbohydrate. While basal insulin is often sufficient for people with Type 2 diabetes where a degree of endogenous insulin secretion remains, people with Type 1 have absolute insulin deficiency and short-acting insulin to maintain more physiologically normal insulin levels throughout the day, according to their specific goals, dietary intake, and activity. Where people with diabetes have capacity to do so, carbohydrate counting is a means to accurately determine their insulin requirements and may permit a more normal approach to eating than restrictive diets of the past. Blood samples from a finger prick to measure BGL real time and carbohydrate counting are both used to safely adjust insulin dosage. An extension of this is the introduction of insulin pump therapy which remains in situ, reading the BGL and administering insulin subcutaneously according to individual patients' needs and BGL targets.

In the past two decades, pancreatic and islet cell transplants have emerged as an alternative to lifelong insulin therapy however this remains an option available to few; such as those with recalcitrant, recurrent or severe hypoglycaemia or those with end stage complications already requiring renal transplantation for diabetes-related kidney failure (54, 55).

1.1.4 Self-Management and Patient/Person-Centred Care

Self-management is at the core of effectively controlling diabetes and managing complications to reduce the impact of the disease(56). Active participation on the part of the patient relies on a patient-centred approach. The patient-centred approach is defined as "providing care that is respectful of and responsive to individual patient preferences and needs" as described in the seminal research presented by in the book by Gerteis et al (1993), is now a represented as a key standard in the Australian Hospital Accreditation Standards, and appears in evidence-based guidelines for managing diabetes(50, 57-59). Key principles of patient-centred care are that patients are engaged in their health care decisions. While patients (and families) need a level of health literacy to access to information, there is a responsibility on the health professional to provide them information in a way that can be understood and relates to their circumstances. Patient centred care also means considering health care provision from the perspectives of patients and their experience of illness.

While this is a responsibility of all health care organisations and all health professionals, education of patients on strategies to manage medications and lifestyle changes is optimised with the role of diabetes educators as part of the multidisciplinary team. The recommended focus of diabetes educators is to tailor the education to the individual and engage the patient in goal setting and decisions regarding their care (57, 60). Evidence-based recommendations can be effective when clinicians support patients with treatment decisions and adherence to lifestyle changes that best fit their preferences and individual circumstances(61).

The aims of the research described in this thesis align to the goals of patient-centred care. Information to guide treatment decisions requires evidence on the impact of different treatment approaches on outcomes, in this case, whether there is additional benefit to healing outcomes, of more frequent debridement. The preferences for care are further explored in a simple survey of patients, undertaken as part of this overall project.

1.1.5 Acute diabetes complications

A main, short-term, acute complication of diabetes is the risk of hyperglycaemia causing ketoacidosis in type 1 diabetes and hyperosmolar hyperglycaemia in type 2 diabetes.

Diabetic ketoacidosis (DKA) is life-threatening and mainly only affects people with type 1 diabetes, quite rarely occurring in people with Type 2 diabetes. DKA occurs at any stage of diabetes, whenever there are critically low insulin levels. A lack of insulin leads the body needing to use an alternative form of energy through lipolysis. This process of breakdown fatty acids to produce ketones for energy results in the formation of ketone bodies which are acidic and toxic. A build-up of ketone bodies is potentially fatal without emergency treatment involving rehydration, electrolyte, and parenteral insulin therapy, all being closely monitored in an acute hospital emergency or intensive care setting.

In type 2 diabetes, acute, severe hyperglycaemia with hyperosmolarity can occur but is more likely to occur later in the disease or in older people and is frequently associated with infection or other precipitants, such as myocardial infarction. Although ketones are not produced at the same levels, sufficiently high BGL (>33 mmol/L) will lead to hyperosmolar non-ketotic coma (HONC) which can also be fatal if not treated urgently with carefully managed rehydration and parenteral insulin, again in an intensive care setting (13).

Hypoglycaemia whereby BGLs are dangerously low is another potentially fatal scenario requiring immediate treatment. Hypoglycaemia rarely affects people who do not require insulin to manage their diabetes however some hypoglycaemic medications may also be associated with hypoglycaemia. If energy output is high and there is insufficient dietary carbohydrate, or if insulin (or some other hypoglycaemic medication) is administered at too high a dose (or some hypoglycaemic medications) for the needs of the person at that time, then a dangerous drop in BGL can occur such that there is insufficient glucose for the brain to function normally (13). If the person with diabetes becomes aware of symptoms of low BGL or can detect the drop with testing, then they can manage the event with intake of glucose(62). However if hypoglycaemia goes undetected and is not treated early, a severe hypoglycaemic event or loss of consciousness can occur for which emergency management, including glucagon intravenously or via injection is indicated (62).

1.1.6 Long- term complications of diabetes

The long-term organ complications of diabetes, in contrast to these acute conditions, take years to manifest. For people with Type 2 diabetes, complications can begin to develop before diagnosis due to the more insidious onset of this type of diabetes and because vascular disease is associated with metabolic disease preceding diabetes (63). Diabetes diagnosis is also more likely to be delayed with Type 2 diabetes. For those with Type 1 diabetes, complications are more likely to be delayed until 10 or more years after diagnosis. For both types, longer duration of diabetes, increasing age and higher BGL are positively correlated with risk of complications. The long term complications of diabetes are broadly grouped into microvascular; retinopathy, nephropathy and peripheral neuropathy and macrovascular complications; stroke, heart disease and peripheral vascular disease.

With greater numbers of people experiencing diabetes for longer, the hospital management of complications, including cardiovascular disease, renal and foot disease, consume a significant proportion of health care resources (64, 65). Advancements in the standard of treatment, both in the organisation of care and use of technology such as insulin pumps and continuous blood glucose monitoring and pharmacological advancements will likely continue to improve glycaemic control and reduce the likelihood of complications in the long term (66).

A key consideration in the management of people with diabetes complications is the insidious onset of complications which may develop without overt symptoms . Evidence-based practice guidelines, supported by health policies, encourage regular (mostly annual) screening for complications, using standardised tests, in adults with diabetes. While not all people with diabetes will develop complications, early detection through routine screening for eye, kidney, vascular and neurological complications provides the opportunity for treatment to prevent or delay the onset of conditions which can significantly impact quality of life, cause disability and premature mortality (67).

Gastrointestinal and genitourinary complications of diabetes are related to hyperglycaemia and neuropathy including erectile dysfunction and urinary retention. While these are important conditions, they will not be expanded on in this review.

The mechanism by which hyperglycaemia results in chronic complications continues to be explored. It may be explained by the formation of advanced glycosylation end products (AGEs) and other specific pathological processes such as antioxidant stress on cells and tissues with reduced antioxidant defences and specific cell signalling pathways such as Protein Kinase C. Not all people develop complications with genetic factors implicated in the development of kidney (68), carotid artery (69, 70) and retinopathy (71) with environmental impacts and behaviours (such as smoking) also implicated in the pathogenesis of diabetes complications(72), in particular cardiovascular disease (73).

Lastly, diabetes-complications are not discrete and separate from one another. For example, chronic kidney disease (CKD) and diabetes-related retinopathy will often co-inside with foot complications, both being long-term and microvascular driven complications of diabetes (74). CKD, as it progresses, becomes a greater risk factor for macrovascular disease, in particular myocardial infarction, heart failure and cerebrovascular disease with stroke (75).

Retinopathy

Diabetes is a leading cause of blindness and impaired vision(76). While the early changes which occur with diabetes-related retinopathy (DR) are commonly detected in diabetic complications screening, it is estimated that 1% of people with diabetes will develop blindness due to the condition (77). The pathophysiology of DR is related to several pathways of injury, related to hyperglycaemia: damage to the blood vessels from the formation of AGEs, the polyol pathway, protein kinase and hexosamine pathways and inflammation causing damage from leucocytes within the vessels and retina (76). The UKPDS and ACCORD studies showed a reduction in the progression of early DR with tight blood glucose control and the latter, including a benefit from fenofibrate (36, 78). This highlights the importance of eye examination at diagnosis of diabetes and regularly (at least every 2 years) thereafter to detect retinopathy when it is mild(77, 79). In the early stages of retinal damage, non-proliferative retinopathy, can be detected with retinal examination involving fundal dilation to detect signs of microaneurysms, haemorrhages and hard exudates (76). As DR progresses to severe or vision threatening proliferative retinopathy or macular oedema, more frequent monitoring is necessary so that treatment with photocoagulation therapy, intravitreal anti-vascular endothelial growth factor pharmacologic agents (anti-VEGF), or lastly, vitreous surgery can be used to prevent or delay more severe vision loss, however only anti-VEGF can improve vision lost to DR (76, 79) and more effective treatments are needed.

Vision impairment or blindness resulting from DR impacts many aspects of life, including capacity for self-care. A simple, yet relevant example being that poor vision is an impediment to visual inspection by one's own feet to detect foot problems. Retinopathy increases the risk of foot complications in the presence of neuropathy where neither sight nor sensation can alert the person to the presence of a foot injury. A strong association between foot ulceration and the presence of DR (with and without macular oedema) has been found in studies of foot ulcer risk in people with diabetes (80-82).

Chronic Kidney Disease (Diabetic Nephropathy)

Another serious complication related to microvascular disease is nephropathy which, if left untreated, can progress to end stage renal disease (ESRD), dialysis and premature death. This complication is particularly prevalent in Aboriginal Australians (with and without diabetes) with the rate of death from ESRD, 11 times than of non-indigenous Australians (83). The terminology has more recently changed to chronic kidney disease (CKD) in people with diabetes as this term better encompasses the reduced kidney function which is indicated by the presence of high blood creatinine or low glomerular filtration rate (GFR), which precedes end stage renal failure (84).

Early detection of CKD again relies on proactive screening and testing. The first sign is elevated urine microalbumin. Nephropathy follows a reasonably predictable course in people with Type 1 diabetes, with half of those who develop microalbuminuria experiencing progressive decline to macroalbuminuria. In Type 2, microalbuminuria may be present at time of diagnosis of diabetes and is more often associated with hypertension. In addition to early, tight glycaemic control, management can include pharmacotherapy to manage hypertension, in particular ACE Inhibitors which act to reduce glomerular perfusion pressure to reduce the loss of protein through the renal glomeruli to prevent progression to macroalbuminuria. Once macroalbuminuria is established, a gradual decline in renal function ensues, irrespective of glycaemic control and some patients will experience end stage renal disease where renal function becomes so low that dialysis is needed to prevent death.

Management is focused on balancing renal replacement with dialysis using peritoneal or hematologic treatment with the latter being possible to administer at home where the environment and supports are available. In Australia, there has been recent focus on renal supportive care which is essentially an option for palliative care, avoiding dialysis. Lastly, renal transplants may be available to a small proportion of younger people with ESRD pending the availability of a donor kidney and this is sometimes in addition to pancreatic transplant. Renal and pancreatic transplants will affect cure for both kidney disease and diabetes. However, lifelong immunosuppressive treatment required.

It is now understood that patients with ESRD have a similar risk of foot ulceration and amputation as people with diabetes and peripheral neuropathy, independent of having diabetes (85, 86). For people with Diabetes, the presence of ESRD is a significant risk factor for DFU and is a predictor of non-healing and mortality outcomes in this population(87-89).

Cardiovascular Disease

Diabetes is a major risk factor for macrovascular disease which is the most common cause of death in people with diabetes (90). The pivotal "Framingham Heart Study" in the United States (US) showed increased long term prevalence and worse cardiovascular disease outcomes in people with both Type 1 and Type 2 diabetes (91). The association between diabetes and macrovascular complications, through hyperglycaemia however is not so closely linked by causation as microvascular complications is with hyperglycaemia (36, 38). While interventional studies, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) trials have to date, not found improved glycaemic control very effective in preventing cardiovascular mortality or treating established cardiovascular disease, with only non-significant reduction in cardiovascular mortality (43, 92). Importantly, longer term follow-up of the ACCORD participants found a reduction in myocardial infarction in the intensively treated group (93) but longer term follow-up of the ADVANCE study did not show a difference (94).

More important than glycaemic control, in the prevention and management of cardiovascular complications in people with diabetes are modifiable risk factors; hypertension, obesity, dyslipidaemia, reduced physical activity and tobacco smoking which are all important in the pathogenesis of cardiovascular complications in Type 2 diabetes in particular (95).

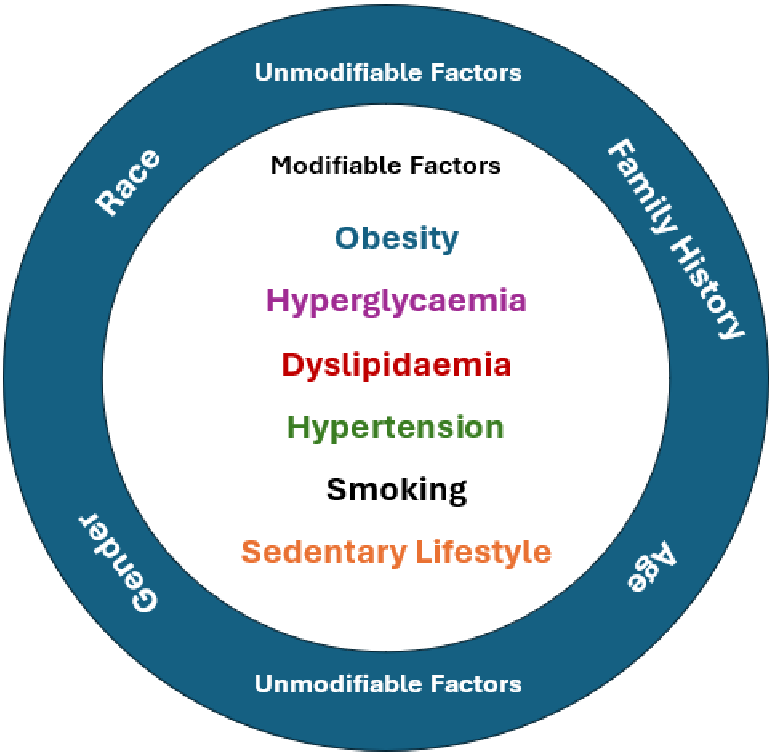
The pathologic process of atherosclerosis begins with low density lipoprotein (LDL) passing through arterial endothelium and depositing within the arterial wall. Oxidation of the LDL leads to local inflammation and further oxidation of the LDL which eventually results in macrophage activation and presentation of foam cells which are the hallmark of atherosclerosis and lead to “fatty streaks” on the vessel wall which represent the pre-curser to atherosclerotic plaques(96). This may be accelerated in diabetes due to increase vascular permeability making it easier for LDL to pass through the endothelium and the increased density of the LDL and the pro-inflammatory conditions of diabetes (97). The endothelial damage and associated inflammation encourage platelet aggregation at the site with thrombus formation which becomes incorporated into the vascular wall (98). Progression of atherosclerosis leads to progressive narrowing of the arteries (99).

While inflammation plays a role in the pathogenesis of atherosclerosis in people with and without diabetes (100), the pro-inflammatory state of diabetes may explain part of the earlier onset and more rapid progression which is seen in people with diabetes(98). Atherosclerotic plaques may also be more unstable in diabetes due to increased secretion of metalloproteinases which degrade collagen at the vessel wall (96). Diabetes is also associated with a propensity for thrombosis due to impaired fibrinolysis(101) and increased platelet activation(102) accelerating platelet adhesion and aggregation at the vessel wall.

In addition to the gradual narrowing of the vessel wall, acute embolic events may also occur if atheroma becomes detached. Atheroma can detach from the vessel wall, flow through the artery and lodge at site too narrow for it to pass. Depending on its location, myocardial infarction, stroke, or acute lower limb ischaemia distal to the blockage will result (98).

Figure 1: Risk Factors for Vascular Disease

Adapted from Lansang et al (2023) Diabetes and Vascular Disease (103)



Overt signs and symptoms will typically accompany such acute ischaemic events, however, gradual, and insidious hardening and narrowing of arteries in PAD may progress to an advanced stage with little or no symptoms (99).

The possibility that advanced macrovascular disease can occur without symptoms, highlights the essential role of complications screening which can detect changes in asymptomatic adults with diabetes, leading to investigation and treatment.

In routine complications screening of people with diabetes, any symptom of cardiovascular disease warrants investigation, initially with non-invasive tests such as doppler ultrasound to investigate flow in the major arteries and standard blood pressure measurement. Coronary angiography, as an invasive test and carries some risk but is indicated when there is high suspicion of significant myocardial ischaemic and the need for intervention is likely (104).

The management of cardiovascular risk in people with diabetes centres on supporting patients to undertake dietary changes and moderate exercise, together with pharmacotherapy in people with diabetes at higher risk of macrovascular disease targeting blood pressure, dyslipidaemia, and the hypercoagulable state(105). A low dose aspirin is used to reduce blood viscosity and the likelihood of thrombus formation in people with known atherosclerosis or those at increased risk (adults with > 10 years of diabetes). Statins are used to reduce hypercholesterolaemia, more specifically high LDL due to the high level evidence of benefit in reducing cardiovascular related deaths, all-cause mortality, and major vascular events in people with and without diabetes (106).

Angioplasty of vessels with significant narrowing, provides an opportunity to open a vessel lumen, narrowed by atherosclerotic blockage and is used in place of bypass surgery in the many cases. Stents, used to retain the patency and opening of the artery post angioplasty are commonly used, some containing agents to reduce the risk of re-stenosis. Patients with atherosclerotic disease may undergo multiple and repeated angioplasties in their lifetime. Coronary artery bypass surgery is indicated in people with diabetes who have had three or more major vessels involved with significant coronary artery disease or if the main left coronary artery is diseased (107).

Peripheral arterial disease

The development of atherosclerotic macrovascular disease in diabetes, will involve peripheral arteries of the lower limb. While peripheral arterial disease (PAD) in the general population mostly affects people over 50 years of age, and often in association with smoking(108), PAD is more prevalent, presents at an earlier age and progresses more rapidly in people with diabetes (109-111). Pooled relative risk ratios (RRR) for for PAD from 7 cohorts in people with diabetes have shown that diabetes doubles the age-adjusted RR of PAD in both men (1.84%) and women (1.96%) (112). A range of other confounders were to adjust the RR across these studies.This differs from the data on relative risk of cardiovascular-related mortality in people with diabetes which has shown than women have a threefold increase in risk of death from stroke or ischaemic hear disease compared to a twofold increase for men (113).

A feature of PAD in people with diabetes is preponderance for the distal tibial vessels to be affected (111) and there is both clinically significant narrowing, and calcification of the vessels, both of which have implications for ulcer risk and healing outcomes (114-117).

The UKPDS demonstrated the link between diabetes and PAD with both duration and extent of hyperglycaemic to be independent risk factors for PAD(118). Other long term population studies show higher HbA1c% is associated with a five-fold increased rate of PAD related hospitalisation, even when other CVD risk factors (smoking, dyslipidaemia and adiposity) were controlled (119, 120). As with other cardiovascular complications related to atherosclerosis, the main, modifiable risk factors for PAD in people with diabetes apart from hyperglycaemia are smoking, hypertension, dyslipidaemia, and obesity (in particular central adiposity) (97, 99). The management of these risk factors relies substantially on lifestyle modification; smoking cessation, dietary changes and exercise form the basis of treatment with pharmacotherapy and vascular interventions are also used to manage PAD (99).

In addition to atherosclerosis which narrows and may ultimately occlude the arteries, medial arterial wall calcification (MAC) of medium sized arteries and thickening of the basal membrane of small vessels and capillaries also contribute to PAD in diabetes. MAC is prevalent in people with symptomatic PAD, in particular people with both diabetes and chronic kidney disease (121) which is due to disruption in the normal homeostasis; increased expression of proteins which enhance MAC and reduced expression of proteins which inhibit calcification (121).

Calcification, which affects the intimal layer of the arteries and arterioles restrict their flexibility, and hence expansion of the vessel wall during systole. Tibial vessel calcification is associated with foot ulceration and amputation (114, 115), independent of atherosclerosis and complicates vascular assessment by falsely elevating blood pressure readings due to the incompressibility of the vessel(122).

Assessing PAD in People with Diabetes

This section will deal with the screening for PAD in people with diabetes and the assessment and grading of PAD in the management of DFU will be discussed following this.

It is a strong recommendation of the Australian evidence-based guidelines for diabetes-related foot disease, that screening for PAD be provided for all adults with diabetes and including a thorough history of symptoms and palpation of pedal pulses (123-125). The reasons are twofold; PAD is a marker of cardiovascular disease which is leading cause of premature mortality, and the presence of PAD is an independent risk factor for foot ulceration and amputation.

The Australian National Diabetes Audit (ANDA) for 2019 reported the prevalence of PAD as 7.3% based on 3.8% in people with Type 1 and 9.5% in those with Type 2 diabetes(126). Prevalence increases with age and duration of diabetes, hence for those with a 10 year diabetes history, prevalence is higher at 98.5% and 74.8% for those with Type 1 or Type 2 Diabetes respectively(126). The ANDA definition of PAD in this audit is; the absence of both dorsalis pedis and posterior tibial pulses in either foot, symptoms of peripheral vascular disease (e.g. intermittent claudication, rest pain, tissue loss/ gangrene), Ankle-Brachial Index<0.9, confirmatory arterial duplex scan or angiography or previous revascularisation procedure (incl. angioplasty, stent insertion or surgical bypass). Prevalence of PAD (Ankle brachial index < 0.9) , based on the community-based Fremantle Diabetes Study of 1294 people with Type 2 diabetes was 13.6% and data from those with 5 years of follow-up, show PAD was independently associated cardiac-related death (67%) (127). A diagnosis of PAD should therefore prompt examination of coronary arteries and risk mitigation strategies discussed earlier.

The presence and severity of PAD is also predictive of DFU and associated with poor outcomes, including delayed healing, hospitalisation, and amputation (116, 128, 129). Important longitudinal studies of people with diabetes have all found clinical measures of PAD predictive of DFU. In the Seattle study published by Boyko et al (1999), claudication, self-reported PAD, reduced ankle pressure and perfusion determined by transcutaneous oxygen tension, were all found to be risk factors (130). In the North-West study, reduced pulses were identified as risk factor for DFU (131). In the Australian Freemantle Diabetes Studies, the absence of one or more pedal pulses carried a high incident ration for hospitalisation with or for a DFU (132). In another recent Australian study of patients attending university podiatry clinics, PAD identified by abnormal toe-brachial indices carried an eight fold increased likelihood of foot complications(133). Hence the screening and testing for PAD is significant in both prevention and treatment of DFU and for assessing patients' overall risk cardiovascular-related death.

Systematic reviews have led to the recommended minimum screening for all people with diabetes that involves taking a history of symptoms and palpation of pedal pulses(124). A thorough history includes; symptoms of claudication and rest pain, smoking and PAD history and is interpreted alongside clinical assessment of the signs of PAD; the absence of hair, cool temperature, colour changes and delayed capillary filling time and weak or absent foot pulses (62, 134). While it is clear from previous studies that an absence of foot pulses, is associated with DFU and amputation risk, the test lacks the sensitivity and specificity to detect or exclude PAD with a high degree of confidence (131, 135-137). Hence the recommendation that, where possible, additional testing be undertaken and that a low threshold for referral for definitive test, such as arterial duplex scanning be undertaken when there are clinical signs, symptoms or a lower extremity wound in people with diabetes.

Systematic reviews by Forsythe et al (2019) and Pasha (2021) both investigate the evidence for different bedside clinical tests to reliably detect PAD in people with diabetes, using slightly different inclusion criteria and methodology however both reporting high levels of bias in the included studies (138, 139). Forsythe (138) analysed the results of 15 studies in 2019 reporting on the performance and reliability of tests to determine PAD in people with diabetes and Pasha included fewer (n=11) studies and performed an analysis of pooled data to calculate their own sensitivity and specificity (139). Pasha's results; ABI (Sensitivity 63.5% and Specificity 89.3%, TBPI (Sensitivity 83% and Specificity 66.3%) and Continuous Wave Doppler Assessment (Sensitivity 82.8% and Specificity 86.8%). The results largely concur with the Forsythe et al regarding the inability of either pedal pulse palpation or ABI to reliability detect or exclude PAD, the value of TBI in excluding it and the emerging importance of continuous wave assessment with high sensitivity and specificity (138, 140).

The chairside use of continuous wave doppler (CWD) effectively detects PAD and can be readily available as a hand held device which can detect pulses in the presence of swelling, oedema and/or anatomical differences affecting palpation. It is most reliable when waveforms are visualised (141). Tehan et al have compared the results of CWD to the reference standard of colour duplex ultrasound results in 396 participants with and without diabetes and compared 66 to angiography, finding that in people with diabetes (and without) that CWD predicted duplex ultrasound confirmed PAD with high sensitivity and specificity (140). While these results are important, the overall number of participants for assessing with CWD in the currents studies is still considered to be low and more research into predicting clinically significant PAD in people with diabetes is recommended.

The current recommended approach for screening for PAD is based on the interpretation of results together. Ankle-brachial indices are still advised in the assessment of PAD in the 2020 International Working Group on the Diabetic Foot (124) despite the known issue of MAC falsely elevating results (122). Interpretation can be enhanced when considered alongside pulse palpation in which a weak or absent pulses is considered as indicative of PAD according to a cross sectional study of n=200 participants with diabetes at high risk of PAD published by Aubert et al (122). In this cohort, pedal pulses were palpated, and ankle-brachial indices, duplex scanning and multi-slice computed tomography of the tibial vessels to assess for both occlusive arterial disease and arterial calcification were performed (122). Their results support the use of both pulse palpation and ABI in screening for PAD due to high sensitivity (92.3%) of these tests when using the parameter of the patient having a weak or absent foot ulcer and/or abnormal ABI (< 0.9). They found that tibial artery calcification scores were significantly higher in participants with false negative results, thus indicating that when arterial calcification is present, assessment of pulses and ABI will miss a significant proportion of patients with significant PAD who have > 70% stenosis in a lower limb artery(122). Chuter et al have since published a systematic review of studies investigating the diagnostic accuracy of ABI in people with diabetes concluding that while the test is highly specific, the mean sensitivity of 0.60 (95% CI 0.48-0.71) is too low for the test to reliably exclude significant early PAD (142).

Returning to history of symptoms and clinical assessment of pulses which is the recommended minimum screening (124, 125), standard history includes questioning patients about claudication symptoms (134, 143). Claudication symptoms are more prevalent in people with diabetes and typically occur in the lower limb, particularly with exertion such as occurs with walking up hill or stairs, as a sign of significant PAD (144, 145) It a consequence of inadequate blood flow to meet the tissue demands for (146). Claudication symptoms are differentiated from musculoskeletal and neuropathic pain by its predictable pattern of onset, with the pain rapidly alleviated when the person stops to rest. Clinically, the presence of PAD may co-inside with loss of protective sensation and so in people with peripheral neuropathy and also those who do not walk sufficiently to experience claudication, the presence of painful symptoms is not a reliable indicator of PAD (99, 124, 147).

Rest pain indicates a more severe occlusive disease such that pain occurs when the legs are elevated during rest and sleep (148, 149). The pain and disability associated with claudication can be highly impactful and an indication for treatment with revascularisation or other interventions to manage pain when vessels are not amenable(149).

The literature pertaining to assessment, grading and management of PAD in people with DFU is covered in the section on management of DFU.

Diabetic distal symmetrical sensorimotor polyneuropathy

This section will focus now on Distal symmetrical sensorimotor polyneuropathy (DSPN), the most common and impactful type of neuropathy experienced by people with diabetes which is a strong predictor of DFU. Painful neuropathy and other forms of neuropathy which are more common in people with diabetes, such as mono mononeuropathies and acute axial neuropathy will not be discussed in this review or thesis.

DSPN is a chronic complication of diabetes, categorised as microvascular but which has a complex aetiology involving the deleterious effects of hyperglycaemia and cardiovascular disease on the peripheral nerves. The mechanisms under investigation for their role in DSPN pathogenesis include the polyol pathway for converting excess glucose with aldose reductase, activation of protein-kinase C, non-enzymatic glycation, over-production of reactive oxygen species, however no treatment has been as yet proven to reverse DSPN (150-152).

The role of hyperglycaemia is evident from pivotal, longitudinal studies. In the DCCT, intensive treatment and reduction in hyperglycaemia delayed and prevented DSPN in people with Type 1 Diabetes, with a 50% reduction in the incidence of neuropathy in those intensively treated (37). Additional data from the 13-14 year follow up study, NeuroEDIC, demonstrated evidence of sustained benefit from early intensive treatment(153). In NeuroEDIC, 25% of participants developed clinically confirmed neuropathy in the DCCT intensive treatment arm compared to 35% for those receiving conventional treatment ($p = < 0.001$) (153). In the UKPDS study of intensive versus conventional treatment for Type 2 diabetes, risk of microvascular complications was also positively correlated with poor glycaemic control with a slowing of progression of neuropathy however less impressive than the DCCT(154). Reduced risk of microvascular complications was sustained in 10 year follow-up(155). The UKPDS also showered the impact of hypertension on microvascular complication with reduced prevalence of neuropathy associated with lower systolic blood pressure(156). In the Fremantle Diabetes Study population (Type 2 Diabetes), multiple logistic regression higher blood glucose was positively associated with DSPN, as was systolic blood pressure and with lipid lowering fibrates and statins associated with reduced incidence of neuropathy over 5 years (157). The studies showing associations between neuropathy and vascular risk factors; hypertension, obesity, dyslipidaemia, and smoking provide evidence that to prevent and slow progression of DSPN, clinicians need to address cardiovascular risk reduction in addition to optimising glycaemic control(158-160).

Prevalence data will vary with the population studied but also the assessment criteria are used to define its presence, which vary significantly(135). While clinically relevant and of meaning to patient quality of life, symptoms alone cannot be relied on to determine the presence of DSPN with its main feature being loss of sensation which develops insidiously and frequently without symptoms (161). Widely adopted evidence-based tests include use of the 10g monofilament and tuning fork or neurothesiometer to detect vibratory perception (135, 162). These and several other tests, instruments and scoring systems which include both signs and symptoms have been documented, each with their own method(s) and merit based on convenience, predictive value and suitability to the task, be it population screening or for clinical research (151). A review of monofilament testing highlights the lack of consensus regards the specific approach to testing and the number of people diagnosed will vary depending on the method used (163, 164).

Overall, the median prevalence in community-based diabetes populations, has been estimated to be 28-29%(165). Some important population studies to note include; Katon et al (2004) in a large cross sectional study of US National Health and Nutrition Examination Survey (NHNES) of 7818 adults over 40 years in which DPSN was present in 27% of people with diabetes, 18% of those with undiagnosed diabetes, 16% of this with pre-diabetes and 11% of people without diabetes(166). Diagnosis in this study was based on monofilament insensitivity at ≥ 1 site. In Australia, Tapp and Shaw et al as part of the Ausdiab study, found 13.1% of adults over 25 years with unknown diabetes had DSPN with prevalence increasing with duration of diabetes(167). It is worth noting that the criterion for neuropathy was based on extensive testing with patient classified as having neuropathy on the basis of two or more abnormal results using the following scores; Pressure Perception (monofilament), the Neuropathy Symptom Score, Neuropathy Disability Score and Autonomic Neuropathy with an ≥ 20 mmHg drop in blood pressure with standing (167). This prevalence is less than the community population in the Fremantle Diabetes Study of which 30% of participants (without DFU) were found to have neuropathy, although a positive screening for DSPN in this study was based on 2 or more items using the clinical criterion in the Michigan Neuropathy Screening Instrument comprising of: DFU presence, Abnormal appearance, Ankle reflexes and Vibration perception (168). In adult patients attending diabetes services in Australia, the ANDA 2019 report indicated 18.9% of the patient population had peripheral neuropathy (126).

Despite the range of methods and variable numbers diagnosed, one test, insensitivity to the 10g monofilament stands out as a consistently identified indicator of loss of protective sensation due to DSPN, useful in predicting risk of DFU based on prospective studies and systematic review (130, 131, 135, 169) with vibration (tuning fork at hallux) or vibratory threshold at the malleoli alone or as part of the neuropathy disability score also proving predictive (131, 135).

The methods for assessing DSPN in the Diabetes Debridement Study were outlined in a diabetes treatment protocol agreed to and shared with participating sites. In this protocol, neuropathy is presumed on the basis of clinical assessment and testing with the 10g monofilament and vibratory perception using biothesiometer, neurothesiometer or 128 Hz tuning fork which is consistent with the guidance at the time and remains so with the latest (2023) guidelines on the prevention of DFU (162). Insensitivity to the monofilament was defined as the inability of the patient to detect one of both sites using the plantar first and 5th metatarsal heads, a method shown to be predictive with good sensitivity and specificity(164). Vibration perception is assumed to be abnormal if patients cannot detect the 128 Hz tuning fork according to the IWGDF guidance (170) or biothesiometer/neurothesiometer below 25 V. Concordance between the biothesiometer and neurothesiometers is good and correlates with tuning fork results (171, 172) and this approach is consistent with guidelines recommending at least two tests be used (170, 173).

The clinical impact of DSPN is broad and varied. Some individuals will experience painful neuropathy symptoms including a dead or numb feeling, pain, paraesthesia or pain which is transient or permanent and may or may not occur with loss of protective sensation(151) but around 50% will have no symptoms(161). DSPN presents distally but progresses proximally in stocking and glove distribution, affecting both limbs similarly and involving the sensory, autonomic and motor nerves(174, 175), with the latter more likely to be detected in advanced disease(176). Once established in the lower limb, the hands will be become affected.

The presence of DSPN is associated with significant physical impairment. People with advanced DSPN have accelerate reduction in muscle strength which contributes to altered biomechanics and balance deficits which place them at increased risk of falls and is detrimental to physical functioning and quality of life(176). Strotmeyer et al (2008) studied the effect of peripheral nerve function on physical abilities in a large group (n=2364) of people participating in the Health, Ageing and Body Composition study, finding lower performance in people with diabetes in common functional tests; chair standing, standing balance, 6m walk, narrow walk and single foot standing was assessed(177). The difference was explained by measures of peripheral nerve function as determined by vibratory perception, sensitivity to the 10g monofilament and nerve conduction studies in this group (177). In another population study, Chiles et al (2014) using data from the InCHIANTI Study found that in people over 65 years, those with diabetes have clinically significant, reduced physical functioning scores compared to age and sex matched peers (178). Reduced scores on the Short Physical Performance Battery were associated with indicators of DSPN, reduced nerve conduction and neuropathy scores in those with diabetes (178). In the Fremantle Diabetes Study, neuropathy was predictive of impaired mobility in participants followed up an average of 4.8 years(179). The causes of functional impairment are linked to muscle dysfunction. While the aforementioned studies show associations with diabetes and neuropathy, other studies show a broad range of factors related to diabetes and other disease processes (180).

A systematic review and meta-analysis of data on physical function in older people with foot disease (predominantly people with DFU) found higher rates of poor physical functioning, as defined by a broad range of measures, in older adults with diabetes-related foot complications compared to their peers (181).

In clinical studies of strength, Almurdhi et al (2016) compared knee and ankle extension and flexion, and muscle volume in people with type 2 diabetes to age, sex and BMI matched controls(182) reporting that strength but not volume were reduced in the diabetes, related to DSPN severity. In related research, Brown and Handsaker (2014), studied stepping accuracy, gaze behaviour and stability in stair climbing to explore the impact of diabetes and DSPN on lower limb functional deficits and falls risk in patients (183-188). Their series of investigations have shown that people with diabetes and DSPN have lower extremity weakness, compared to people with diabetes and no DSPN, that there is more exertion in this group who must use a greater proportion of their range of strength to manage activities of daily living such as stairs and that both step placement accuracy and steadiness are impaired (183-188). The implications of this are that people with diabetes and peripheral neuropathy face greater challenges in physical functioning which impacts adherence to pressure offloading in their treatment of DFU.

Other researchers have linked reduced physical functioning to patients' quality of life and depressive symptoms. The latter was measured in a study by Vileikyte et al (2009)(189). Baseline depression and neuropathy scores and repeated measures at 9 and 18^{th} months in were analysed from 388 people with DSPN (189). While painful symptoms have been the focus of some research, not all people with DSPN or DFU experience painful symptoms (190). The longitudinal study was specifically designed to elucidate data on the impact of neuropathy symptoms related to unsteadiness and to other parameters such as the neuropathy disability score and painful symptoms. In this study, participants had high baseline scores on the Hospital Anxiety and Depressive subscale for anhedonia, the HADS-D, consistent with other reports (191). The longitudinal study found that depressive symptoms scores increased over time and even with HADS-D controlled at baseline, with unsteadiness and painful symptoms predictive of higher HADS-D scores, more so than the Neuropathy Disability Score with 60% of variance explained by neuropathy scores (189). The authors concluded that unsteadiness was the symptom most strongly associated with depression, likely linked to feelings of low self-worth.

While reduced physical function in people with diabetes and DSPN has now been widely studied a comparative body of evidence to address management has lagged. Newer research showing benefits to neural function, postural control, and strength in people with diabetes and DSPN undergoing aerobic and resistance training (192, 193). With careful selection of exercises in those patients who are willing to participate, there may be benefits to physical functioning (194) however more research is needed in this area.

The implications of poor physical functioning in people with diabetes on their quality of life are significant and likely to impact patients' ability to travel to and attend treatment visits (195, 196).

In the feet, marked intrinsic muscle atrophy has been shown to occur in people with diabetes, in association with DSPN when compared to controls (197-199). While traditionally, this atrophy was considered to cause digital clawing, progressively prominent metatarsal heads, and forward displacement of the forefoot plantar fat pad which is associated increase in forefoot plantar pressure(197), direct evidence of causation has not been found(200) .

The manifestations of autonomic neuropathy in diabetes range from coronary artery neuropathy (CAN) to gastrointestinal, urogenital, and sudomotor dysfunction(201). While important complications which impact quality of life and in the case of CAN, may result in death, most are unrelated to foot complications, with the exception of sudomotor changes. Sudomotor dysfunction is associated with DSPN, correlating with reduced vibratory perception(202, 203), and is shown to be more prevalent in people with diabetes and foot ulcers compared to people with diabetes and those with diabetes and DSPN(204). Dry skin resulting from an absence of sweating, makes it is more prone to callus and fissures, hence the contribution to foot ulcer risk.

Notwithstanding the combined impact of irreversible motor, autonomic and sensory impairment on patients' quality of life, the most impactful aspect of neuropathy in the pathogenesis of DFU, is loss of protective sensation (LOPS). LOPS is present in almost every patient with DFU. Not only does LOPS render the foot vulnerable to trauma, it denies the patient the stimulus to seek help during which time DFU can become deeper, larger, and infected. During treatment, patients with LOPS often continue to walk without adequately protecting their foot, with low adherence to offloading an unresolved issue in people who cannot tolerate or choose not to use an irremovable device.

Adherence to wearing pressure offloading devices is likely impacted by the relative absence of pain as well as proximal muscle weakness and poor proprioception causing loss of stability and confidence to use some offloading devices. Postural instability increases risk of falls injury and this is particularly relevant when using devices which result in significant changes to gait, such as knee-high devices. For these reasons, knee-high offloading was not uniformly enforced as the offloading strategy in the Diabetes Debridement Study.

It is apparent from the available evidence that many people with DFU have significant physical limitations due to neuropathy and that would impact their ability to travel to treatment centres. At the same time, those with neuropathy are more likely to have other microvascular and macrovascular complications, further impacting their independence in terms of driving ability and walking distance.

1.2Diabetes-related Foot ulcers

Diabetes-related foot ulcers arise as a complication of diabetes, primary due to the impact of diabetes peripheral neuropathy (DSPN), as a microvascular complication, and peripheral arterial disease (PAD), a macrovascular complication, both long term sequelae.

It is important to note that other complications hitherto discussed will often be clinically present to some degree in people with DFU, meaning that for many, the overall disease burden is high and DFU and other co-morbidities will be negatively impacting quality of life and capacity to manage DFU.

People with DFU are impacted already by frequent medical appointments, complex treatment regimens of lifestyle and pharmacologic interventions and the need for vigilance in self-care and monitoring.

As a common complication of diabetes and a leading cause of hospitalisation, foot ulceration is associated with lower extremity amputation are high mortality. The available data on the epidemiology of diabetes-related foot complications will be discussed.

1.2.1 Epidemiology of foot disease in people with diabetes

Calculations from a United Kingdom (UK) Community cohort and United State (US) Veterans with diabetes estimates the lifetime incidence of Distal Symmetrical Polyneuropathy (DSPN) for people with diabetes is between 19.6 and 34 % with 8% of US Medicare Beneficiaries with diabetes having a history of diabetes-related foot ulceration(205, 206). In the US Medicare Beneficiaries are predominantly people over 65.

The population prevalence of DFU in Australia is not known but a study of NSW residents enrolled in the 45 and up Study provides some estimates. In this study, NSW admissions and emergency department data were linked for a random population sample of people 45 years of age and over. The study found that 10.8% of people with Diabetes in NSW (the most populated State), were admitted or attended an emergency department for a diabetes-related foot complication (2006-2012) (207). Of these, around half (5.4% of those with diabetes) had a DFU or diabetes-related foot infection. This is likely underestimation of the overall prevalence because people presenting to non-admitted services or primary care for treatment (and not admitted) were not captured(207).

Another source, the Australian National Diabetes Audit (ANDA) conducted under the auspices of the National Association of Diabetes Centres reported in 2015, that 22.5% of adult patients with diabetes had peripheral neuropathy (based on clinical judgement), 3.4 % had a current and 6.7% a past foot ulcer (208).The trend according to the NADC data is for an increasing prevalence of foot disease, compared with lower rates 4 years prior in 2011 when they reported that 21.9% adult patients had peripheral neuropathy, 2.1% a current and 5.5% a past foot ulcer (209). Thus, while NADC data is cross sectional only, and based on a snap shot, it suggests that foot disease in diabetes is not decreasing and may be increasing. Furthermore, as Type 2 diabetes is increasingly being diagnosed in younger people, it is noteworthy that peripheral neuropathy prevalence of 20-36% has also been reported in younger Australian and Americans with diabetes (210, 211). Across the two time periods of the Freemantle Diabetes Study, 1993-1996 and 2008-2011, hospitalisations rose slightly with incident rate ratio of 2.4 to 2.6 per 1000 patient years (132).

Both internationally and here is Australia, Aboriginal people are disproportionately affected by diabetes prevalence and most likely rates of DFU are higher (212). In their meta-analysis and review of six studies, Isa et al found that worse outcomes were found in indigenous versus non-indigenous populations, in particular with regards to major amputation, however not all studies accounted for non-urban place of residence which is associated with poor health outcomes (212).

In several populations studied in Australia, rates of diabetes-related foot ulceration are higher in Aboriginal people compared to non-Aboriginal with lower limb amputations also associated with Aboriginality (213-215). Furthermore, foot complications in Aboriginal people appear to develop at a younger age (214) with Aboriginality, independently associated with DFU risk in the Freemantle Diabetes Study (168). While some of this may be explained by some Aboriginal populations living in more rural and remote areas, the review by Singh et al suggests Aboriginality per se, is a risk factor for increased amputation risk (216) . In their audit of 4832 patients presenting with DFU to services in Queensland, Australia, Zhang et al found 10.5% of patients identified as Aboriginal (217) which is twice the state's population average for Aboriginal and Torres Strait Islander people (218). In a single service in the Australian Northern Territory, where 30% of the population identified as Aboriginal or Torres-Strait Islander on the government Census, 50% of the patients attending the interdisciplinary foot service identified as Aboriginal or Torres-strait Islander (219).

Most recent national data on amputations reported by the Australian Institute of Health and Welfare in 2017 indicates there were 4,402 diabetes-related lower limb amputations (LLA) 2012-2013, representing 23 per 100,000 people (208). For evaluating clinical care, the incidence of minor and major amputations in a defined population is recommended, ensuring both can be reported separately and expressed as a ratio of high (above knee amputations) to low (distal to the ankle) (220, 221). Australia's diabetes related high: low amputation ratio is reported as ~ 50:50 (208).

Amputation incidence can serve as a relatively reliable indicator of the population health and performance in the health care system tasked with the prevention and management of diabetic foot complications (222-224). Nationally, the incidence rate of diabetes-related amputation is higher in some areas and populations suggesting inequitable access to quality care which can improve outcomes (225). Diabetes-related amputations are four times higher in remote areas (compared to the Cities and Inner Regional areas), 1.8 times higher in the lowest socioeconomic group (compared to the highest) and 3.8 times higher in Indigenous people compared to non-indigenous (208). The Northern Territory has almost triple the age adjusted amputation incidence rate compared to the Australian Capital Territory (ACT) and this is likely to be driven by these three factors; regionality (and remoteness), socioeconomic factors and the proportion of Aboriginal versus non-Aboriginal people with DFU (224).

Around 50% of all lower extremity amputations (LEA) are diabetes-related, however there is some additional data available on trends for LEA which includes both diabetes and non-diabetes related. Dillon et al has highlighted the relative stability of overall age-adjusted incidence of lower limb amputation in Australia between 2000 and 2010 with an overall incidence of 37.41+/-1.01 amputation procedures per 100,000 population (226).The reduction in the major (above ankle) amputations and relative increase in minor (distal to the ankle) amputations is demonstrated with the ratio of 0.61 to 0.34 from 2000 to 2010 respectively. This shift is consistent with that noted in other regions in response to improved care (226). Notably, in Australia, three quarters of minor amputations are distal and involve only the toe or toe and metatarsal (as the same procedure). While partial foot amputations of this nature of are limb saving, and the functional outcome far better than for a major amputation, the residual foot has an extremely high risk of re-ulceration and re-amputation due to the addition of iatrogenic deformity to other, primarily irreversible risk factors (205).

The seriousness and impact of foot complications is also reflected in mortality data for people with DFU and Diabetes-related lower extremity amputation (LEA) (88, 206, 219, 227-233). The association with DFU and increased, all-cause mortality is confirmed in meta-analyses by Brownrigg (2012) and updated by Saluja and colleagues in 2020 (88, 234). Data from 11 studies shows that people with DFU are found to have a greater than 2.45 increase risk of all-cause mortality when compared to people with diabetes (and no foot ulcer) with cardiovascular disease a common cause of death in people with diabetes both with and without foot ulceration (88). In their systematic review of studies published until August 2001, Jupiter et al (2016) estimated the 5 year mortality rate for people with DFU being around 40% (235). Data pooled from mortality studies published since 2007 by Armstrong et al, showed the mean 5 year mortality rate for people with DFU to be 30.5% and for those with minor and major amputation 46.2 and 56.6% respectively which they found to be on a par with most cancer diagnoses (233).

Premature death relating to DFU has been reported since 1993 with data from a cohort of 553 patients with DFU and those who had DFU and amputation (227). They found 5-year mortality rates of 42 and 73%, 2-4 times higher than their age and sex matched peers(227). Boyko et al (1996) also reported a two-fold increase in mortality rate in their population of 725 (mostly) male, US Veterans with DFU who were prospectively studied and compared to those with DM alone (228). This difference was detected while adjusting for age as well as type, duration, and treatment of diabetes(228). South-East Asians with DFU were also found to have increased risk of pre-mature death compared to age-matched peers with diabetes (n=2880) followed prospectively for 14 years whose 5 year mortality of 22%, is lower than the European populations studied(87). Given the likelihood of comorbid cardiovascular and renal disease in people with diabetes who develop foot ulceration, it is expected that cardiovascular complications would explain pre-mature death (236). Lin et al (2021) found the combination of cardiovascular disease, foot complications and LEA, predictive of mortality in their 15 year, nation-wide observational study in Taiwan. In their study, they adjusted for major cardiovascular co-morbidities at baseline reporting an overall 5 year mortality rate of 19% with an adjusted hazard ratio of 1.43 for people with diabetes-related foot complications without major CVD prior to foot complication and 1.98 in people with PAD and CVD present before first foot complication, signalling that foot disease is associated with increased mortality, with and without major CVD (237). Nonetheless advances in management of cardiovascular disease (CVD) risk in people with diabetes, should mitigate risk of premature death to some extent in this group. The implementation of more aggressive, evidence-based strategies to address cardiovascular risk resulted in a partial reversal of this trend in mortality was seen in the study by Young and colleagues with a 50% reduction in mortality in DFU patients(229). Of note, heart failure was prevalent in the cohort of patients with DFU attending our Sydney-based Diabetes centre and was associated with failure to heal (238). Notwithstanding the importance of a strong multidisciplinary team approach to managing people with DFU which addresses the risk factors for death from cardiovascular disease, it remains the case that DFU per se is associated with increased risk of premature death(88, 230), not only through its association with CVD.

A retrospective audit of 644 DFU patients attending outpatient services in Portugal (2002 to 2010) found DFU to be an independent risk factor for premature mortality (230). Using univariate analysis, they found that age, visual or physical impairment, diabetes duration, cardiovascular complication history, total count of complications, ESRD and foot complications including DFU showed an association with rate of death with age, complication count and history of DFU remaining predictive in multivariate analysis, concluding that DFU history and complication count (combined) were strongly predictive (AUC 0.81) (230). Subsequently, Walsh and colleagues published their data which also found DFU to be an independent risk factor(231). Using their database of 14, 523 patients with diabetes and controlling for known diabetes complications associated with mortality, the 5 year mortality rate for those with DFU was 42% with DFU associated with a 2.5% higher risk of death compared to those with diabetes (231). Other factors strongly associated with mortality in this population were age and co-morbidity index, the latter being the best independent predictor of death in this group, supporting the earlier finding that these patients are experiencing multiple health problems in association with their DFU which contributes to mortality (231). Social determinants of health may also play a part with one study measuring deprivation scores in association with DFU and mortality finding that people in the lower quintiles of social deprivation have both higher DFU prevalence and risk of mortality(239). The association with financial disadvantage and death in people with DFU was also reported in the meta-analyses by the Brownrigg and Saluja (88, 234).

Australian mortality rates associated with DFU in a single study are reported as 24.6%. In this patient population studied from 2003-2015, Jayaraman et al found age and plasma albumin levels predictive of mortality in their final multivariate analysis with chronic kidney disease the cause of death for 24.6% of their DFU patients (219). CVD (19.6%) and sepsis (19%) were the other leading causes of death in this young cohort with average age of 55.9 years of whom 50% were Indigenous and 30% lived remotely (219).

1.2.2 Aetiology of Diabetes-Related Foot Ulcers (DFU)

Prevention and management of diabetes-related foot ulceration begins with primary prevention of the diabetes complications as discussed in the first section of this literature review. In this section, the aetiology and management of DFU will be expanded on with discussion of the main tenets of treatment.

Foot complications include loss of sensation caused by distal, symmetrical polyneuropathy (DSPN) and peripheral arterial disease PAD), small nerve disease as well as deformity caused by muscle wasting and limited joint mobility. Distal symmetrical polyneuropathy (DSPN) is the most potent risk factor for first time foot ulceration (131, 135, 240) and the presence and extent of peripheral arterial disease is highly predictive of non-healing and amputation (241, 242). The effect of DSPN on the foot includes deformity, due to muscle wasting, skin changes due to the sympathetic denervation and loss of sweating but most importantly, sensory loss which permits injury to the feet such as repetitive pressure, to go on undetected and develop into limb threatening ulceration. The inability to detect injury to the feet delays the affected person from seeking treatment and allows them to continue to walk on their injured foot, exacerbating the injury and leading to ulceration and infection. Additional factors relating to diabetes as well as extrinsic factors will impact on the clinical outcome, however the loss of “protective” sensation from advanced peripheral neuropathy is invariably the pre-curser and a major factor in the pathogenesis (135, 162, 243, 244).

Injury to the foot, either through chronic pressure or friction (or both) related to the presence of foot deformity or acute trauma on a neuropathic foot is the main mechanism by which foot ulceration occurs(117). While DSPN is almost always required for DFU to occur, the impact of reduced blood flow and other factors strongly impact on the ability of the DFU to heal readily and contribute to risk of non-healing and amputation (217, 245, 246). Loss of sensation is not only required for the initial injury in many cases, but it also contributes to ulcer deterioration. The absence of pain permits the person to continue to walk on the injured foot, often without any initial warning that they have sustained trauma. Moreover, reduced sensation including to infection symptoms will result in the person with DFU believing their condition is less serious that it potentially is in-reality. Therefore, delayed seeking of care is commonly associated with DFU and its deterioration (116, 246).

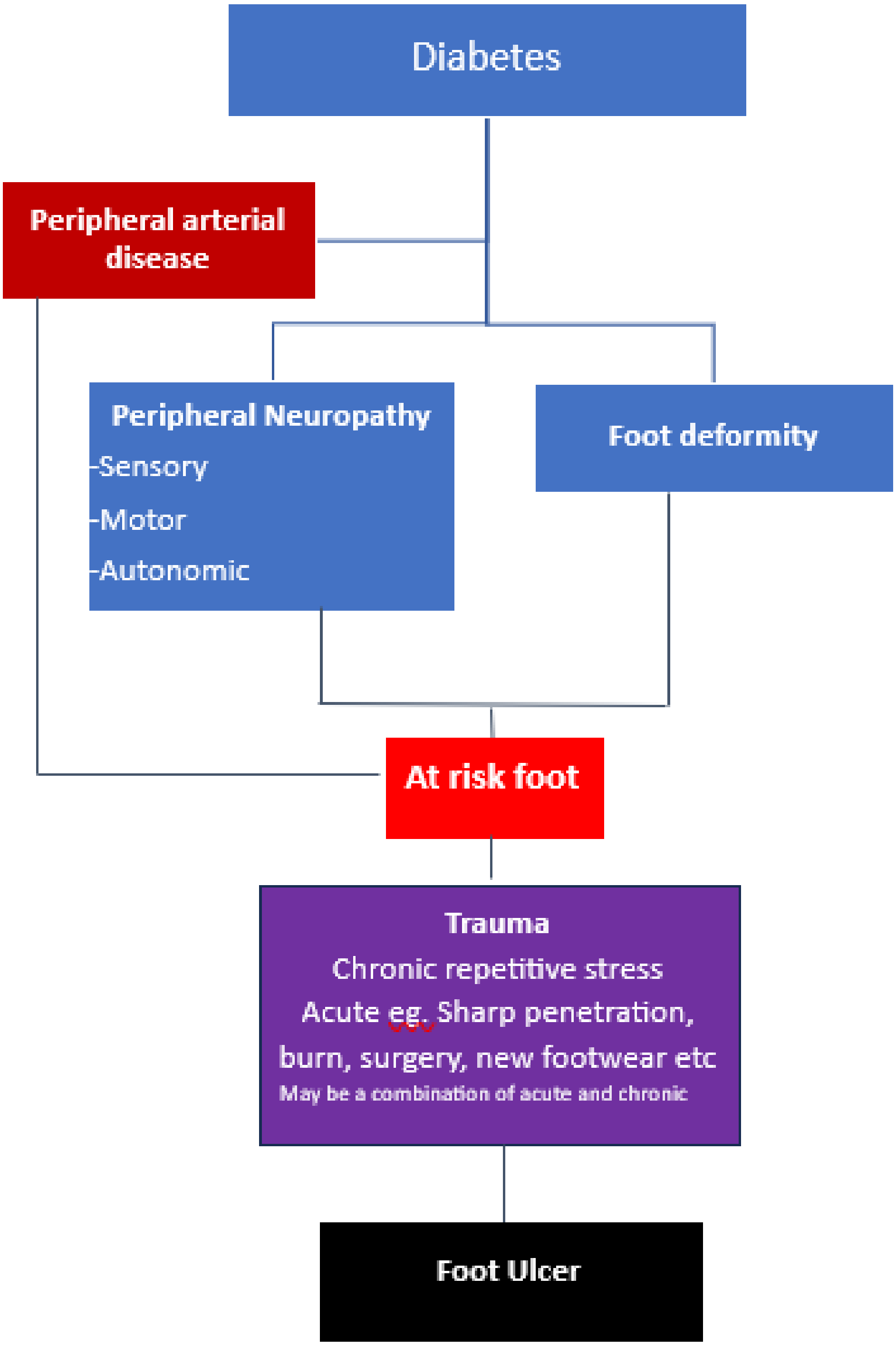
The impact of pressure and foot deformity explains why DFU typically occur on the plantar aspect of the foot. Treading on a sharp object or because of an area of high pressure under a bony metatarsal head or hallux (117, 136, 244) are common precipitants, as is injury to the toes or forefoot from footwear which is too tight (247). Thermal injury from warming the foot in some way such as sitting to near a radiant heat source and walking barefoot on hot ground surfaces are other pathways to DFU (248, 249).

Biomechanical factors can predict to some extent, where increased plantar pressures will localise (135, 250, 251) and plantar pressure are also measurable, providing an opportunity to identify and manage areas of focal pressure (252-254). A common deformity, associated with distal symmetrical polyneuropathy is clawing of the toes. Clawing of the toes may be a consequence of wasting of intrinsic foot muscles which occurs in people with diabetes and DSPN. Tightening of the gastroc-soleus muscle complex, contributes to muscle imbalance which favours the digital extensors pulling the toes into a retracted position but studies have not confirmed this(200) . Rigid claw toes are a risk factor for ulceration from footwear pressure as shoes are generally made too shallow to accommodate the toe deformities (135). Furthermore, the metatarsal heads become more exposed to plantar pressure as a consequence of anterior displacement of the forefoot plantar fat pad when the toes are clawed (197). Owing to the propensity for deformity and the peak of plantar pressure experienced at the forefoot in gait, the forefoot (including toes) is the most common site of DFU(255, 256).

In contrast to specific sites of increased pressure, the mere presence of peripheral neuropathy is associated with higher plantar pressures when people with diabetes and peripheral neuropathy are compared to people with diabetes and no neuropathy (257).

In addition to the impact of motor and sensory neuropathy on the aetiology of foot ulcers, other contributing factors include PAD, described in the previous section. In additional to occlusive PAD, microcirculatory changes relating to shunting of blood flow due to sympathetic denervation may also be detrimental to healing due reduced oxygen concentration to the skin and wound. These major contributing factors to the aetiology of DFU are summarised in Figure 2.

Figure 2: Pathway to Diabetes-related Foot Ulceration.
Adapted from Boulton AJM (2018)(258)



In terms of the direct impact of hyperglycaemia of DFU, hyperglycaemia impairs cell mediated immunity which increase susceptibility to infection and altered healing at a cellular level (259) which likely contributes to wound chronicity. While there is evidence that surgical site infections are more likely in people with diabetes (260) and hyperglycaemia is associated with higher amputation risk(261) evidence to show that improvement in glycaemic control promotes healing is lacking(262).

Finally, but no less important is the impact of patient behaviours on aetiology and healing which is of course influenced by a complex and interplay of factors. These include, but are not limited to depression, cognitive dysfunction, low health literacy and access to self-care education(263-266), factors which contribute to ulcer occurrence and adverse healing outcomes. Development and use of Patient Interpretation of Neuropathy (PIN) score which helps explain foot care behaviours based on patients' illness specific beliefs and Perrin et al found 3 clusters with different sets of beliefs linked to DFU prevalence in people with DM and DSPN) (263, 266).

While depression is risk factor for pre-mature death in people with diabetes (adjusting for complication (267) individual studies have identified that people with DFU are at further risk of depression or depressive symptoms compared to people with diabetes and no foot complications (264, 265, 268). Two single centre studies of DFU patients, using the Patient Health Questionare-9 found the survey identified 40-52% of patients had depressive symptoms (264, 269). While this may be bi-directional, the Williams et al (2010) diabetes population-based study (n=4839) found a two-fold increase rate of incident DFU (in people with no prior DFU or amputation history) in those who were determined to have major but not minor depression based on the Patient Health Questionnaire-9 (265). Depression in DFU patients is also associated with poor healing (270), amputations (271) and premature mortality. With regards to mortality, the cohort study by Ismail (2007) et al found a third of their patient population (n=253) with DFU had depression. Both minor and major depression was associated with a three-fold higher risk of mortality at 18 months when adjusted for co-variates age, sex and marital status and socioeconomic status in this cohort (272),. A small Australian study including 60 participants with DFU, used the Patient Health Questionare-9 to assess for depressive symptoms which found around half reporting symptoms however no association was found between symptoms and with poor healing or recurrence at 6 months (264).They did however detected an association with symptoms and poor self-care with regards to diet, exercise and foot care behaviours which is likely to impact health status over the longer term (264).

The challenges of having psychological problems as well as cognitive deficits were appreciated by health professionals interviewed and surveyed in a qualitative study by Nguyen et al (2021) (273) who were cognisant of the prevalence of psychological problems in their patients and the impact on their capacity to engage in treatment. The authors highlighted the importance of tailoring treatment and developing positive relationships in order to respond to these challenges faced by patients (273).

Cross sectional studies in Italy and Australia both found that people experiencing DFU are more likely to have reduced global cognition (274, 275). Marseglia et al (2014) compared people with DFU over and under 65, finding that cognitive impairment was more likely in the older group and in those with amputation (274). Corbett et al (2019) compared their participants' cognitive test results to those of age matched general population as well as early dementia samples, finding that people with DFU were more similar to the latter in their cognitive functioning (275). Both studies lacked a control group. More recently, a Perth study compared DFU patients with those attending a complex diabetes management service and did not find a difference in cognitive function between groups when DFU patients' results were compared to those of similar age and education status as well as other likely variables which would likely affect results, including depression score (276). Mild cognitive impairment was however common, and affected around half of participants in both groups (276).

Chen et al (2023) have published prospective data, showing cognitive impairment as an independent predictor of first DFU in a cohort of patients with established diabetes but not previous DFU (277). These studies highlight the potential impact of cognitive impairment on people with DFU. While assessment using the Montreal Cognitive Assessment (MOCA) or Mini-Mental State Examination (MMSE) is suggested as a means to identify patients, another approach is that of applying universal precautions approach to communicating and educating patients to mitigate the effects of poor health literacy which can be related to a variety of factors (278).

Health literacy is increasingly recognised as an important consideration in patient engagement and health outcomes. Chen's (2018) systematic review on health literacy and its role in diabetes foot outcomes found a lack of evidence to determine the impact of DFU incidence (279). In their subsequent prospective study of health literacy, n=191 participants with established diabetes, but no history of DFU, were followed up for four years. A range of predictive factors were assessed and participants' health literacy measured with the Functional Health Literacy Score (FHLS) and Health Literacy Questionnaire (FHQ) (277). Over the follow-up period, 13 developed a DFU, with higher scores on two HLQ domains, reducing the odds of foot ulcer by 77% when other factors such as age, gender, BMI and education level were controlled (277). Health literacy is particularly important for patients' capacity to understand self-care advice and follow treatment advice, particularly with to the use of pressure offloading strategies.

Another factor associated with incidence of DFU is socio-economic (SE) disadvantage. A large United States (US) study of 13,955 participants showed that people in 5th quintile of disadvantage were more likely to develop a DFU than those in the first (lowest) quintile (280). Once DFU is present, SE disadvantage can further impact treatment outcomes as determined in two Australian studies. Bergin et al (2011) studied hospital separations for diabetes and related foot complications across Victoria. Significantly more people (per 1000 population) in the lowest SE areas were admitted with diabetes with greater differences in DFU and below knee-amputation admisssions. Of note was the preponderance for males who were also admitted at a younger age from the lower SE areas (281). The outcomes of 30 day re-admissions and amputations at 1 year follow-up in another US-based study, including 7415 patients who underwent an amputation, also shows that people living in areas of SE deprivation are more likely to be re-admitted and have further, minor amputations (282). Major amputations were not associated with higher SE deprivation, possibly because of the importance of PAD as a risk factor for major amputations. In a small, multi-site, prospective study by Tehan et al (2023) a significant, between group difference was found between people with DFU who healed and those who did not, with SE disadvantage based on residential post-code associated with higher odds of not healing (283).

Patient age and diabetes duration are not consistently predictive of DFU in meta-analysis but testing with the monofilament to detect LOPS and an absence of at least one pedal pulse, as an indicator of PAD is strongly predictive of DFU and males are more likely to experience DFU(169). In assessing for DFU risk, the most potent predictors; loss of sensation from DSPN, PAD and deformity (169) are recommended for screening of all people with diabetes, however further examination and consideration of other aforementioned risk factors become important in people with diabetes who are screened as being at risk(162).

Once a person has experienced DFU, the irreversible nature of the risk factors, and advancing age ensure a high risk of recurrence (205, 284). Hence recently, authors have begun to refer patients with DFU as being in "remission" in the periods of time without active DFU (285).

1.2.3 Management of DFU

The aetiology of DFU is multifactorial, thus its management must address where possible, those processes which cause and perpetuate DFU. As described by Edmonds in 2000, the following "controls" need to be in place to promote healing(286); Mechanical (referred to as pressure offloading), Microbiological (infection), Vascular, Metabolic, Educational and Wound.

Pressure Offloading for Mechanical Control

Systematic reviews have been used to guide the most recent international and now Australian adaptation of guidelines on the management of DFU(287-289) with regards to pressure offloading. While there is clear rationale for patients wearing devices or footwear which protect the non-plantar aspects of the foot from pressure and sheer, available data pertains almost exclusively to protecting the plantar aspect of the foot, mainly the forefoot. This part of the review will focus on the aspects of pressure offloading which apply to DFU on the plantar aspect of the foot. There is little data to report outside of this scope except for surgical offloading for clawed toes and this is not applicable to the studies included in this thesis.

Mechanical control in the management of plantar DFU requires the net weight-bearing trauma to be reduced to a level which is not detrimental to healing. While no precise threshold has been determined for the amount of peak pressure reduction is necessary to support healing, it is understood that any offloading device must reduce pressure to a substantial degree at the ulcer site (referred to as the region of interest), the device must be worn preferably at all times whenever the patient is weight-bearing and the overall time spend standing and walking (and step count) should be minimised. The pressure offloading threshold under which DFU can heal has not been determined however research has shown that a pressure reduction of around 200kPa is consistent with prevention of foot ulcers (290, 291). Owings et al measured the average in-shoe peak plantar pressure in a subset of patient with previous DFU who had remain healed for longer than 90 days(290). In this study, barefoot pressures were substantially reduced (av. 36.5%) in the prescribed therapeutic footwear, although with high variability between participants. People who remained healed had a pressure reduction to 200kPa or less (290). As determined in their systematic review of the literature, a decade later, Jones et al presents the evidence to support the goal of reducing peak plantar pressure at the ROI to less than 200 kPa or less to assist in the prevention of DFU recurrence(291).

With regards to weight-bearing activity, there is limited evidence that weight-bearing activity impacts healing outcomes in people with DFU, wearing offloading devices(292). Of the six studies identified in a recent review of the topic, only one study including 49 participants found a statistically significant impact of delayed healing in association with increased weight-bearing activity(293). The issue of reducing activity is challenging. Patients must be able to walk to some degree to maintain activities of daily living or those activities that remain necessary such as to earn income and care for dependents. It is also important for social engagement, cardiovascular and mental health. Current evidence is insufficient to recommend weight-bearing exercise as safe for a patient with a foot ulcer and a prospective study is needed to determine what type and amount of exercise is beneficial and what may cause harm(294-296).

A less documented factor in plantar pressures is patients' gait, type of activities and walking speed and adaptation of gait is not associated with any evidence. It is however known that faster walking speeds increase plantar pressure (297) hence slower walking may provide some protection.

Systematic reviews and evidence-based practice guidelines recommend irremovable knee-high devices as it is these which have the most robust evidence for facilitating healing(288, 298, 299). While original reports showed greatest efficacy with total contact casts (TCC), recent studies have shown that there the pressure relieving capability of prefabricated knee-high devices are similar (300-303) and when rendered irremovable by casting material, studies show similar healing outcomes to TCC (300, 304, 305). In a systematic review and meta-analysis comparing RCT's of TCC and removable cast walkers, the authors found TCC superior to RCW across the 5 included studies however highlight the small number of study participants overall (n=169) and an unclear risk of bias (306).

The first RCT, by Armstrong et al (2001) randomised 75 participants with uninfected, non-ischaemic DFU, excluding heel, rearfoot and non-plantar DFU. With data from 65 participants across 3 groups, the authors showed that a knee-high RCW which was rendered irremovable healed more patients than the RCW and a half shoe (300). Participant age is not reported. Armstrong (2005) in a separate study randomised 50 participants to receive RCW removable or modified to make irremovable. The age of participants was 65.6 years and results strongly favoured the irremovable device with 82.6% versus 51.9% healed, showing the benefit of making these pre-fabricated devices irremovable (304). Katz (2005) also studied the efficacy of knee-high RCW made irremovable comparing healing outcomes with patients wearing a TCC in a randomised study with 29 participants (307). The results showed equivalent healing between the two treatment devices. Importantly, Katz documents that the patients included in the study were those whom the "treating physician felt casting appropriate"(307). It is of course expected people who could not tolerate or declined TCC would not have been included in the previous studies and patient selection is critical in the use of irremovable devices, however with none of the previous studies referred to such selection processes. None of these studies included the CONSORT flowchart expected in contemporary RCT's (308).

The efficacy of both casts and knee-high devices is attributed to the features of immobilisation at the ankle to prevent the peak of pressure associated with toe-off, and the a moulded and/or cushioned sole (or innersole) which redistributes plantar pressure more evenly on the sole of the foot and total contact casts also transfer load through the walls of the cast(309). The third mechanism is the imposed adherence of a cast or irremovable device that the patient themselves remove (292). This forced adherence is particularly relevant to management of patients with loss of sensation who, due to the effects of neuropathy and other factors may opt not wear devices at all times when weight-bearing (301).

A range of pressure offloading modalities, predominantly removable, remain in common use clinically and in research protocols with irremovable devices including TCC infrequently prescribed in most patient populations (310-314). Some studies have also shown comparable efficacy of removable devices. Randomised offloading studies by Faglia (2010) and Piaggesi (2016) both found similar healing outcomes between groups of participants randomly assigned to either TCC or one of two commercially available removable devices or a commercially available irremovable device (305, 315). Bus (2018) assessed the outcomes of participants with DFU randomly assigned to one of three removable devices(316). The highly informative study reported healing outcomes at 12 weeks but also step count and adherence, two key factors in cumulative stress on the affected wound. The results showed similar healing between groups in terms of percentage completely healed and percent wound closure with an ankle high device showing overall highest proportion healed and the BTCC the largest reduction in ulcer size (316). With 20 participants in each group, the differences were not statistically significant for healing outcomes. Other data reported showed optimal pressure offloading was achieved with the BTCC, higher drop-out rate and a non-statistically significant higher number of complications in this device (316).

Two observational studies of patients attending specialised services reflect very different practices. Birke et al (2002) reported the results of 120 consecutive patients with forefoot DFU, uncomplicated by ischaemic or osteomyelitis as with the RCT’s (317). Clinicians chose the offloading strategy in line with their assessment of the patient with devices ranging from compressed felt, walking splints and TCC. Overall, 94% of participants healed and 81% within 12 weeks irrespective of the offloading used.

Another observational study conducted in Australia reported very high proportion of patients treated with TCC. The demographics of the patient population are remarkable with a high proportion of Aboriginal people 48.1% included, due to the location and over-representation of Aboriginal people with diabetes. Despite geographical challenges, the service reported using TCC in 53.5% of patients requiring pressure offloading with the outcome that a higher proportion of DFU healed in TCC (93.1%) compared to removable devices (83.5%), with the TCC wounds being larger (318).

Evidence for the use of healing sandals for healing DFU is largely absent in the research literature (288). These devices are however, widely used, with and without additional insoles and deflective padding (311, 319). The features which attract patients and users to these devices include; stiffened and curved rocker sole with the potential to dampen the forefoot peak pressure at toe-off, cushioned or moulded foot bed to redistribute pressure, fastening to hold the foot in, width and depth to accommodate swelling and dressings, easy to don and doff, washable or replaceable when soiled from exudate, very light weight. The offloading effectiveness of these devices and RCW has been shown to be augmented with addition of deflective paddings (320). Paddings made of semi compressed felt and felted foam effectively reduce pressure at the ulcer site (319, 321-323), they are customised to accommodate the specific foot shape and placed on the foot or within the post-operative shoe with similar healing outcomes (324). Felt padding require frequent replacement because they flatten and lose effectiveness within days (323). Felt in combination with foam lessens the edge effect which is where pressure can be increased at the edge of the padding (321, 322). Patient acceptability, at least anecdotally, is high with ankle high devices, with or without paddings. Data published on the pressure offloading capacity on specific ankle high healing sandals used in the randomised study, is limited to a pilot project conducted within the author's district which showed that when used with an insole pressure was reduced to an average of <200 kPa (325).

Given the importance of adherence to the wearing off commonly used offloading devices, clinicians will select from a range of devices to achieve a strategy that provides pressure offloading, while also being acceptable to patients(311, 317). There is comparatively little data on factors associated with non-adherence and strategies to overcome the barriers, and on the commonly used alternatives. Crews et al (2016) analysed data from activity monitors simultaneously placed on the offloading device and patients' hip to objectively measure adherence and conducted a broad range of measures focused on the impact of neuropathy, depressive symptoms, and quality of life measures(314). The data from 79 participants was used to assess factors which were associated with adherence and non-adherence with the results showing that high scores for postural instability (from the NeuroQol predicted non-adherence (326). Predictors of adherence were larger wounds, painful symptoms (314). A recent qualitative study exploring adherence to wearing similar devices has recently been published and identifies a broad range of factors influence patients' behaviours around wearing RCW including psychosocial, physiological and environmental factors (327). The results of these studies support what is commonly practiced. Ultimately what is accepted and worn by the patient, involves a broad range of considerations related to wound pain and severity, patients access to social and physical supports, strength, and balance, motivation, and beliefs.

Plantar pressure reduction throughout healing and beyond is indicated to help prevent recurrence as elevated PP is known to persist (328). Long-term pressure offloading with appropriate footwear is therefore a key component of lifelong foot protection (329, 330)

Patient selection has played an important role in the design of studies of pressure offloading in which the data on total contact casts and irremovable knee-high devices has shown their superiority in promoting healing (288). In reality, many patients, as a consequence of their instability and psychological factors are unable or reluctant to wear such devices. We believe this explains their relatively low uptake which was evidenced in US and Australian surveys (310, 311). This reluctance to apply irremovable knee-high devices in the management of the of patients is also reflected in the choice of standard care and interventions in well-designed, contemporary clinical trials (312, 313). Notwithstanding the effectiveness of the treatment, the capacity for many patients to wear them is a limitation which is insufficiently acknowledged.

Control of Infection

Infection of an acute or chronic foot ulcer in a person with diabetes represents the main precipitant of deterioration of the wound and without rapid and effective management, can lead to hospital admissions and amputations. In particular, the combination of infection and PAD are potent predictors of poor outcomes (116, 241, 255, 331, 332), hence the importance of simultaneous assessment of PAD in patients presenting with Diabetes-related foot infection (DFI) (333). The reasons for the increased risk of infection exists due the interplay of treatment delay in the presence of loss of sensation, the effect of hyperglycaemia on impairing the immune response and in the presence of PAD which reduces oxygenation of tissues and is likely to reduce the perfusion of antimicrobials to the affected tissue. An Australian study by Jia et al (2017) attempted to determine the incidence of infection in patients presenting with uninfected DFU using data which is systematically collected across the State (334). In a 12 month period, 40.1% of DFU became infected. Longer DFU duration > 3 months, deeper DFU, patients with DSPN, previous ulcer history, foot deformity, being female and younger age were associated with DFI (334).

It is proposed that the management of infection begins with addressing bacteria present within a chronic wound, often present as biofilm. Debridement of the non-viable and "unhealthy" tissue from DFU has been cited as having a role in the overall management of infection with the expectation that with removal of non-viable tissue, reduces the potential "reservoir" for bacterial growth according to expert consensus (335, 336). The role of non-surgical debridement in the management of bacterial load within the wound will be further discussed in the debridement section.

In order to manage an infection, it must first be detected. Detection of infection relies on clinical signs and symptoms related to inflammation; warmth, erythema, swelling and pain (241, 255) which can be dampened or absent in the presence of PAD and DSPN, making detection of infection more challenging in these patients (337). The Infectious Diseases Society of America and International Working Group on the Diabetic Foot have been aligned in their descriptions of the clinical features used to diagnose and grade infection severity for some years and the newer grading system WIfI are also similar. In the 2023 IWGDF guidance, consensus has been reached on key recommendations regarding the identification, grading, and treatment of infection. Systemic inflammatory markers may be elevated and indicative of severe infection however are not reliable indicators on their own (337). Table 1 described the clinical features of infections by grade.

Once infection has been diagnosed clinically, systemic antibiotics are prescribed and due to the need for rapid treatment, recommendations are for these to be prescribed empirically with the choice of antibiotic based on the likely organisms based on presentation and history (338, 339). Culture of the wound at presentation, following initial debridement is best practice, used for the culture and testing of sensitivities to treat the infecting organism(s) using a narrower spectrum antibiotic. This strategy is designed to best target treatment and minimise the broader risk of emerging resistant strains of bacteria. Organisms detected using superficial wound swabs were found to correlate closely with those detected using deep swabs taken post debridement for superficial but not deep (to bone) DFU according to Slater et al (2004) (340). In the case of mild to moderate infections where there are no factors to suggest an increased risk of infection with resistance organisms, the IWGDF suggests it is safe to use empiric antibiotic choice and not undertake a wound culture (333). The evidence on optimal collection of tissue or wound surface bacteria for analysis has been investigated. A large, multi-site, cross-sectional study, CODIFY aimed to quantify the degree of agreement between the results of pathogens detected from wound swab and tissue sampling of infected DFU. The results showed 58% of paired results differed with the tissue sampling method detecting more organisms and more of those likely to be pathogens, but with no difference in the detection of multi-resistant organisms (341). Most commonly detected organisms were Staphylococcus aureus (43.8%), Streptococcus (16.7%) and other aerobic Gram-positive cocci (70.6%) (341).

Table 1: Clinical Signs of Different Grades of Infection

Adapted from IWGDF (2023)(333) and Mills (WIFI)(241)

	Clinical signs and symptoms
IWGDF Mild ISDA 2 WIfI 1	2 or more signs: • Local swelling • Erythema > 0.5 and < 2cm • Local pain or tenderness • Local warmth • Purulent discharge In the absence of other causes of inflammation eg. Fracture, Charcot arthropathy,
IWGDF Moderate ISDA 3 WIfI 2	Infection (as above) with the addition of; • Erythema ≥ 2cm from the wound margin and/or • Tissue deeper than skin and subcutaneous tissues eg tendon, muscle joint and bone. In the absence of systemic signs of infection
IWGDF Severe IDSA 4 WIfi 3	Any infection with x 2 systemic manifestations of inflammatory response syndrome ; • Temp > $38\ ^{0}$ C or < 36^{0} C • Heart rate > 90 beats/min • Respiratory Rate > 20 breaths/min or PaCP2 < 4.2 kPa (32mm Hg) • While blood cell count > 12,000/mm’ or < 4G/L or > 10% immature (band) forms Infection involving bone
The IWGDF recommends the addition of “O” when documenting when there is Osteomyelitis associated with the DFI Grade 3 or 4. If osteomyelitis is diagnosed and there are no signs of inflammation grade as 3 or 4 dependent on whether systemic signs are present or not.	

Choice of antibiotic has been a challenging area to study and a paucity of evidence and wide variation in clinical practice has resulted (342, 343). Only two comparative studies comparing agents according to IWGDF which has led to the recommendation that local guidance should be followed (333). The recommended duration is 1-2 weeks of systemic antibiotics for a mild infection, 2-4 weeks for moderate to severe and 6 weeks for osteomyelitis with clinical response to be monitored (333).

The management of osteomyelitis (OM) has traditionally involved surgical resection of bone. Given the importance of early treatment to avoid higher level amputation, OM should be considered with a high index of suspicion, particularly in patients with DFU which are longstanding, deep, have exposed bone or caused by trauma as they are associated with higher risk. Detecting OM clinical involved a history and Positive Probe to bone test (PTB). PTB is a useful clinical examination which in combination with plain x-ray in patients with DFI has high predictive value in a study which compared the use of these tests in combination, compared to results of resected bone histopathology, which the most effective method to diagnose OM (344). Best practice guidelines indicate that bone biopsy through intact skin percutaneously and away from the ulcer site be used to reliably determine the true infective organism (333, 335) and differentiate from wound bacteria. Two main barriers to implementing these practice recommendations are access to clinician skilled and credentialled to perform the procedure, the cost if performed by a surgeon and reluctance to undertake an invasive procedure in a compromised foot (345). In separate studies by Bernard et al (2011) and Malone et al (2013), good concordance between bone biopsy detected organisms and those obtained from taking a deep swab (to bone), suggesting that when bb is not feasible or acceptable to the patient, that a deep swab may provide a substitute in performing culture and sensitivities needed to guide treatment (345, 346).

Systemic inflammatory markers are not considered useful alone in diagnosis of OM but pro-calcitonin has been demonstrated to be elevated in OM with a systematic review and meta-analysis showing the highest test accuracy with some evidence that is can be used to aid diagnosis. CRP and ESR are elevated with and have potential usefulness in diagnosing and monitoring OM (347, 348)

The recommendations for duration of treatment for soft tissue and bone infections varies and until recently, there was little evidence that conservative treatment with systemic antibiotics could successfully treat OM without surgical removal of infected bone or partial foot amputation. There is now data supporting a non-surgical approach in some cases such as those with forefoot OM who may respond to systemic antibiotics of 90 days based on one randomised study (349). Depending on which bone is affected, there may be an increased risk of future DFU if the surgery results in iatrogenic foot deformity (349). This may be due to a loss of surface area creating localised plantar pressure on the residual foot or loss of foot stability.

In the management of moderate to severe DFI, rapid surgical review is indicated. Two studies have focused on the impact of rapid surgical debridement for severe DFI. Both retrospective, single centre studies, they report of patients admitted with “serious” or deep space DFI. In Tan et al (1996) patients were grouped as those who were treated promptly with surgical debridement and intravenous antibiotics and those who were initially treated with intravenous antibiotics and surgery delayed three days (350). While the authors report that all feet were adequately perfused and that PAD did not play a major role in predicting the outcome, they also point out that clinical documentation was incomplete. It would be unusual for a cohort of 112 patients admitted for severe DFI not to include a proportion of participants with PAD. The main results of their study were that a higher proportion, 27.6% compared to 13% of patients underwent subsequent above ankle amputations in the group whose surgery was delayed 3 days (350). Faglia et al (2006) retrospectively reviewed the outcomes of 106 patients admitted for treatment of deep space infections comparing the results of those admitted directly from the hospital’s outpatient clinic to those of patients who were transferred to the facility from other hospitals (351). The hospital’s approach was described as providing urgent surgical intervention and same day evaluation of perfusion. Patients found to have reduced TcPO2 < 50mmHg or significant disease on duplex ultrasound scan, were revascularized the following day. Of the patients whose surgical intervention was delayed, there was higher incidence of osteomyelitis (radiologically) and higher amputation levels in those whose surgery was delayed (351). IWGDF guidelines recommend that for moderate DFI in people with ischaemic and all severe DFI, urgent surgery and vascular review given the current evidence (339).

Assessment and Grading PAD in People with DFU

Both occlusive peripheral arterial disease and MAC are associated with the pathway to foot ulceration in people with diabetes (115, 117) and the presence and severity of PAD is positively correlated with the risk of non-healing of DFU and amputation (116, 129, 255, 352).

International guidelines adapted for Australia (2021), advise continuous wave doppler (used to assess pulse waveforms) in the pedal vessels, together with ankle pressure and ankle-brachial pressure indices (ABI) or toe pressures and toe-brachial pressure indices (TBPI) be used in people with diabetes to determine the presence of PAD with the use of toe pressure more specifically indicated in the presence of DFU (123, 353). The 2023 update, a collaboration of the IWGDF, European Society for Vascular Surgery and the Society for Vascular Surgery, recommends people with a DFU undergo assessment with continuous wave dopper of the pedal vessels as well as having measurement of the ankle-brachial index (ABI) and toe-brachial index (TBI) to assist in identifying whether the patient has PAD (352). In the absence of any one test showing strong negative likelihood ratio, guidelines and systematic reviews of the evidence, emphasize that no single, bed-side test can reliably predict or exclude PAD with a high degree of accuracy (123, 138). The aforementioned tests however have reasonable positive predictive value in assessing for the presence of significant PAD in people with DFU, helping to determine which patients require more definitive tests (such as arterial duplex scanning) and potential vascular intervention (122-124, 352, 354). In calculating ABI, using the lowest reading of the ankle pressure improves the sensitivity of diagnosing PAD according to a study by Jeevananthan (2014) et al, hence current guidance recommends this method (354, 355). Further consideration highlighted in the systematic review by Chuter et al (2023) is that the bedside tests for PAD (ABI, toe pressures and TBI) also have significant error margins which should be considered when interpreting results (354).

Evidence used to inform these recommendations comes from Vriens et al (2018) in which the investigators assessed PAD in the feet of n=60 participants with DFU attending a single Multidisciplinary clinic (137). They calculated the positive and negative likelihood ratios of ABI, ankle pressure, TBPI, toe pressures, the pole test, and waveforms to detect of PAD diagnosed by duplex ultrasound (137). The lowest (best) negative likelihood ratio (NLR) was obtained for distal tibial waveform assessment (0.15) and TBPI (0.24) leading them to recommend these tests, however cautioning that this testing will still fail to detect some patients with DFU who have significant PAD (137). They argue the importance of NLR in the context of managing DFU, given the potential for increased risk of non-healing and major amputation when PAD is present and the need for intervention (137). A high index of suspicion should prevail in the care of people with DFU and formal investigations should be performed when PAD is suspected on the basis of clinical tests or when DFU fail to heal with standard care. In the case of ABI, low pressure, below 0.8 is indicative of disease, normal pressure ratio is ~1.0 and 1.3 or above is indicative of a calcified and incompressible artery, and the test is uninterpretable (356). The cut-off of 0.8, widely used to Grade DFU as ischaemic (255), it is now known to underestimate the presence of PAD in people with diabetes, especially those with renal disease, due the complication of MAC reducing the vessels' capacity for compression, yielding a falsely elevated ankle pressure (142, 356).

While in screening for risk of DFU, defining PAD as being more or less likely has value, when an ulcer is present, the use of toe pressure and transcutaneous oxygen provides more information on the adequacy of perfusion to the foot, which is required for healing (123, 124). Where there is adequate perfusion for healing is demonstrated with toe pressure or $TCPO_2$, it is likely that sharp debridement can be performed safely. When there is low toe pressures or oxygen concentration, additional investigations are indicated to determine whether re-vascularisation is required and feasible for healing and limb preservation.

Which tests are used to determine healing potential is an important question. To a large extent, a "healable" DFU is one in which sharp debridement is considered safe and appropriate treatment in the hands of podiatrist or suitably trained nurse. No specific studies have been found that address the question of what degree of PAD represents an absolute contraindication for sharp debridement. Still, it is valid to consider a DFU associated with insufficient perfusion to heal, as one in which sharp debridement would be restricted to loose, non-viable tissue and surrounding callus, and not that which could extend the wound base or margin. For the purpose of the randomised trial, PAD associated with significantly reduced healing potential is considered a relative contra-indication for sharp debridement. To align with known evidence, the protocol for the research participants in the randomised debridement study used clinical assessment of pedal pulses together with ABI and toe pressures with ischaemia graded according to the WIfI grading system (241).

The critical question of what tests for PAD can be used to predict healing or non-healing of DFU has been investigated in a systematic review and meta-analysis by Wang et al published in 2016 (242). Wang et al (2016), found insufficient data from the 37 included studies to evaluate most of the tests in common use, except for ABI and TcPO2, which had sufficient data to pool results. In their assessment, only TcPO2 was useful in predicting healing, with a sensitivity and specificity of 0.72 impact healing (242). A later systematic review and meta-analysis by Linton et al published in 2020, analysed the data from 10 studies which examined the role of toe pressures in predicting healing after minor foot amputation, finding that ≥ 30mmHg at the hallux is associated with healing a two-fold reduced likelihood of healing(357).

The use of digital vessels, being less likely to be calcified, has become widely adopted due the growing body of evidence that toe pressures provide more reliable prognostic data (123, 124) than ABI alone which has poor predictive value(242). Point of care devices now reliably measure digital pressure, typically at the hallux and can be performed chair-side within a short time period (358). Other tests include the use of transcutaneous oxygen tension which is used to quantify the oxygenation of an area of tissue and may be clinically valuable to assess healing potential but is not diagnostic for PAD (99).

The detection of PAD is broadly important in determining wound aetiology, a vital consideration for direction care decisions (359). The presence of PAD has included in grading systems for classifying DFU for many years however, more recently, the severity has become are key criterion in more sensitive ulcer grading systems used for classification of DFU.

Classification of DFU is a key recommendation of best practice guidelines. Researchers have been investigating prognostic indicators to develop optimal classification systems that can support communication between health professionals, benchmarking for audit and research, to guide treatment and predict healing (360, 361). Most gradings include a composite score based on evidence-based predictors of outcome, including ulcer size or depth, the presence of infection and PAD, duration of ulcer and site (location) (360). Grading systems include the University of Texas wound classification system (UT) (255), the MAID score derived from the parameters of wound area, assessment of ischaemic, wound duration and the presence of multiple ulcers (362), the SINBAD score derived based on six criteria; Ulcer site, presence of ischaemic, neuropathy, bacterial infection and the ulcer area and depth (363) and the Wound Ischaemic and foot Infection score (WIfI) (241). While the benefits and applicability of each to specific scenarios are different, the WIfI system is most thoroughly validated for PAD. It is recommended in Australia and by the International Working Group of the Diabetic Foot for use in grading PAD and the in determining the need or potential benefit of revascularisation (128). Grading the severity of DFU and PAD for the purpose of directing clinical care, communication and research is embedded into the practice of DFU management.

The classification system, WIfI, an initialism of; Wound, Infection and Ischaemia, first published in 2014 by the Society of Vascular Surgeons (SVA), relies on the grading of ischaemic based on toe pressures or transcutaneous oxygen tension($TcPO_2$) from; 0 (Toe or $TcPO_2 \geq$ 60mmHg), 1 (40-60mmHG), 2 (30-39mmHg) and 3 (< 30mmHg) (241). Grading the severity of ischaemia in the ulcerated foot in people with diabetes using WIfI is recommended in Australian and International guidelines for use in people with DFU with evidence that it predicts healing outcome and amputation(364, 365). In their systematic review, Forsythe et al concluded that a toe pressure >30,mmHg (or $TcPO_2 \geq$ 25mmHg) represented the most useful prognostic marker of healing(138), the corollary of which is that a foot with a toe pressure below this threshold is unlikely to heal without revascularisation.

Interventional management of PAD in people with DFU

In people with PAD, secondary prevention involves smoking cessation, anti-platelet and lipid-lowering medication together with management of hypertension (366). Such strategies while important cannot reverse the effects of PAD on perfusion to the foot to promote healing. For people with DFU complicated by severe PAD (toe pressure < 30mmHg) and those who have rest pain, critical limb threatening ischaemia is present and revascularisation is indicated (124).

The aforementioned colour duplex ultrasound is the first line investigation when planning intervention, followed by angiography; magnetic resonance angiography, computed tomographic angiography or intra-arterial digital subtraction angiography (124). Angiography also presents an opportunity for the interventional radiologist or endovascular surgeon to perform an angioplasty and during the same procedure employ stents to support the vessel to remain open.

An International Working Group of the Diabetic Foot (IWGDF) systematic review reported the majority (84-91%) of people with DFU in which angioplasty was first line treatment, underwent technically successful procedures (367) however long terms outcomes measured by ulcer healing time and ulcer-free time following revascularisation are also important and one study has shown better outcomes for surgical revascularisation compared to an endovascular approach(368). In their most recent systematic review, IWGDF report that using available data from randomised studies with wound healing outcomes, 60% of wounds healed at 12 months overall; 75% following endovascular procedures and 52% following open bypass surgery (369). Long term limb survival may be slighter higher following bypass however differences in outcomes may be due to patient selection (369).

Angioplasties are inherently less invasive hence treatment decisions are based on the assessment of both risk and benefit with guidelines recommending endovascular procedures in preference to open procedures, when the patient is a higher surgical risk due to age and/or co-morbidities (370). The time to restenosis can be unpredictable and anticoagulant therapies are provided systemically and sometimes within the stent to mitigate the risk of thrombosis.

When performing revascularisation to promote the healing of DFU, both direct (or angiosome directed) and indirect approaches are considered. Traditionally, the most viable, or best vessel was targeted. However, when considering the angiosome that perfuses the ulcer site more directly, the approach may be taken to select the vessel which best feeds the relevant angiosome, particularly when there is a lack of collateral vessels to compensate for the diseased vessel (369, 371, 372). Chae et al undertook a meta-analysis including four, non-randomised studies of angioplasty procedures comparing direct and indirect approaches, finding in favour of angiosome (or direct) approach to revascularisation for healing DFU (371). Spillerova et al (2017) have since published their report on outcomes of 545 cases with DFU undergoing revascularisation including both open bypass and endovascular procedures (373). The results of this study are included in the 2020, IWGDF systematic review and while direct versus indirect was associated with better healing outcomes (60.5%) than indirect, better outcomes overall were achieved with direct bypass surgery (77% healing) (373) (369).

Structural and function changes to the microcirculation are also evident in people with diabetes and have been observed and are associated with advanced peripheral neuropathy(374, 375). Reactivity of capillaries to occlusion and warming is reduced and another mechanism “capillary steal syndrome”, can occur where sympathetic denervation leads to blood flow through arterioles failing to perfuse normally into the vascular bed(375-377). These observations will not be further explored in this thesis but are potentially impactful in DFU pathogenesis and healing. However, conclusive studies regarding the role of microvascular changes in DFU healing are a lacking (378, 379).

Wound Management DFU

The preparation of the wound bed to support healing is one of the fundamentals of wound care(359). It involves the removal of non-viable tissue which has the potential to impede granulation and epithelialisation. While there are indeed many different modalities available to achieve wound debridement, guidelines support the use of sharp debridement as the main to achieve rapid, concise removal of nonviable tissue from the base and callus from the periphery of DFU (380-383). The procedure uses low cost instruments and due to the nature of DFU being most often related to loss of sensation, it can be achieved without pain for most patients.

This section will focus on dressings and topical agents applied to the wound bed to facilitate healing and sharp debridement will be covered in detail in section 1.3.

There are however relatively few randomised studies and high quality evidence on which decisions regarding topical treatment and dressings can be based (384). Only three recommendations in the IWGDF guidance are rated as moderate, these being; the use sucrose-octasulfate impregnated dressings for non-infected, neuroischaemic DFU in addition to standard care when there is poor healing(312), the use of autologous combined leucocyte, platelet and fibrin as an adjunctive treatment in addition to standard care for DFU failing to heal(385) and the use of systemic hyperbaric oxygen for non-healing ischaemic DFU (383, 386).

The goal of dressing the wound is to provide a degree of protection of the exposed tissue from external contaminants and infection, absorb exudate but retain a level of moisture that can allow for cell migration, and be easy to apply and remove (384). EBPG cite an absence of high quality evidence to demonstrate the superiority of any particular dressing. Clinicians select dressings based on their assessment of the wound characteristics such as exudate, patient factors and dressing features such as absorbency, ease of use, cost, cost-effectiveness and availability (384).

The role of antimicrobial dressings is an area of controversy. Given the implications of infection of DFU to wound healing outcomes, hospitalisation, and amputations, it seems appropriate that agents with efficacy in reducing the culture medium for bacteria, or directly killing bacteria would be of benefit to wound healing. Despite these agents being in common use (387, 388), the evidence remains unclear as to the direct benefit of antimicrobials on healing outcomes due to a paucity of studies without bias (389). IWGDF guideline specifically state "do not use topical antiseptic or antimicrobial dressings for wound healing of diabetes-related foot ulcers" with the recommendation being strong, based on a moderate strength of evidence and upheld in the Australian version (383, 386). However some expert groups have formed consensus that emphasises antimicrobials in conjunction with debridement to minimise bacterial colonisation of chronic wounds including DFU (390). The approach of the IWGDF is to review randomised trials and grade the quality and certainty of evidence, while other guidance is based on studies which include animal models, in-vitro research, and clinical studies on humans together with expert consensus.

Some work that has crossed over into human studies is that of Johani and Malone et al (2018) who measured the effect of a range of agents used to manage bacteria in DFU on invitro biofilms and also in ex-porcine models and human DFU (391). While the agents; melaleuca, povidone iodine, chlorhexidine and cetrimide, polyhexamethylene biguanide and superoxidised solution all showed varying but effective reduction or complete eradication of bacteria, including biofilm, the results did not translate to clinical in vivo effectiveness. Only the melaleuca based antimicrobial and surfactant were tested on human participants but the results showed a stark difference with no reduction in DFU bacterial load despite 15 minutes of exposure, daily for seven days. The authors use this data to highlight the difference in the performance of antimicrobials between the invitro and vivo conditions and further concluded that clinicians seeking to use antimicrobials to reduce bacterial load in chronic DFU should adopt a “multifaceted approach” including sharp debridement.

A systematic review and meta-analysis by Dumville et al (2017) sought to determine whether more DFU healed with antimicrobial dressings compared with non-antimicrobial dressings using data pooled from the 5 available RCT’s (392). They reported studies had small patient numbers and were mostly poorly designed, weakening the strength of the evidence however they found a Risk ratio of 1.28 (CI 1.12-1.45) with ulcers slightly more likely to heal with use of antimicrobial dressings (392). Based on the low quality of evidence, the IWGDF and our National guidelines do not recommend use of antimicrobial over standard care(383, 386). Hussey et al (2019) published compelling data on the rapid and significant rise in prescription of antimicrobial dressings and associated their high costs, largely driven by the use of topic silver dressings, despite a lack of evidence of their efficacy in improving healing, highlighting the importance of determining where costly dressings can add value in high quality randomised studies (388).

Subsequent to the publication of the most recent guidelines, an RCT of a silver impregnated dressing, Acticoat has been published. The bactericidal effect of silver ions(393) is harnessed in nanocrystalline form, which provides slow release of ions in concentrations considered non-toxic to cells such as fibroblasts however data is conflicting on whether there is an effect (394, 395). In their RCT, Lafontaine et al (2023), 118 people with 167 DFU of less than 6 weeks duration were randomised to receive standard care or standard care plus Acticoat, a silver impregnated dressing (387). Standard care for all participants included sharp debridement, antibiotics, revascularisation if required and offloading which was individualised (not standardised). DFU complicated by PAD and infection were included. The study found no statistically significant difference between groups in terms of ulcers completely healed at 12 weeks with 75% of those who received silver impregnated dressing and 69% of those who did not (387). Given the increased cost of silver dressings compared to standard dressings, the latest randomised study is unlikely to change the recommendation regarding the use of silver dressings to improve healing.

Hyperbaric oxygen treatment has been proposed as a means to improve oxygenation and stimulate angiogenesis. The latest guidelines suggest that as a treatment, it may improve healing outcomes in patients with ischaemic DFU as an adjunct to standard care (383, 386). Given the time, expense and limited access to centres providing HBO2, studies other topical therapies that can increase the oxygenation of tissue to support healing have been undertaken.

Other examples of agents which have evidence of benefit include nitrous oxide. Edmonds et al (2018) ProNox1 study randomised 114 patients with 124 chronic DFU, including those with PAD (inclusion criteria ABI > 0.5 or a palpable pulse) and infection to receive treatment with a nitric oxide delivering device or standard care alone (396). There was a pragmatic design with regards to the use of antibiotics, choice of dressing, debridement and offloading at clinician discretion with weekly visits for 4 weeks and every 2 weeks until 12 week analysis of healing outcomes of complete healing and percent wound reduction, the primary outcome. The primary outcomes were determined by assessors blinded to treatment allocation and data analysis following intention to treat principles, showing a 40% percent wound reduction (PWR) in the intervention group compared to 26% in the controls(396). The difference was attributed primarily to the improvement achieved in DFU > 1cm^2 which with subgroup analysis showed am 82% PWR for the intervention compared to 29% for the controls. In a separate multi-site randomised study of a topical oxygen deliver system, Frykberg et al (2020) randomised 73 patients to receive the intervention or standard care and a sham device, including patients with chronic DFU > 1cm^2 including those with PAD (ABI > 0.7 and TCPO2 >30mmHg or Toe pressure >30mmHg and infection(397). Dressings were standardised to foam and hydrogel and DFU offloading with a removable below knee device with weekly visits including debridement. The outcome based on intention to treat analysis showed a higher proportion healing with the administration of topical oxygen with 15 (41.7%) healed in the intervention group compared to 5 (13.5%) in the control group(397). In their report, further described on page 100, Lavery presents post-hoc data from a separate study of topical oxygen in which the impact of more frequent sharp debridement is presented(398). This suggests that frequent sharp debridement supports better outcomes with this type of therapy.

The range of topical products which deliver cells and growth factors to the wound have been explored with the replacement of these cells, or the matrix, being a large field of study and an expanding range of products. As a high cost treatment, they are not widely accessible or recommended to replace standard care. A systematic review and meta-analysis by Mohammed (2022) found an overall increased likelihood of healing at 12 weeks and improved percent wound reduction using placental-derived products (399) and these are recommended conditionally in the IWGDF guidelines (386). The indications for when to use these advanced products remains an important question.

1.2.4 Normal and Impaired Healing

Normal wound healing and chronic wounds

It is expected that most acute wounds, will heal via the process of normal tissue repair process whereas "chronic wounds" fail to progress and healing is delayed. The normal wound healing process is described in terms of the following overlapping but sequential stages (400) This process starts immediately post-injury with **haemostasis.** During primary haemostasis, the injury to the blood vessel stimulates platelets aggregation, promoted by the release of von Willebrand factor, rapidly followed by secondary haemostasis, in which thrombosis occurs (401). During platelet aggregation, platelet alpha granular contents are activated and release cytokines and growth factors; platelet derived endothelial, epidermal, fibroblast and transforming growth factors which will help mediate inflammation (402). They also act as chemoattractant, bringing inflammatory cells; the neutrophils and monocytes, stimulating the proliferation of important epithelial, fibroblast and vascular endothelial cells for the next stages of healing and repair. At the same time, the fibrin provides a scaffold for red blood cells and platelets to form a clot to stop any bleeding (403, 404).

The **inflammation** phase occurs within minutes of injury and is characterised by vasodilation and increased capillary permeability which facilitates the passage of polymorphonuclear leukocytes and macrophages to the injury site (404) and is regulated by mast cells. While a key role of these cells is destruction of bacteria which potentially contaminate the wound, macrophages also release of proteolytic enzymes (Collagenous and Elastase), cytokines and growth factors for the ongoing healing process. The proteases break down the extra-cellular matrix (ECM) in a carefully modulated process, facilitates new ECM (405). The inflammatory phase lasts hours to several days in normal healing however chronic wounds are characterised by persistence of this inflammatory stage (406, 407). The matrix metalloproteinases (MMPs) and how their balance is related to healing of chronic and acute wounds and will be further discussed in later sections.

The **proliferation phase** should follow, during which inflammation subsides and the formation of new capillaries and extra-cellular matrix (ECM) takes place. During this stage, fibroblasts proliferate, mediated by macrophages from day three to seven in normal healing and continues for weeks. Fibroblasts migrate to the wound and together with keratinocytes, vascular endothelial and epithelial cells become the source of growth factors responsible for ongoing formation of the ECM which deposits to form a fragile scaffold on which granulation tissue will form(408, 409).

MMPs released from the fibroblasts and other cells, facilitate granulation tissue by degrading the basement membrane around endothelial cells (401). Granulation tissue is recognised as red, highly vascular tissue at the base of the wound, over which the epithelial cells and keratinocytes will migrate across the wound to close or heal the wound. Wound care providers view a granulating wound bed and the absence of inflammatory signs as a signal of a healthy wound bed capable of healing.

With progression of normal healing and process of apoptosis, the cells involved in the inflammation phase reduce. A balance of ECM breakdown and synthesis is still needed and fibroblasts continue to be active in these later phases of repair, synthesizing the collagen, elastin and proteoglycans for the ECM and releasing MMPs to degrade ECM and tissue inhibitors of the metalloproteinases (TIMPs) in careful balance (403). During this **epithelialisation and maturation phase** endothelial and epidermal cells migrate across the granulation tissue and the scar tissue will be remodelled and strengthened by the formation of collagen fibril cross-linkages over a period of weeks to months (403).

Impaired healing in DFU

DFU area chronic wounds and often do not progress through the normal phases of tissue repair, exhibit delayed healing, or may fail to heal altogether. Indeed, a chronic wound has been defined by the Wound Healing Society as " A wound that fails to progress through a normal, orderly, and timely sequence of repair or wounds that pass through the repair process without restoring anatomic and functional results"(410). Diabetes-related foot ulcers (DFU) are among the most prevalent of all chronic wounds (410, 411).

Dysregulation of the repair processes involving fibroblasts, the regulation of angiogenesis, collagen depositions, quantity of granulation tissue, as well as production and remodeling of extracellular matrix (ECM) has been shown in types of chronic wound such as DFU(412). Fibroblasts in DFU have delays in cellular proliferation and migration and induction of senescence (413) ECM from DFU derived fibroblasts compared to control fibroblasts exhibit increased, immature fibronectin in an in-vitro 3D tissue model (414).

The presence of senescent cells in higher number is chronic, compared to acute wounds has also been investigated as having a role in delayed healing (415). Senescent cells, are those which have ceased replicating but may still produce enzymes such as metalloproteinases, thus contributing to the imbalance of MMPs detected in non-healing wounds.

Matrix metalloproteinases (MMPs) which are important for the breakdown and remodelling of the ECM but need to be balanced in their activity. Persistent, elevated levels of some MMPs, particularly MMP-9 has been found to be grossly elevated in chronic wounds compared to acute wounds(416), as are reduced tissue inhibitors of MMPs. This imbalance is associated with delayed healing, prolonger inflammation and wound chronicity in DFU whereas resolution of certain MMPs to lower levels are associated with healing (417-419). The existence of elevate serum MMP-9 has been detected in people with diabetes and DFU prior to the onset of the ulcer suggesting a pre-existing pro-inflammatory state (419).

Investigations of chronic wounds have detected increased and prolonged presence of macrophages at the wound edges (DFU and venous) but interestingly, without the same prolonged activity against bacteria (420). Fibroblasts in DFU are lower in number and fail to respond to growth factors having low proliferation (421, 422). In-vitro testing of fibroblast activity in the presence of chronic wound fluid suggests an inhibitory effect from chronic wound fluid which does not occur with acute wound fluid (423). Keratinocytes at the edge of DFU also show abnormal activity with proliferation but failure to properly differentiate and migrate across granulation tissue (424).

Bacteria colonise all chronic wounds including DFU (425) are especially prone to bacterial proliferation and infection due to, the effects of hyperglycaemia on cell mediated immune function and healing(426). The presence of ischaemia which complicates many DFU by reducing oxygen and nutrients to the wound, also increases the risk of bacterial colonisation and infection. Concomitant infection and ischaemic which occurs in 5-10% of DFU presenting for treatment and is associated with the worst prognosis for timely healing without amputation (116, 241, 255).

How bacteria retard healing begins with their of nutrients and oxygen within the wound and their production of endotoxins into the wound which stimulates elevation of pro-inflammatory cytokines which leads to increased MMPs which retard the formation of mature ECM which is required for normal healing (425, 427, 428).The most common infecting organisms are Staphylococcus aureus and Pseudomonas aeruginosa(429), both capable of also forming into biofilms.

Considerable focus has been placed on the study of biofilms within wounds. Biofilm is a construct of bacterial colonies whereby bacteria attach to each other and sometimes to a surface. They are encased within a self-produced matrix comprised of extracellular polymeric substances (EPS) including proteins, polysaccharides, nucleic acids, and lipids which binds and protect the polymicrobial bacterial colonies within (428, 430). Biofilms can be non-pathological such as those found in the gastrointestinal tract. However, biofilms as a phenotype, are more resistant to antibiotics than those planktonic bacteria and considered responsible for the chronic inflammation and infection associated with chronic wounds (431). The structure and function of biofilms means they are resistant to the host’s immune response and can be impervious to antibiotics and contribute to antibiotic resistance (428, 432-434). Some topical antimicrobials have demonstrated limited efficacy against biofilms and but biofilms are not readily removed with traditional wound cleansing and debridement also may not substantially remove them.

The immune response to high levels of bacterial concentration is believed to contribute to a chronic state of inflammation within a wound, even in the absence of overt clinical signs of infection and acts to prevent the normal phases of tissue repair, proliferation, and epithelialisation. Debridement is promoted as a means to reduce bacteria and their pro-inflammatory impact on the wound, thus supporting healing (435).

1.3 Sharp Wound Debridement in DFU

Sharp debridement has a long history in the management of wounds. This section describes some of the history of the use of sharp debridement and contemporary practice by clinicians. The definitions, evidence from studies of humans and purported benefits are explored.

1.3.1 History of sharp debridement in wound care

Ambroise Paré, a 16th Century barber-surgeon made significant surgical advancements based on his experiences treating soldiers on the battlefield has been quoted (In Porter 1998) as saying “There are five duties of surgery: to remove what is superfluous, to restore what has been dislocated, to separate what has grown together, to reunite what has been divided, and to redress the defects of nature” (436). According to Helling, it was Henri Francois Le Dran in the 18th Century who first described debridement (meaning to unbridle) using the term to refer to surgical incision to drain and reduce tension under the skin (437) and Le Dran who, during the battles of World War 1, helped to re-introduce the approach in management of infected and traumatic wounds (437).

Earliest descriptions of non-surgical sharp debridement in the treatment of chronic wounds appear in the nursing literature in the 1990’s (438, 439) and in the published study protocols for emerging bioengineered wound products (440, 441). Gentzkow states “The protocol specified sharp debridement, with removal of all necrotic tissue and callous down to a bleeding bed…" and Steed describes the preparation of DFU in their study as "…the target ulcer was aggressively surgically debrided to remove all callus, necrotic tissue and chronic granulation tissue…1-2 weeks before randomisation…surgical debridement could be performed as required throughout the treatment period"(440, 442). These descriptions are important since data from the patients in these studies provides most of the limited evidence available for sharp debridement in DFU management. By 1999, the first systematic review of debridement of chronic wounds was published by Bradley and Sheldon as a Health Technology Assessment (443). A further 12 reviews have focused on sharp debridement of chronic wounds, including DFU. Table 2.

Edmonds et al (2014) describes key domains of control to effectively manage DFU. With regards to debridement, Edmonds et al states the practice, provides the following benefits (444).

Debridement:

- enables the true dimensions of the ulcer to be perceived.
- allows drainage of exudate and removal of dead tissue; both render infection less likely.
- enables a deep swab to be taken for culture.
- encourages healing, by restoring a chronic wound to an acute wound

Debridement is also described in the broader context of Wound Bed Preparation (WBP) in all chronic wounds, including DFU. The theories and practice of WBP has been extensively described and popularised following a 2002, Expert Working Group meeting and subsequent publications which reference the paradigm (445). The acronym, TIME, later changed to DIME, became the mechanism to focus clinician attention to the four aspects of a wound that need to be addressed to support endogenous healing of chronic wounds and optimise outcomes from advanced wound healing treatments.

The initialism TIME or DIME, used by Sibbald (2000), Schultz (2003) and Ayello (2004) stand for ; **T**issue Removal of non-viable tissue / **D**ebridement, **I**nflammation and **I**nfection, **M**oisture balance and **E**dge of wound (non-advancing or undermined) (446-448). These have now used for over twenty years and made popular in educating clinicians engaged in wound management by Sibbald who established the organisation, WoundPedia, and by faculty members who have co-authored publications on the topic. Earlier versions did not address the broad principles of wound management, to determine the wound aetiology and treat the underlying and contributing factors. Addressing aetiology is important for successful management of all wounds, and for DFU in particular; identification and management of trauma pressure offloading, ischaemia and other relevant factors including infection, nutritional deficits and oedema are important. TIME also omitted reference to objective monitoring which can help to identify delayed healing trigger intensification of treatment and or referral to a more specialised team.

Baker (2002) describes the role of the podiatrist with regards to sharp debridement of DFU, both in terms of the removal of callus and wound bed, as part of their role in the multidisciplinary team in the UK(449), following the first descriptions of these services by Edmonds (1986) at Kings College and Thomson (1991) in Manchester (450, 451). While agreeing that the practice is important and common practice, he aptly refers to the practice of callus debridement being “empirical based on experience” and its effect on wound healing as “conjecture” in the absence of quality evidence (449).

In 2003, Smith and Thow published an update on Smith (2002) Cochrane systematic review of debridement of DFU, from which it was concluded that “research is needed to evaluate the effects of a range of widely used debridement methods and of debridement per se” having found the only quality evidence related to the use of hydrogel over standard care of dry gauze (452, 453). A survey of clinicians was planned but the results of this do not appear in the published literature.

By 2012, there was reference to Australian nurses with specialised training performing conservative sharp wound debridement (CSWD) in a survey by Rice et al (454). The current “state of play” they reported was that while nurses do debride when they consider themselves to have the relevant skills and experience, the undergraduate courses aim to provide theoretical knowledge only and do not assess debridement competence (454). There was consensus among those surveyed that specific modules of learning are required for those who wish to gain competence in debridement as either nurse practitioners of clinical nurse consultants in wound management. Similarly in Canada, there is documented practice of CSWD in the care of chronic wounds, including DFU by Rodd-Neilson (2013) and the Canadian Agency for Drugs and Technologies citing the cost effectiveness of debridement of DFU, preferencing sharp debridement in 2014 (382, 455).

While it appears that sharp debridement is routine practice anecdotally, there is very comparatively scant description in the literature on debridement as part of podiatry practice (456) possibly because of the relatively small size of the profession. According to workforce data from the national registration of podiatrists, there are 19.9 registered podiatrists per 100, 000 population in NSW, lower than the National ratio of 22.2 per 100,000 (457). Most (8/9) podiatrists work on a fee-for-service basis in private practice (458), making frequent debridement expensive and potentially cost prohibitive for people with DFU who are most likely to be on financially disadvantaged or on low incomes (281, 283). Potentially more of the DFU debridement and care is providing in the public sector where there is no consultation fee however there is no data to confirm this.

With sharp debridement in the management of chronic wounds a consistent recommendation is wound EBPG, it is expected that it is widely practiced. In their global survey of health professionals involved in wound care, Swanson et al (2017) reported variation in the proportion of health professionals using sharp wound debridement between health settings and countries (293). The survey was distributed through the Wounds International and Smith and Nephew TM contacts yielding 2614 respondents involved in wound care, of which nearly a third were Australian. Discipline was not collected but given the relatively small numbers of podiatrists compared to nurses, it is likely the majority of respondents were nurses. One third of respondents indicating treating wounds was their primary role and the remainder indicated wound management was part of their role. The countries where sharp debridement was performed the most, were the US where 79.6% of respondents indicated they frequently sharp debride, followed by Australia and the UK where 46% and 44% frequently sharp debride (293). The similarities with Australia and UK may reflect similarities in how wound care is organised within our health care systems with inpatient, community and outpatient services supporting wound care which aims, at least, to be interdisciplinary and is publicly funded.

On the published recommendations for debridement as part of wound bed preparation, published updates of the model by Sibbald in 2021 followed their survey of “key opinion leaders” (n=21) who were selected as representatives from a range of disciplines and from each continent, as well as recent graduates from the International Interprofessional Wound Care Courses (n=66) (359). Treatment of the cause, the need for vascular assessment for healing potential is highlighted, management of pain and evaluating wound healing progress are now included in key consensus statements. The focus on wound bed preparation is retained and statement five is directly relevant to the area of debridement. It states “5 A: Consider sharp surgical debridement (to bleeding tissue) for healable wounds and conservative surgical debridement for maintenance /non healable wounds. 5B: Evaluate the need for alternative debridement modalities: autolytic with dressings, enzymatic, mechanical or biologic”(359). While wound bed preparation deserves focus, sharp debridement of DFU has goals beyond the wound edge, with the removal of callus at the wound edge and peri-wound also potentially beneficial in promoting healing.

Table 2: Published Reviews of Sharp Debridement.

YEAR	AUTHOR (FIRST)	TOPIC	WOUND TYPE
1999	Bradley(443)	Systematic review: Debridement	CW
2003	Smith(453)	Update of systematic review: Debridement	DFU
2010	Edwards (Cochrane Review)(459)	Debridement	DFU
2010	Wound Healing and Management Node Group. JBI.(460)	Surgical & Conservative Sharp Debridement	CW
2012	Hoppe(461)	Debridement	CW
2013	Strohal. European Wound Management Association(462)	Debridement: An updated overview and clarification of the principle role of debridement	CW
2016	Elraiyah(463)	Debridement	DFU
2017	Liu(464)	Combined Debridement Techniques	CW
2019	Michailidis(465)	LFU versus non-surgical sharp debridement	DFU
2021	Thomas (466)	Debridement	CW
2021	Dayya(467)	Debridement Narrative review summarising systematic reviews from 2017-2021. No studies of Sharp Debridement.	CW
2022	Nowak(468)	Wound Debridement products and techniques:	CW
2023	Chen(386)	IWGDF Systematic Review: Randomised Studies of Interventions to improve healing	DFU

Systematic and literature reviews of debridement of diabetes-related foot ulcers (DFU) and Chronic wounds (CW). Excludes reviews limited to non-sharp debridement modalities; biological, enzymatic, laser and ultrasonic debridement and reviews which do not include debridement of DFU (for example debridement of surgical wounds or venous leg ulcers only).

From the first systematic review and randomised study conducted by Bradley (1999) (443) to the present by Nowak (2022)(468), and the systematic reviews of the International Working Group on the Diabetic Foot (IWGDF) (386), only two prospective randomised studies of debridement are documented; Piaggesi (1998) involving surgical sharp debridement (469) and the present study to assess the outcomes of weekly versus second weekly debridement. The efficacy of debridement, compared to no debridement has not been determined in any randomised study.

Between 1999 and the present, 2023, reviews of sharp debridement practice have drawn on observational data from studies by Steed et al (1996) (441), Cardinal et al (2009) (470), Saap and Falanga (2002)(471) and Wilcox (2013) (472). These will be discussed in more detail, along with the recent data reported by Lavery (398).

Of particular importance in the field of diabetes-related foot complications are the International Working Group on the Diabetic Foot (IWGDF) series of reviews and evidence-based guidelines written for global implementation, since 1996. Evidence and expert consensus-based guidelines are updated every 4 years. Since their first publication and in subsequent systematic reviews sharp debridement has been documented as a key component of treatment for DFU and the preferred method owing to it being precise, rapid, and cost effective (380, 386). Their 2012 systematic review concluded that evidence for sharp debridement was "not strong" however guidance has consistently recommended sharp debridement (473). In 2016, the recommendation was "In general, remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contraindications such as severe ischaemia into account" and rated the level of evidence as low and the recommendation strong (474) with frequency referred to as "Debride the ulcer (with scalpel), and repeat as needed"(475). Only one study is cited to support non-surgical sharp debridement, Saap and Falanga (2002) which is described later (471).

In the latest 2023 review of evidence published as a systematic review of relevant randomised studies on interventions to assist healing of DFU, Chen et al (2023), included ten randomised studies on a range of debridement (not all sharp) interventions which were assessed according to GRADE criteria which assesses quality of evidence (61, 386). The selected clinical questions, reporting in PICO format detail the patient group, intervention under investigation, the control intervention and outcome (PICO). The guidelines refer to best standard of care to be local debridement, offloading, revascularisation, and the treatment of infection when indicated. The review and expert panel concluding that neither autolytic, bio-surgical, hydrosurgical, chemical or laser debridement modalities were recommended in preference to standard care of sharp debridement with the recommendation graded as strong with a low certainty of evidence (386).

Surgical debridement was referenced, with surgical debridement not recommended when sharp debridement can be performed “outside a sterile environment” ostensibly meaning, in an outpatient clinic, not an operating theatre by a surgeon (386). This new recommendation was based on the greater cost associated with formal surgical debridement by a surgeon in the operating theatre and the potential for treatment delay, a recommendation which remains consistent with the European Wound Management Association (EWMA) debridement guidance(462). Importantly, it is noted that extensive necrosis, collections, and gas forming infections warrant urgent surgical opinion due to the limb threatening nature and likelihood that surgical debridement is indicated(386). The evidence from the randomised study, described in this thesis, was included in the ten randomised studies assessed and reported in the guidance document (386). The recommendation of sharp debridement over the routine use of surgical debridement, was a strong recommendation despite a lack of high-quality studies which resulted in a low certainty of evidence (386).

1.3.2 Types of sharp debridement and providers

There is a spectrum in the extent and level of debridement which is described in the management of DFU, which is, in part, related to local models of care and the discipline of the provider. We believe the terms conservative, maintenance, serial, and sharp debridement are virtually synonymous however variation in the extent of debridement between clinicians, services, and disciplines for both surgical and conservative approaches is also likely, due to training and scope of practice differences. The available literature, centres of the care provided in the US, Europe, Canada, and Australia.

In the US, sharp debridement (both conservative and surgical) may be performed by physicians, nurse practitioners, and physician assistants however conservative sharp wound debridement may be performed by a broader range of disciplines, such as registered nurses depending on State and local laws (https://woundcareadvisor.com/can-perform-sharp-wound-debridement/ Accessed March 2023). Podiatrists in the US graduate as doctors of podiatric medicine with surgical training.

In the **United Kingdom, Canada and Australia**, the care of people with DFU and the performing of sharp debridement falls to podiatrists working as allied health. While the procedure or extent of debridement is not frequently referenced, images available in Baker (2002) (449), the relevant Chapter by Thomson in Edmonds and Foster's book on the management of DFU(444), Saap (2002) (471), Falanga (2008) (476) and in the Murphy et al (2022) (477) on "Wound hygiene", are consistent with what we have described and illustrated in this thesis. The practice of sharp debridement of the wound periphery and base, is core task performed by podiatrists within the health care systems, in particular in organised centres for the management of DFU described in the UK and Australia (450, 451, 478, 479) and possibly also by private clinicians, although this is not documented.

The important differences are between surgical sharp and that which we are referred to as serial, conservative sharp or non-surgical sharp debridement. The latter is typically performed in the non-admitted clinical setting or can be described as a chair or bedside procedure. It is repeated often during a course of treatment. Surgical sharp debridement is performed by those with surgical qualifications and performed in an operating theatre with higher levels of sterility required of this more extensive tissue debridement which is more likely to include excision of bone and a margin of viable tissue. Surgical debridement has a higher per episode cost than non-surgical sharp debridement and is more likely to be undertaken at initial presentation, when significant infection, abscess formation or necrotic tissue is present or when tendon or bone excision is indicated (386) it is not undertaken frequently during the course of treatment although a recent expert panel published suggests initial surgical debridement may need to be repeated before stepping down to a form of weekly maintenance debridement (480).

The one prospective study of surgical debridement is by Piaggesi et al (1998) in which the results of surgical sharp debridement of DFU, involving a single procedure are reported (469).The title of this publication is confusing as it refers to the “Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers…” however, the procedure involves surgical resection of the wound and primary closure.

The Steed study (1996) refers to aggressive sharp debridement followed by what is likely to have been a more conservative debridement thereafter, although a thorough description is absent and the study protocol for the randomised study from which the data was used, did not stipulate how often the DFU should be debrided (441).

Saap and Falanga investigate the extent of a single surgical sharp debridement (471) and the studies by Cardinal (470)and Wilcox(472) which are both retrospective do not define and explore the extent of debridement but report on outcomes related to frequency alone.

The significance of the Cardinal study is that, like in the Steed study, they analysed the data from DFU which were studied in a randomised study of a bioengineered dressing to specifically explore the effect of debridement frequency. In the study by Steed, the frequency that debridement was to be performed was not stipulated in the protocol for the randomised study. In the Cardinal study, frequency was stipulated in the protocol as “patients underwent sharp debridement of the study ulcer to remove necrotic or hyperkeratinized tissue at each visit (Weeks 0–12)”(470).

A paper by Granick et al (481) purports to address the issue of defining what is practiced in their article titled “Toward a common language: surgical wound bed preparation and debridement”. The article describes the conundrum that is our lack of prospective evidence for sharp debridement but discusses surgical sharp debridement in terms of the formal, operating room procedures and the merits of hydrosurgical debridement as an alternative to surgical debridement. Non-surgical or serial sharp debridement is not covered in the article.

While surgical and non-surgical debridement have important differences in the potential extent and level of tissue removed, there are features common to both. In the authors experience, sharp debridement in the non-admitted setting by a podiatrist experienced in the management of DFU can closely approximate the extent of debridement performed in the operating theatre in some instances while at other times, being minimal, as determined by patient and practitioner-related factors. This may also be the reason the IWGDF recommends that surgical debridement not be undertaken when sharp debridement can be performed "outside a sterile environment (386).

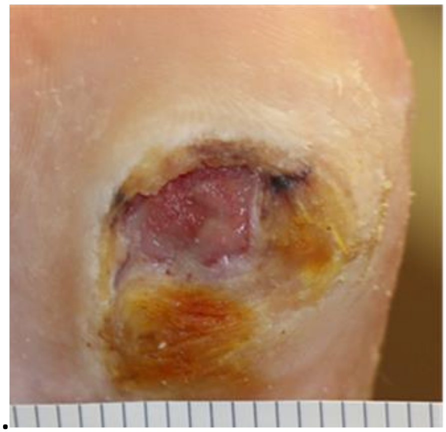
In clinical setting, wound characteristics and treatment goals, vascular status, what is accepted by the patient and the clinician's scope of practice are most likely the determinants of the extent and frequency of sharp debridement individual patients receive.

Table 3 contains a summary of descriptions for sharp debridement of chronic wounds as they appear in key references on the subject. Notably, there are common features to both surgical and sharp debridement and the practice of repeat, serial debridement is rarely referenced. Most of the literature is written from the perspective of surgeons and dermatologists. Only find one article is written by a podiatrist, Malone (2017) (482) which effectively describes the technique followed in our studies.

In this thesis, I consider conservative sharp wound debridement to be the same as sharp, serial debridement. It is defined as the practice of routine, serial, non-surgical debridement, using scalpel and forceps and curettage where tissue such as hyperkeratosis (callus) from the wound edge is removed, along with superficial non-viable tissue from the wound bed to the point of bleeding. While a bleeding edge and base may result from SWD, the aim is not to extend into viable tissue. Sharp wound debridement which excises the wound bed, including the granulating tissue base and margin and may include underlying structure such as bone, are referred to as excisional sharp debridement. The term "conservative" is not used in the IWGDF or earlier EWMA guidance but is the term used in some articles, including those published as part of this thesis. This was done to help distinguish the sharp debridement technique employed in routine practice within the non-admitted setting, from the surgical debridement provided by surgeons. Figure 3 depicts sharp debridement as referred to within this thesis.

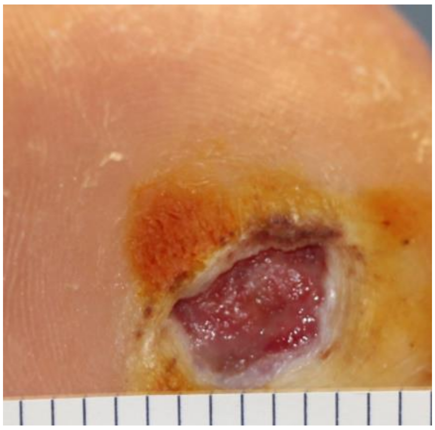
Figure 3 Before and After Images of a Plantar Neuropathic DFU Treated with Sharp Debridement

A



B

C



D

Before and after images of a plantar neuropathic foot ulcer. This patient consented to use of their DFU and was a participant in the randomised study of debridement frequeny. (A) Week 1 before and (B) Week 1 after (C) Subsequent week before debridement and (D) after debridement.

Table 3: Definitions of Sharp Debridement of Diabetes-related Foot Ulcers

Author, Country	Year	Discipline	Term(s) used	Details	Description of sharp debridement (quoted)
Steed (441) USA	1996	Surgeon	Sharp debridement	Observational (retrospective) study of debridement frequency	“Aggressive sharp debridement of callus and necrotic tissue down to bleeding tissue as needed at the time of their office visit….bony prominences found in the wound can be resected….excising the tissue with the highest bacterial counts”
Piaggesi (469) Italy	1998	Surgeon	Conservative Surgical Debridement	Randomised study	“…excision of ulcer, the debridement or removal of any involved bone and the surgical suture of the wound margins” Alternative / standard care debridement is described only as “initial debridement of lesions and elimination of surrounding hyperkeratosis”
Vowden (483) USA	1999	Nurse	Conservative Sharp Wound Debridement	Evaluation of new model of care with nurses performing CSWD	“Excise callus until punctate bleeding tissue is seen”
Saap (471) USA	2002	Dermatologist	Surgical debridement	Observational Study	“Surgical Debridement. Defined according to Debridement Performance Index (DPI) score: a) removal of callus; b) removal of ulcer's edge undermining; and c) removal of wound bed necrotic or infected tissue”
Attinger (484) USA	2006	Plastic Surgeon	Serial Debridement	Article	“To the point of bleeding, soft or normal-coloured tissue is reached"
Falanga (476) USA	2008	Dermatologists, nurses, a surgeon and internal medicine specialists	Surgical/Sharp debridement and Maintenance debridement which may or may not be sharp/surgical	Article – Expert Panel Consensus recommendations	Surgical/Sharp debridement “Removal of callus, frankly non-viable tissue, eschars and fibrinous wound bed” with maintenance being the use of a range of modalities from autolytic, enzymatic, mechanical, and sharp to ”maintain readiness of the wound for healing”.

Wolcott (485) USA	2009	Surgeon	Sharp debridement	Article	"… opening all undermining and tunnels, removing all devitalised and poorly perfused tissue, and shaping the wound topography. The resulting smooth, well-perfused wound bed will inhibit biofilm adhesion"
Cardinal and Eisenbud et al (470) USA	2009	Biomedical engineer and vascular surgeon	Serial Surgical Debridement	Observational (retrospective) Study	"patients underwent sharp debridement of the study ulcer to remove necrotic or hyperkeratinized tissue at each visit"
Wound Healing Management Group Australia	2012	NA	Sharp debridement	Joanna Briggs Evidence Review	"Removal of foreign matter and devitalised / necrotic tissue from a wound using either a sterile scalpel or sterile scissors….until the surrounding healthy tissue is exposed".
Lebrun (486) USA	2013	Dermatologist	Excisional debridement and Maintenance debridement	Commentary	"Excisional debridement of the bed and edges with a scalpel initially…thereafter maintenance debridement regularly (weekly or second weekly) using surgical or non-surgical techniques"
Strohal: EWMA (462) Europe	2013	Eds. Dermatologist and Nurse	Sharp debridement	Evidence Based Practice Guideline	"sharp debridement' as a minor surgical bedside procedure, involving cutting away tissue with a scalpel or scissors. 'Surgical debridement' is defined as a procedure performed under general anaesthesia, using various surgical instruments"
Schwartz (487) USA	2014	Surgeon	Surgery Surgical debridement	5 DFU treated with sharp versus hydrodebridement. Evaluating the	"Sharp debridement uses steel instruments to remove necrotic tissue from the wound bed"

				reduction in planktonic bacteria	
Malone (482) UK	2017	Podiatrist	Sharp debridement	Article	"The removal of dead or necrotic tissue or foreign material from and around a wound to expose healthy tissue using a sterile scalpel, scissors, or both. Bedside debridement undertaken in an outpatient clinic environment often performed using a sterile scalpel, dermal curettage. Surgical (as above) undertaken in a theatre…more aggressive approach involving superficial and deep structures…often large surfaces or the requirement to debride to deeper structures needing haemostasis"
Nakagami (488) Japan	2019	Nurse	Conservative sharp wound debridement	Preliminary, retrospective study evaluating detection of biofilm post	"CSWD performed if slough or eschar hindering healing. Minimally invasive technique using scissors and /or scalpel"
Hajhosseini (489) USA	2020	Surgeon	Sharp debridement	Randomised study of sharp debridement compared to YAG Laser. N=22 Venous leg ulcers and 0 DFU	"Scalpel and /or curette…all fibrinous as well as necrotic tissues were cleared and debridement was complete once healthy, bleeding tissue was encountered".
Panuncial-man and Falanga (405) USA	2007	Dermatologist	Surgical Debridement	Review article	"Traditional approach is to debride to bleeding tissue….without injuring viable tissue based…. Surgical debridement is the fastest way to debride a wound, but it is not selective because it removes viable tissue as well. "Maintenance debridement" in between surgical debridement interventions may be achieved by other methods, such as autolytic, chemical, or biologic means."

					No reference to non-surgical sharp debridement
Eriksson (480) USA	2022	Medical/Plastic Surgeon and Nursing Researcher	Surgical	Consensus document	“Surgical debridement at the first or second visit followed by enzymatic debridement (common practice). “substantial surgical debridement followed by maintenance debridement” quoting Falanga (2008)

Descriptions of sharp debridement and nomenclature used between key publications by author, country, and discipline. EWMA = European Wound Management Association.

1.3.3 Human studies evaluating the effect of Sharp Debridement and Frequency

The following studies with outcomes in humans, represent the main body of evidence on sharp debridement in the treatment of DFU and will be explored here in more detail.

Piaggesi and Schipani et al (1998), randomised 41 participants (from 234 screened) who met the study criteria of uncomplicated (non-ischaemic and non-infected) neuropathic DFU, and agreed to participate. All participants were managed as non-admitted. The surgical group underwent resection of the ulcer and underlying bony prominence, were given prophylactic intravenous antibiotics for 5 days and treated with rest, crutches, medical grade footwear and orthoses (MGF) for 3 weeks then permitted to weight-bear with the MGF and orthoses without the crutches. The new, surgical wound was sutured for healing by primary intention. Participants in the standard care group underwent "initial" debridement at baseline, were not closed, were managed with dressings, twice weekly clinic visits and utilised the same type of offloading devices. The standard care DFU do not appear to have had any further sharp debridement. The wounds were large, ~ 4cm in diameter, uninfected and without severe peripheral arterial disease (PAD). Interestingly, the treating clinicians of patients in the standard care group were not made aware that their patients were in the study. The surgically treated DFU were more likely to heal (21/22) compared to the standard care (19/24) and did so in a much shorter time 46.7 verses 128 days with fewer recurrences, defined as a subsequent ulcer at the same site. The healing outcomes experienced by the participates who received surgery may have been improved in part, due to surgical "off-loading" achieved with removal of underlying bone and the addition of parenteral antibiotics administered for 5 days in this group. Overall, it is clear that in the surgical group, the DFU was converted to acute surgical wounds, healing by primary intention. The standard care DFU were left to heal as chronic wounds by secondary intention. While this was a study with low patient numbers and a high degree of bias, the effect size is large and provides evidence that successful treatment of DFU can be achieved with surgical removal of the wound and with good patient satisfaction in those patients who agree (469).

Steed and Donohoe (1996) et al published their observations on the impact of debridement frequency in patients enrolled in the multi-site randomised controlled study (RCT) investigating the effect of topically applied recombinant human platelet-derived growth factor (RhPDGF). In their study which was a *post-hoc* analysis of the main RCT, the outcomes of 118 patients with DFU recruited across 10 participating centres were analysed according to how frequently the wounds were debrided. Inclusion criteria for the study was participants with a neuropathic DFU of minimum 8 weeks duration (without healing), adequate blood flow for healing (TCPO2 >30mmHg) and an absence of infection, renal failure, liver failure or poor glycaemic control. In addition to the statistically significant benefit of RhPDGF, they observed a higher rate of healing at 20 weeks in those centres that performed more frequent debridement. The opportunity to detect this difference was present because there was no explicit advice in the study protocol on debridement frequency, hence variability between participating treatment centres in debridement frequency occurred. There is no statistical analysis of these results and they are reported by centre, rather than at the patient level. In the main study report, published first, the authors, Steed et al (1995) indicated that "no treatment by centre interaction showed statistically significant differences in the number or percentage of DFU healed during which debridement occurred"(442). The post-hoc analyses however pooled participants from the five sites with less than 10 participants enrolled and looked for an association between frequency of debridement performed at each centre and proportion of wounds healed at the study end, 20 weeks across the now, six groups (441). By referring to the 1995 publication detailing the schedule of office visits, it can be estimated that there were 12 study visits (following randomisation) where there was an opportunity to debride (442). Participants attended weekly for the first four weeks and then every two weeks until 20 weeks. The protocol required aggressive sharp debridement of all participants' wounds one to two weeks prior to randomisation, a procedure which according to their definition could include bone. It is not known whether participants underwent this extent of debridement and whether the depth and extend of debridement differed between sites. It is also unclear, precisely how many times the wounds were debrided in the 20 week study period. The decision to debride was left to the discretion of the investigator. The authors conclude that more frequent sharp debridement enhanced the effectiveness of the advanced wound healing modality, RhPDGF (441).

Despite these study weaknesses, the results have become the most cited incentive for recommending frequent SWD. The author later reports that "Despite the fact that most physicians, and certainly all surgeons, know what debridement is, there is no universal agreement on how to debride, when to debride, or how much tissue to take" (490). Indeed, there are few studies which address this clinical question.

Saap and Falanga (2002) et al reported their study on the effect of debridement on healing outcomes, specifically assessing the extent of debridement performed. Their study was another retrospective analysis of DFU's enrolled in a randomised study of an advanced healing product, a bilayered, bioengineered skin construct (BSC). In this study the extent of debridement at baseline was graded in terms of the presence of callus (at the periphery), undermining of the wound edge and necrosis on the wound bed. Their novel Debridement Performance Index (DPI) (Table 3) is the first and only study to the author's knowledge to attempt to classify wound debridement. Blinded assessors retrospectively analysed the available images of 143 images of DFU, taken at the baseline, before and after what was described as surgical debridement. For this analysis they grouped participants who received BSC with those who did not. In the images, it is evident that the edge of the wound was excised and the base debrided however it appears that the new margin is not substantially different to the original. The images illustrate the level of debridement is en par with that used in the randomised study (471).

Saap and Falanga found a statistically significant, positive association was found between DPI and complete wound closure. Using a cut-off of for low (0-2) and high (3-6) DPI, wound healing rate was 34.5% for those with low DPI and 55.3% for high (p=<0.05). These results suggest that the extent of debridement performed is important overall, with more thorough removal of non-viable tissue having a beneficial effect to healing at week 12. The sample size was too small for comparison of between group differences for those receiving standard care and those receiving BSC however BSC recipients were 2.4 times more likely to heal by week 12.

It should be noted that the scoring system allocates maximal points where there is no clinical indicator for debridement. This leaves the possibility that wounds healed better because they were required less debridement. DFU requiring less debridement would feasibly have less callus due to more effective offloading and lower bio-burden and have a better prognosis, irrespective of debridement performed(471). A subsequent study by these authors, focused on the VLU's, in which they refined their criteria for this wound type(491). Overall, the work by Saap and Falanga shows that the effect of debridement is dose-dependent and it is a variable which affects healing outcomes of chronic wounds (471, 491).

Cardinal and Eisenbud (2009) published data on the healing of DFU and VLU, using patients enrolled in two randomised controlled studies of a bioengineered dermal substitute (BDS), Dermagraft ™, to determine any effect of debridement frequency on the participating wounds. The study was completed in 2000 and included 310 DFU's treated at one of 35 centres (470). The characteristics of the ulcers or participants reported with the primary outcomes of the study (492). The method and findings are similar to the study by Steed et al and contain similar limitations, being retrospective and not designed to examine the effect of debridement frequency (441). A key difference is that the protocol of the 2000 BDS study specified debridement of DFU at every visit, while the earlier by Steed study had not. In both studies, the investigators divided the participants by treatment site, defining sites according to how often debridement was performed. In their study, Cardinal et al defined treatment centres by whether which debrided all DFU at every visit 75% (or more), or less than 75% of the visits. Where debridement was frequent (n=231 patients at 20 sites), the percentage healed at 12 weeks was 29%. Less frequent debridement (n=74 patients at 10 sites) 15% healed at 12 weeks (p=0.015), a non-statistically significant difference. A predictive Kaplan-Meier analysis performed at the patient level (between patients) did not detect a statistically significant difference (Wilcoxin: p=0.102). Interestingly, the study of VLU did produce a significant difference with more frequent debridement associated with higher healing rates, however the VLU were debrided less frequently overall and serial debridement frequency was at the discretion of the treating clinician (470). This is in contrast to observations of a subsequent study by Wilcox (472).

A group of researchers from US have published data on visit and debridement frequency in chronic wounds, using data collected and entered into the Healogics database, used across wound treatment centres in the US and Puerto Rico. The first of these articles, published by **Williams et al (2005)** involved non-healing venous leg ulcers**.** The 20 week, observational study was conducted to document and assess the safety of CSWD of VLU in an outpatient setting. Wounds that were non-healing and had features of slough (and without granulation tissue) were sharp debrided by the same clinician using a curette. Wounds with granulation tissue present were not debrided. Both groups received standard care. The sample sizes were small (28 and 27 patient wounds) and the intervention was not assigned randomly. The results were not statistically significant, thus did not show that CSWD accelerates healing (493). The authors concluded that the procedure was safe and associated with reduced rates of clinical infection at week 4. Their graphical representation of wound size suggests a positive effect of debridement on the previously non-healing, debrided ulcers. Of interest, the authors explained their decision not to conduct a randomised study based on the unethical risk that ulcers that needed debridement might be randomised to not receive this mainstay of treatment. As described in this thesis, our research group had similar ethical concerns which led us to decide on randomising to two different frequencies of debridement.

Warriner and Wilcox (2012) et al analysed data from the episodes of care of n=206 patients with a variety of chronic wound types, across 9 centres treated between 2009 and 2010. They included DFU where the healing outcome was known and grouped the wounds by visit frequency, those which were treated weekly compared to those treated every second week, during the first four weeks of care at the centre (494). Debridement frequency, described as excisional, was counted but those patients who did not undergo excisional debridement of their DFU were excluded. Controlling for important co-variates including depth and duration of the wound, time to first debridement and number of visits, visit frequency was the dominant variable impacting healing outcome with 63.8% of weekly visiting patients DFU healing in a median of 21 days compared to 2% of patients healing in a median of 79 days. The weekly visit group were older being 71.6 years on average, had less PAD (25%), a median of 5 visits and 2 excisional debridements. The second weekly group were younger, being 64.5 years on average, had more PAD (52%), attended 7 visits, and underwent 4 excisional debridements. Those who attended every second week also had larger wounds, an average 3.72cm^2 compared to 1.2cm^2 for those seen weekly (494). It is not possible to understand the impact of frequency of debridement since the more debridements in the weekly group occurred over a longer time period. It is not known whether conservative debridement was provided in between excisional debridement. Despite the selection bias (healed wounds), there is evidence that visit frequency is an important variable to control in any investigation of DFU treatment (494).

Wilcox and Carter et al (2013), present the largest observational study of the effect of debridement on healing. Through retrospective analysis of data extracted from the wound database, the same as used by Warriner (2012) where the effect of consultation frequency was assessed, Wilcox reports the healing outcomes based on ulcer debridement frequency. The large dataset included records from the database of 525 US wound care centres (472). The opportunity to collate and present this large dataset occurred due the use of a web-based database and the requirement that clinicians complete the data collection on all patients. They excluded records where there were obvious errors (nil or negative wound size) and cases where there was no follow-up, with the final number of 312 832 records available for analysis, including 59464 (19%) for participants with a "diabetic foot ulcer". DFU represented the second most frequently recorded wound type, second to venous leg ulcers. Wound duration size and duration, frequency of debridement and some key parameters were investigated for their relationship to healing outcomes. The average frequency of debridement for all wounds was 2 (1-138) and 70.8% healed with more frequent debridement associated shorter time to healing. (p= <0.001). Variables affecting wound healing were analysed using the Cox Proportional Hazards Regression Model which detected that weekly (or more frequent than once a week) debridement had a odds ratio for healing of 4.26 (4.20-4.31) compared to 1-2 weekly debridement 1.22 (1.21-1.23). The other variables such as wound duration, size and patient age were associated with slower healing, as would be expected. Other potential confounders such as pressure offloading prescribed and worn, clinical infection and its treatment were not systematically reported or considered and visit frequency was not discussed in this study(472).

The greatest impact of debridement frequency on wound healing was noted for DFU. When categorised as weekly (or more frequent), every 1-2 weekly or second weekly (or less often), the mean time to healing was 21, 64 and 76 days respectively (p=0.001).

Carter and Fife (2017) returned to the subject of visit frequency using the same database as the previous two studies. In this recent dataset, they included new presentations for treatment of DFU. The 12 month healing endpoint was defined as wound epithelialized, without exudate or less than 2mm in size to substitute for healing outcome for patients who failed to return for their final visit. They excluded patients who healed in the first 2 weeks.

Their final analysis included 29696 DFU from 115 clinics, with the mean patient age of 63.5 years and wound size 5.2cm^2. It was not possible to interpret the HR for debridement frequency with the categorical data groupings overlapping (1-2 weekly, 2-4 weekly) and with the likelihood that only excisional debridements were recorded (based on earlier protocol). Of note, visit frequency dominated again in this larger study, although the HR is lower. Other co-variates age of wound, treatment with hyperbaric oxygen or negative pressure wound therapy and initial area were also important. HR results: 4–7.5 visits per 4 weeks: 0.66 (95% CI: 0.69– 0.79); 2–4 visits per 4 weeks: 0.51 (95% CI: 0.48–0.54); ≤2 visits per 4 weeks: 0.18 (95% CI: 0.16–0.20) show a small to medium effect size between the lowest and highest number of treatment visits (495).

More frequent treatment visits may benefit healing for a great many reasons; improved adherence to treatment through patient education, better quality of wound care when provided by the clinicians at the centre, more thorough wound bed preparation through non sharp debridement methods or more prompt identification and management of infection. It is also possible that those patients who attend more frequently are healthier, better supported by family and carers or more engaged and adherent to treatment, hence present to more appointments.

It is challenging to interpret these data, reported retrospectively with the potential effect of these and other confounding variables.

Data used was not collected for the purpose of finding a relationship between healing and debridement frequency. The strength of the Wilcox study is the high numbers of participants included and the opportunity to compare the effect of debridement of DFU compared to VLU. Of additional note is that the mean healing time of 21 days in the most frequently debrided ulcers is a very short time to healing raising the possibility that these were superficial ulcers, not complicated by infection or ischaemia. The extent of sharp debridement, excisional or conservative, was not reported in the 2013 study (472).

It is not clear in the Wilcox study, whether debridement was performed at every consultation and how often patients attended, hence the outcome measure may be as much an indicator of how frequently the patient presents for treatment as whether how often debridement was provided, with the latter being significant. Clinical activities which occur during a treatment visit such as education, dressings, management of infection and implementing and monitoring of pressure off-loading may also have been improved with more frequent visits and since attendance reflects patient access to care and all that influences this, such as patient adherence and engagement with treatment, financial barriers, distance and access to transport, it raises questions as to whether debridement frequency as an intervention explains the substantially better clinical outcomes. These considerations emphasize the need for a definitive, prospective randomised study to test the effects of sharp debridement frequency on healing of DFU in the context of standard care, controlling for visit frequency.

Lavery et al (2019), represents the most recent clinical study reporting on healing outcomes related to debridement. The authors return to the question about debridement frequency and the impact on the effectiveness of advanced wound healing modalities. In their study Lavery et al examined the impact of surgical sharp debridement frequency on healing outcomes of topical oxygen therapy (398). In this retrospective post hoc analysis, they included data from 146 participants with DFU, enrolled to a randomised, double blind, placebo-controlled study to evaluate the effectiveness of continuous diffusion of Oxygen. Differences in surgical sharp wound debridement between sites afforded the authors the opportunity to evaluate debridement frequency as a variable. Debridement was described as surgical debridement and the included ulcers were those graded as 1A (superficial and without ischaemia or infection) which failed to reduce by 50% in the four-week run in period of the study. Most of the 34 participating treatment centres debrided the DFU every week, however one site ((90% overall) however one site (Site X) debrided ulcers only 41.3% of the weekly study visits compared to 98.4% of the other sites. While the number of DFU in the final analysis was only 15 for site X, the impact of less frequency debridement was potentially impactful with a lower proportion of DFU healed in both active and placebo groups at this site compared to the other sites. Owing to a difference in the ethnicity, with most of site X participants being Hispanic, the authors specifically analysed the impact of debridement frequency on healing outcomes in the Hispanic participants and found that 81.8% of DFU debrided weekly in the active arm healed, compared to 21.4% ($p = 0.005$) of DFU of Hispanic patients in the placebo arm which represented a greater between group difference compared to the results of other sites where 51.2% of DFUs in the active group healed compared the

11.3% (p= 0.006) in the placebo group (398). The limitations are the small number of participants and the retrospective design however the authors have detected a difference which potentially supports their hypothesis that frequent surgical debridement prepares the wound bed for the application of oxygen therapy.

As established, sharp debridement is a mainstay of standard care in the management of DFU but with some notable exceptions. DFU established to be unhealable may be more conservatively managed without sharp debridement, using gently methods to remove surface and loose slough and debris. Unhealable DFU are most often those complicated by chronic limb ischaemic with perfusion below that which is required for healing. While there is no single measure used to determine this, expert assessment and the use of vascular investigations are used to guide this decision in consultation with the patient's goals and acceptance. There is some evidence that wounds where the toe pressure is below 40mmHg or Ankle-brachial index below 0.6, that healing is at least delayed and, in some cases, not expected. When restoration of perfusion is not available, feasible or accepted, the goals of wound management may be to maintain or palliate in which case sharp debridement may not be recommended. This is more likely true of an ischaemic DFU with intact eschar and no-exudate or infection when clinical dictum is generally to leave the eschar intact. In the authors experience, these scenarios may result in some form of peripheral debridement for comfort and to prevent deterioration in consultation with the interdisciplinary team and patient.

Overall, the results of the aforementioned, observational studies signal that the approach to debride DFU often, such as weekly, will promote healing. It appears that the benefits of advanced healing agents are improved when sharp debridement is more often.

1.3.4 Specific Benefits of Sharp Debridement in DFU

In the majority of DFU, sharp debridement is considered to provide the following benefits, for which the evidence will be discussed;

- Removal of necrotic tissue and slough from the base
- Reduction of bacterial burden
- Reduction of callus (and pressure)
- Removal of senescent cells

Non-viable tissue and slough are thought to provide an optimal medium for bacterial growth, detrimental to healing (496, 497). Debridement to remove non-viable tissue is therefore linked to the goal of removing bacteria from the wound. The capacity for sharp debridement to remove necrotic tissue can be verified visually, however the effect on bacteria is less straightforward. The assumption that bacteria are effectively removed in this process has been challenged by Schwartz (2014) (487), Kim (2018) (498) and Hajhosseini (2020) (489). Furthermore, the extent to which removal of bacteria from the wound is required for healing is also unclear since wounds with high bacterial load can still progress to healing Hajhosseini (2020) (489).

DFU are often complicated by infection which leads to worse healing outcomes, particularly in the presence of underlying ischaemic (116, 241, 255, 499). Bacteria, present in all chronic wounds, cause infection when they multiply to a concentration of 10^5/g with microbial invasion into the tissues causing inflammation (333, 348). Evidence-based practice guidelines recommend that clinical signs of infection be used to determine the presence of infection, for which prompt antibiotic therapy is indicated (333). Limited evidence for the use of antibiotics based on microbiological evidence comes from a study by Foster and Edmonds et al (2004) in which more DFU with positive cultures healed when antibiotics were prescribed compared to those with positive culture and antibiotics in the absence of clinical signs of infection (500). The justification for antibiotic use in the absence of overt clinical signs is explained by the dampening of the inflammatory response in people with neuropathy and PAD in particular (500).

At our High Risk Foot Service in Sydney, bacterial load was quantified from wound fluid in a series of 32 patients with DFU with the number of bacterial colony forming units correlating with delayed healing (501). Despite large datasets and research from this centre showing an association, there has yet to be high level evidence that infection is independently predictive of poor healing according to a systematic review by Norman et al (2021) which sought to determine the evidence for the impact of infection or other aspects of the wound biome on healing outcomes of chronic wounds including DFU (389). Despite the lack of clear evidence, identification and treatment of infection is fundamental in the management of DFU, with antibiotic therapy and surgical debridement the key strategies(333). The evidence for the role of non-surgical sharp debridement in the prevention and management of infection is less clear but still recommended (383, 386).

While bacterial burden is considered problematic and associated with increased risk of infection which predicts poor healing outcomes, biofilms are more specifically associated with chronic wounds, having been shown to be present in a far greater proportion of chronic wounds such as DFU (482, 502). Biofilms are polymicrobial communities of bacteria which excrete an extracellular polymeric substance (EPS) which coats and adheres bacteria together and to tissues. The bacteria within the biofilm have a reduced replication rate and owing to this and their EPS, are relatively impervious to antimicrobial therapy and host immune responses (503, 504). The deleterious impact of biofilms relates to their capacity to form functioning communities of bacteria which embed deep within the wound bed, reduce availability of oxygen within the wound and contribute to a pro-inflammatory environment in which cytokine release is increased (505, 506). The biofilm in this way remains as a reservoir of bacteria from which planktonic bacteria detach to form new colonies. Biofilms, their behaviour, and role in chronic wounds is an extensive topic and their importance and management will not be adequately covered in this review however these aspects are relevant to the practice of sharp debridement.

Does debridement remove bacteria?

While there is expert consensus promoting regular and frequent sharp debridement as the most effective modality for reducing bacterial load to support healing in wounds with sufficient blood flow(380, 383, 386, 390), the evidence that this is due to effective removal of bacteria from the wound is less clear.

With the presence of bacteria in biofilm being prevalent in chronic wounds and resistant to antibiotics(507), sharp debridement has been considered as a way to physically remove it. Davis et al (2008) published results of their studies using an animal wound model to observe the impact of antimicrobials on newly infected tissue with planktonic bacteria and that with mature 48 hour biofilm formation (508). Their model showed that the agents could exert effect at 24 hours but were less effective on the more mature 48 hour biofilm. As the understanding and measurement of biofilms in wounds was growing, a model of biofilm based wound care was proposed and authors, Wolcott et al, published a case series applying this to non-healing wounds complicated by critical limb ischaemic (509). The model proposes that sharp debridement and maintenance debridement, together with agents with suppress biofilm formation be used (390, 482, 485, 510), not to eradicate bacteria from the wound, but to disrupt the biofilm, providing a therapeutic window for healing to occur and other agents to act on the immature biofilm (511). In a group of 190 patients with chronic wounds and CLI, sharp debridement was used in combination with ultrasonic debridement and agents (patented by the author) specifically targeting biofilm management, showing 75% of patients who chose to participate in the treatment approach, healed (510). The direct changes in wound bacterial load were not quantified in this study.

Wolcott et al (2010) subsequently published a series of biofilm maturity studies, in which they measured biofilm susceptibility to antibiotics using in vitro, animal and clinical wounds in the form of three clinically infected venous leg ulcers (2010) (511). Biofilm was sharp debrided at baseline and then treated with wet to dry dressings, with biofilm collected from three sites over subsequent days which was tested for antibiotic resistance. Compared to mature, baseline biofilm, the newly formed and immature biofilm demonstrated a nine-fold reduction in bacterial concentration when treated. Two of the three wounds exhibited prolonged susceptibility up to 48 hours. Their mouse model biofilm showed improved antibiotic susceptibility for up to 72 hours. The results, albeit very small numbers, provide initial evidence that sharp debridement disrupts biofilm and that during the time it takes to mature, that the bacteria, possibly due the increased metabolic activity required to reform, are able to be killed by antibiotics. The study illustrates the effect of sharp debridement on VLU wound bed and it may be inferred that similar effects are occurring in the sharp debridement of DFU.

To assess the impact of sharp debridement of bacterial load within the wound, Nusbaum (2013) measured the results of four different debridement modalities, sharp debridement, and plasma-mediated bipolar radiofrequency ablation (PBRA) at two different intensities and hydro surgery and sharp using a porcine wound model, infected with MRSA to form a 48 hour biofilm. The authors detected a better reduction in bacteria in the order of 99% with PBRA intensive debridement, with no statistical difference between the modalities based on histologic and microbiologic measures with the pathologist blinded to treatment group but by day 21, all wounds healed irrespective of reduction of bacteria (512).

Schwartz et al (2014) compared the reduction in planktonic bacteria following debridement, comparing surgical sharp debridement to hydro surgical debridement with, in 12 human participants with chronic wounds (n=5 DFU), sequentially assigned (487). All debridements were performed in an operating theatre with pre and post debridement tissue samples sent for 48 hour culture (487). While not a statistically significant difference, surgical sharp debridement reduced bacteria by 93% compared to hydrosurgery (75%) with neither substantially reduced the bacterial count according to microbiological standards. This is despite the post-debridement wounds being reported as visibly devoid of necrotic tissue. Biofilm specifically, was not measured. While debridement was not shown to have a significant, direct impact on planktonic bacteria within the wound, authors believed disruption of biofilm with sharp debridement would provide some beneficial effect (487).

Kim et al (2017), measured before and after bacterial burden using autofluorescence, semi-quantitative cultures and qualitative assessment of bacterial species in a cohort of 36 patients with chronic wounds, primarily DFU (75%) treated with non-surgical sharp debridement which they described as “clinic-based” debridement to mirror what is standard care (498). The technique was described and included the use of “curette, scissors and/or surgical blade to remove devitalised tissue in bleeding tissue at the wound base and margins were observed. All wounds were gently cleansed with normal saline prior to debridement." The reduction in bacterial colony forming units from 6.7 x 10^4 +/- 1.4 x 10^6 CFU/g down to 1.7 x 10^4+/- 3.1 x 10^6 CFU/g in quantitative assessment however the authors report that by microbiological standards, a significant reduction in bacterial count was not observed, with reduction in the order of log(s) required for there to be a significant change. Considering the autofluorescence results and semi-quantitative assessment of pre-and post-debridement tissue, the reduction on bacterial load was not statistically significant. The results neither support or refute those of Wolcott because the techniques used did not differentiate between planktonic bacteria and biofilm containing bacteria. While not discussed in their report, it is not known whether post debridement cleansing of the wound by irrigation or other common methods would have led to more removal of bacteria from the wound post-debridement (513).

To detect whether debridement strategies are impacting bacterial load, either planktonic or within biofilm, is an area of investigation. It has been proposed that using point of care testing for biofilm or associated biomarkers of inflammation be used to guide treatment (514, 515). A technique of wound blotting has been described as a means to detect the mucopolysaccharides present in biofilm (488) and a point of care camera to detect autofluorescence can be used to show high concentrations of bacteria within a wound (516). With the known correlation between MMP concentration and bacterial load, it has also been proposed that MMP concentration be used as a surrogate measure of effective wound bed preparation (417, 517).

The measurement of bacterial autofluorescence has been explored as a method to quantify bacterial levels within a wound, with increased fluorescence correlating with delayed healing and a reduction in fluorescence post-debridement (516, 518, 519). In 2022, Rahma et al published a prospective, randomised pilot study aimed at exploring the use of a point of care device which produces images of bacterial autofluorescence within wounds, in the clinical setting. The investigators sought to understand how the additional data would inform practice and the impact on healing of DFU, with outcomes measured at 12 weeks by assessors blinded to group allocation. Clinicians responded to positive signals of autofluorescence with increased debridement on 40% of occasions. While the study was small (n=56) and underpowered to produce statistically significant differences in the subgroups, more DFU healed in the group where autofluorescence was measured compared to the controls (45% vs 22%) (519). Furthermore, within the intervention group, DFU without signals of autofluorescence had a 100% percent wound reduction in size at week 12, those which were positive and where there was a change in treatment to address bacterial load had a PWR of 84% and those which were positive but did not have a change in treatment had the least PWR of 56.1%. Those in the parallel control group (n=27) had a PWR of 72.8% (519). The results are interesting and suggestive that there is clinical application of the device in directing strategies which address bacteria in DFU, which in turn promotes healing. It is worth noting that the inclusion criteria for this and a case series published by Cole (2020) was an absence of clinical signs of infection, despite which there were high levels of bacterial colonisation within the chronic wounds (519, 520)

In summarising the impact of these studies, sharp debridement reduces the bacterial load within DFU, although this is not to a substantial degree. Evidence from VLU and animal models that show that mature biofilm exhibits resistance to antimicrobials, and that sharp debridement can be used to (at least) partially remove and disrupt biofilm. In doing so, biofilm is rendered susceptible to topical antimicrobials at least until it a mature biofilm re-develops in the 24-72 hours that follow. There are uncertainties about the effect of the extent and type of wound bacteria and infection on healing outcomes is unclear and more research is needed to understand how bacteria impact healing(521). Data supports the practice of frequent sharp debridement on the basis that bacteria within a chronic wound will recover from the effect of debridement and form mature biofilm within a short period, although this is not yet based on clinical studies of DFU Several forms of point of care testing are showing promise as methods to help guide clinicians in their treatment to reduce bacteria within DFU and limited data to suggest this can influence outcomes.

Effect of debridement on senescent cells

It has been suggested that debridement, by the removal of senescent cells from the wound and edge, restores molecular and moisture balance, facilitating cell migration (447, 522, 523)

In vitro studies on the effect of chronic wound fluid (CWF) on fibroblasts by Phillips et al (1998) show that fibroblast proliferation is reduced in response to CWF exposure (524). Chronic venous leg ulcers were shown to have a 10 fold or higher percentage of senescent fibroblasts when compared to tissue biopsies of normal tissue from the same patient, with the proportion of senescent cells associated with delayed healing (525). Liang et al (2016) in other invitro studies compared fibroblasts collected from DFU to non-diabetic fibroblasts and found DFU harvested fibroblasts to exhibit inhibition of cell movement and proliferation and more senescence compared to normal fibroblasts (414). It has been proposed that debridement, by removing senescent cells at the base and edge of the wound, re-starts the normal cascade of healing with cells that are more responsive to endogenous growth factors and advanced healing agents (484, 515, 523). There is some indirect evidence of this, with interventional studies of advanced healing modalities showing greater efficacy achieved when sharp debridement is more frequent (398, 441, 470, 526).

Debridement of the wound edge, specifically addresses migration of epithelial cells, a process necessary for secondary intention wound healing which is hindered by the presence of dysfunctional keratinocytes at the edge (527).

Excisional or surgical sharp debridement involves removal of non-viable tissue include removing a margin of surrounding tissue. With this technique, the original wound margins change and it is plausible to consider a resultant change in wound phenotype from chronic to acute. In our service, a DFU which has been undergone extensive surgical debridement may be re-classified as post-surgical. Sharp debridement which does not fully excise the original wound is less likely to induce more subtle changes. Evidence is needed to understand the changes in cell function and healing outcomes that may result from standard, sharp debridement as performed by podiatrists.

Removal of callus from the periphery

The presence of callus is a characteristic, pathognomoic of neuropathic and neuroischaemic DFU and the presence of callus is predictive of foot ulceration, being associated with the presence of high plantar pressure (244, 528). Hence it is sensible to assume that the removal of callus and dysfunctional keratinocytes from the wound edge would have the benefit of pressure reduction and support healing.

In 1992 Young et al published their findings that barefoot peak pressures at the site of calluses, 43 sites in 17 patients with diabetes, reduced by an average 26% following sharp debridement, with most (37/43) sites demonstrating a reduction (529). Pitei et al (1999) undertook before and after in-shoe plantar pressure measurements in 24 participants presenting for treatment of plantar callus, having a history of DFU and infrequent callus debridement and having previous DFU and frequent callus debridement (530). Those with no DFU history were younger, had lower HbA1C%, lower vibratory perception threshold and shorter duration of diabetes. Debridement of callus resulted in a significant reduction in peak pressure across all groups; 32%, 30.9% and 24.8% respectively (530). Slater et al (2006) was the most recent to measure before and after peak pressure with sharp debridement (531). This study combined debridement with digital orthoses in the treatment of 14 participants with digital callus associated with clawed toes, 13 of whom had diabetes. This showed a similar reduction in peak plantar pressure of 29% following removal (531).

Interestingly, barefoot peak plantar pressures, are not consistently shown to reduce following callus debridement in people without diabetes. In a study of fifteen healthy participants. Potter and Potter (2000), in their study, found only 20% of debrided areas showed a reduction of 25% with no overall significant pre and post debridement difference (532). This is despite the demonstrated increased peak plantar pressure in the subjects with callus. These data suggest that callus in people with diabetes, increases peak plantar pressure in a way that it does affect people without diabetes. Perhaps the glycosylation of collagen, sympathetic denervation and reduced sweating contribute to stiffness and hardening of skin callus compounding the increase in plantar pressure in people with diabetes and neuropathy. Skin hardness and sole stiffness have been found to be associated with the presence of Diabetes and neuropathy (533, 534).

The use of non-surgical sharp debridement, is mainstay of care, recommended in guidelines and is a core skill of Australian podiatrists. Anecdotally, it is the form of debridement most often used in the care of people with DFU. There is however a lack of data on the practice of non-surgical sharp debridement.

1.4 Aims and Hypotheses

The research in this thesis aims to address the deficit in evidence for non-surgical sharp debridement in the management of DFU by undertaking a randomised controlled study using two different frequencies of SWD. The design follows principles of translational research with intention to treat analysis.

By conducting the study within interdisciplinary High Risk Foot Services, recruiting patients who are representative of the patient cohort for whom the treatment is intended, the study is a translation of current evidence regarding sharp debridement, into practice.

To provide context for the research findings of the main randomised study , two original observational studies were also undertaken. They report; a survey of current practice and a survey of patient perceptions of debridement and visit frequency.

Study one

Aims to determine the current local practice, amongst clinicians engaged in the management of people with DFU, with regards to sharp debridement. Specially, the study aims to determine how often they debride and what factors they use to decide this.

The hypotheses are:

1. Standard care for diabetes-related foot ulcers provided by NSW Health Podiatrists, is sharp wound debridement at every consultation for all patients with non-ischemic wounds
2. Debridement frequency is dependent on clinical judgement, workforce capacity and patient's ability to access the service

Study two

The aim of the study is to determine the effect of sharp wound debridement performed at weekly versus second weekly intervals, on the healing of diabetes-related foot ulcers Percentage of diabetes-related foot ulcers (DRFU) healed by 12 weeks.

The hypothesis: That DFU debrided weekly will show a clinically significant 30% improvement in the rate of ulcers healed by week 12 weeks with a sample size of 120 participants with a sample size of at least 85% power with 95% confidence to detect such an improvement allowing for a 20% attrition rate. Healing is defined by complete wound closure without exudate and is documented at the first treatment visit where this occurs. The primary endpoint is the proportion of DFU healed at Week 12 as determined by assessment of outcome by assessors blinded to treatment allocation and the secondary outcome is the percent wound reduction from baseline at week 4 and 12 using a calculation of the wound size as determined by wound outlines recorded on clear acetate and placed over a grid of known size.

Study three

The aims of the study were to:

a) investigate the actual and the preferred frequency of attendance for treatment, including sharp debridement, for patients with DFU

b) understand what patients with DFU value about their clinic attendance at the HRFS

c) determine the extent to which patient-reported mobility may affect attendance

d) document the mode of transport used, duration of time spent on their clinic visit, and any out-of-pocket costs related to attendance.

Hypothesis: That patient preference is for less frequent treatment visits to the High Risk Foot Service however the nature of this study is explorative. The aspects of patient experience of interest are:

1. How far people travel to attend the High Risk Foot Service
2. The costs of attendance, including travel costs, lost time from work etc

3. The level of physical challenge in attending
4. Patients' report of factors which influence their frequency of attendance
5. The aspects of treatment or reasons for attendance that patients report as important to them
6. Preference for treatment visit frequency

Chapter 2: Frequency of Sharp Wound Debridement in the Management of Diabetes-Related Foot Ulcers: an exploration of current practice

This study was undertaken to establish the current practice with regards to conservative sharp wound debridement of DFU within the State of New South Wales (NSW). This is the state in which the author works as a clinician manager. In establishing current practice, the author sought to define the baseline of standard care and clinicians' rationale for this. At the time, the randomised study was planned but the results were not known. Two debridement frequencies were chosen based on local data at the lead site.

Engaging the NSW Health employed podiatrists in this research through asking them to reflect and report on their clinical practice through the survey, aligns with the principles of enabling translation of research into clinical practice. The data from this study has the potential to inform practice change when considered in the context of evidence for specific debridement frequency.

Ethics approval was granted by the Sydney Local Health District Human Research and Ethics Committee, Concord Repatriation and General Hospital (LNR/17/CRGH/112) and the study has been published in the Journal of Foot and Ankle Research and is included here as the published manuscript.

Nube, V. L., Alison, J. A., & Twigg, S. M. (2021). Frequency of sharp wound debridement in the management of diabetes-related foot ulcers: exploring current practice. Journal of Foot and Ankle Research, 14(1), 52–52.

The candidate was responsible for the study concept, developed the survey and protocol, obtained ethics approval, collected, analysed, and interpreted the data and wrote the manuscript, created the figures and tables and was the corresponding author.

Nube et al. Journal of Foot and Ankle Research (2021) 14:52
https://doi.org/10.1186/s13047-021-00489-1

Journal of Foot and Ankle Research

RESEARCH Open Access

Frequency of sharp wound debridement in the management of diabetes-related foot ulcers: exploring current practice

Vanessa L Nube[1,2*], Jennifer A Alison[3,4] and Stephen M Twigg[2,5]

Abstract

Background: Conservative sharp wound debridement (CSWD) is fundamental to wound bed preparation. Evidence-based practice guidelines strongly recommend frequent CSWD of diabetes-related foot ulcers (DFU) based on expert opinion and observational studies which suggest that more frequent debridement is associated with better healing outcomes.

Aim: To document current practice with regards to CSWD of DFU and whether this is performed at every visit, how often and what factors determine debridement frequency.

Method: Survey data were collected and managed using REDCap electronic data tools, a secure, web-based application. The survey was distributed through podiatry managers and relevant clinical networks between October 2017 and February 2018.

Results: One hundred clinicians opened the survey and seventy-five surveys were completed by $n = 53$ NSW Health (Australia) employed podiatrists (representing 41% of all NSW Health podiatrists), 11 privately practicing podiatrists, and 11 nurses. Most ($n = 47$) worked in metropolitan areas versus regional/remote ($n = 28$). CSWD was the most frequently used debridement method, performed at every visit by most (84%) of podiatrists. Callus, slough and infection presence were the top 3 most important determinants of frequency, with staff time (a limiting factor) ranking 4th. Regional/remote podiatrists practiced less frequent debridement compared with those in metropolitan areas (debridement every 2 weeks or less = 71% regional podiatrists versus 45% metropolitan podiatrists) ($p = 0.024$).

Conclusion and clinical implications: CSWD was the predominant form of debridement used with debridement occurring at every treatment visit for most of the clinicians surveyed. Debridement frequency was determined by clinical wound indications and staffing resources, with regional/remote podiatrists providing debridement less often than their metropolitan colleagues.

Introduction

Diabetes-related foot ulcers (DFU) are a highly prevalent, chronic wound type which place considerable burden on the healthcare system, the patient, and often their family. Prompt access to interdisciplinary management is critical to address the aetiological factors and to promote healing. Debridement of the wound to prepare the wound bed for endogenous healing is a fundamental component of care and several potential methods of debridement are described including surgical and non-surgical modalities [1, 2].

* Correspondence: vanessa.nube@health.nsw.gov.au
[1]Department of Podiatry, Royal Prince Alfred Hospital, Sydney, Missenden Rd, Camperdown, NSW 2050, Australia
[2]Faculty of Medicine and Health, Sydney Medical School (Central), The University of Sydney, Camperdown, Australia
Full list of author information is available at the end of the article

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Current evidence for sharp debridement is based on observational studies using retrospective analyses [3–5] and is rated as weak, due to a lack of prospective studies of the efficacy of debridement [2]. Notwithstanding the lack of prospective randomised studies, conservative sharp wound debridement is a mainstay of treatment provided by podiatrists and some nurses with specialised training within the Australian Health Care System. Sharp debridement of DFU is cited in leading management guidelines from European and Canadian and US organisations and the International Working Group on the Diabetic Foot as standard care [2, 6–9] . It is performed using a scalpel, forceps and curette to achieve rapid and concise removal of non-viable tissue and senescent cells from the base and edge of the wound to facilitate healing. While the evidence is unclear about the extent to which bacterial load is reduced with debridement [10], the current consensus is that serial debridement has a key role in managing infected wounds and biofilm which is associated with most chronic wounds [11, 12]. Hyperkeratosis, a particular feature of diabetes-related foot ulcers associated with loss of sensation and chronic repetitive trauma is also managed with sharp debridement. The removal of hyperkeratosis is associated with a reduction in plantar pressure [13, 14] which is likely to support healing.

Retrospective studies suggest a positive, dose-dependent relationship between the extent and frequency of debridement. Performed serially when there is adequate blood flow for healing, several studies have shown as association between more frequent sharp debridement and improved healing outcomes. This has provided incentive, if not direct evidence, for thorough and frequent, sharp debridement of DFU [3–5, 15].

The model of care for providing treatment of DFU involves clinic visits to assess and manage the wound and factors associated with healing such as offloading, management of infection, diabetes and education of the patient. The provision of CSWD is likely to be strong determinant of visit frequency, for which there is no direct substitute. More frequent treatment visits for the purpose of CSWD places more demand on the clinical workforce which would need to considered in the context of a small and finite workforce. Current clinical practice regarding debridement frequency and factors that influence clinical decision making concerning debridement are not known.

The aim of this survey was to document current debridement practice in the management of diabetes-related foot ulcers by podiatrists, and factors associated with debridement frequency. The objectives of the survey were to determine debridement type and frequency, specifically: whether CSWD is the most frequently used method of debridement; how often DFU are debrided; whether DFU are debrided at every clinic visit; whether there are differences in debridement frequency between the regional and metropolitan areas what factors influence clinicians' decisions with regards to how often ulcers are debrided. These data were collected while a randomised study of debridement frequency (Clinical trial registration: ACTRN12618000703202) was being undertaken by the authors. The findings of the survey were planned to inform implementation strategies for translation of evidence from the randomised trial into practice.

Method

The survey was quantitative, cross-sectional and respondents were recruited through relevant networks via an email invitation which provided a link to the online survey. The online survey was developed de novo by the first author (VN). The prototype survey was provided to 10 podiatrists including the site investigators of the aforementioned randomised debridement study who manage DFU from both metropolitan and regional areas, and a podiatry academic. Feedback as to what aspects of the prototype survey could be modified to minimise ambiguity was provided. Respondents indicated which questions should be modified in order to enable a refined survey to adequately address the study aims and this was incorporated into the final version (Additional file 1: Survey Questions). In addition to closed questions and discrete data, survey participants were asked to "Please make any additional comments here regarding the factors that influence your debridement frequency, the enablers or barriers".

The online survey was developed using REDCap, an electronic data tools and secure, web-based application hosted at the Sydney Local Health District. Survey data were subsequently managed using REDCap [16] An invitation to participate including a URL to the final version of the online survey was distributed between October 2017 and February 2018.

To target New South Wales (NSW) Health podiatrists, the survey invitation was distributed to Podiatry Managers and to individual podiatrists known to be engaged in the care of people with diabetes-related foot complications within High Risk Foot Services via the state-based Community of Practice. Members of the Community of Practice are clinicians with an interest in management of patients with diabetes-related foot complications. While the membership is not exclusively podiatrists, they are the main discipline represented. So as not to exclude private practitioners or nurses involved in debridement, the survey was also distributed to 30 NSW private practice attendees at a Diabetes Foot Education session, and wound care nurses within the lead site were also provided a link which they could disseminate to their peers.

The invitation advised potential participants that they were invited to participate on the basis that they were involved in the management of diabetes-related foot ulcers, that the project was funded by the Ministry of Health to help improve understanding about current debridement practice and that it could be completed anonymously and take approximately 10 min to complete. An email address was provided for additional information.

No identifying information, name practice or institutional details were required for the survey. A URL was provided at the end of the survey in which participants were invited to provide their contact information. This URL was not linked to the survey responses and was to aid the researchers in knowing who had responded. Twenty three participants submitted their details using this URL.

Data were included for analysis if participants responded 'yes' to managing non-ischaemic DFU with conservative sharp wound debridement and if they provided responses to the following: number of DFU treated on average each week; how often they debrided individual foot ulcers; whether they debrided at every treatment visit; whether they were located (rural, regional or metropolitan); and their clinical discipline.

Participants were also provided the option to obtain and use a simple audit tool to record information relating the ulcers treated, the frequency of debridement, and healing presence at 12 weeks. Consent to participate in the audit relied on an additional layer of approval from their site Governance and Research office. The protocol, audit tool, questionnaire and participant information sheets were approved by the Sydney Local Health District Human Research and Ethics Committee – Concord Repatriation and General Hospital (LNR 17CRGH112 CH 62/6/2017–076). The information sheet available from the survey link advised that consent to use the respondents' survey data was enacted when the participant proceeded to complete the survey.

Results

One hundred participants opened the survey link, seventy five met the inclusion criteria, and 70 completed all questions. Characteristics of the participants are detailed in Table 1.

Table 1 Characteristics of participants who opened and those whose responses were included in the analysis

	All participants (who opened survey) *n* = 100	**Participants included in analyses** *n* = 75
Location of service		
Metropolitan	58 (64.4%)	47 (62.7%)
Rural	24 (26.7%)	22 (29.3%)
Remote	8 (8.9%) N = 10 missing data	6 (8%)
Health sector		
Public – Community Health	16 (18%)	11 (14.7%)
Public – Hospital	61 (68.5%)	52 (69.3%)
Private	12 (31.5%)	11 (14.7%)
Other	N = 1 missing data	N = 1 missing data
Discipline		
Podiatrist	66 (77.6%)	64 (85.3%)
Nurse	19 (22%) *N* = 15 missing data	11 (14.7%)
Years of podiatry experience		
Mean	13.3	13.3
Median	13	13
Range * Podiatrists only	1–45 years	1–45 years
Number of clients treated with DFU each week		
< 1 per week	17 (20%)	13 (17.3%)
1–4 per week	15 (17.6%)	12(16%)
> 4 and < 10 per week	17 (20%)	15 (20%)
10 or more per week	36 (42.4%) N = 15 missing data	35 (46.7%)

Most of the respondents were podiatrists, the majority (83%) of whom were employed by NSW Health. The number of NSW Health employed podiatrists who completed the survey ($n = 53/129$) represented 41% of the NSW Health podiatry workforce according to 2018 data provided by the NSW Department of Health, Workforce Branch. For podiatrists employed in the public sector, half reported that more than 60% of their caseload was the management of DFU and 28% reported DFU management was 90% or more of their caseload. Podiatrists employed in the private sector and nurses treated proportionally fewer people with DFU (Table 2).

All respondents performed CSWD in their management of DFU with CSWD being the predominant method of debridement used. Most (73%) reported using other forms of debridement infrequently. The exception was hydrogels which were used at least occasionally by most respondents (Table 3).

Frequency of conservative sharp wound debridement

Most respondents performed CSWD at weekly (29%) or fortnightly intervals (39%) with a small number of respondents (7%) debriding their patients' DFU more frequently than this or at longer intervals of up to 5 weeks (16%) (Fig. 1).

Debridement at every treatment visit

Most respondents (79%) performed CSWD in the treatment of DFU at every visit if the patient had adequate blood flow. Of the podiatry respondents, 84% performed CSWD at every visit and of the NSW Health employed podiatrists, 92% debrided at every visit. NSW Health employed podiatrists who reported not debriding at every visit ($n = 4$), debrided their patients' ulcers fortnightly ($n = 2$), weekly ($n = 1$) and one debrided more frequently than once a week. Nurses were less likely to debride at every visit.

Differences between rural/regional and metropolitan clinicians

Regional/remote clinicians were more likely to debride their patients' ulcer less often with 71% reporting performing CSWD of their patient's DRFU every 2 weeks or less often compared with 45% of metropolitan clinicians $z = 2.25$, $p = 0.024$. Using data for NSW Health employed podiatrists; regional/remote practicing podiatrists practice less frequent debridement with 68% reporting performing SWD of their patients every 2 weeks or less often compared to 35% of metropolitan podiatrists $z = 2.35$, $p = 0.019$.

Factors that determined frequency of conservative sharp wound debridement

In reporting the relative importance of different factors to consider when determining debridement frequency, callus was rated as very important by most respondents (97%) followed by slough (76%), infection (59%), lack of clinical staff time (51%), patient non-adherence to attendance (44%), transport access (33%), consultation fee (23%), and transport/parking costs (20%).

Respondents were also asked to rank (in order of importance), the factors they considered in determining debridement frequency. Potential indications of callus and slough were combined for this question. The presence of callus and slough, infection, and clinical staff time/resources were more frequently ranked in the top three considerations for determining debridement frequency of non-ischaemic DFU (< 10% missing data) (Fig. 2).

Discussion

Based on NSW Health reported numbers, the respondents represent 41% of NSW Health employed podiatrists, which for a survey process is a high percentage. This high response rate indicates that the survey sample is likely to be representative of the public podiatry workforce in NSW. The number of private podiatry and nurse respondents was low and less likely to be representative of these groups however they were not the main target populations for this study. Notably, NSW Health employed podiatrists represent a small proportion (11%) of the registered podiatrists in NSW and are more likely to be engaged in the care of DFU than their private practice colleagues [17].

Previous surveys have explored clinician practice and have reported on wound debridement. In their online survey of Australian podiatrists designed to determine adherence to evidence-based practice guidelines for managing DFU, Quinton (2015) asked respondents if they performed sharp debridement on non-ischaemic

Table 2 Number of diabetes-related foot ulcers treated per week (on Average)

Weekly patient number treated (average)	Public Sector Podiatrists ($n = 53$)	Private Sector Podiatrists ($n = 11$) 10% missing data	Nurses ($n = 11$)
Less than 1	3	7	3
Between 1 and 4	6	2	5
From 5 to 10	12	1	2
More than 10 patients	32	1	2

Table 3 Use of other (non-sharp) methods of wound debridement

	Never		Occasionally		Sometimes		Often		Always	
	Podiatrists NSW Public sector	All	Podiatrists NSW Public sector	All	Podiatrists NSW Public sector	All	Podiatrists NSW Public sector	All	Podiatrists NSW Public sector	All
Hydrogel	3	5	30	36	13	18	3	8	1	2
LFUD	44	60	2	3	4	6	4			
Versajet	49	68	1	1						
Larvae	48	62	2	6				1		

Missing Data Podiatrists NSW = 3
Missing Data Overall = 7
LFUD = Low frequency ultrasonic debridement
Versajet = Hydrosurgical debridement therapy

wounds. The median response from public sector employed podiatrists nationally was "always" and their private practice colleagues reported debriding "very often". The respondents ($n = 310$) included 48 NSW podiatrists (18 public: 30 private). An international survey of clinicians engaged in management of chronic wounds, reported by Swanson (2017) found that 57% of clinicians frequently used sharp debridement, and 46% of Australian clinicians frequently used sharp debridement in the management of biofilm [18]. The respondents ($n = 2614$) represented a broad cross section of clinicians; while not reported, the proportion of podiatrists as a small profession, would be expected to be low.

The results of this study indicate that conservative sharp wound debridement is a mainstay of treatment and the predominant modality used to remove non-viable tissue in the management of DFU. Other modalities were rarely used, with the exception of hydrogel which was used at least occasionally. Due to the frequent debridement performed, it is likely that hydrogels are used as an adjunct to sharp debridement and/or to restore moisture to a dry wound.

CSWD is currently provided at every treatment visit to a NSW Health employed podiatrist for a patient with diabetes-related foot ulceration. While treatment visits are most commonly every 1 or 2 weeks, clinical indications are used to determine frequency, together with consideration of the available clinic resources to provide care. In the case of rural and regional areas, patients are more likely to receive the treatment less often and this is likely to be a consequence of staff resources and potentially distance from the patients' homes to the clinic. The latter has not been explored directly with patients but relatively few of our respondents rated transport issues as very important in this survey.

Conclusions

Podiatrists employed within the public health system are providing conservative sharp wound debridement to all patients with non-ischaemic diabetes-related foot ulcers

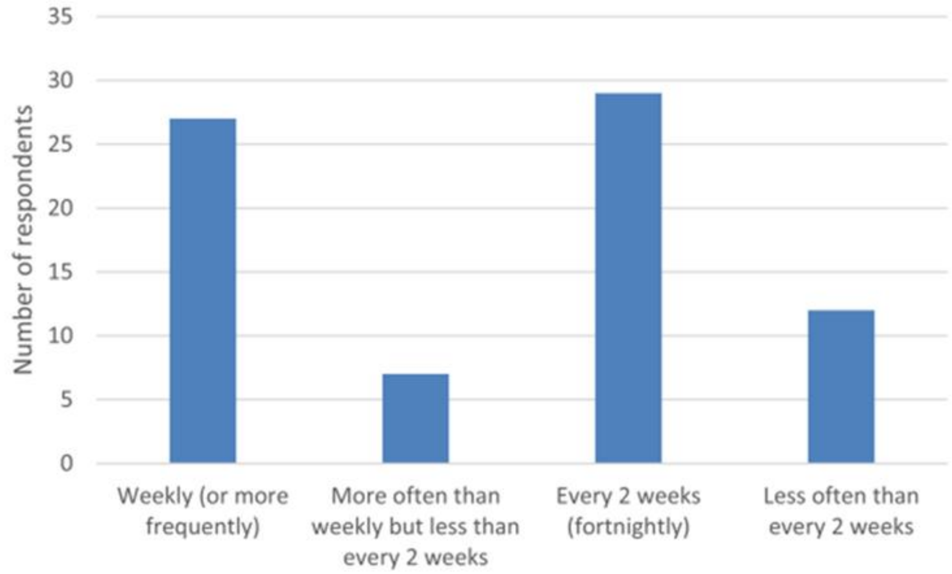

Fig. 1 The average frequency of conservative sharp wound debridement of diabetes-related foot ulcers as reported by clinicians

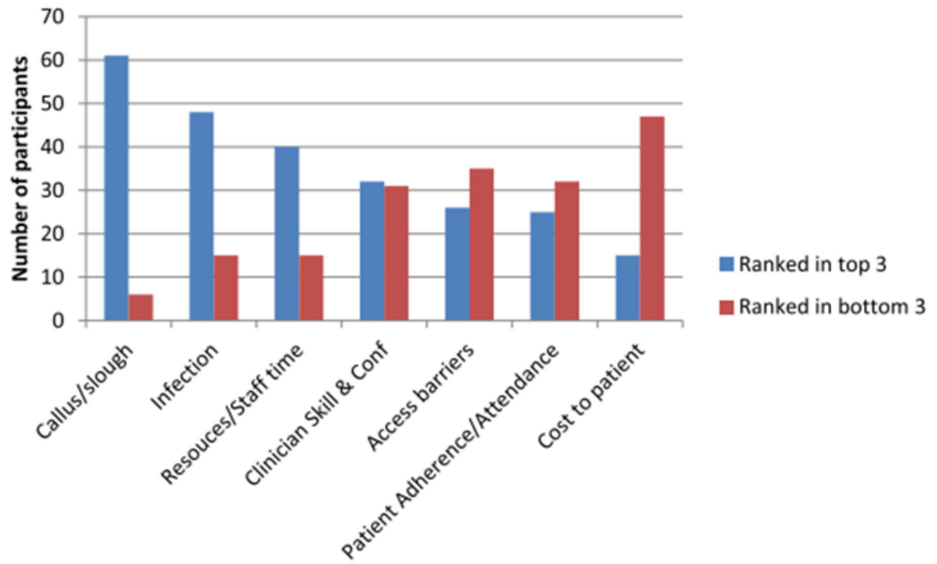

Fig. 2 Respondent ranking of importance of the variables influencing debridement frequency. The top 3 rankings and bottom 3 rankings combined for each variable and data ordered from those ranked as most important (blue) to least important (red)

as the predominant modality to remove non-viable tissue to promote healing. The frequency of debridement is virtually synonymous with treatment visit frequency as wounds were debrided at every visit, with frequency determined by clinical indicators but limited in some cases by available resources.

Patients receiving care in rural and regional settings were also provided with this treatment however they were most likely to receive debridement every 2 weeks or less often when compared to those attending metropolitan based services who were more likely to receive weekly debridement. While this data is informative as to current practice, whether such debridement frequency of weekly vs less often impacts ulcer healing in people with diabetes, will require a prospective, randomised trial to address this key clinical question.

Abbreviations

CSWD: Conservative sharp wound debridement; DFU: Diabetes-related foot ulcer; NSW: New South Wales

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13047-021-00489-1.

Additional file 1.

Acknowledgements

The authors thank Vivienne Chuter, Sarah Manewell, Diane Brooks, Cindy Meller, Georgina Frank, Jessica White, Julie Zwarteveen and Kate Carroll each for reviewing and testing the survey.
These people have provided email consent to be named in acknowledgements.

Authors' contributions

Vanessa Nube designed the survey and protocol, obtained ethics approval, collected, analysed and interpreted the data and wrote the manuscript. Jennifer Alison provided input into the design of the survey and protocol and also read and contributed to the writing of the manuscript and approved the final version. Stephen Twigg provided input into the design of the survey and protocol and also read and contributed to the writing of the manuscript and approved the final version. The author(s) read and approved the final manuscript.

Authors' information

Vanessa Nube is the Director of Podiatry at the Sydney Local Health District and practices as a clinical podiatrist with an interest in management of diabetes-related foot complications with over 20 years experience caring for people with DFU, predominantly within the Royal Prince Alfred Hospital Diabetes Centre, High Risk Foot Service. Previous publications in the field, including original research conducted as part of a Masters of Science in Medicine and this current work has also been undertaken as part of her current PhD candidature. Vanessa has been involved in the development of standards of care for people with diabetes-related foot complications within the NSW Agency for Clinical Innovation and National Association of Diabetes Centres.

Funding

At this time this survey was conducted, the author had received a NSW Ministry of Health Translational Research Grant to conduct a study of debridement frequency and this survey was part of the overall project but was not directly funded by the grant.

Availability of data and materials

Please contact author for data requests.
We did not request data sharing in our original ethics application however if required, we can seek approval for the dataset to be made available on reasonable request to the author.

Declarations

Ethics and consent to participants

This project has been approved by the Concord Hospital Human Research and Ethics Committee. CH62/6/2017 LNR/17/CRGH/112.

Consent for publication

No individual persons' data is included.

Competing interests

None of the authors have any competing interests to declare.

Author details
[1]Department of Podiatry, Royal Prince Alfred Hospital, Sydney, Missenden Rd, Camperdown, NSW 2050, Australia. [2]Faculty of Medicine and Health, Sydney Medical School (Central), The University of Sydney, Camperdown, Australia. [3]Faculty of Medicine and Health, Sydney School of Health Sciences, The University of Sydney, Camperdown, Australia. [4]Allied Health, Sydney Local Health District, Camperdown, Australia. [5]Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Camperdown, Australia.

Received: 9 May 2021 Accepted: 25 July 2021
Published online: 12 August 2021

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Chapter 3: A randomised controlled study of sharp debridement by Podiatrists in the Management of Diabetes-Related Foot Ulcers.

Both second weekly and weekly debridement frequencies are commonly practiced with contemporary interventional studies of DFU describing weekly debridement as standard care. Evidence-based practice guidelines recommend regular sharp debridement over other modalities in the management of DFU however there is a lack of interventional studies to determine optimal frequency. This study was designed to compare the effect of non-surgical sharp debridement performed weekly to every second week.

This study was approved by the Sydney Local Health District Human Research and Ethics Committee, Royal Prince Alfred Hospital (X14-018 & HREAC/14/RPAH/242) with site Governance approval at all participating hospitals.

Two publications relating to this study, and an extended discussion of the methods are included in this chapter.

1. Nube, V. L., White, J. M., Brewer, K., Veldhoen, D., Meler, C., Frank, G., Carroll, K., Featherston, J., Batchelor, J., Gebski, V., Alison, J. A., & Twigg, S. M. (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*(12), e203–e205. https://doi.org/10.2337/dc21-1454

The candidate was involved in the study concept and design of the randomised study, developed the final protocol, obtained ethics approval for amendments, wrote the funding application, collected data, oversaw the conduct of the study and investigator meetings, participated in the development of and agreed to the final statistical analysis plan, collected data, prepared the data for analysis by the NHMRC Clinical Trials Centre.

Supervisor, Stephen Twigg was the corresponding author on the *Diabetes Care* publication.

2. Nube, V. L., Alison, J. A., & Twigg, S. M. (2023). Diabetic foot ulcers: weekly versus second-weekly conservative sharp wound debridement. *Journal of Wound Care*, *32*(6), 383–390. https://doi.org/10.12968/jowc.2023.32.6.383

For the Commentary in the *Journal of Wound Care,* a completers (per protocol) analyses was undertaken with ethics approval. The candidate analysed and interpreted the data and wrote the manuscript, created the figures and tables.

The candidate was the corresponding author on *the Journal of Wound Care* publication.

Introduction and background

Diabetes-related foot ulcers (DFU), are a serious and prevalent complication of diabetes, most often experienced by people with a long duration of diabetes, poor glycaemic control, and peripheral neuropathy (135, 168, 535). To promote healing, avoid unnecessary hospitalisation and prevent amputation, regular and intensive treatment is needed to address aetiology and prepare the wound bed for healing. Care is optimally delivered in the clinic setting by a multidisciplinary team with a key component of treatment being podiatry intervention including sharp debridement (456, 536-538).

Sharp wound debridement for the purpose of this study is defined as the use of scalpel and forceps to achieve rapid and concise removal of non-viable tissue from the base and callus from the periphery of the wound using and is considered standard care in the management of DFU Sharp debridement facilitates wound drainage and inspection and reduces the medium for bacteria to proliferate (380, 381, 490, 539, 540). It disrupts biofilm, transforming bacteria to the planktonic phenotype, temporarily more susceptible to topical and systemic antimicrobial therapy (390, 511) This potentially reduces the deleterious effect of bacteria on delayed wound healing otherwise occurring through perpetuation of pro-inflammatory metalloproteinases and chronic inflammation within the wound(417, 541). In addition, the removal of senescent cells and callus which is typically present at the wound margin in DFU, promotes cell migration for secondary intention healing and reduces local plantar pressure (529, 542).

There is however no published prospective, interventional study confirming the effect of non-surgical sharp debridement or optimal time between treatments on DFU healing (381, 459, 461, 463, 467, 543). Current Australian and international guidelines for DFU management, recommend regular non-sharp debridement of DFU over other methods for ulcers where there is adequate blood flow for healing (380, 381, 383, 386). These recommendations are based on data from retrospective post-hoc analyses of studies and audits reporting a positive association between more frequent (or extensive) sharp debridement and better healing outcomes suggesting a debridement dose-dependent relationship (398, 441, 470-472). Considering the potential differences in healing outcomes related to frequency of debridement, it is important to investigate debridement frequency in a prospective study.

A paucity of evidence to guide debridement practice is likely to contribute to unwanted variation is clinical approach, outcomes, and patient experience. Given its integral role in treatment, debridement frequency may determine how often patients need to present to a clinic for treatment. This has significant implications for patients, their families and for healthcare providers in terms of cost and workforce requirements.

The current study was designed to test the hypothesis that weekly sharp wound debridement of DFU promotes improved healing rates compared with second weekly debridement, with the primary outcome being the proportion of DFU healed at 12 weeks.

Research Design and Methods

The study design was a randomised trial including patients recruited from multiple High Risk Foot Services in the state of New South Wales to support study generalisability and recruitment. The study protocol was registered on the Australian New Zealand Clinical Trials Registry https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367998 and approved by the ethics committee (X14-0184&HREC/14/RPAH/242) as the lead site with local site Governance approval at each participating centre.

Sample size

Local historical data from the lead site showed that 50% of DFU treated, healed by 12 weeks (median 10 days between treatments with sharp debridement). To show a clinically significant 30% improvement in the rate of ulcers healed by week 12 weeks, a sample size of 120 participants will have at least 85% power with 95% confidence to detect such an improvement allowing for a 20% attrition rate. The local data also revealed that DFU were debrided on average every 1.5 weeks and clinicians consulted, indicated the majority of patients were recommended to attend every week or every second week for debridement, with exception of palliative wounds which were likely to have less frequent care. It was on this basis that the two frequencies of debridement were chosen for comparison.

A pragmatic approach was taken to balance the need to control factors that would influence the healing outcome between sites and participants with the imperative that the results, if favorable, would be translatable into clinical practice. The design therefore involved an inclusive and representative patient cohort and participating sites were selected which were representative of the model of care. Treating teams were afforded some scope to make clinical decisions regarding treatment while agreeing to adhere to locally adapted, practical and evidence-based guidelines on assessment, treatment and documentation. All participating sites adhered to a State approved model of care for interdisciplinary High Risk Foot Services (544).

Participants

Adults with diabetes mellitus, a plantar neuropathic foot ulcer of at least 2 weeks duration and equal or greater than $0.5cm^2$ and up to $10cm^2$ in size, were considered eligible if there was adequate blood supply to safely perform sharp debridement (WIfI Ischaemia Grades = 0-1) (241). Ulcer exclusion criteria were any of the following: non-healing despite 6 months (or longer) duration of care at the treating centre, moderate or severe ischaemia (WIfI = ABI < 0.6, or Toe pressure < 40mmHg) (241), moderate or severe infection grades (IDSA/IWGDF Grades = 3-4) (128, 348), or non-plantar location. Neuropathy was assessed locally using 10 g 5.07 gauge S-W monofilament and vibration perception threshold (164, 353). Patients were excluded if they did not provide consent or were unable or unwilling to follow the study protocol. This included participants living geographically distant from the treatment centre who would not agree to weekly visits. Towards the end of the study, the exclusion criteria of non-plantar location were removed to facilitate recruitment and two non-plantar foot ulcers were subsequently randomised to the study.

All participants provided informed consent prior to computer generated and block randomisation to either weekly or second weekly debridement with stratification for treatment centre and DFU size being smaller than 3cm or $\geq 3cm^2$. The randomisation process was run by an independent, off-site, clinical trials centre.

Standardised care

Weekly treatment visits were scheduled on the same day of each week for participants in both groups to control for the potential impact of frequency of visits to the treatment centre on healing outcomes, which has shown to have a positive association(494). A +/- 3 days was accepted within the protocol to allow for sick days, competing commitments or reduced adherence to appointment attendance.

Standard care provided at the weekly visits for both groups included management according to a shared, practical, evidence-based treatment protocol used at the lead site. A HbA1c% and assessment of perfusion to grade for peripheral arterial disease was required of all participants. Infection was assessed and managed with systemic antibiotics as needed. Patients had access to Endocrinology consultation for diabetes management and foot and wound care including debridement and offloading provided by senior, registered podiatrists. Dressings were performed according to individualised treatment plans for each participant determined by the treating team with foam dressings predominantly used. While some autolytic debridement would be expected with this moist wound healing approach, products that cited debridement as their function, negative pressure wound therapy or other advanced healing products were not used.

The technique of sharp debridement involved the use of scalpel, forceps and/or curette to remove callus from the wound margin and necrotic tissue from the wound base. To assist in the standardisation of the debridement practice between clinicians and sites, before and after images of debridement were shared with participating sites. Debridement was performed at every (weekly) visit for the participants in the weekly debridement group and every second visit (fortnightly) in the second weekly debrided group.

Options for pressure offloading were limited to two different types of removable knee-high cast walker or an ankle-high healing sandal with rocker sole. Devices were fitted with either a custom moulded 10mm thick Plastizote^{TM} insole or a prefabricated cushioned insole of similar thickness and material type. Minimal additions of 3mm Poron^{TM} and compressed felt to reinforce the arch were allowed. In many cases, patients were issued with both a knee and ankle high devices. All participants were educated on the use and benefits of the devices and continuous wear was encouraged. Patient self-reported adherence to wearing the offloading devices was monitored by treating clinicians and recorded as the percentage of waking hours that the device was worn.

Reasons for study discontinuation were written in the study protocol to improve patient safety. These were either that: the wound had undergone a >50% increase in size; callus had completely covered the ulcer, there were signs indicative of underlying purulence or abscess; foot infection had deteriorated >grade 2 (IDSA/IWGDF) including whether clinically definite osteomyelitis was present; or participant appointment cancellation occurred with inability to reschedule their appointment within ± 3 days of the planned debridement schedule.

Outcome measures

Digital images were taken at baseline, 4 and 12 weeks or when the treating clinician deemed the ulcer had healed (whichever came first) and uploaded into the study database. These data were used to determine the primary outcome at 12 weeks. Healing was defined as complete epithelialisation of the wound with no exudate that would require dressing. The outcomes at 4 and 12 weeks were assessed by 2 independent assessors blinded to treatment allocation. Both assessors were experienced wound care nurses who had access to single images of the wound sites taken at 4 and 12 weeks (or healing if this occurred prior). Neither assessor was involved in providing treatment to the participants at the clinical service.

The pre-defined secondary outcome measure of percentage of wound area reduction (PWR) from baseline to weeks 4 and 12 was calculated as percent wound size reduction from the original size based on planimetry. The use of these surrogate endpoints was included as these represent sensitive time points, shown to be predictive of healing overall (545-548). Following debridement, the treating clinician performed wound tracings by using clear acetate. PWR data was calculated by a central research co-ordinator and assistant using the tracings from participants' medical records, as submitted by the local site investigators.

Participant study completion was when the clinical team determined that the ulcer had healed. Healing outcomes were recorded in the medical record and data entry forms by the treating clinicians and this outcome is reported as a site assessed outcome.

Data on hospital admissions, infections, reasons for any study withdrawal, and amputations, were recorded by the clinical team in the medical record as well as in the research data entry form.

Statistical analyses

A statistical analysis plan (SAP) was developed prior to any data unblinding and comparisons of the primary and secondary outcomes between the two debridement schedules for the debrided DFU were analysed according to the principle of intention to treat.

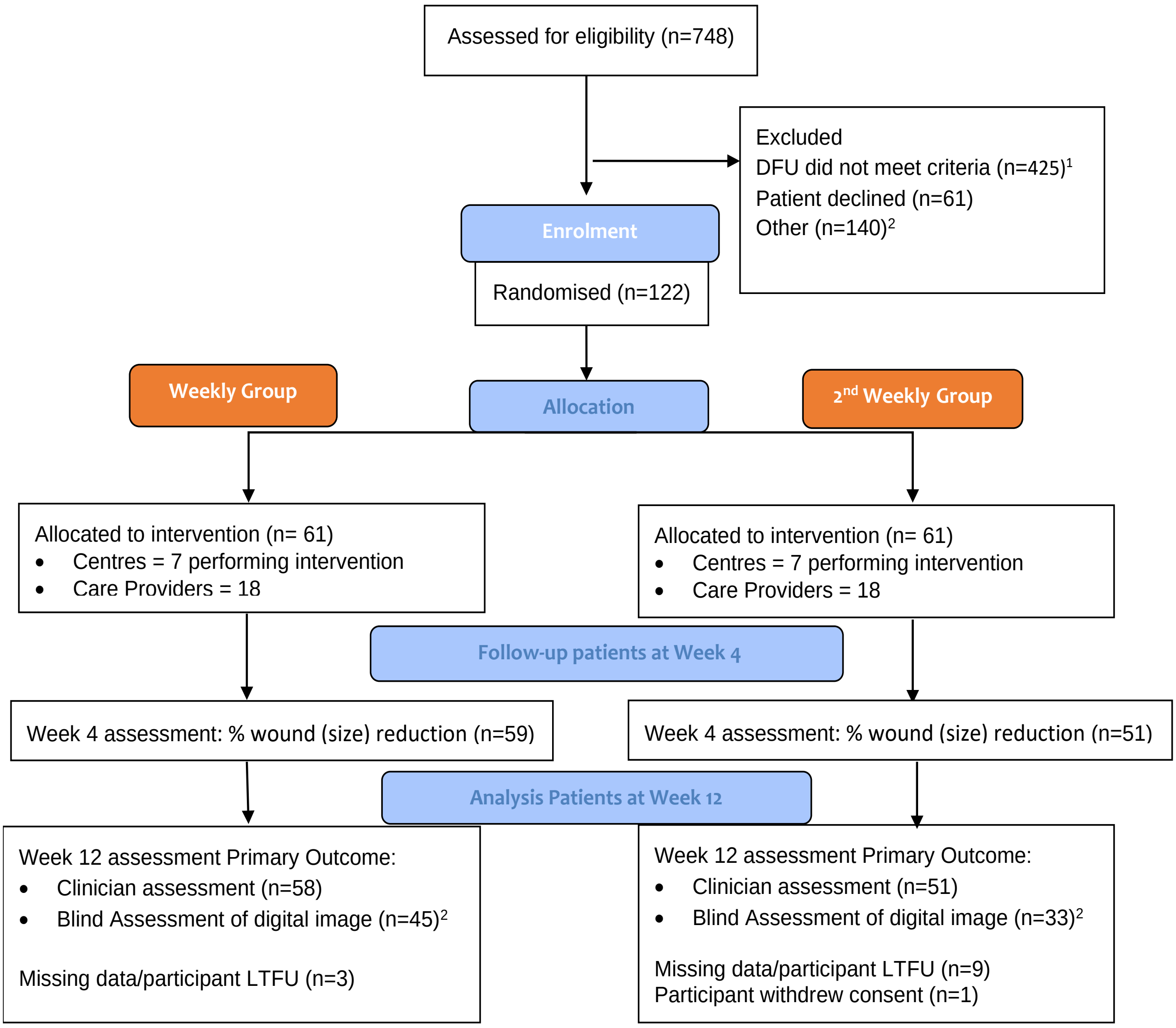
Summary statistics were used to describe the data and, if the data, after a test of normality were deemed not to be normally distributed, appropriate transformations were used (eg. log) to achieve a more symmetrical distribution.

All comparisons were two-sided using the Pearson Chi-squared test together with the corresponding 95% confidence intervals, and p-values of less than 0.05 were considered statistically significant.

Results

Patients attending the participating High Risk Foot Services with foot ulcers (n=748) were screened for inclusion in the study. A total of 122 participants (61 in each group) were recruited from 7 treatment centres between October 2015 and 2019, with the majority recruited from three sites which included two metropolitan and one regional hospital High Risk Foot Service, recruiting 35, 32 and 33 participants, respectively. Thirty participants (24.6%) discontinued for reasons given in the study protocol, related to deterioration in wound or infection or inability to attend visits. Thirteen participants who were site assessed as healed by week 12 did not have a week 12 photo available for blind assessment of the primary outcome and one patient withdrew consent.

Figure 4 Consort Flow Chart for the Randomised Trial of Sharp Debridement Frequency



Definitions: Diabetes-related foot ulcer (DFU), Lost to Follow-up (LTFU). Reasons for exclusion.
1. DFU too small, ischaemic, or non-plantar location. 2. Patient too old, lives out of area to the service and is attending for a once-off consultation, non-ambulant, no diabetes or receiving negative pressure wound therapy. 3. Participants whose digital images were available for assessment by wound expert blinded to treatment allocation.

Participant and wound baseline characteristics are shown in Table 4. The groups were well matched.

The primary outcome, based on an intention to treat analysis of the blind assessment of wound photos, showed no between group difference in the proportion of ulcers healed by 12 weeks, with 53% (n=24/47) healed in the weekly group and 52% (n=17/33) healed in the 2nd weekly group, mean difference 1.8 %(95% CI -16.3 to 20.0), p= 0.84). Figure 5.

Using site assessment of healing outcome by 12 weeks, the proportion healed was 52% (n=30/58) for weekly and 45% (n=23/51) for second weekly debrided wounds, mean difference 6.6% (95% CI -7.9 to 21.1% p=0.37). Figure 5.

The pre-defined secondary outcome of percent wound reduction at week 12 showed a non-significant 15% higher wound closure rate (65.6 versus 80.6) in the weekly debrided group (mean difference 15% (95% CI-11.6-41.7) p=0.27). Figure 6. Three participants in each group had a deterioration in infection, 3 in the weekly debrided group and 5 in the second weekly debrided group had a deterioration in wound size of > 50% and 2 participants in the weekly group were admitted to hospital for reasons unrelated to the study. No participant underwent an amputation during the study.

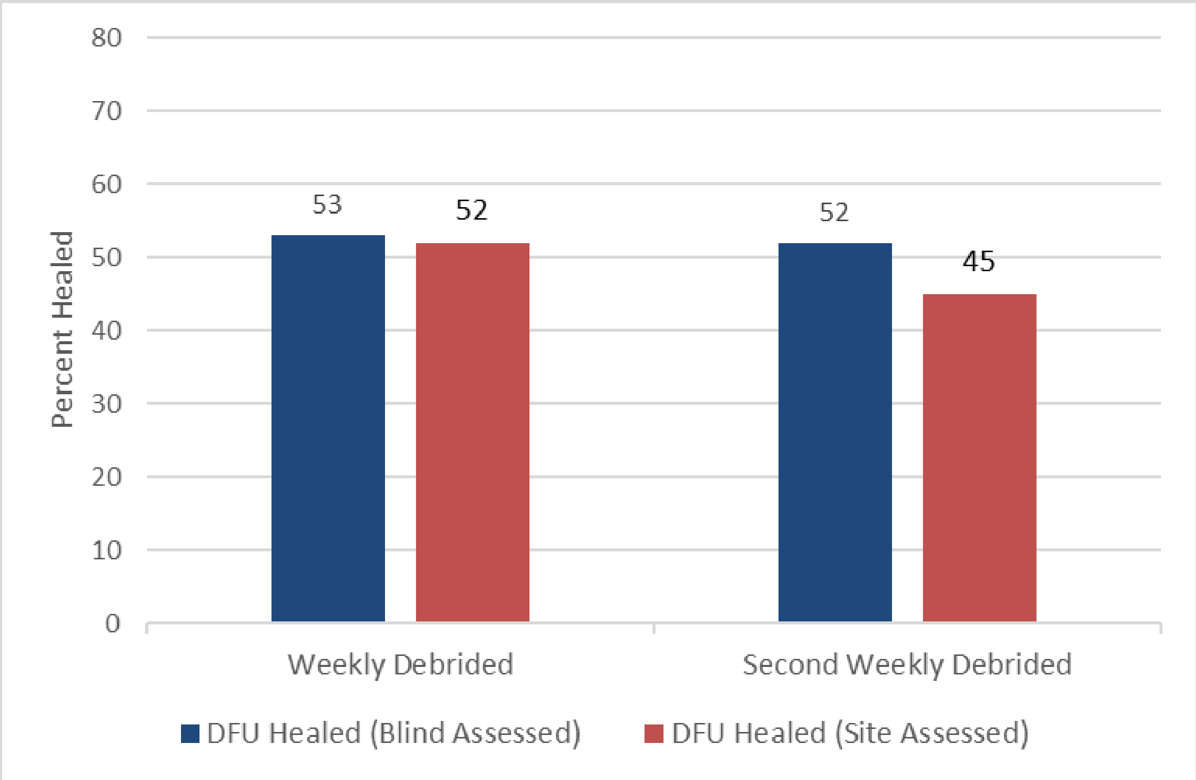
The number of participants whose primary offloading was a knee-high removable cast walker was 32/61 and 28/61 in the second weekly group. Overall, better adherence as determined by patient reporting of the average number of hours a day occurred with use of the ankle-high device. The number of participants who reported wearing their device more than 9 ½ hours a day on average was 26/61 in the weekly and 30/61 in the second weekly groups.

The impact of age, male gender, wound duration, and treatment group on outcome were explored. Only longer wound duration (>3 months) was associated with failure to heal at 12 weeks, p=0.01.

Table 4: Patient Demographics and Wound Characteristics

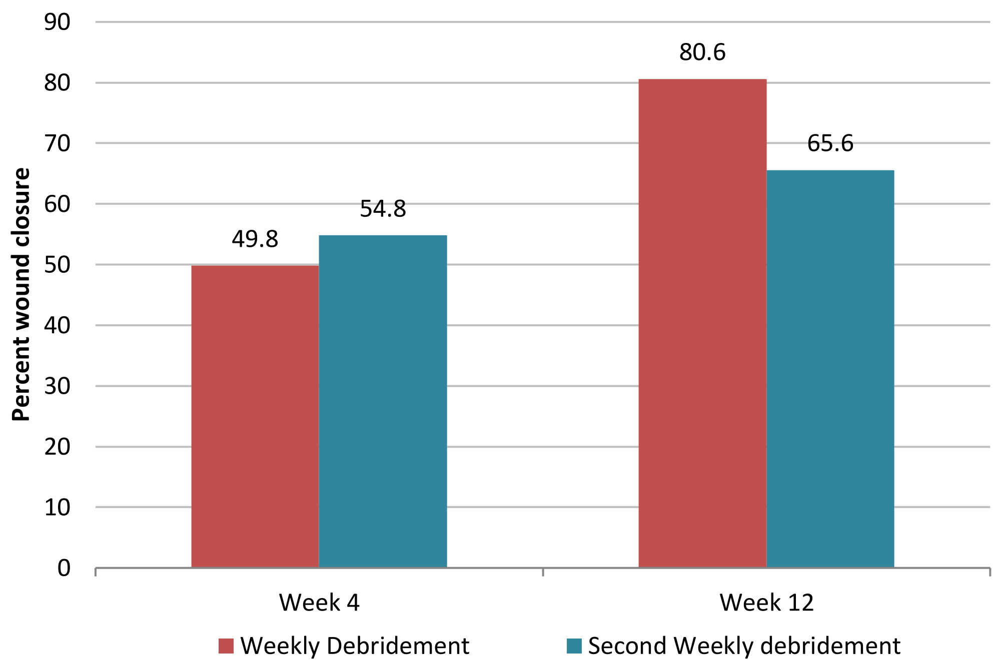
	Weekly	Second Weekly
Randomized patients	61	61
Age in years	59.4 (10.0)	60.1 (11.4)
Female (n)	12 (20%)	7 (11%)
Male (n)	49 (80%)	54 (89%)
Type 1 diabetes	1/61 (2%)	6/60 (10%)
Type 2 diabetes	60/61 (98%)	54/60 (90%)
Duration of diabetes in years	13.8 (8.8)	16.4 (10.4)
HbA1c% (NGSP Units) & SD Mmol/mol	8.1 (2.2) 65 (17.65)	8.9 (2.0) 74 (16.63)
Wound duration in months:		
<3 3-<6 6-<12 12+	41/55 (75%) 9/55 (16%) 2/55 (4%) 3/55 (5%)	37/57 (65%) 14/57 (25%) 5/57 (9%) 1/57 (2%)
Wound Size		
< $3cm^2$ > $3cm^2$	50/61 (82%) 11/61 (18%)	47/61 (77%) 14/61 (23%)
PEDIS classification:		
1 2 3	38/60 (62%) 21/60 (34%) 1/60 (2%)	43/61 (70%) 18/61 (30%) 0
WIfI classification:		
0 1 2	54/61 (89%) 6/61 (10%) 1/61 (2%)	47/60 (78%) 13/60 (22%) 0
Wound location:		
Forefoot Hallux Heel Midfoot Toes	34/61 (56%) 18/61 (30%) 2/61 (3%) 6/61 (10%) 1/61 (2%)	42/61 (69%) 10/61 (16%) 4/61 (7%) 4/61 (7%) 1/61 (2%)
Offloading		
Knee-high removable cast walker Optimal adherence to offloading	32/61 (52%) 26/61 (43%)	28/61 (46%) 30/61 (49%)

Figure 5: Proportion (%) of diabetes-related foot ulcers healed by week 12



DFU debrided weekly vs those debrided every second week with the outcome (blue) based on independent assessment by wound expert blinded to treatment allocation and the treating clinician outcome (red).

Figure 6 : Percent Wound Closure at Week 4 and 12



Percent wound closure as a percentage of baseline DFU size for DFU debrided weekly (red) and second weekly (green). Week 4 95% Confidence interval (-24.0, 13.9%), p= 0.61, and Week 12 95% Confidence interval (-11.6, 41.7% p=0.27)

Discussion

In this, the first prospective, randomised, trial to investigate the effect of sharp wound debridement frequency on healing outcomes, an important aspect of care has been investigated for which high quality evidence has been lacking (381, 459, 463, 543). We have explored the dose effect of this therapy when provided as part of standard care and shown there is no significant difference in the outcome of proportion of ulcers healed by 12 weeks when sharp wound debridement was performed every week or every second week. The secondary outcome of average percent wound closure showed a 15% greater wound closure rate in weekly debrided wounds. This difference was not statistically significant.

Considering the multi-factorial nature of wounds and the variables that will impact healing, a 30% between group difference was ambitious however, a retrospective audit conducted at the lead site prior to this study, and published observational studies suggested the potential for a substantial effect size. Wilcox (2013) conducted a retrospective audit of files for 59464 DFU and found that weekly (or more frequent) debrided wounds healed in 21 days compared to 76 days for those debrided fortnightly or less often (p=0.001) (472). The earliest report from Steed et al (1996) used post-hoc analyses from the multi-site randomised, controlled study of PdGF, to show that the treatment centres providing more frequent debridement of DFU (n=118), had better healing rates at 20 weeks compared to centres that debrided less often(441). Similar post-hoc analyses from a subsequent RCT of dermal replacement involving 310 patients across 35 centres, showed that centres that debrided ulcers at every weekly visit, >75% of the time, also had a higher healing rate compared to those with less frequent debridement with 29% and 15% healed at 12 weeks (470). The same study did not find a statistically significant difference between individual participants. Our data, collected prospectively, controlling for visit frequency and other factors, also did not find a difference between treatments of weekly treatments versus second weekly treatment.

The main strengths of this study were the prospective, randomised design, use of intention to treat principles and independent assessment of healing outcome by clinicians blinded to treatment allocation which reduced the risk of bias. A further strength was the inclusive patient recruitment criteria and the implementation of the study across multiple centres, improving generalisability of results. Participants were recruited from the clinical services which routinely manage DFU and included patients with wound infection and/or ischaemia. People with common co-morbid conditions such as heart disease, renal disease and high HbA1c%, were similarly, not excluded for this study and the cohort are of an age and with a duration of diabetes which reflects the true patient population.

The results of the study results indirectly support ongoing sharp debridement weekly or second weekly based on the healing outcomes of this cohort of patients for whom there was adequate blood flow for healing. The outcome of 52-53% healing by 12 weeks across the two groups in this study is commensurate with good healing outcomes compared to others with similar patient and wound characteristics, which reported 30% and 24% healed by 12 weeks and recently presented meta-analysis of DFU healing from randomised controlled trials reporting 33.4% of DFU healing at 12 weeks (549, 550). The current study contributes to benchmarking contemporary healing rates in the context of our model of care and patient population.

It has been demonstrated that wounds of longer duration and less than 50% healing at 4 weeks have a low probability of healing (246, 545, 548). Our data showed that ulcers > 3 months in duration were less likely to heal which supports recommendations that early access to the interdisciplinary team, including podiatry consultation, improves wound healing outcomes (246, 456, 538, 551).

The pragmatic approach to the offloading of pressure on DFU in this study meant participants wore removable, knee high cast walkers and ankle high healing sandals (with orthoses) consistent with standard care and contemporary interventional studies involving DFU (312-314). While studies on irremovable knee-high devices have shown superiority in healing outcomes and recommended, the participating centres infrequently prescribe irremovable devices which is consistent with reported practice (310, 311). In this study, to impose irremovable knee-high devices, would have resulted in a study cohort less representative of the patient population since many would not tolerate wearing the irremovable devices due to postural instability or other reasons.

The main limitation of this study was the lower than expected number of digital images available for independent blind assessment. Furthermore, there was imperfect concordance

(0.7) between site assessment and blind assessment. The difference is explained as follows; one DFU deemed healed by blinded assessors was not healed based on assessment of the treating clinician, n=13 ulcers that healed (as determined by the treating clinician) were not deemed healed by the assessors using digital images. This imperfect agreement highlights the issue of assessing an outcome based on digital images (alone) compared to real-time clinician assessment. Clinician assessed healing outcomes, were used to perform sensitivity analysis. This included available data from participants who were discontinued. Across both groups, more DFU were deemed healed based on clinician assessment compared to an independent assessment of digital images. Ultimately, analysis of the healing outcomes assessed from blinded and clinician reported outcomes gave the same result of similar healing between groups.

Some expert consensus suggests that ulcers presenting with a higher burden of non-viable tissue would require more frequent debridement, at least initially (390). Our study was not powered to detect differences in sub-groups of patients.

The study does not answer questions such as whether a longer or shorted interval between debridements would be more beneficial or detrimental to healing. Whether debridement every 3 weeks would be negatively associated with healing was not explored. To extend debridement frequency to this longer interval would have represented a significant departure from our standard care which we could not ethically justify.

Future research on point of care measures of bacterial burden and other parameters to more concisely direct the extent and frequency of sharp debridement has the potential to individualise treatment.

In conclusion, sharp debridement performed by podiatrists to remove non-viable tissue from the base and margin of chronic, non-ischaemic DFU can be performed at weekly or second weekly intervals, with similar healing outcomes achieved with either treatment frequency. In the absence of indicators for more frequent debridement and where acceptable healing trajectories are observed, clinicians may consider extending treatment visits to every two weeks. This has the potential to ease some of the treatment burden for patients and reduce treatment costs.

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

Vanessa L. Nube,[1,2]
Jessica M. White,[1] Kate Brewer,[3]
Danielle Veldhoen,[1] Cindy Meler,[4]
Georgina Frank,[1] Kate Carroll,[5]
Jill Featherston,[6]
Jacqueline Batchelor,[7] Val Gebski,[3]
Jennifer A. Alison,[8,9] and
Stephen M. Twigg[2,10]

Diabetes Care 2021;44:e203–e205 | https://doi.org/10.2337/dc21-1454

Current guidelines strongly recommend regular, sharp debridement of diabetes-related foot ulcers (DFU) when blood flow is adequate (1). Sharp debridement disrupts biofilm and removes nonviable tissue, callus, and senescent cells, preparing the wound for endogenous healing (2) and advanced wound-healing therapies (3). Despite a reported association of more frequent debridement with improved healing outcomes (4), published prospective, randomized studies to inform optimal debridement frequency are absent, and existing evidence is rated as low (1).

A prospective, multicenter intervention study was conducted to determine the effect of sharp debridement frequency on healing outcomes in participants with DFU, randomized to weekly debridement or every second week debridement.

Adults with diabetes and a plantar neuropathic foot ulcer of ≥2 weeks' duration and ≥0.5–10 cm^2 in size were included. Exclusion criteria were nonhealing despite ≥6 months of treatment, moderate or severe ischemia, moderate or severe infection, nonplantar location, and/or inability to follow the protocol, including weekly visits.

Computer-generated, block randomization, 1:1 to either weekly or every second week debridement, with stratification factors of treatment center and DFU size (<3 cm^2 or ≥ 3 cm^2), was used. A participant sample size of 120 was sought, with 85% power to detect a between-group 30% healing difference at 12 weeks, allowing for a 20% study dropout.

All study sites adhered to a state-approved model of care for interdisciplinary high-risk foot services (5) and documented treatment standards: pressure offloading using removable knee-high or ankle-high devices both with rocker soles and insoles (standardized), oral antibiotics when indicated, dressings (excluding those that debride), and systemic diabetes care. The debridement method was removal of nonviable tissue from the wound base and periphery using scalpel, curette, and forceps. Self-reported adherence to wearing the offloading devices was recorded as the percentage of waking hours that the device was worn. All participants attended weekly.

Digital images were taken at baseline, 4 weeks, and 12 weeks or when the treating clinician deemed the ulcer had healed (whichever came first). Healing was defined as complete epithelialization of the wound with no exudate that would require dressing. All digital images were assessed by two independent wound experts, blinded to treatment allocation. Healing outcomes were recorded in the medical record by treating clinicians and reported as a site-assessed healing outcome. The predefined secondary outcome measures of percentage of wound area reduction at weeks 4 and 12 were calculated from real-time wound tracings.

A statistical analysis plan was developed prior to any data unblinding, and comparisons of primary and secondary outcomes between groups were analyzed according to the principle of intention to

[1]Royal Prince Alfred Hospital Department of Podiatry, Sydney Local Health District, Sydney, Australia
[2]Faculty of Medicine and Health, Sydney Medical School (Central), The University of Sydney, Sydney, Australia
[3]Clinical Trials Centre, National Health and Medical Research Centre, The University of Sydney, Sydney, Australia
[4]Bankstown Hospital, Sydney, Australia
[5]John Hunter Hospital, Newcastle, Australia
[6]St Vincent's Hospital, Sydney, Australia
[7]Hornsby Hospital, Sydney, Australia
[8]Sydney Local Health District Professorial Unit, Sydney, Australia
[9]Faculty of Medicine and Health, Sydney School of Health Sciences, The University of Sydney, Sydney, Australia
[10]Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia
Corresponding author: Stephen M. Twigg, stephen.twigg@sydney.edu.au

Received 12 July 2021 and and accepted 2 September 2021
Clinical trial reg. no. ACTRN12618000703202, www.anzctr.org.au

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treat. All comparisons were two-sided together with corresponding 95% CI, and P values of <0.05 were considered statistically significant.

The study protocol was registered on the Australian New Zealand Clinical Trials Registry (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367998) and approved by the Royal Prince Alfred Hospital ethics committee (X14-0184&HREC/14/RPAH/242) as the lead site, with local-site governance approval at each participating center.

In total, 122 participants (n = 61 per group) were recruited between October 2015 and September 2019 from seven treatment sites. Between-group participant and wound baseline characteristics were well matched (Table 1). Thirteen (11%) participants dropped out of the study with no outcome data for analysis (n = 3 in the weekly and n = 10 in the every second week debridement group). Overall, 75.4% (n = 92) completed each protocol. Digital images were available for assessment for only n = 78 participants.

Using a modified intent-to-treat analysis excluding participants whose healing outcome was not known, 53% (n = 24/45) in the weekly group and 52% (n = 17/33) in the every second week group healed by 12 weeks (mean difference 1.8%, 95% CI −16.3–20.0%, P = 0.84), according to assessment of digital images. Using clinician, site-assessed outcomes, 52% (n = 30/58) healed in the weekly and 45% (n = 23/51) in the every second week group (mean difference 6.6%, 95% CI −7.9–21.1%, P = 0.37). The secondary outcome of percentage of wound area reduction at week 12 showed a nonsignificant higher clinical closure rate (80.6% vs. 65.6%) in the more frequently debrided group (mean difference 15%, 95% CI −11.6–41.7%, P = 0.27). No on-study amputations occurred.

Study strengths include its pragmatic design with representative patients receiving contemporary management. Study limitations include use of removable pressure-offloading devices (Table 1); however, use of irremovable devices would have limited recruitment only to participants able to accept and use such methods.

Sharp debridement is optimally provided by skilled clinicians in the multidisciplinary setting, necessitating recurrent presentation to a clinic. Consequently, debridement frequency and clinic presentation are closely aligned. Debridement frequency has substantial implications for patients, their families, and health care provider cost and workforce requirements. While weekly debridement may be of benefit if individual wound and patient factors warrant it, this study shows that weekly debridement is not superior to debridement every second week. A good rate of ulcer healing is achieved with standardized care that includes both weekly and every second week debridement regimens.

Table 1—Baseline characteristics by randomized treatment group to weekly or every second week debridement

	Value by debridement frequency group	
Parameter	Weekly	Every second week
All randomized patients (n)	61	61
Age in years, mean (SD)	59.4 (10.0)	60.1 (11.4)
Female, n (%)	12 (20)	7 (11)
Male, n (%)	49 (80)	54 (89)
Type 1 diabetes (%)	2	10
Type 2 diabetes (%)	98	90
Duration of diabetes in years (SD)	13.8 (8.8)	16.4 (10.4)
HbA_{1c} % (NGSP units) (SD)	8.1 (2.2)	8.9 (2.0)
HbA_{1c} (IFCC units) mmol/mol (SD)	65 (17.7)	74 (16.6)
Wound duration (months), % of patients		
<3	75	65
≥3 to 6	16	25
≥6 to 12	4	9
≥12	5	2
Wound size (cm^2), % of patients		
<3	82	77
≥3	18	23
PEDIS classification, % of patients		
1	63	70
2	35	30
3	2	0
WiFi classification, % of patients		
0	89	78
1	10	22
2	2	0
Wound location, % of patients		
Forefoot	56	69
Hallux	30	16
Heel	3	7
Midfoot	10	7
Toes	2	2
Pressure offloading, no./total no. (%)*		
Knee-high removable cast walker	32/61 (52)	29/61 (48)
Ankle-high offloading method	29/61 (48)	32/61 (52)
Adherence to offloading (≥10 h/day)	26/61 (43)	30/61 (49)

Group ulcer healing outcomes are provided in the text. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; PEDIS, perfusion, extent, depth, infection, and sensation; WiFi, wound, ischemia, and foot infection. *This was the routine use of a knee-high prefabricated removable cast walker plus either an instant custom-molded total contact orthotic (iTCO) or self-molding prefabricated insole. If the participant was unable to mobilize safely or be accommodated in such a device, then a Darco post op shoe or a Darco cast shoe and iTCO were fitted.

Acknowledgments. The following clinicians supported the conduct of the study: Anna Crawford, Jessica Kronenberg, Sarah Manewell, Purnima Rao, and David Wong. Purnima Rao collated and entered data. Michelle Barakat-Johnson and Jana Pinkova assessed digital images for

the primary outcome. Participating site investigators include Danielle Veldhoen and Louise Pfrunder (Royal Prince Alfred Hospital), Georgina Frank (Concord Hospital), Cindy Meler, Luke Taylor and Ashish Gargya (Bankstown Hospital), Julie Zwarteveen and Kate Carroll (John Hunter Hospital), Alan Kennedy (St. George Hospital), Jill Featherston and Joel Lasschuit (St. Vincent's Hospital), and Jacqueline Batchelor and Catherine Stephens (Hornsby Hospital).

Funding. Funding support came from NSW Health, Office of Health and Medical Research, competitive Translational Research Grants Scheme, recipient number 96. There was no funding body involvement in study conduct, with the exception of the rules governing ethical conduct of the research. This funder did not have a role in the analysis or interpretation of the data, writing of the manuscript, or decision to submit for publication. There was in-kind support from the Sydney Local Health District and participating hospitals. The funding was used for consumables, offloading, partial clinical backfill for investigators, a study coordinator, external randomization, and data analysis services from the National Health and Medical Research Council Clinical Trials Centre, The University of Sydney. There has been no payment to write this article.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. V.L.N., D.V., and S.M.T. designed the study protocol and prepared submissions for ethics. V.L.N., D.V., C.M., G.F., J.F., and J.B. collected data and provided oversight of the study at their site. J.M.W. contributed to coordination and data management of the study. V.L.N., K.B., V.G., and S.M.T. contributed to and approved, and K.B. and V.G. wrote, the statistical plan. K.B. and V.G. analyzed the data. V.L.N., V.G., J.A.A., and S.M.T. interpreted the data. V.L.N. wrote the manuscript, and S.M.T. contributed to the manuscript and discussions. All authors approved the manuscript. S.M.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the Australasian Diabetes Congress, 11–13 November 2020.

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Diabetic foot ulcers: weekly versus second-weekly conservative sharp wound debridement

Abstract: Diabetic foot ulcers (DFU) are a serious and costly long-term complication of diabetes, and are one of the most prevalent hard-to-heal (chronic) wound types. Conservative sharp wound debridement (CSWD) is a mainstay of care. It is performed regularly until healing is achieved (when there is adequate blood flow for healing) to support endogenous healing and improve the efficacy of advanced healing therapies. CSWD is supported by evidence-based treatment guidelines, despite a lack of prospective studies. The first prospective randomised study to compare different frequencies of CSWD—the Diabetes Debridement Study (DDS)—showed no difference in healing outcomes at 12 weeks between those ulcers debrided weekly and those debrided every second week. A DFU may require more or less frequent debridement according to individual wound characteristics; however, the new data from DDS can inform clinical decisions and service provision. The implications of weekly versus second-weekly debridement are discussed.

Declaration of interest: The authors have no conflicts of interest to declare.

conservative sharp wound debridement • debridement • diabetes • diabetic foot ulcer • podiatrist • ulcer • wound • wound care • wound dressing • wound healing

Foot ulceration is a serious, long-term complication of diabetes, associated with peripheral neuropathy, increased plantar pressure and/or peripheral arterial disease. It has an estimated lifetime incidence of between 19–34% in people with diabetes.[1] Diabetic foot ulcers (DFUs) develop at a stage when other complications and comorbidities, such as retinopathy and cardiovascular disease, cognitive dysfunction and depressive symptoms, are also frequently present.[2,3] The high disease burden experienced by people with a DFU is evidenced by their ~2.5-fold increased risk of all-cause mortality compared with people with diabetes who do not experience a DFU.[4,5]

The central tenets of foot ulcer care in patients with diabetes aim to address aetiology and expedite healing while avoiding unnecessary hospital admissions and amputation. They include:[6]

- Debridement
- Pressure offloading
- Management of infection
- Restoration of blood flow
- Control of glycaemia
- Other comorbidities
- Wound dressings
- Patient education including aspects of self-care.

Prompt, effective treatment by a skilled interdisciplinary team is considered the best approach to improve outcomes in people with a DFU.[7–10] Despite improved standards of care, only around three-quarters of all wounds will heal[11,12] and amputation, preferably distal and limb-saving, may be indicated for some patients.

As recommended in national and international guidelines,[13–16] sharp debridement of a DFU is a mainstay of therapy. How often clinic visits are necessary for debridement and other aspects of treatment remains an important unresolved question, with implications for patients and carers as well as healthcare resources.[17] This article aims to discuss the evidence for conservative sharp wound debridement (CSWD) in the management of DFUs, with a focus on the randomised study of CSWD frequency—the Diabetes Debridement Study (DDS).[18] Herein, we will discuss the strengths, limitations and practical implications of this research for clinical services and patients.

Defining the role of conservative sharp wound debridement

Sharp debridement, both surgical and conservative, promotes healing by: removing non-viable tissue and potential bacterial burden within the wound; allowing for drainage of exudate; facilitating assessment of the wound dimensions; and providing the opportunity to take tissue for culture.[19–21] Sharp debridement also removes calluses, thereby reducing pressure at the wound margin.[22,23] Debridement of senescent cells, including fibroblasts, epithelial and keratinocytes, known to characterise hard-to-heal (chronic) wounds, may restore normal differentiation and migration of cells to support healing by secondary intention,[24,25] as

Vanessa L Nube,[1,2] Master of Science in Medicine*; **Jennifer A Alison**,[3,4] Doctorate; **Stephen M Twigg**,[2,5] Doctorate
***Corresponding author email:** Vanessa.nube@health.nsw.gov.au
1 Royal Prince Alfred Hospital Department of Podiatry, Sydney Local Health District, Australia. **2** Sydney Medical School (Central), Faculty of Medicine and Health, The University of Sydney, Australia. **3** Sydney Local Health District Professorial Unit, Australia. **4** Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney. **5** Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia.

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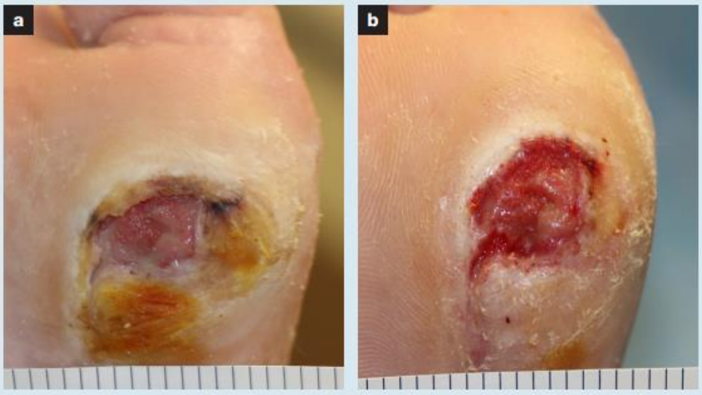
Fig 1. Neuropathic diabetic foot ulcer before **(a)** and immediately after **(b)** conservative sharp wound debridement. Image reproduced with permission from the original Diabetes Debridement Study[18]



well as improve responsiveness to advanced wound healing agents.[25–28]

In acute infection, surgical debridement is urgently required to remove all devitalised tissue, including bone, and drain any purulence.[29] This form of debridement is typically performed in the operating theatre by a surgeon. Unless there is primary closure of the post-surgical wound, serial sharp debridement, referred to here as CSWD, is usually required thereafter.

CSWD following surgical debridement, or as a standalone method, is readily performed in the outpatient or clinic setting by clinicians skilled in the procedure.[13] Forceps, scalpel and curette are employed to remove all devitalised tissue to a bleeding base and leave smooth, normal skin at the margin.[20,21] This is performed serially until ulcer healing is achieved (Fig 1a and 1b). The procedure is rarely well described in the research literature. The study by Saap et al.,[30] as well as the text by Edmonds and Foster,[21] and the more recent article by Murphy et al.[31] all provide images and descriptions consistent with the procedure and extent of debridement used in the DDS. Fig 1 is a before-and-after image of a debrided DFU from the DDS. (Patient consent was given for the taking and use of photographs of this wound at the time of the original DDS.) It is worth noting that CSWD is not routinely undertaken in people with insufficient blood flow for healing but is indicated when wounds are deemed 'healable'. CSWD has a limited role in DFUs associated with critical limb ischaemia but may be undertaken in the context of vascular consultation and restoration of blood flow or as an emergency limb- or life-preserving procedure, preceding revascularisation.[13,14,32]

CSWD forms part of the podiatrist's role within the interdisciplinary high-risk foot service, wound clinic or standalone podiatry service.[33] Nurses with advanced wound management training and medical doctors in general practice may also perform CSWD where local professional standards and local guidelines permit.[13,20,34,35]

Other methods of debridement, each with their specific indications and strengths, include larvae (biological), collagenase, hydrogels, hydrosurgery, ultrasonic debridement and, potentially, a monofilament product.[20,36] These are described in other useful reviews.[20,37–39] Sharp debridement remains the most often used and preferred method for DFU debridement as no other method achieves the same level of selective, rapid removal of non-viable tissue from the wound base and callus from the wound periphery, using minimal and readily available instruments in an outpatient setting.[13–15,17,40] The characteristics of DFU (periwound callus, loss of protective sensation and high risk of infection), make CSWD particularly important and easier to perform without anaesthesia in an outpatient setting compared with other wound types.

Emerging evidence regarding the role of biofilms in DFUs and other hard-to-heal wounds reinforces the role of debridement, particularly CSWD, to promote healing.[41,42] Biofilms complicate most DFUs and are associated with delayed healing.[40,41,43,44] Owing to their inherent ability to form structured and organised communities of bacteria, and to reduce their metabolic activity within a protective, extracellular polymeric substance, biofilms can effectively defend themselves against host immune responses, systemic antibiotics and topical antimicrobials.[40,43,45,46] The bacteria within the biofilm create a proinflammatory wound environment, secreting and stimulating the release of metalloproteinases in a way that perpetuates inflammation and breakdown of extracellular matrix and delays healing.[40,41,44,47] CSWD disrupts biofilm which adheres to and embeds into the wound, transforming bacteria to the planktonic phenotype potentially more susceptible to topical and antimicrobial treatments.[42] However, the effect of sharp debridement on biofilm is incomplete and temporary, with biofilm shown to reform rapidly, hence the recommendation that CSWD should be performed frequently.[40,42]

How often should CSWD be performed?

How often CSWD should be performed has been explored in retrospective studies, suggesting a dose-dependent relationship, with improved healing when performed more often or more aggressively.[12,26–28,30] Steed et al.[26] conducted post hoc analysis of data from participants (n=118) in a study of platelet-derived growth factor. Participants' DFUs were debrided prior to randomisation and they attended weekly for one month, and every two weeks thereafter, with debridement performed 'as needed' during the 20-week study period.[48] The authors reported that centres which performed sharp debridement more frequently had significantly better healing rates.[26]

In a subsequent randomised study of dermal replacement therapy which recruited participants (n=310) across 35 centres, Cardinal et al.[27] included weekly sharp debridement in the study protocol. Centres that debrided DFUs at weekly office visits at least 75% of the time had healing rates of 29% at 12 weeks compared with 15% for the centres which did not debride wounds weekly during at least 75% of visits.[27] Wilcox et al.,[12] in a large US study, audited a cohort of patients with wounds, including 59,464 DFUs, and found weekly (or more frequent) debrided DFUs healed in 21 days compared with 76 days for those debrided fortnightly or less often (p=0.001). While a strength of the Wilcox et al.[12] study was the number of DFUs included, its retrospective design means the effects of confounding factors cannot be assessed.[49] Lavery et al.,[28] in their study investigating the effect of continuous diffusion of oxygen on DFU healing, also reported that weekly debridement (compared with less frequent debridement) was associated with improved healing outcomes.

Despite these observational reports, the level of evidence for debridement frequency and sharp debridement per se remains low due to the lack of prospective randomised studies.[37,50] The recommendation of frequent CSWD in evidence-based practice guidelines is based on limited evidence and expert opinion,[13–16] and is standard care in contemporary, interventional studies.[27,28,51–54] A survey of clinicians managing DFUs showed weekly or second-weekly CSWD is common practice but that resource to provide weekly debridement is a constraint.[33]

Randomised study comparing weekly to second-weekly CSWD of DFUs

In contrast to these previous observational studies, the DDS[18] is the only prospective, randomised study to investigate debridement frequency. The study was specifically designed to determine the difference in DFU healing outcomes, comparing wounds debrided weekly with those receiving second-weekly (less frequent) CSWD. Results of the DDS were reported according to intention-to-treat principles using assessors blinded to group allocation. Independent wound experts, who were not involved in the care of the patients, reviewed stored digital images of the wounds and deemed the DFU healed if it appeared closed with an absence of exudate, such that a dressing would not need to be applied. Based on the assessment of available images (n=78), second-weekly debridement was shown to result in similar healing outcomes compared with weekly debridement in chronic neuropathic DFUs. Due to the higher than anticipated drop-out rate, a sensitivity analysis was also conducted using the healing outcomes for DFUs (n=109) based on the degree of healing reported by clinicians in participating centres. This analysis confirmed the findings from the analysis of digital images.

The participants (n=122) in the DDS were representative of those with DFUs and the two groups (weekly versus second-weekly debridement) were well matched, with similar DFU characteristics.[18] Participants were recruited from seven treatment centres, improving the generalisability of results. The DFUs were small on average, with 80% <$3cm^2$ and many of long duration.[18] The majority were located on the plantar aspect, and all were associated with peripheral neuropathy.[18] People with mild ischaemia were included if there was adequate blood supply to safely perform CSWD (Wound, Ischaemia, foot Infection (WIfI) Grades=0–1).[55] DFUs that had been treated at the centre for ≥6 months without healing were excluded.

The design followed the principles of a translational research design, testing weekly debridement in the context of usual care. In line with this, treating teams were afforded scope to make clinical decisions regarding treatment, such as dressing and antibiotic choice, while agreeing to adhere to a set of practical, evidence-based guidelines covering assessment, treatment and documentation and which were provided by the lead site. Visit frequency was controlled, with all participants attending weekly.

Standards for reporting randomised studies of DFUs by Jeffcoate et al.[56] were followed and the study adhered to CONSORT recommendations.[57] The CONSORT Flowchart was included in the trial registration with the Australian and New Zealand Clinical Trials Register,[58] which contains information about the study protocol and predefined outcomes. Independent off-site randomisation, the use of predefined outcomes, and intention-to-treat analyses with outcomes determined by assessors blinded to treatment allocation reduced potential bias in the study.

Reporting standards recommend information on pressure offloading be provided for trials of patients with DFUs.[56] DDS participants were limited to one of two different types of removable knee-high cast walker or an ankle-high healing sandal with a rocker sole. All devices were fitted with either a custom moulded 10mm thick Plastazote (Polyformes Ltd., UK) insole or a prefabricated cushioned insole of similar thickness and material type. Minimal additions of 3mm Poron (Rogers Corp., US) and compressed felt to reinforce the arch

Fig 2. Knee-high removable device pictured with instant total contact orthosis (ITCO) **(a)**. Ankle-high removable device pictured with prefabricated insole (PI) **(b)**. The ITCO or PI could be used in either device

were allowed. The devices used in this study have been assessed as reducing plantar pressures by >50% and below the 200kPa threshold[59] (Fig 2).

Devices used in the study protocol were aligned to best practice recommendations and other contemporary interventional studies of DFUs in which participants wore devices which included ankle- and knee-high removable devices.[28,52,53,60,61] Adherence to wearing the offloading devices was also recorded, with participants asked to report the percentage of waking hours that the device was worn throughout the study. Overall, only half of participants wore their devices for most of the day.[18]

The type of offloading and relatively poor adherence to offloading in this study need to be considered in interpreting the results. Non-adherence to offloading is a known phenomenon that could have been addressed by prescribing irremovable knee-high devices to ensure adherence and which are more effective.[62,63] Had the use of irremovable devices been made a requirement in the study, only those participants willing and able to wear irremovable devices would have been included and this would not have been representative of the patient population. Notwithstanding this, healing outcomes would almost certainly have been improved if participants had worn knee-high, irremovable devices and the need for debridement may not have been the same. Thus, the results of the DDS may not directly translate to patients using irremovable knee-high devices.

The DDS focused on an important aspect of care for which high-quality evidence has been lacking.[13,17,37,38] Overall combined healing rates at 12 weeks for both the weekly and second-weekly CSWD groups was 53% based on digital images and 49% based on clinician assessment. Of the participants who completed study visits (until healed or up to 12 weeks) 58% healed. These healing rates were commensurate with good healing compared with meta-analyses showing 33.4% healed at 12 weeks,[64] recognising that the phenotype of the wounds included in the DDS may have been less severe.

It is possible that debridement frequency prior to recruitment was influential in the healing outcome or that the long duration of wounds meant they were less responsive to debridement frequency as performed during the study. It has been demonstrated that wounds of longer duration and with <50% healing at four weeks have a low probability of healing and the DDS also showed that ulcers of >3 months' duration were less likely to heal.[18,65,66] This supports recommendations for early access to the interdisciplinary team, including podiatry consultation to improve wound healing outcomes.[67] The DDS did not explore or answer questions such as whether a longer interval (>2 weeks) or <1 week between CSWDs would be more detrimental or beneficial to healing. To extend the time interval between debridement to >2 weeks may not be ethically justified when practice guidelines, standard care in other studies, observational data and clinician reports suggest weekly debridement is common.[12,28,33,54] Potentially, some DFUs, such as those with a higher bacterial burden, would have responded better to more aggressive debridement or debridement performed several times a week. However the DDS was not powered to detect differences in subgroups of DFUs, such as those with high bacterial burden.[40]

The results indicated that for people with a DFU, such as those recruited to the DDS who commonly present to high-risk foot services, two-weekly debridement would not appear to adversely impact healing.

The DDS protocol was registered on the Australian New Zealand Clinical Trial Registry and approved by the Royal Prince Alfred Hospital ethics committee (X14-01 84&HREC/14/RPAH/242) as the lead site, with local site governance approval at each participating treatment centre).

Considerations for implementation of CSWD

Topical agents to augment sharp debridement

A potential benefit of CSWD is reduction of high bacterial load and disruption of biofilm to facilitate this.[40] The available data, however, are not definitive on whether planktonic bacteria can be effectively removed with debridement alone.[68,69] Study on the impact of topical agents, including surfactants and antiseptics, on biofilm and healing, mostly using in vitro and animal models, continues[70–76] but findings so far suggest that surfactants developed for use in wounds may work in synergy with antimicrobials to reduce the bacterial burden in wounds.[75–77] Similarly, antimicrobials used following sharp debridement may kill or suppress bacteria in the planktonic state[40,42] but further research is needed.

How to determine effectiveness of debridement

Clinicians experienced in the management of DFUs will assess infective signs and visualise non-viable tissue, callus and slough to guide debridement. However, in the absence of clinical signs of infection and non-viable tissue there is no simple means whereby clinicians can identify biofilm and assess the effectiveness of their debridement on biofilm without biopsy and microscopy.[78] Future directions include point-of-care visualisation of many common bacteria which can be achieved with a commercially available camera that detects autofluorescence of bacteria at moderate-to-high levels within a wound. While the output image does not distinguish between biofilm and planktonic bacteria, it does provide clinicians with additional information about the microbial burden to target debridement.[79] Other techniques being studied include blotting[80,81] to detect biofilm components or detection of elevated matrix metalloproteinase-9 (MMP-9). Persistent high MMP-9 in post-debridement DFU fluid occurs in wound inflammation, and is associated with delayed healing and biofilm presence.[47] This represents another potential point-of-care test to assess the impact of debridement.

Impact of less frequent debridement on service providers

How the research findings of the DDS are interpreted and implemented will vary between services and patient cohorts. However, for services routinely providing weekly debridement, cost-effectiveness and efficiency of healthcare delivery can be improved with implementation of these research findings.

If weekly debridement is not specifically indicated, extending the time between clinic visits to two weeks for some patients, could increase appointment availability, enable the inclusion of patients from broader geographical areas, reduce waiting times for new presentations or allow longer visits. Fewer appointments could alternatively increase time for other vital activities such as quality improvement, research and staff development.

To ensure patient safety is maintained with less frequent clinic visits, systems for remote monitoring via telehealth could be implemented. While remote monitoring does require resourcing, the costs for patients and staff would be reduced compared to weekly face-to-face treatment.

Impact of less frequent debridement on patient and carer experience

While many patients value frequent appointments and have the capacity to attend, there are several reasons why physically attending a clinic appointment can be challenging. Cost of travel, time away from employment or other activities, poor mobility, carer burden and the amount of walking required to get to and from a clinic represent likely challenges and barriers experienced. Patient preference and capacity to attend should naturally inform decisions regarding visit frequency, alongside clinical recommendations. If more frequent patient follow-up is deemed necessary for management other than the provision of sharp wound debridement, remote monitoring using wound images may reduce some of the burden of frequent clinic visits on patients and carers.[82] Future research could explore patient experience and preferences with regard to sharp debridement.

Recommendations

In the absence of more precise tools to guide practice, we recommend that where good healing trajectories are observed using objective measures of wound size (for example, 50% wound size reduction in four weeks),[65] that second-weekly debridement supports healing of DFUs that are receiving standardised care in an interdisciplinary setting. As per published guidelines, delayed healing should prompt clinicians to reconsider and act on those factors which can impede healing, chiefly, failure to mitigate trauma (such as pressure), ischaemia, uncontrolled infection, chronic inflammation and inadequate debridement. **JWC**

Acknowledgement
The authors would like to thank Anita Hood and Georgina Frank for their critical review of the manuscript before submission, and our colleagues Anna Crawford, Purnima Rao and Sarah Manewell, who shared their views on the implications of this research to their practice.

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Reflective questions

- How accessible is thorough and frequent conservative sharp wound debridement for people with diabetic foot ulcers (DFUs) in your area or health service? What could be done to make it more accessible to patients?
- How often is conservative sharp wound debridement provided for your patients with DFUs? Why has this frequency been chosen?
- What evidence is there that sharp wound debridement and antimicrobial treatment supports the healing of DFU?

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Extended discussion of study design

Reporting Standards

Consolidated Standards of Reporting Trials (CONSORT) guideline 2010 for parallel-group randomised controlled trials (RCT) was referred to in the design and reporting of the randomised Diabetes Debridement Study (DDS) (552). A key principle of the CONSORT guideline is that authors adhere to the guideline, providing the level of transparency regarding study design that consumers need to be able to discern its quality and validity. The flowchart for the completed study using the online tool has been completed (http://www.consort-statement.org/consort-statement/flow-diagram) and included in the Diabetes Care 750-word publication of this study (355).

The study protocol was further guided by the "reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes" that were developed to improve the quality of research and reporting in this field (553). The DDS broadly followed this guidance with the exception that the measurement of the effect of pressure offloading and the recording of quality of life.

The study protocol was submitted to the Australian New Zealand Clinical Trials Registry as a single site study, later registered as a multisite study following funding for additional treatment sites to be included.

Ethical considerations

The main ethical consideration for this study was determining which frequencies of debridement to compare. The investigators agreed that weekly and second weekly treatment were both standard practice and that it would be meaningful to determine the difference between these two frequencies. Third weekly was also considered but as this represented a significant departure from standard care in some centres, it could not be ethically justified without assessing the safety of second weekly debridement.

Sample size

To show a clinically relevant, 30% difference between groups for the primary outcome, it was estimated that a sample size of 120 participants was needed to achieve 85% power with 95% confidence with p-value of 0.05, assuming a 20% attrition rate. Historical data from the lead site, based on retrospective audit showed that 50% of DFU healed at 12 weeks with the median days between treatments being 10 days. This estimated dropout rate of 20% is consistent with those reported in other studies of patients with DFU (554, 555).

Randomisation

Patients were randomised following baseline assessments, sharp debridement, and measurement of wound size, using an off-site clinical trials centre offering statistical and randomisation services, to either weekly or second weekly debridement. Block randomisation by treatment centre was used and wounds were stratified as smaller than 3cm or ≥3cm with the aim of achieving similar wound sizes between groups. Treatment visits were scheduled on the same day each week however, +/- 3 days was accepted within the protocol as this would allow for patients to miss an appointment as is often the case due to sickness, competing commitments or deliberate non-adherence.

Blinding

Treating clinicians entering in the medical record and study data forms and patients were not blinded to group allocation. The primary outcome was determined from stored digital images taken of the wounds at 4 and 12 weeks and when healed, which were viewed by two independent wound experts who were blinded to group allocation. The panel of two experts were asked to document in the database (with access limited) whether the wound was healed or not with healing defined as wound closure with an absence of exudate, such that a dressing would not be required. Wound experts also entered the week that the ulcer healed.

Statistical analysis

A statistical analysis plan (SAP) was developed prior to any data unblinding and comparisons of the primary and secondary outcomes between the two debridement schedules for the debrided DFU were analysed according to the principle of intention to treat.

Summary statistics were used to describe the data and, if the data, after a test of normality were deemed not to be normally distributed, appropriate transformations were used (eg. log) to achieve a more symmetrical distribution.

All comparisons were two-sided using the Pearson Chi-squared test together with the corresponding 95% confidence intervals, and p-values of less than 0.05 were considered statistically significant.

Data collection

Treating clinicians were provided data collection forms to record all the data required to describe the participant, wound characteristics and outcome measures. Data also included he presence or absence of infection and wound grade recorded at each visit along with data on whether the patient had been admitted, and any adverse events, study withdrawal, and amputations. This data was entered by the research assistant or co-ordinator into the study database, REDCAP, which was housed on the District's server.

Digital images of wounds were taken by standard digital cameras before and after debridement at baseline and post debridement at weeks 4 and 12,common and when healed. Images contained a small disposable ruler, date and UIN of the participant. Investigators used a technique described in the study investigator manual which involved taking a well-focused, post-debridement digital image with the camera 30cm from the wound surface at the same plane as the DFU (556). Images were uploaded by site investigators, into the study database.

Participant study completion was when the clinical team determined that the ulcer had healed. Healing outcomes were recorded in the medical record and data entry forms by the treating clinicians and this outcome is reported as a site assessed outcome.

Blinding

Wound experts who were used to assess the healing outcome had limited access to the database fields, which permitted them to view the wound images, UIN and ruler and document the outcome but they could access group allocation or other data fields describing the wound or participant. Healing was defined as complete epithelialisation of the wound with no exudate that would require dressing.

The pre-defined secondary outcome measure of percentage of wound area reduction (PWR) from baseline to weeks 4 and 12 was calculated as percent wound size reduction from the original size based on planimetry. The use of these surrogate endpoints was included as these represent sensitive time points, shown to be predictive of healing overall (545-548).

Standard Care and Assessment

All participants were scheduled for weekly consultations and standard care as part of the study protocol. Participating sites agreed to adherence to the Practical Diabetic Foot Treatment Protocol developed for use in the health district of the lead site, based on contemporary evidence-based practice guidelines.

A detailed investigator folder containing the treatment protocol, the technique for wound tracing, calculation of DFU size and wound digital photography was developed, discussed at investigator meetings and provided to each participating site. The folder also contained before and after images of sharp debridement to help illustrate the expected standard of sharp debridement. Additional images were share during investigator meetings.

Aspects of standard care included the following (in brief):

- Sharp debridement undertaken by a podiatrist skilled in the procedure, using a scalpel, curette and forceps and including removal of periwound callus and non-viable tissue from the base of the wound.
- Infection is determined on the basis of clinical signs of inflammation and purulence according to the IWGDF and IDSA criteria.

- Ischaemia is assessed on the criteria for lower limb ischaemia described in the IWGDF guidance on PAD and WIfI score with an ABI of < 0.6 or toe pressure of < 40mmHg indicating moderate to severe ischaemia.
- Neuropathy is assessed using monofilament (using the plantar first and 5th metatarsal sites) and vibration perception using a biothesiometer, neurothesiometer with DSPN present if the reading at the hallux was > 25 volts or the patient was unable to detect the 128 Hz tuning fork.
- Patients are education included wound self-care advice to
    - Clean the wound with normal saline.
    - Cover with a non-adherent dressing recommended by their podiatrist and change at the recommended frequency and to tape securely down all sides of the dressing.
    - Keep the foot dry when showing and clean the wound and foot at dressing changes.
    - Monitor for any signs of infection or wound deterioration and contact their treating centre promptly with any changes to suggest the above.
    - Always wear the prescribed offloading device when standing or walking.
- Access to medical care. Review by a physician experienced in the management of diabetes and foot care was part of the model of care at all participating centres with access to referrals for investigations, management of infection and diabetes.

Glycaemic control

Glycaemic control was recorded for all participants and a HbA1c% measured within 3 months of study entry was used. While observational studies to determine the relationship between glycaemic control and healing have given different outcomes, Chrisman et al have most recently shown that higher HbA1c % is predictive of delayed healing in patients with diabetes and chronic wounds, resulting in slower wound closure in those patients with concomitant peripheral arterial disease (PAD)(557). Why this difference was only demonstrated in the subset with PAD is unclear however and the patients in the poor glycaemic control group ($\geq$ to 8%) had significantly smaller wounds which in the authors experience will often demonstrate less rapid total area closure than larger wound. Given the possible contribution of suboptimal glycaemic control on the cell-mediated response and defective healing, this variable was measured and reported.

Dressings

Dressing choice and frequency was at the discretion of the treating clinician, in accordance with the agreed clinical treatment protocol which included non-adherent foam or absorbant dressings. The use of dressings which specifically stated in their indications that they would debride or de-slough the wound, were discouraged and clinicians had to document the use of these in the study data form. Dressing changes could be done by the patient, family or a nurse. It is worth noting that sucrose octasulfate was not in use at the time in the participating centres and the use of negative pressure wound therapy, bio-engineered or skin replacement wound products were also not used on study participants.

Pressure Offloading

The recommendation of the reporting standards by Jeffcoate et al is that pressure offloading for interventional studies on plantar DFU report details of the devices. In accordance with this recommendation, the study protocol allowed for the following offloading (553).

- Removable Below-Knee Cast Walker (RCW)– Initial selection – the Prowalker by Johnson&Johnson™. If the foot was too wide, then the secondary option was the MaxTrac™
- As the foot/shoe interface, an insole was used in addition to the RCW.
    - At the SLHD sites, there is capacity for devices to be made using heat moulded Plastazote™ of 1cm thickness.
    - At the other sites, the OAPL™ brand pre-made diabetic insole of 1cm thickness was used. This device was similar in function because it moulds to the foot over time. The same allowing modifications were used at discretion of the clinician based on their assessment of the foot.
    - Allowable modifications to the devices were made at the discretion of the clinician and based on their assessment of the foot.

    - The addition of felt to reinforce the arch
    - Heel raise to accommodate a fixed equinus of plantigrade foot.
    - Deflection with 10mm felt for plantar lesions under 1.5cm
- If patients were too unsteady or the RCW could not safely accommodate the foot, patients were provided a removable ankle-high device, the "All Purpose Healing Shoe" by Darco^{TM} to which the orthosis was applied.
- In most cases, patients were in the RCW were provided the Darco^{TM} shoe and insole as their secondary device.
- All devices were fitted in accordance with study and treatment protocols by the treating podiatrist and could be replaced when worn, up to twice during the study period.
- Participants were asked to self-report on the number of hours each day that they wore the device, on average and this was recorded at weeks 4 and 12.

The OAPL device has been evaluated in a small pilot study by the Concord Hospital site investigator and it was demonstrated that the pressure relief obtained from the use of the pre-made insole was similar but slightly inferior to the custom moulded devices(325).

The offloading in the study was aligned with recommendations of the International Working Group on the Diabetic Foot (IWGDF) and our Sydney Local Health District Clinical Treatment Protocol which was developed by the lead District and shared with the participating sites in an effort to standardize the treatment between participating clinical sites(330). The IWGDF states that "To heal a neuropathic plantar forefoot ulcer without ischemia or uncontrolled infection in a patient with diabetes, offload with a non-removable knee-high device with an appropriate foot–device interface. (GRADE strength of recommendation: strong, Quality of evidence: high)." These guidelines have been adapted for Australia and a point of difference is the downgrading of the reported strength of evidence for non-removable knee-high devices compared to ankle high devices. In the current study, investigators determined that if irremovable knee-high devices were made a requirement of inclusion in the study, that few patients would be eligible to enroll, and the participating treatment centers infrequently made the knee-high devices irremovable.

Our adaptation to this guidance for the study protocol was to use knee-high devices that could be removed but participants were strongly encouraged to always wear the device when standing or walking. If the participant was unable to safely use the knee-high device, an ankle high device was used. The rationale for this approach is that it was not our routine clinical practice or that of the other participating site investigators due to the clinical experience of patients having complications from their RCW when they were not removed for regular inspection. As we needed to standardise the treatment, it was decided that all patients would be provided with the offloading as “removable” but with intense education of patients, intended to promote adherence to using the devices prescribed.

Expected Time to Healing

It is well recognised that DFU are hard to heal and associated with delayed healing and risk of amputation. Early referral for non-healing or complex wounds to a specialised center where the barriers to healing can be addressed, expedites healing and helps to avoid unnecessary hospitalisation and amputations(558-560). The predicted healing time for diabetes-related foot ulcers varies, depending on case-mix variation, chiefly the presence and severity of PAD, wound duration, infection and size as well as the quality of care (Table 6). Some benchmark for time to healing can be derived from large randomised, controlled studies (RCT) and wound registries with approximately 66-77% of DFU healing reported by 12 months(116, 205, 561). Given the potential impact of wound duration, PAD, infection and wound size, these characteristics were recorded and reported, and all participating centres adhered to the same standards and model of care.

Table 5: Healing Outcome Data

Examples of healing outcomes of DFU from large datasets.

Author and publication year	Cohort. Patients with DFU	Outcome
Fife, CE et al (2016) (561)	US Wound Registry, Healogics. (n=6440)	66.1% healed overall
Prompers, L et al (2008)(116)	Eurodiale Study Participants (n= 1232)	77% at 12 months
Margolis DJ et al (2005) (549)	Patients Curative Health Services (CHS) Registry (US) (=n=3261) for the year 2000	48.4% healed with mean time to healing of 2.1 months, mean size 1.5cm
Zhang et al (2021) (217)	4709 DFU patients, Qld Australia	41.5% at 3 months

Measurement of the Healing Endpoint and Percent wound reduction

The main outcome measure for the study was percentage of wounds healed at 12 weeks in the two groups. Healing was defined as complete epithelialisation of the wound with no exudate and not requiring a dressing which is consistent with most studies(562) and our protocol required that for the pre-determined primary outcome, that wound healing would be determined by a panel of two wound experts who were blinded to treatment group allocation. The evaluation was undertaken when data collection was complete and stored digital images were used. The intention was to eliminate any risk of bias. The US FDA defines wound healing as above however requires that the wound be assessed over two consecutive visits and needs to be healed at both visits to meet their definition of healing(563). In the DDS, clinician assessed healing was also reported and these healing outcomes, using data from the medical records and study data sheets.

The secondary outcome measure was percentage wound reduction PWR from baseline at weeks 4 and 12. The use of these surrogate endpoints are valid because the rate of wound change at these sensitive time points has been shown to be predictive of healing overall and provide a pragmatic and comparable outcome measure used in other clinical trials.(546, 564)

The 12 week point was chosen as this is a sensitive endpoint, used in many clinical trials of wound interventions and as such, there are datasets to compare against. (554, 564) In our local data (unpublished) of DFU at the RPAH High Risk Foot Service, 50% of ulcers treated weekly (to 10 days) heal at 3 months compared to 76% of those treated weekly determined by a retrospective audit of our database. The median time to treatment was 10 days.

In their meta-analysis, Margolis and Kantor included patient cohorts where the ABI was >0.7 (or toe pressure >30mmHg) closely resembling our inclusion criteria of ABI >0.6 (or toe pressure >40mmHg) and reported the average healing rate of DFU at 12 weeks to be 24.2% (CI 19-5-28.8)(564).

Sheehan and colleagues in 2003 provided evidence from a dataset of 203 chronic DFU's enrolled in a clinical trial across 11 treatment sites, that healing at the 4 week point is predictive of healing at 12 weeks(548). In their paper the authors reported 82% wound closure was achieved at week 4 in wounds that healed, compared to only 25% wound closure in those that failed to heal at 12 weeks. They propose that using the median reduction in wound size of 53% (healing) from this patient group, it can be predicted that 58% of wounds that achieve greater than this at 4 weeks should heal at 12 weeks with a sensitivity and negative predictive value of 91%. In comparing this cohort of patients, it is important to note that they excluded patients with PAD and Infection, which needs to be considered when using this predictive model for our patients in this study (548).

Additionally, the 4 week point is often used as a surrogate end point because the percentage of wound closure at this point is highly predictive, 82.2% according to one study with a specificity greater than 90% (565). In their examination of the role of wound closure rates in the trial of Dermagraft™, Cardinal et al determined that the graphed, wound healing trajectory for DFU's and Venous Leg Ulcers (pooled data) at 4 weeks, based on percentage of area reduced was 82.2% predictive of healing at 12 weeks, with a sensitivity of 90%. The Percentage Area Reduction (PAR) method is a calculation of difference in wound size between successive weeks, expressed as a percentage (565).

Snyder and colleagues retrospectively analysed the healing rates of study participants with DFU enrolled across 2 studies and multiple sites, confirming the high sensitivity and specificity of 50% PAR at 4 weeks as a predictor of healing at 12 weeks (566). In this review of data, they were also able to determine that this is consistent across patient groups with differing ulcer size.

Measuring wound size for Percent Wound Closure

Both wound tracings performed after debridement, and photographs were used to determine wound size and healing outcome. Tracings were performed by the treating clinician at every study visit. The clinician was aware of the treatment group and was therefore not blinded. To reduce the risk of bias, wound size was calculated by the research assistant and entered into the study database. Furthermore, the outcomes at 4 and 12 weeks were validated independently by 2 wound care experts who were blinded to treatment allocation.

The method used in recording and measuring wound size for calculation of baseline size and PWR is manual planimetry. The technique was in use across the participating centres and is in common use for recording wound size(567), being inexpensive, simple and accessible. The original description of the acetate and grid method describes the use of a fine marker to trace the wound onto a double layer of transparent acetate film(568). The piece adjacent to the wound is discarded and the upper most film containing the outline is kept. The acetate is then placed over grid-paper and the number of 1mm diameter squares within the outline, counted to determine the area. In the case of this study, the outline is taken and labelled with the date, week, and unique patient identifier for wound area calculation by the research assistant and co-ordinator.

Evaluations of the range of wound measurement techniques have confirmed the acetate outlines and grid paper used to calculate wound area is both accurate and reliable with good inter and intra-reliability (568-570). Several authors have compared the accuracy of this technique against newer technologies concluding the former to be valid, accurate and reliable (567, 571) The main potential sources of inaccuracy is determining the wound edge (568).

Chapter 4: Treatment Frequency for Diabetes-related Foot Ulcers: Exploring patient experience and preferences

It is evident from studies on physical strength and mobility in people with diabetes and DSPN and the high morbidity and mortality recorded in this patient population, that clinic attendance for many of our patients with DFU is likely to require considerable effort.

During the conduct of the randomised study, it was also apparent that the commitment to weekly attendance was challenging for some of our patients who declined to participate and some who agreed and could not meet the schedule of visits.

In implementing any practice change, it is important to consider the implications for patient outcomes but also their experience. For these reasons, a small additional study was undertaken to capture patients' experience of what they value, how often they prefer to have treatment and whether the 15% faster rate of healing, found in the randomised study, was sufficient to change patients' preferences for frequency of treatment. A quantitative survey was undertaken.

This study was approved by the Sydney Local Health District Human Research and Ethics Committee, Royal Prince Alfred Hospital (2020/ETHO3244) and has been published in *Wound Practice and Research Journal* and included here as the published manuscript.

Nube, V. L., Zwarteveen, J., Frank, G., Manewell, S. M., Cocks, M. L., Rao, P., Twigg, S. M., & Alison, J. A. (2023). Challenges faced by people with diabetes-related foot ulcers in attending hospital-based high risk foot services: results of a consumer survey. *Wound Practice & Research*, *31*(3). https://doi.org/10.33235/wpr.31.3.99-105

The candidate designed the study and survey, prepared the ethics submission, collected data, analysed data, wrote the paper, consulted with other authors for their review and input into the final submission, prepared the submission, is responsible for the integrity of the work and is the corresponding author.

RESEARCH

Challenges faced by people with diabetes-related foot ulcers in attending hospital-based high risk foot services: results of a consumer survey

Vanessa L Nube[1,2]*, Julie Zwarteveen[3], Georgina Frank[1], Sarah M Manewell[1], Molly L Cocks[4], Purnima Rao[1,4], Stephen M Twigg[4–6], Jennifer A Alison[6,7]
[1]Department of Podiatry, Sydney Local Health District, Missenden Road, Camperdown, NSW, Australia
[2]The University of Sydney, Faculty of Medicine and Health, NSW, Australia
[3]Department of Podiatry, Hunter New England District, Community and Aged Care Services, Greater Newcastle Sector, Newcastle, NSW, Australia
[4]Diabetes Centre Royal Prince Alfred Hospital, Camperdown, NSW, Australia
[5]Diabetes Centre, Department of Endocrinology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia University of Sydney, NSW Australia
[6]The Faculty of Medicine and Health, Sydney Medical School, University of Sydney, NSW Australia
[7]Allied Health Professorial Unit, Sydney Local Health District, Camperdown, NSW, Australia
*Corresponding author email vanessa.nube@health.nsw.gov.au

Abstract

Introduction Diabetes-related foot ulcers (DFU) are optimally managed with a team approach to addressing infection, ischaemia, pressure offloading and sharp debridement. Treatment frequency is commonly every 1–2 weeks.

Aim To investigate the actual and preferred frequency of treatment of patients, and potential factors affecting treatment attendance including perceived benefits, mobility and mode of transport.

Method A convenience sample of patients attending urban or regional high risk foot services (HRFS) for treatment were invited to participate in the survey via a QR code, on paper or via phone. The study had ethics approval No X20-0550 2020/ETH03244.

Results A total of 60 participants from three centres completed the survey. Eight (13%) attended weekly, 28 (47%) every 2 weeks, and the remainder (40%) less often; 51 (85%) indicated they would attend weekly if this hastened healing; 33 (45%) had some level of difficulty in mobility impacting their ability to attend, with 11(18%) requiring a carer or family support for them to attend; most (84%) participants drove or were driven.

Conclusions Physical mobility deficits impact patients' ability to attend for treatment, with the majority relying on private transport to attend appointments. Family support to enable attendance was common. These factors should be considered by providers and commissioners of services.

Keywords access, chronic wound, diabetes-related foot ulcer, high risk foot service, podiatry

For referencing Nube VL. Challenges faced by people with diabetes-related foot ulcers in attending hospital-based high risk foot services: results of a consumer survey. Wound Practice and Research 2023; 31(3):99-105.

DOI https://doi.org/10.33235/wpr.31.3.99-105

Submitted 21 May 2023, Accepted 14 July 2023

Introduction

Interdisciplinary high risk foot services (HRFS), which include podiatry, vascular and endocrinology interventions, are known to improve outcomes for people experiencing diabetes-related foot complications[1,2]. The aim of these coordinated interdisciplinary teams is to provide rapid access to optimal care to help avoid unnecessary hospital admissions and amputations[3–7]. Key tenets of care provided within the HRFS include management of infection, local wound care including sharp debridement, assessment and management of peripheral arterial disease, pressure offloading of the wound, patient education and management of their chronic disease[8]. Standards for care and clinical guidelines are outlined in state, national and international documents which emphasise the need for the model of care to include rapid access and on-site teams[3,4,8,9]. Interdisciplinary teams are advantageous due to the emphasis on coordination and communication which may minimise the number of visits to health facilities by bringing together clinicians from different disciplines for joint consultation.

In a health environment which is seeking to deliver more care outside the hospital facilities and through telehealth, particularly in the COVID-19 era[10], the need for patients to attend face-to-face appointments to receive sharp debridement and detailed wound assessment remains necessary. From the clinicians' perspective, the recommended frequency of sharp debridement is a key determinant of how often patients with diabetes-related foot ulcers (DFU) attend a HRFS for care, with visit and debridement frequency being virtually synonymous[11]. Sharp debridement is standard care in the management of DFU, typically undertaken serially to facilitate healing[12–15], with weekly or second-weekly intervals representing the usual frequency when there is adequate blood flow for healing[11,16]. The procedure is routinely performed in the outpatient setting of the HRFS which can satisfy the requirements for infection control as well as the safety and comfort of both patient and clinician. While there is a lack of data on patients' reasons for attending or non-attendance to HRFS, a systematic review on reasons why people with diabetes could not attend diabetes education programs identified lack of transport, distance and parking, duration of appointment and other commitments, along with physical disabilities and financial reasons, as barriers to attendance. Patients' perception of the benefits of the consultation also influenced their decision of whether or not to attend[17].

Given the high rate of co-morbidities, depressive symptoms and poor physical functioning in people with DFU[18–21], the capacity of some patients to physically attend a hospital service may be a limiting factor and have a negative impact on the quality of life for some[22]. Patients' preferences regarding treatment frequency, the perceived benefits, impact of mobility and how they travel to appointments are potentially meaningful areas to investigate.

The aims of the study were to: a) investigate the actual and the preferred frequency of attendance for treatment, including sharp debridement, for patients with DFU; b) understand what patients with DFU value about their clinic attendance at the HRFS; c) determine the extent to which patient-reported mobility may affect attendance; d) document the mode of transport used, duration of time spent on their clinic visit, and any out-of-pocket costs related to attendance.

Methods

A survey was developed *de novo* by the investigators and tested by two consumers whose input was incorporated. The study was approved by the Human Research and Ethics Committee of the lead site, with local site-specific governance approval at each of the three participating services. A patient information sheet was provided to all potential participants. Consent was enacted when the participant agreed to answer the survey questions. The three sites included two hospitals based in a capital city and one regional city hospital. Their models of care were consistent with the state-wide standards for HRFS[3]. All services were located within a hospital, non-admitted patient setting coordinated by a senior podiatrist and with interdisciplinary team consultations with relevant disciplines.

The estimated clinic population was n=150 patients, of which 60 participants was considered as a reasonable sample of eligible clinic patients. A convenience sample was used, with clinicians being requested to recruit to a target n=20 participants for each site. Inclusion criteria were people with DFU of minimum 4 weeks duration, attending one of three HRFS for wound management. Potential participants were given an information sheet with a QR code linked to the online survey. Participants could alternatively complete a paper version, have the treating clinician document their responses, or request that the investigator phone them to complete the survey by phone. This choice was provided to improve the uptake of the survey and eliminate the potential barriers of poor literacy, use of technology or a preference not to provide responses to their treating clinician. All responses were entered into a password protected electronic database, Research Electronic Data Capture (REDCap)[23], which was generated for the study and open to the site investigators.

Survey questions were predominantly multiple choice, with the exception of home suburb, distance walked and time taken to attend location of care, and cost of parking. One multiple choice question, "How important do you believe these are to you?", asked participants to rate the perceived importance using a 3-point Likert-style scale from 'not important' to 'very important' (and including 'not applicable') for the following: debriding with a scalpel (cleaning) of my foot ulcer to remove dead skin, slough etc; changing the dressing on my foot ulcer; offloading (special shoe, boot, cast or padding to protect my foot); getting a doctor to treat my infection; getting a doctor to treat my diabetes; getting a diabetes nurse educator to help manage my diabetes; learning about my feet and how to care for them. Open-ended questions asked why (if applicable) participants preferred to attend the HRFS more or less often, and lastly a question asked participants to write about the benefits and challenges of attending for treatment of a foot ulcer. The questions regarding whether participants would wish to attend more frequently if this meant their ulcer might heal faster was posed as follows:

> *About half (50%) of foot ulcers heal within 3 months. Whether a foot ulcer heals and how long it takes, depends on a number of factors. These can include how severe the*

ulcer is and how long it has been present, circulation and treatment effectiveness. If attending the foot clinic every week meant that you were likely to heal 15% faster, would you attend more often?

The multiple-choice answers were: yes, no and "I already attend every week (or more often)".

Results

Participant demographic data

During a 10-week period (July to October 2021) clinicians approached patients to participate in the survey. Since this was during the COVID-19 pandemic, the participating HRFS followed state and national guidance with regards to hospital appointments (ref DFA). All face-to-face consultations were maintained for all initial and most follow-up consultations, with follow-up consultations replaced with telehealth where clinically indicated and deemed safe[24]. A total of 60 participants completed the survey from a possible 462 people who attended the services during the data collection period. Demographics for participants is given in Table 1. All participants were between 40 and 65 years of age and only eight (13%) were employed.

Frequency of attendance: actual and preferred

Frequency of attendance was every second week for almost half the participants (n=28). Table 2 indicates the frequency of attendance reported by respondents and their preference for how frequently they preferred to attend. A total of 12 of the 15 reporting 4-weekly attendance were from the regional city HRFS. When asked whether they would prefer to attend weekly if this were to hasten healing time by 15%, 51 (85%) indicated they would attend more often.

What patients valued about their consultation

Table 3 summarises the findings of the value to participants of attending the HRFS. Receipt of sharp debridement, dressing changes, pressure offloading and the education they received on foot self-care were the most highly rated. Not all participants were aware of or valued diabetes management as part of the service. It should be noted that five people who did not have diabetes completed the survey.

How participants perceived the impact of health and mobility on ability to attend the clinic

Around half of the participants (n=33/60) reported being "well and mobile enough to attend without difficulty"; 11 (18%) reported that they required the assistance of a family member or carer to attend the appointments (Figure 1).

How participants travelled to the clinic

Eight (13%) participants travelled by public transport to the HRFS and reported walking an average 462 metres; seven (12%) travelled by ride-share or taxi, walking an average of 218 metres; 21 (35%) drove themselves by car, walking an average of 308 metres; 19 (32%) were driven by a family member, walking an average of 276 metres; and one walked 2km from their home to the service. Five participants used a wheelchair or scooter instead of walking from their main mode of transport into the clinic. One participant used Commonwealth Aged Care funded transport and one used their National Disability Insurance-funded support worker (Figure 2).

The median time participants spent on their overall visit (travel and treatment time) was 2 hours; this was the same for all centres. Those attending the large capital city centres lived predominantly within a 10km radius of the hospital, with three (8%) travelling greater than 30km. The median distance from the participants' home to the regional city hospital was 19km and six (30%) travelled over 30km. In addition, a total

Table 1. Survey participant demographics

Variable	Participants n (%)
Age (%)	
Over 40 and less than 65 years	25 (42%)
Over 65 and under 85 years	32 (53%)
Missing data	3 (5%)
Gender (%)	
Male	42 (70%)
Female	18 (30%)
Diabetes type (%)	
Type 1	6 (10%)
Type 2	47 (78%)
Don't know or other	2 (3%)
Nil diabetes	5 (8%)
Diabetes duration (%)	
Less than 5 years	10 (17%)
5 or more (less than 10) years	6 (10%)
10 or more (less than 20) years	15 (25%
20 years or more	24 (40%)
Employment status (%)	
Employed full-time	3 (5%)
Part-time or casual employment	5 (8%)
Unemployed	3 (5%)
In receipt of disability pension	15 (25%)
Retired	32 (53%)
Missing data or declined to answer	2 (3%)
Marital status (%)	
Married	35 (58%)
Unmarried	25 (42%)
Carer status (%)	
No carer responsibilities	52 (87%)
Caring for a family member (not a child)	4 (7%)
Caring for a dependent child	4 (7%)

of 13 participants (22%) were aware of the parking fees they had paid, with an average spend of $13 per visit. Additional comments from participants are shown in Figure 3.

Discussion

This consumer survey found that most participants rated debridement, dressing changes, pressure offloading, management of infection, and learning about caring for their feet as very important. Management of diabetes was somewhat or very important for 82% of those with diabetes. Second-weekly attendance for treatment was most common, and weekly or second-weekly visits were preferred, which is consistent with other reports[11,16]. There was an indication that some participants attending less often would attend weekly if this would hasten healing by as little as 15%, suggesting this is a meaningful difference for at least some participants. However, as this question was potentially leading, the result is not conclusive.

One quarter of the participants attended every 4 weeks or less often, which may not represent standard care[14]. It is not known to what extent treatment every 4 weeks is based on clinician recommendation, time constraints of the service (appointments unavailable), or due to patient factors but a similar number of participants also reported 4-weekly care as their preference. In previous qualitative research, reliance on family for travel to appointments, the indirect treatment costs which include travel and parking, as well as the challenges of maintaining employment with frequent visits, have been described as having negative effects on the quality of life for people with DFU[25–27].

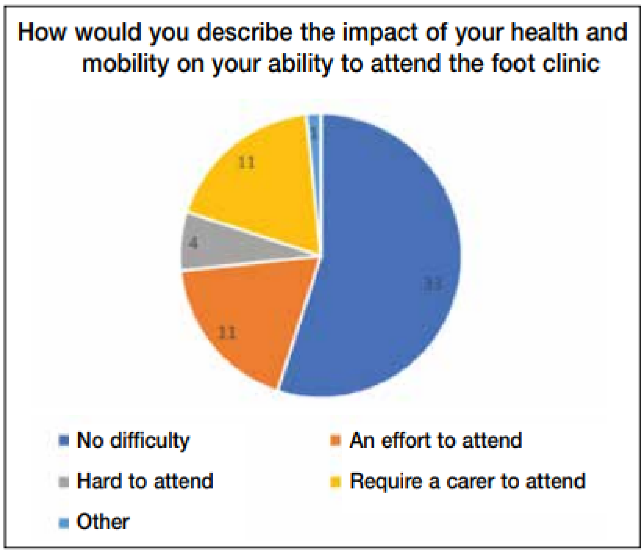

Figure 1. Participant-reported impact of health and mobility on clinic attendance

Table 2. Patient-reported visit frequency and preferred frequency

	Patient-reported visit frequency	Patient preference for visit frequency
More often than weekly	0	1
Weekly	8	18
Every 2 weeks	28	17
Every 3 weeks	9	5
Every 4 weeks (or less)	15	14
Don't know / no preference	–	5

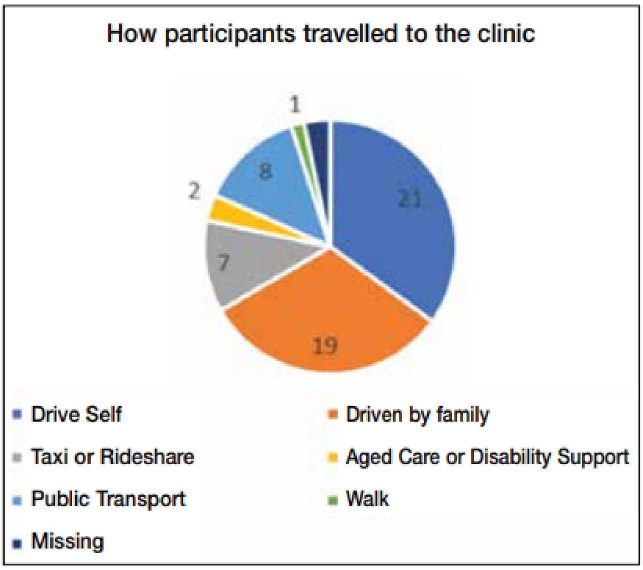

Figure 2. How participants travelled to their clinic appointments

Table 3. Participant responses to how they rated the importance of different aspects of care within the HRFS

Aspect of care	Very important	Somewhat important	Not important	Not available	Missing data
Debriding with a scalpel	53	3	1	–	3
Changing the dressing	53	3	1	–	3
Offloading	53	3	1	–	3
Getting a doctor to treat my infection	47	6	1	3	3
Getting a doctor to treat my diabetes	37	8	2	9	4
Getting a diabetes nurse educator to help manage my diabetes	30	15	3	10	2
Learning about my feet and how to care for them	52	4	0	1	3

While there is observation data and indirect evidence that more frequent debridement is beneficial in the management of DFU[16,27–30], the one prospective study of sharp debridement, which controlled for visit frequency (weekly), found weekly and second-weekly sharp debridement to have similar outcomes at 12 weeks[28]. There was also a high drop-out rate, suggesting that the regimen of weekly visits was not acceptable or feasible for all participants. In practice, some wounds are likely to require more aggressive debridement than others due to the presence of infection, callus or more non-viable tissue[11,13]. The patient's capacity and desire to attend as well as clinic resources will also impact frequency of attendance[11].

A key finding of the current survey was the high number of participants who relied on a private vehicle (car) to attend the HRFS, with few using other means such as public transport. Private car was the main modality used by 84% (n=50) of respondents, and 100% of those attending the regional city hospital. Furthermore, the driving responsibility was conferred to family members of 33% of respondents.

Loss of lower extremity function for people with DFU and the restriction to mobility as recommended treatment are known issues for those experiencing foot complications[20–22]. Almost half of the participants in our survey reported having physical limitation affecting attendance, and travelling by car was associated with less walking, particularly if someone else drove them to the appointment. Only two respondents indicated they used age and disability supports to travel to the clinic. Reliance on social supports for transport was also identified as a key theme in small qualitative study by Palaya et al (2018)[27]. Our survey data further highlights the needs of this patient group with respect to transport support. This should be further explored to determine why participants, many of whom would be eligible for this assistance, were not using these supports.

In terms of access, these results suggest that not having the use of a car is a limitation for those needing HRFS care. In our survey, a quarter of study participants were in receipt of a disability pension and only three reported being in full-time employment. Both the cost of running a car (not reported) and parking costs are potential barriers to those on low incomes who would already be burdened with costs of treatment[29]. While there can be many influencing factors determining ease of access to services and how often, research on geographical access to healthcare services shows that distance and transport availability are important determinants of healthcare utilisation, with people in disadvantaged groups likely to rely on public transport[30,31]. The geographical distribution of current HRFS means that many patients are not within close proximity[32,33]. Where clinics exist, consideration as to distance from car parking and extending clinic hours to accommodate patients who rely on working family members to drive them to appointments may warrant consideration.

- Treatment is always changing so new learning for me all the time.
- …great podiatrists and they really know their job.
- It's just mobility is the problem. Knee and lower back pain.
- I also use a disability scooter. It's an outing for me and the podiatrists are so kind and so good. It's a pleasure for me to come in.
- The treatment I get here is very specialised and you do not get it in any other department.
- Thank you for the disability parking.
- I can't use community transport because I travel from outside your District and there is too much walking to use public transport.

Figure 3. Comments from participants

International data show that timely presentation to specialised services is associated with better outcomes for people with DFU[34]. However, Australian data suggests a significant proportion of patients with DFU admitted to hospital have not accessed specialised a HRFS prior to being admitted. Manewell et al[35] reported that 43% of patients admitted for DFU were not known to have attended the HRFS, and Plusch et al[36] found 75% of people admitted for diabetes foot infection had not accessed the HRFS. These represent missed opportunities to avoid admissions and amputations. It is not known whether physical access or transport were barriers in these instances but understanding and mitigating any impediments to access are likely to improve healing outcomes.

These survey results highlight a potential problem with physical accessibility to services and raises the question as to how accessible the services are for people with chronic illness and poor mobility who are without family, aged care or disability supports to enable attendance.

Limitations of this study is the use of non-random sampling and the higher-than-expected patient clinic numbers which meant the sample size was proportionally small. Both factors limit the generalisability of the results. There is an inherent bias towards those participants who were able to attend the HRFS. Patients with DFU who did not attend or who rarely attended were not captured in the survey. Some bias toward valuing different aspects of care is also likely. While the participants' identifying information was not included in the responses, the majority chose to complete the survey via the phone or during their treatment visit with the clinicians, hence they were not fully anonymous. The option to complete electronically via a QR code link to the survey would have provided anonymity but was not preferred by participants, and only one participant elected to complete the survey this way. Provision of phone or treatment visit options for completing the survey enabled participation for those with impaired vision, reduced cognition, low literacy and anyone without the access or capacity to use a smart phone or computer. However, we acknowledge that participants would have been disinclined to respond in a way which was negative towards the service while in the presence of their treating clinician. Results of the question "How important do you believe these are to you?" should be interpreted with respect to the likelihood of bias.

Other variables were also not explored in this study such as unavailability of appointments, time constraints for people working or with caring responsibilities, cultural safety of the HRFS for the culturally diverse patients who attend the clinics, or preferences towards particular provider(s). Moreover, while the survey was used across three HRFS sites in the current research, it has not been validated or tested with regard to reproducibility.

Lastly, our study enrolment included five respondents (across the sites), who were being treated for chronic foot ulcers related to neurological or vascular complications but who did not have diabetes. The data from these participants were retained in the study as their non-diabetes foot care requirements were closely aligned to those of people with DFU, hence their admission under the care of the HRFS for interdisciplinary management, including debridement by a podiatrist.

Conclusions

Attending specialised interdisciplinary teams for non-admitted care of foot ulcers has been shown to help reduce the risk of hospitalisation and to improve clinical outcomes; however, in this survey, a high proportion of participants had challenges in mobility impacting their capacity to attend and used travel by private vehicle to attend, with a significant number being reliant on others to drive them. While telehealth in DFU care is becoming more commonplace post the COVID era, some aspects of care such as sharp debridement need in-person HRFS specialist care. Further research to understand the reasons for non-attendance (or infrequent attendance), potential solutions and the impact on admissions and healing outcomes is needed.

A recommendation from these data is that HRFS providers aim to mitigate potential barriers to access for new and existing clients and seek to draw on supports which may be available to patients to help attendance. Government commissioners of HRFS should consider the clients for whom they are targeted. Distance required for patients to travel to services, proximity of parking, availability of drop-off bays, public transport access and opening hours should be considered, with the aim of maximising the reach and utilisation of services which can minimise hospitalisation and amputations.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

The study was approved by the Royal Prince Alfred Hospital Research Ethics Committee (2020/ETH03244) with local site governance approval from Royal Prince Alfred, Concord and John Hunter Hospitals.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. In-kind support was given by the hospitals of the participating authors.

Author contribution

VN designed the study, prepared the ethics submission, collected data, analysed data, wrote the paper, consulted with other authors for their review and input into the final submission, prepared the submission and is responsible for the integrity of the work. JZ was consulted and agreed to the design of the study, was responsible for conduct of the study at John Hunter Hospital, contributed substantially to the acquisition of the data, reviewed and approved the final version of the work, and shares responsibility for the integrity of the work. GF was consulted and agreed to the design of the study, was responsible for conduct of the study at Royal Prince Alfred and Concord Hospitals, collected data, reviewed the paper and shares responsibility for the integrity of the work. SM, MC and PR collected data, reviewed the submission, approved the final submission and share responsibility of the integrity of the work. ST and JA provided academic oversight as academic supervisors of VN (PhD candidate) and had input into the research design, JA is the coordinator PI on the ethics submission, ST and JA contributed to the critical review of the manuscript, approved the final submission and share responsibility for integrity of the work.

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Chapter 5: Integrating Discussion

This thesis examines the use of non-surgical sharp wound debridement in managing Diabetes-related Foot Ulcers (DFU), a late complication of diabetes associated with high comorbidities and pre-mature mortality. The evidence for sharp debridement, albeit derived from observational data, has led to regular sharp debridement being accepted as standard care and the preferred method of debridement to promote healing of DFU (386). Despite the emergence of newer techniques and agents, sharp debridement is widely promoted as being the most rapid, selective, and cost effective in the treatment of DFU and can be undertaken with minimal and inexpensive instruments. Furthermore, some retrospective studies suggest a dose dependent relationship with more frequent sharp debridement associated with better healing (441, 470, 472). However, there was no prospective data on which to base decisions about frequency of treatment. In healthcare, more so in publicly funded services, resource constraints necessitate the provision of evidence-based care that demonstrates the value and efficient use of resources, particularly in the public health setting. For patients, how often they need to travel to a clinic to receive treatment, is also potentially important. The studies in this thesis focus on the frequency of debridement provided by podiatrists as part of their scope of practice in podiatry and High Risk Foot Services (HRFS).

The first study explored current practice through an online survey of clinicians, mainly public sector employed podiatrists, who perform sharp debridement in their routine clinical practice. The survey found that NSW Health employed podiatrists use sharp debridement as their mainstay method of debridement in all healable wounds, performing sharp debridement of DFU at every visit (572). The correlation between visit and debridement frequency meant that treatment and debridement frequency are virtually synonymous. The results also indicated that both weekly and second weekly regimens are commonly practiced (572). The factors ranked by clinicians as the most influential in determining frequency were the clinical indicators (slough, callus and infection) with staff resources being a constraint (572). The latter may explain why podiatrists practicing in more regional and rural areas debrided their patients' DFU less often than their metropolitan colleagues, as found in the survey.

The second study, a randomised study of two different frequencies of sharp debridement included 122 participants, across seven treatment centres, with participants randomised to receive sharp debridement weekly or every two weeks. Healing outcomes were assessed at 12 weeks (573). Modified intention to treat analyses of the data, using independently assessed digital images of the participants' DFU, found no between-group difference in the proportion of DFU which healed completely at 12 weeks with approximately half in each group, achieving complete healing (573). Sensitivity analyses using clinician assessed outcomes and per-protocol analysis of participants who completed the study, also did not show a statistically significant between-group difference, although there was a non-significant 15% higher wound closure for the group that received weekly debrided DFU compared to the group whose DFU were debrided every second week (573).

The final study, a survey of 60 patients attending one of three High Risk Foot Services and receiving sharp debridement, was undertaken to provide insights into their experiences of treatment. Sharp debridement was a valued aspect of their treatment and some were prepared to attend more often if they thought it would provide even modest improvement in healing (574). However, the survey found a significant proportion of participants experiencing mobility deficits with a high reliance on travel by car to appointments, much of which was provided by a family member (574).

The contribution and implications of these findings to the field, on providers and consumers will be discussed and future research directions proposed.

Staffing Resources and Sharp Debridement

Services providing care for people with DFU must balance their resources to provide sufficiently intensive treatment for existing patients of the service while also maintaining capacity to accept urgent, new presentations. Prompt access to specialised interdisciplinary teams, including podiatrists, for managing DFU is reported to improve patient outcomes such as reduced hospital admissions and amputations (225, 456, 538, 575-577). Both timeliness and specialisation are important (536, 551). Specialised teams typically consist of clinicians with expertise in infection and peripheral arterial disease management, diabetes, wound care, patient education, pressure offloading, and sharp debridement, as these are the central tenets of evidence-based treatment (286). Nutritional support and psychological interventions may also be included as there are some associations with malnutrition and nutritional deficits (283, 578) and depression with DFU (264, 579). Specialised clinical teams, to manage specific health and medical conditions is part of contemporary best practice more broadly and represents high value compared to treatment delivered by a single discipline(580). In a practical sense, these models of care also have potential to minimise the number of separate visits to a health facility for patients.

With regards to the workforce requirements podiatrists within the interdisciplinary team typically assess and treat every patient with DFU at every visit, often coordinating patient care and the service(232, 456, 538, 544, 581, 582). The unique skill set and scope of practice of podiatrists means they provide offloading, assessment of infection, and ischaemia and provide local wound care, including sharp debridement with elements of patient education and care co-ordination in their role (456, 582). The survey responses in this thesis confirm the hypothesis that NSW Health employed podiatrists use sharp debridement as their mainstay method of debridement in all healable wounds and debride at every visit. Prior to this study, Quinton et al., in their survey of Australian podiatrists, also found that podiatrists in public sector roles would "always" perform sharp debridement on healable DFU (582), while Swanson et al., in their broader, global survey of wound care clinicians from all disciplines, reported only half of Australian respondents were using sharp debridement frequently (583). The results of these two previous surveys, while less targeted to sharp debridement by podiatrists, support the view that podiatrists (as a discipline) are more likely to perform sharp debridement than other wound care practitioners.

Since NSW Health employed podiatrists debride at every treatment visit, treatment and debridement frequency are synonymous in the context of these public sector podiatry and HRFS (572). The time intervals between sharp debridement treatments were shown to vary, however patients were most likely to have their wounds debrided either every week or every second week according to 68% of clinician participants who debridement every week (29%) or every two weeks (39%) (572). Clinicians reported clinical evidence of callus, slough, and infection guided their decisions about treatment frequency, with staff time, being a limiting factor in debridement frequency (572). Placing these findings in the context of the availability of podiatrists as a workforce, it is important to evaluate whether weekly debridement improves the speed and degree of healing or whether equivalent healing times can be achieved with less frequent debridement. If fewer patients required weekly debridement or if weekly treatment was provided for a shorter period of time , there would a potential cost benefit to the health system and a reduction in clinician time required for direct patient care. The availability of more clinician time may enable new patients to be seen more quickly, or clinicians could be redirected to other important activities such as quality audits and research. The results of the randomised study presented in Chapter three are therefore potentially impactful to the individual patient, patient populations, clinicians, and the health system more broadly.

Internationally, podiatrists are a reported to be a limited resource with variable access even within countries where podiatrists are trained and employed (232, 456). Recently published Australian and NSW Government workforce data shows numbers of podiatrists are lower in NSW, and projected supply unable to meet the current and projected demand for public sector podiatry care (457, 458, 584). Within NSW, where the studies included in this thesis were conducted, there are 20 registered podiatrists per 100, 000 population, the majority of whom work in private practice, both at the State and National level (457, 585). In their PAIGE study, Couch et al (2023), surveyed both private and publicly funded podiatrists in a sample representing 21% of all registered podiatrists (585). They reported low numbers in rural areas with rural podiatrists indicating that patients were more likely to wait > 15 days for an appointment (585). Our findings that rural and regional podiatrists debride their patients' DFU suggests less appointments are available outside metropolitan areas and are consistent with these findings (572).

In the relative absence of detailed descriptions of podiatric practice (456, 585), the clinician survey presented in Chapter two provides useful baseline data on sharp debridement practice and the clinical reasoning of clinicians who commonly perform sharp debridement. In the current study, it was evident that podiatrists were following the best practice guidelines of the time (380-382) and more contemporary guidance from the 2023 IWGDF which advocates non-surgical sharp debridement over other modalities, including surgical sharp debridement (386). Our clinician respondent rarely used other modalities except for hydrogels, which were sometimes or occasionally used, with results suggesting this was used as an adjunct to sharp debridement (572).

The survey response rate (n=75) included 41% of the State's podiatrists, including 28 (37%) practising in regional or remote areas (572). This participation rate means the results are likely to be a true reflection of the current state of practice amongst NSW Health-employed podiatrists but may be less representative of debridement practice in other Australian states or other countries.

Fewer respondents rated factors unrelated to the wound, such as patient adherence to appointment attendance, transport access, consultation fees, parking and transport costs impacted debridement frequency as important to debridement frequency, when compared to clinical indicators and staff time (572). These non-clinical factors relating to patient access did not reach the top four determinants as ranked in importance by clinicians. The majority of clinician respondents were podiatrists employed in the public health system. As such, their consultations were provided at no cost to the patient. The targeting of public sector podiatrists, explains why respondents ranked cost lower as a factor in determining debridement frequency, compared to other variable. However, even when consultation fees are not required, there are indirect transport-related costs to clinic attendance. Furthermore, the low workforce numbers and maldistribution of podiatrists in Australia, would mean that many people with DFU would be reliant on the services of private podiatrists. There is substantial uptake of Government rebates on private consultations for podiatry which is included in the cap of five for allied health consultations. Additional consultations may be approved for Aboriginal and Torres Strait Islander people. Most podiatrists charge a gap fee (585). The need for effective use of publicly funded podiatry services particularly pertinent in the context of local data from a study by Tehan et al (2023) finding socioeconomic disadvantage is a predictor of poorer healing outcomes in people with DFU (283).

Impacts of frequency of sharp debridement on patients

The high drop-out rate in participants of the randomised study suggests that for some patients, frequent, weekly attendance could not be sustained. There are broad-ranging patient and service-related factors, that impact service accessibility and whether patients will choose to attend. As described by Horigan et al (2017) patient choice of attendance will be based on the beliefs regarding the benefits (195, 196) weighed against the barriers of time, cost, travel, and competing commitments. Our patient survey was designed to explore these and provided insights into the challenges of attendance extending HRFS.

Sixty patients receiving sharp debridement at one of three High Risk Foot Service (HRFS) participated in the survey. Relatively few(13%) reported attending weekly, with half attending every second week and the remainder, less often. The earlier clinician survey results suggested around a third of patients would receive weekly debridement. There are several possible reasons for the apparent difference between clinician and patient reported sharp debridement frequency. One third of patient respondents were receiving care at a regional city hospital which provides service to broader geographical area. Access for regional dwelling patients is more challenging due to the longer distances travelled compared to patients attending the two major city hospitals hence a higher proportion of patients might be expected to attend less often. Secondly, the patient survey was undertaken after the results of the randomised study were published, hence clinicians (many of whom had been involved in the RCT) may have modified their practice in-line with new evidence comparing weekly and second-weekly debridement. Lastly, the patient survey was undertaken during the late stages of the Covid-19 pandemic during a period of workforce challenges. While HRFS remained in operation, there was pressure to minimise any unnecessary hospital visits and this may have led to less frequent attendance.

The patient survey also intended to explore potential logistical barriers such as cost and mobility which have been identified in systematic reviews as being associated with non-attendance (195, 196). The survey revealed a patient cohort that relied heavily on car travel to attend appointments, with 84% travelling by car and few (13%) using public transport. This may be due to the impact of poor physical function. Nearly half (45%) of those surveyed, reported poor mobility and of these, half required assistance from a family member or carer to attend. Poor physical condition reduced physical activities and co-morbidities experienced by people with diabetes and in those with foot complications are widely documented (181, 586) and likely contribute to the high rate of car usage for travel to appointments. It is also true that patients of the clinic would have been educated to minimise walking. In addition, according to standard care, the majority would be wearing pressure offloading devices which might make walking more arduous. As such, being driven to the hospital would be more desirable.

The walking distance from carpark to the clinic, being around 300 metres may explain the need for a family member to drive, allowing the patient to be “dropped off” nearer to the entry of the service, although the difference in the estimated distance was small. Despite the physical barriers to attendance, aged care and disability transport supports were rarely used despite half of participating patients being over 65 years of age and 40% has diabetes duration over 20 years.

Driving distance was not excessive for most participants which is expected since two are in a major City, well serviced with regards to HRFS access. A third of participants however were attending a regional City and of these, 30% were travelling 30km or further to attend the clinic with a median distance to the clinic of 19km. The impact of distance to a service was highlighted in a study by Linton et al (2021) (587). In their audit, the majority of patients admitted for partial foot amputations had not accessed the District’s HRFS prior, and fewer than half had accessed the publicly funded podiatry services (587). This represents missed opportunities for earlier intervention that may have avoided the admission. While there was an increase in use of services post amputation, this utilisation appeared to be linked to proximity of the service to patients’ place of residence highlighting how distance can impact access for patients with foot complications (587).

Despite participants of this current patient survey attending less often than was expected (from the estimates of the clinician survey), many patients responded that they would attend every week, if it meant even a small increase in the speed of healing. Overall, respondents highly rated the care they received across all aspects of treatment and this may explain their desire to attend more often.

It is of interest that so few participants were employed. This may reflect the age and poor health status of the patient population. It may also be due to inability of those employed to access the service due to the competing work commitments. None of the HRFS provided after hours consultations. From the current data and what is known from related research, it can be inferred that having a sufficient number of services in locations near patients with high prevalence of diabetes, transport assistance, closer parking and extended hours of operation would improve opportunities for access to treatment for prevention and management of DFU.

The major limitation of the data on patient preference is that the population surveyed were those who were attending HRFS. People for whom clinic attendance was challenged by lack of transport access, physical limitations or competing demands are likely to be under-represented in the survey respondents. Furthermore, people with DFU who could not overcome these barriers to attend, were not captured at all. There is also likely to be some bias in the responses regarding what patients valued about the service. Patients may have felt more inclined to respond favourably when clinicians were recording their responses, as was often the case.

Does more frequent (weekly) debridement improve healing outcomes?

Before the prospective randomised study in this thesis, published data from observational studies suggested that weekly debridement would be better for ulcer healing than less frequent debridement, such as every second week (441, 470, 472). Steed et al in 1996, were the first to document that sharp debridement of a chronic DFU was not a one-time event and that services providing frequent maintenance or serial debridement could positively impact healing outcomes (441). Saap and Falanga (2002) investigated whether DFU, which needed and received more complete removal of non-viable tissue, would heal faster and found a positive association between higher scores of effective debridement and complete wound closure (471). The study by Cardinal et al (2009) (471) that followed over a decade later than Steed's was again, a post-hoc analysis, and showed a positive association between more frequent debridement and better healing(470). Wilcox (2012) published retrospective data from 59464 participants with DFU showing an odds ratio off 4.26 (4.2 – 4.31) for healing when debridement occurred weekly (or more often) (472). Only one prospective study of sharp debridement has been published in which Piaggesi et al., surgically debrided DFU in procedures which included bone resection and primary closure (469). As this was a single surgical debridement, this study does not inform the practice of serial sharp debridement and healing by secondary intention.

In reviewing the literature on sharp debridement and images contained within, it became apparent that we need to differentiate between non-surgical sharp debridement performed repeatedly (serially) and surgical debridement, which falls under the surgeon's domain and is not intended to be performed regularly. When writing about wound debridement, authors use different terms with 'conservative sharp', 'sharp', 'maintenance' and 'serial' to describe a type of sharp debridement which removes non-viable tissue to some level of bleeding base but which does not extend into the viable tissue. Some authors refer to both sharp and non-sharp debridement methods as maintenance (405, 476). Throughout the clinician survey and randomised study, the term 'conservative sharp wound debridement' was used to make a clear distinction between sharp debridement and surgical sharp debridement. While this is consistent with some authors, the procedure that is commonly practised and that which was used during the randomised study could also be described as sharp debridement. This terminology, 'sharp debridement', is used in the IWGDF guidance and has been adopted in the latter stages of writing this thesis.

Clinical guidelines have, for many years, recommended frequent sharp debridement be performed often and serially but without any prospective clinical studies of this type of sharp debridement to guide how often it should be repeated. Standard care, as described in research protocols, were investigated in the literature review to help us understand how this standard care is interpreted. Four recent, randomised interventional studies for treatments to improve ulcer healing were explored, all published in 2018. These reports referenced sharp debridement as standard care for participants; one reported "weekly treatment during intervention period with frequency of debridement at investigator discretion", another reported investigator discretion was used resulting in an average of 5.3 debridements in 20 weeks, one indicated that usually debridements were performed once a week and another indicated that "patients visited a local study centre weekly for the duration of the study for wound assessment, debridement"(312, 313, 397, 588). From these reports, it could be interpreted that the clinical judgement of the treating clinician prevailed, but weekly treatment with sharp debridement is more often the expected frequency.

In the absence of prospective data on the optimal dose of debridement, the randomised study included in this thesis chose to measure the effect of weekly sharp debridement compared to sharp debridement performed every two weeks. The aim was to determine whether there was a benefit in more frequent, weekly sharp debridement. The study findings would be highly meaningful for patients and from the perspective of service providers working with finite resources.

The hypothesis that weekly debridement would promote healing more than second weekly, with a 30% between-group difference, was tested. While this was a substantial effect size to propose, there was limited data on which to base our effect size. A large, three-fold difference in the proportion of wounds that healed with weekly (or more frequent) debridement compared to debridement every two weeks was detected in the audit by Wilcox et al (2013) (472) and data from the lead centre in our randomised study (unpublished) showed a 36% difference in healing at four weeks between DFU debrided weekly, compared those debrided every second week. The current study however did not detect a difference between the two groups, with the results upheld in both sensitivity and completers analyses. The secondary outcome of per cent wound closure showed weekly debrided wounds had a 15% higher wound closure rate than those debrided every two weeks but this was not statistically significant (573).

The study's strength is the prospective design which allowed variables such as visit frequency to be controlled between groups. Subjects were well matched including by ulcer size, assisted by stratification of ulcers by size at randomisation. The pragmatic design, closely following standard care, which was defined and agreed on by the participating investigators and aligned with evidence-based practice and other contemporary reporting of interventional studies of DFU. The study was multi-site with seven participating centres, with most participants recruited from four hospitals. The number of participating centres required to meet recruitment numbers, also improved the validity and generalisability of the results.

To reduce potential bias, digital images of the wounds were taken to validate the outcome. The primary outcome was based on the assessment of these images by wound care clinicians. The number of assessable outcomes based on these images was 78, because some participants did not have an image. By using the clinician assessed outcome, the healing outcome of a further 31 participants were available for analysis which returned the same outcome (573).

Given the current evidence-based recommendations for pressure offloading in irremovable knee-high devices, it may be considered a weakness of the study, that pressure offloading used was not fully optimised. The choice of pressure offloading used in the study was limited to ankle or knee-high devices, both removable. As expected, when a removable device is used, the adherence to wearing the devices in the study was both variable and sub-optimal. The decision to use removable offloading was made to align with standard care and that which is employed routinely in the participating centres. Imposing the requirement for non-removable devices would be a significant barrier to patient participation in the study, to the extent that participants would no longer be representative of the patients we treat with sharp debridement in centres which participated in the study. A similar approach was taken with other randomised, interventional studies published in recent years where few participants are reported as wearing irremovable knee-high devices and offloading choices being at the discretion of the investigators (312, 385). Overall, half the participants' DFU healed at 12 weeks. This is a favourable outcome (comparable to other studies) and suggests that standards of care at the participating centres, including removable offloading, were acceptable. Interestingly, some reports of patients with DFU treated with irremovable devices have also shown better healing outcomes when used (298). It is expected however, that limiting the trauma to the DFU by using more rigorous offloading such as irremovable knee-high devices, would substantially alter the wound environment, reducing inflammation, callus, and the requirement for debridement. In this regard, the randomised study results are relevant to DFU treated with removable offloading and may not directly apply to patients whose wounds are treated in irremovable knee-high offloading devices.

What is the impact of sharp debridement on the wound?

Within this thesis, I also sought to explore the existing evidence for how sharp debridement may support healing and prepare the wound bed for healing to prosecute the belief that it stimulates healing by removing non-viable tissue, senescent cells, callus, and bacteria. The level of sharp debridement routinely performed in the non-admitted setting does not, according to the study by Kim et al (2018), substantially reduce bacterial load, and even more extensive surgical debridement may fail to achieve a wound free of bacteria(498). This is likely due to the invasive nature of biofilm presence deep within the tissue of a chronic wound. Based on in-vitro animal models and a small number of human participants, there is some evidence that sharp debridement plays a role in disrupting biofilm, a complex organisation of bacteria within a polymer, resistant to host immune defences and most antimicrobial treatments. It is hypothesised that sharp debridement interferes with the biofilm and removes some, but not the majority, of the bacteria from the wound. Combined with antimicrobial and anti-biofilm agents, this may be sufficient to mitigate the pro-inflammatory effect of high bacterial load within the DFU or at least allow antimicrobials to be more effective alone or in combination with surfactants which might impede biofilm adherence (390, 511, 589).

Callus at the wound edge is a particular feature of DFU when compared to other chronic wound types and effects of callus removal from the wound edge is recommended (383, 386, 444, 590). Data shows that removal of callus per se can reduce plantar pressure, which is one of the goals in healing DFU (529, 530, 542) however the studies reporting this, did not include active DFU. The effect of callus removal from an active DFU remains unproven. It is however likely that sharp debridement is more beneficial for DFU than other forms of debridement due to its capacity to remove callus, reduce plantar pressure and also to facilitate cell migration.The effects of sharp debridement of callus on the wound environment and healing warrant further investigation.

Future Research Directions to target sharp debridement

The participants in the randomised study were typical of patients who can access existing HRFS and their wounds were chronic and on average relatively small. They were receiving an acceptable standard of care, evidenced by the 50% rate of healing at 12 weeks. In the clinical setting, the extent and frequency of debridement would not be determined by randomisation, but the wound characteristics, service resources, clinician’s judgement, and patient preference which we understand will be influenced by mobility, transport access and other factors. In practice, DFU debridement may be more frequent than once a week in DFU with a high, visible burden of non-viable tissue and less than fortnightly when a clean granulating base is present and less callus and the survey of clinicians confirmed they use these indicators to guide debridement frequency. Saap and Falanga's debridement performance index (DPI) study suggests that DFU that need and received more aggressive debridement are more likely to heal (471). It was not used in the current study. The DPI is not a measure of the extent of debridement per se as it includes a scoring system which assigns the highest scores to wounds that do not have callus, undermining or necrotic tissue. It is however of interest and it is possible that images used in the current randomised study could be used to grade the visible extent of debridement by a modified but similar criterion. There is also scope for more research to better target the extent of sharp debridement that is indicated. The current study was not powered to detect difference in sub-groups of wounds but a larger randomised study testing the effect of debridement on healing and other markers of debridement effectiveness could determine the indications for intensified sharp debridement and additional agents or indeed when sharp debridement can be stepped down. Techniques to measure debridement effectiveness and better target treatment are being investigated.

Nakagami (2019) have reported on the use of a blotting technique for detecting the presence of mucopolysaccharides present in biofilm, before and after sharp debridement, in a preliminary study(488). The technique was evaluated on a small number of pressure ulcers (9). Their results are of interest as the blotting and staining technique can be conducted within a few minutes, after debridement, potentially helping to target and individualise sharp debridement. In their study, wounds without biofilm (determined by blotting), reduced in size by 14.4% (4.6-20.1), and those with biofilm increased in size by 14.5% (9.6-25.3) in 1 week (488).

Other research has used point of care devices to detect bacterial autofluorescence as guide sharp debridement (518, 519, 591-593). This technique does not differentiate biofilm from planktonic bacteria but warrants further investigation as means to detect levels of bacteria > 10^4CFG/g which is associated with delayed healing even without clinical signs and symptoms of infection (519, 593). Armstrong et al have recently published their post-hoc analysis of 138

DFU in which they measured clinical signs and symptoms of infection, bacterial autofluorescence and bacterial load as determined by gold standard quantitative methods (bacterial count > 10^4 CFU/g) from punch biopsies of the DFU. The technology improved the sensitivity of assessing for high bacterial load associated with delayed healing. This data, together the study by Rahma et al suggest a role in determining whether sharp debridement has effectively reduced bioburden during the treatment visit (519, 593).

Current research aimed at evaluating wound fluid from DFU for markers of inflammation, potentially some matrix metalloproteinases may also advance to serve as a surrogate measure to guide the extent and frequency of sharp debridement(417, 501, 594). Data from these techniques have potential to help us to better target sharp debridement, individualise the required frequency and intensity and understand its effects.

Conclusions and future research

The evidence from the robustly designed, randomised trial of weekly versus second weekly sharp debridement shows that these debridement frequencies are equivalent for wound healing. Therefore, in the absence of specific wound features that would necessitate more frequent debridement and without other reasons for additional patient visits to the service, second weekly debridement of DFU can be justified.

The results, while most applicable to the NSW and Australian models of care and podiatry scope of practice, would have implications wherever the standard practice of sharp debridement is to serially sharp debride the base and periphery of DFU. The latest International Working Group on the Diabetic Foot Guidelines reference the study included herein with a specific, new recommendation regarding frequency of debridement. This was the only randomised trial to investigate sharp debridement and the recommendations are consistent with ours.

With the evidence supporting rapid access to interdisciplinary specialised care (551), including sharp debridement for people with DFU, efforts to understand and address barriers to access at both individual and service provider levels are important. Future research should focus on people with DFU who are not attending HRFS to understand the reasons why, through choice or inability, they are not making use of these services. Understanding and addressing access barriers could significantly reduce morbidity and costs of DFU.

Emerging technologies which provide point-of-care data on the presence of potential impediments at the wound level, can allow for more individualised sharp debridement. With reliable and valid indicators to guide the extent and frequency of sharp debridement for individual wounds, treatments can be more concisely directed.

Reducing sharp wound debridement to second weekly for some patients has the potential to reduce the cost of care for service providers and burden of care for patient and families. Perhaps more importantly, finite resources may be redirected to provide rapid access for more patients.

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Appendices

1	Accepted Abstract to the 23rd International Symposium on the Diabetic Foot- Diabetes foot ulcer healing outcomes and patient adherence comparing ankle and knee-high devices
2	Publications – additional

1. Abstract – 9th International Symposium on Diabetic Foot (ISDF) The Hague, The Netherlands

Diabetes foot ulcer healing outcomes and patient adherence comparing ankle and knee-high devices

Nube VL [1,3], Frank G [1,2], White JM [1,2], Twigg SM [1,3].
1 Diabetes Centre, Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
2 Department of Podiatry, Royal Prince Alfred Hospital, Sydney, NSW, Australia
3 Sydney Medical School (Central), Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney

Background: Pressure offloading for diabetes-related foot ulcers (DFU) promotes healing, and irremovable knee-high devices, are recommended in guidelines. In practice, it is only a subset of patients who can and will accept wearing them, with a lack of data on the outcomes of other devices. This study aimed to determine what proportion of participants agreed to wear knee-high devices, the level of patient adherence to their use and healing outcomes at 12 weeks.

Method: Data from a recent randomised study of debridement was used, including participants who completed study visits. Inclusion criteria and method are detailed in the original published study (1) including adults with plantar DFU, excluding those with severe ischaemic or infection. Participants from five centres attended weekly for 12 weeks. Clinicians prescribed ankle-high or knee-high devices with a custom or non-moulded insole. Data on device selection, healing outcomes and self-reported adherence to wearing devices were available for reporting. Self-reported adherence was based on participants indicating the average time they spent wearing the device each day.

Results: Ninety-two participants were included, with wearers defined as those who reported wearing the device greater than av.> 6.5 hours/day, and non-wearers defined as those who reported wearing the device for less time than this. Knee-high devices were prescribed to 44 participants (48%), and 77% wore the device >6.5 hours/day. Other participants were prescribed ankle-high devices and 75% wore them av > 6.5 hours/day. Two participants had missing device data. Ulcer size in non-wearers (n=22) was 1.4cm2 (median 0.9cm^2) and 2.0cm^2 (median 1.1cm^2) in wearers (n=70). Proportion healed by 12 weeks; 58% overall, 57%

for the wearers and 59% for the non-wearers, 59% for wearers of the knee-high device and 53% for wearers of the ankle-high device.

Conclusion: These results suggest that in patients with small, plantar ulcers receiving weekly, specialised care, 53-59% will heal within 12 weeks in either ankle or knee-high devices. Poor healing trajectories should be identified early and necessitate optimising all aspects of care, including pressure offloading. The selection of offloading strategy must be based on DFU and patient factors as well as demonstrated efficacy.

Reference:1. Nube VL, Diabetes Care. 44 (12) 2021.

2.Publications – additional

Contributions to published work during this PhD candidature. These are in addition to the publications included in this thesis and cited in the relevant chapters. These papers are not part of this thesis.

1. Min, D., Nube, V., Tao, A., Yuan, X., Williams, P. F., Brooks, B. A., Wong, J., Twigg, S. M., & McLennan, S. V. (2021). Monocyte phenotype as a predictive marker for wound healing in diabetes-related foot ulcers. *Journal of Diabetes and Its Complications*, 35(5), 107889–107

2. Fernando, M. E., Horsley, M., Jones, S., Martin, B., Nube, V. L., Charles, J., Cheney, J., & Lazzarini, P. A. (2022). 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(1), 31–31.

3. McDonogh, C., Nube, V. L., Frank, G., Twigg, S. M., Penkala, S., Holloway, S., & Snyder, R. (2022). Does in-shoe pressure analysis to assess and modify medical grade footwear improve patient adherence and understanding? A mixed methods study. *Journal of Foot and Ankle Research*, 15(1), 94–94.

4. McMorrow, R., Nube, V. L., & Manski-Nankervis, J.-A. (2022). Preventing diabetes-related foot ulcers through early detection of peripheral neuropathy. *Australian Family Physician,* 51(11), 833–838.

5. Manewell, S. M., Aitken, S. J., Nube, V. L., Crawford, A. M., Constantino, M. I., Twigg, S. M., Menz, H. B., Sherrington, C., & Paul, S. S. (2023). Timing of minor and major amputation in patients with diabetes-related foot ulceration admitted to two public tertiary referral hospitals in Australia. *ANZ Journal of Surgery*, *93*(6), 1510–1516.