Technological developments in the assessment and management of diabetic foot ulcers

Thesis submission for Master of Philosophy (Surgery)

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ABSTRACT

There are more than 4,400 amputations every year in Australia because of diabetes. In 2005, more than 1000 people with diabetes died as a direct result of foot ulcers and lower limb wounds which accounts for 8% of all diabetes related deaths. The rates of diabetes-related amputations have increased by over 30% between 1998 and 2011 which reflects a concerning trend.

In 2019, the International Working Group (IWGDF) on the Diabetic Foot released guidelines focused on the main facets of diabetic foot management: offloading, infection control, wound healing interventions and peripheral artery disease.

Complex diabetic foot wounds and chronic wounds are at very high risk of limb loss due as they are difficult to heal and are at higher risk of infection. However, there remains limited options for treatment of these wounds. When diabetic foot ulcers develop in patients with peripheral arterial disease it often results in chronic, non-healing ulcers exacerbated by ischaemia with lack of oxygen and nutrition to facilitate tissue repair. The advancements in endovascular technology for treatment of peripheral arterial disease have been rapid, but the nomenclature and classification systems have remained antiquated and risk inappropriate treatment. All diabetic foot wounds need to be monitored closely as rapid infection and deterioration may occur without early intervention but improvements in the accessibility and accuracy of measurement tools needs to be developed.

This thesis is aimed at developing new technologies to prevent diabetic foot wound deterioration for limb salvage and reducing mortality.

The aims of this research are:

1. To evaluate the efficacy of using BTM in the reconstruction of complex diabetic foot wounds.
2. To use the NDKare phone application to assess its accuracy and practicality for diabetic foot ulcer wound size assessment
3. To critically evaluate the historical classification and management of chronic limb ischaemia and critical limb ischaemia with the development of the latest GVG guidelines

Research from this thesis has evaluated a new dermal template (biodegradable temporising template – BTM) which demonstrated in our prospective cohort study that all the patients with complex, chronic diabetic foot wounds were able to heal with BTM. Whilst it is difficult to extrapolate given the small number of patients within the study, the results were suggestive of potentially a relatively low infection and re-ulceration rate.

The NDKare phone application was able to accurately measure wound size in 2-dimensions and it was a practical new technology to use in the clinical setting as users with different smartphones were able to obtain similar results.

Evaluation of the history of the classification and nomenclature of chronic limb ischaemia and critical limb ischaemia will contribute to increased awareness of the the significance and need for the development of the Global Vascular Guidelines and the Global Limb Anatomic Staging System.

DECLARATIONS

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS

Kuang B, Pena G, Szpak Z, Edwards S, Battersby R, Cowled P, Dawson J, Fitridge R. Assessment of a smartphone-based application for diabetic foot ulcer measurement. Wound Repair Regen. 2021 May;29(3):460-465. doi: 10.1111/wrr.12905. Epub 2021 Mar 3. PMID: 33657252.

ORAL PRESENTATIONS

Kuang B, Pena G, Damkat-Thomas L, Cowled P, Fitridge R, Greenwood J, Wagstaff M, Dawson J. Use of NovoSorb® Biodegradable Temporising Matrix (BTM) in the reconstruction of diabetic foot wounds: a pilot study
Royal Australasian College of Surgeons RP Jepson Medal and Justin Miller Prize, 2021, Adelaide, Australia.

POSTER PRESENTATIONS

Kuang B, Pena G, Damkat-Thomas L, Cowled P, Fitridge R, Greenwood J, Wagstaff M, Dawson J. Use of NovoSorb® Biodegradable Temporising Matrix (BTM) in the reconstruction of diabetic foot wounds: a pilot study. Australian and New Zealand Society for Vascular Surgery Annual Scientific Meeting, 2021, Gold Coast, Australia.

Kuang B, Pena G, Damkat-Thomas L, Cowled P, Fitridge R, Greenwood J, Wagstaff M, Dawson J. Biodegradable polyurethane matrix in the reconstruction of diabetic foot wounds
Diabetic Foot Australia conference, 2019, Brisbane, Australia.

CHAPTER 1 – INTRODUCTION

1.1 The Impact of Diabetes Mellitus

The World Health Organisation (WHO) defines diabetes mellitus as a chronic, metabolic disease resulting in the body's inability to either produce or utilise insulin effectively.(1) Diabetes mellitus results in unregulated high levels of circulating glucose with subsequent multiorgan damage to the vascular system (angiopathy) due to micro- and macrovascular damage, nervous system injury and an immunocompromised state.

The microvascular complications include diabetic retinopathy, neuropathy and nephropathy. The macrovascular complications consist of accelerated atherosclerotic disease causing premature coronary artery disease, cerebrovascular disease, renovascular disease and peripheral arterial disease (PAD).(2)

There has been a dramatic increase in the prevalence of diabetes mellitus which has risen from 108 million in 1980 to 422 million people in 2014.(3) The rise in incidence has been most significant for diabetes mellitus type 2 which increasingly affects children, teenagers and young adults and it now accounts for 85-90% of all cases of diabetes worldwide.(4) This is largely attributed to the calorific-dense Western diet and sedentary lifestyle which has also contributed to the obesity epidemic.(5) As a result, an increasing number and younger people are developing these complications including PAD with development of claudication or chronic limb threatening ischaemia (CLTI).

1.2 DIABETIC FOOT DISEASE

1.2.1. Aetiology

Diabetic foot disease is an advanced complication of diabetes where ulceration, infection or destruction of tissue within the foot occurs in association with neuropathy and/or peripheral artery disease of the lower limbs.(6) The underlying aetiology of diabetic foot disease is estimated to be neuropathic (35%), ischaemic (15%) and neuroischaemic (50%).(7)

Figure 1.1. Diabetic foot heel ulcer secondary to neuroischaemia
Subject provided consent for the use of this photograph.

Peripheral neuropathy comprises of sensory, motor and autonomic neuropathy, all of which contribute to the development of diabetic foot ulceration. Sensory neuropathy secondary to diabetes mellitus typically begins distally and extends proximally resulting in a 'glove and stocking' pattern of distribution. Loss of protective sensory function can result in loss of protective response to even minor traumatic events, such as that occurring with new or ill-fitting shoes. Motor neuropathy tends to affect the small muscles in the foot with alterations in the structure, stability and biomechanics of feet resulting in foot deformities. This causes abnormal pressure distribution, increased friction and when combined with sensory neuropathy, subsequently potential ulceration. Autonomic neuropathy causes sudomotor dysfunction with loss of sweating and dry skin resulting in skin cracking and potential breakdown with risk of infection.(8)

Peripheral artery disease (PAD) is an atherosclerotic disease with symptoms, signs or abnormalities which result in impaired circulation to an extremity.(6) When diabetic foot ulcers develop in patients with PAD it often results in chronic, non-healing ulcers exacerbated by ischaemia with lack of oxygen and nutrition to facilitate tissue repair. Chronic ulcers are at higher risk of infection, which once infected, demand more circulating blood to generate an immunological response and for delivery of antibiotics to the treatment area.

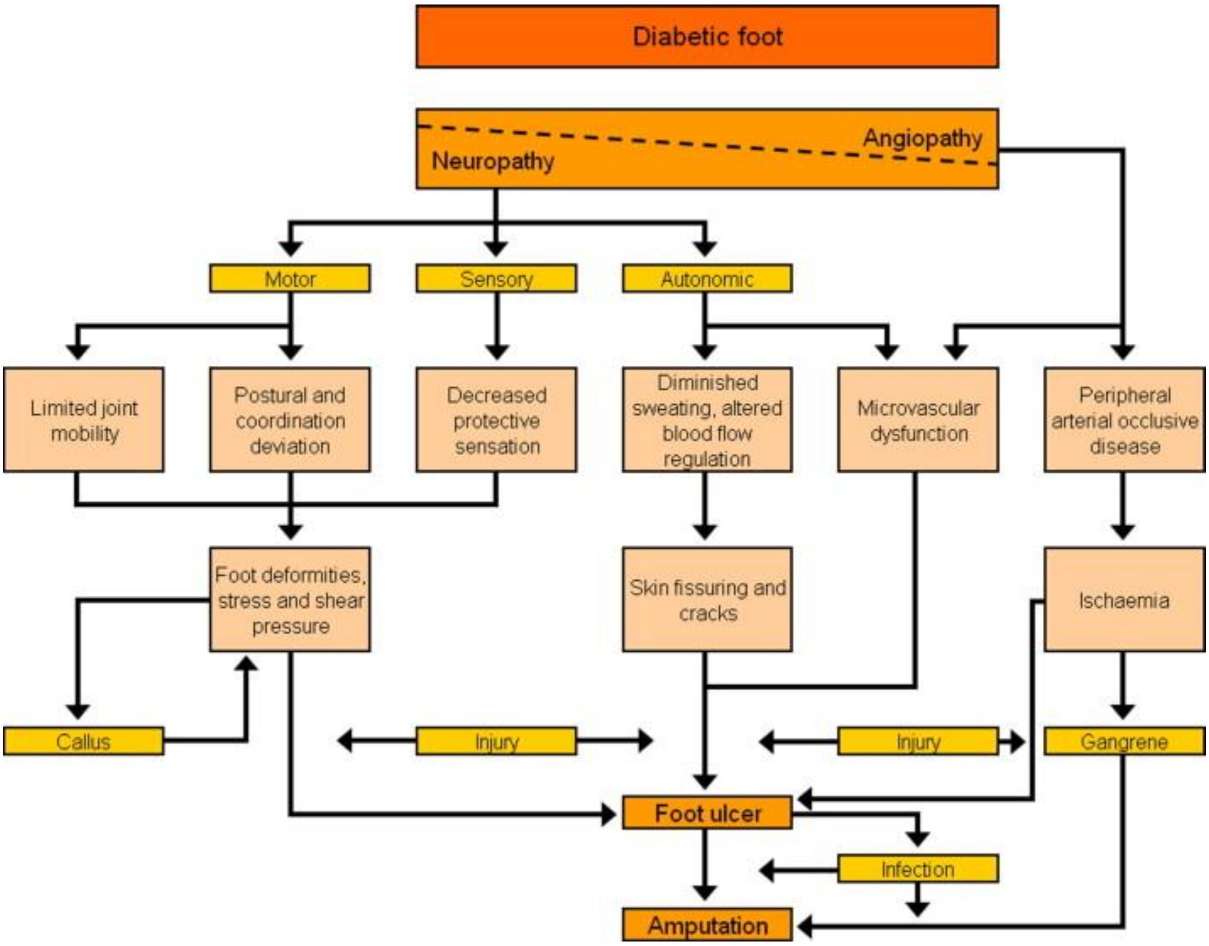

Figure 1.2. The development and natural history of a diabetic foot ulcer.
Source: Lepäntalo, M. et al. Chapter V: Diabetic Foot. European Journal of Vascular and Endovascular Surgery, Volume 42, S60 - S74, with permission.(9)

1.2.2. Severity of disease and impact

The global prevalence of diabetic foot is 6.3%, with a higher preponderance for type 2 diabetes mellitus patients.(10) An estimated 25% of patients with diabetes will develop foot ulceration during their lifetime.(11) In addition, re-ulceration rates are high at 40% within one year and 65% within five years of ulcer healing.(12) 85% of amputations on diabetic patients are preceded by a foot ulcer which has deteriorated to severe infection or gangrene.(13) In Australia, each year diabetic foot disease results in 10,000 hospital admissions, approximately $875 million spent and 4,400 limb amputations.(14)

As a chronic disease, there are psychosocial and financial impacts of foot ulceration and amputation on the individual.(15) Psychologically, there is the stress of complex care regimens, family burden, loss of ambulation and independence. With loss of mobility, patients physically decondition and are at risk of sarcopenia with progressive and generalized skeletal muscle mass and strength loss and may require rehabilitation or permanent placement in an assisted living facility.(16) Many patients experience economic stress due to job loss, medical and nursing care costs.

1.2.3 Treatment

Diabetic foot disease requires complex management beyond treating the underlying aetiology and optimisation of blood glucose levels. In 2019, The International Working Group (IWGDF) on the Diabetic Foot released guidelines focused on the main facets of diabetic foot management: offloading, infection control, wound healing interventions and peripheral artery disease.(6) To comprehensively coordinate management of these issues, multidisciplinary team care has been widely adopted as it has been demonstrated to reduce the rates of major limb amputation.(17) The composition of the multidisciplinary team varies in accordance with hospital policy and available speciality services.

Offloading, in addition to glycaemic control and patient education, are the main preventative strategies for avoiding the development of diabetic foot ulceration. However, once an ulcer is established, it becomes essential to prevent progression and allow healing to occur. Mechanical stress on the ulcer is composed of pressure on the plantar aspect of the foot, and repetitive shear stress with weightbearing.

Pressure offloading relieves this mechanical stress with footwear, surgery or other offloading devices.

Infection in diabetic foot ulcers need to be detected and treated early to prevent progression to a limb-threatening condition. In particular, the development of deep tissue abscess or progression to osteomyelitis increases the risk of minor or major amputation. Depending on the severity of disease, minor infection in the absence of a focal septic source may be treated with oral or intravenous antibiotics in combination with antimicrobial dressings. Due to their immunocompromised state and the presence of PAD in up to 50% of patients, infection can spread rapidly with sepsis and potentially death with surgical intervention warranted for sepsis control.

Wound healing interventions encompass treatments which provide localised treatment to the wound bed. This includes limited sharp debridement which can be performed in the outpatient or ward-based setting by nurses or podiatrists. Topical agents may be used such as placental derived products and autologous combined leucocyte, platelet and fibrin for chronic non-healing wounds may also be available in some specialised diabetic foot services.(18) Dressings should be tailored to the wound for maintaining a moist environment but managing exudate control, mechanical protection and antimicrobial properties as required.

1.2.3.1 – Surgical management of infected diabetic foot ulcers

Non-infected foot ulcers may be able to heal without surgery but, in selected cases, it may be beneficial to correct foot deformities and remove bony prominences.(19) Surgical intervention for infected diabetic foot ulcers are commonly semi-urgent or emergency procedures which may involve debridement, minor digital and ray amputation or major limb amputation. Clinically it is often difficult to discern the extent of infection due to the immunocompromised state of the patient and penetration of infection into the deep tissues. It is estimated that 10-20% of mild to moderate infections and 50-60% of serious diabetic foot infections have underlying osteomyelitis.(20) The goal of surgery in infection is to clear the septic source by removal of infected or non-viable tissue and drainage of any pus. However, with removal of bone and its tendinous attachments, the foot can become destabilised with abnormal pressure areas, or the foot may become non-functional from a walking perspective in extensive cases.(19)

Figure 1.3. Diabetic foot infection sepsis control with hallux ray amputation and debridement
Subject provided consent for the use of this photograph.

Extensive removal of necrotic or infected soft tissue may result in protracted healing and prolonged wound care or it may not be reconstructable, with exposure of deep structures such as bone, tendon and joint. Moreover, perfusion of the foot needs to be considered to ensure adequate healing can occur and revascularisation in the perioperative period may be required.

1.2.3.2 – Peripheral artery disease: definition, aetiology and management

The demographic of patients presenting with PAD has significantly changed over the years leading to recent revisions in the definition and classification of the disease. Critical limb ischaemia (CLI) was first defined in 1982 by the Working Party of the International Vascular Symposium, which deliberately excluded patients with diabetes as it acknowledged this cohort was more complex with neuropathy and infection rather than ischaemia alone. CLI was defined as patients with rest pain with ankle pressure <40 mmHg and/or tissue necrosis with ankle pressure <60 mmHg.(21, 22) Despite the original definition, the terminology of CLI was widely adopted for patients with diabetic foot disease.

With the subsequent growing prevalence of diabetes, by 2007 Prompers et. al., reported that approximately 50% of patients undergoing revascularisation for limb salvage had underlying diabetes.(23) The need for new terminology and definitions was recognised in 2019 and the term and haemodynamic parameters of "Chronic Limb-Threatening Ischaemia (CLTI)" was developed by the Global Vascular Group (GVG) which consisted of all the major vascular societies: the European Society for Vascular Surgery (ESVS), Society for Vascular Surgery (SVS) and World Federation of Vascular Societies (WFVS). CLTI is defined as objectively documented PAD ***in combination with*** any of the following clinical symptoms or signs: 1) ischaemic rest pain with confirmatory haemodynamic studies, 2) diabetic foot ulcer or any lower limb ulceration present for at least 2 weeks, or 3) gangrene involving any portion of the lower limb or foot.(24) Without effective revascularisation, 22% of patients with CLTI will require a major amputation at 12 months.(25)

The development of PAD is multifactorial with the distribution of atherosclerotic disease based on the underlying pathology (Figure 1.4). Smoking use was once far more prevalent, but following extensive public health campaigns about its adverse effects and government taxation, the prevalence of smoking has steadily decreased worldwide since 1990, particularly in more affluent countries.(26) Nonetheless, tobacco use remains one of the most significant risk factors for the development of PAD, increasing its risk of symptomatic disease by 2.3-fold.(27)

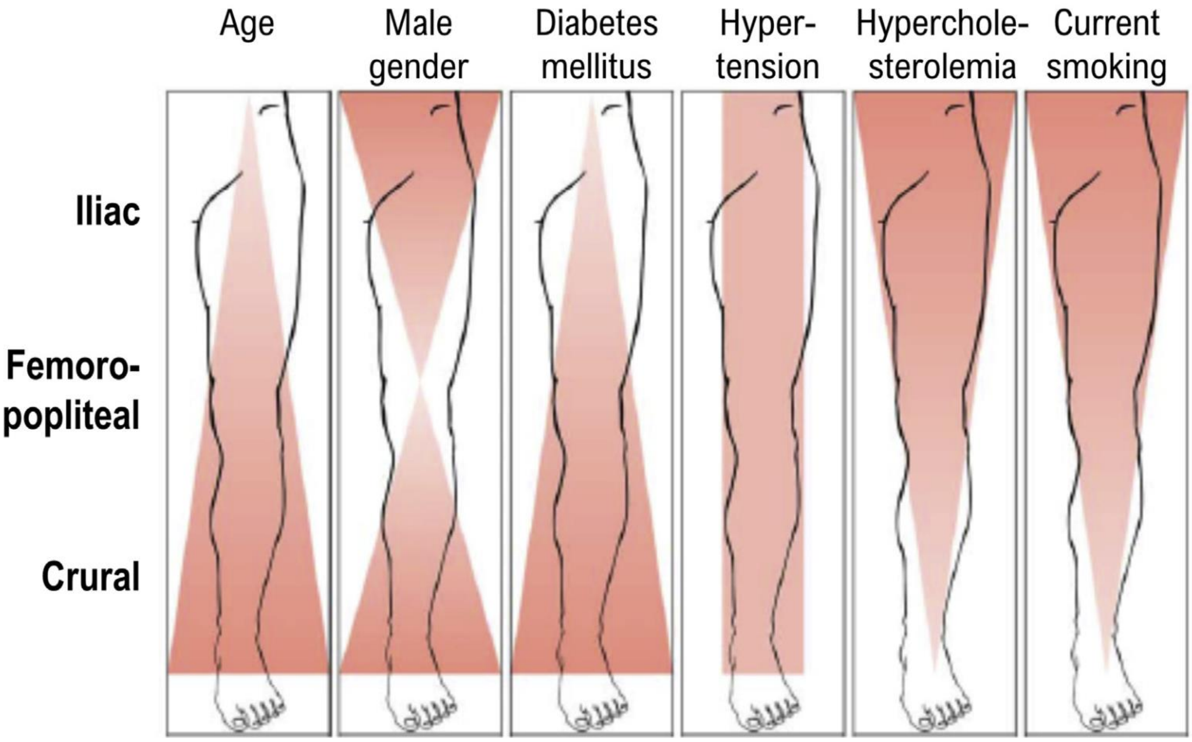

Figure 1.4. Association of risk factors with the level of atherosclerotic target lesions. The red overlay on the anatomic cartoon illustrates the association of risk factor with patterns of atherosclerotic disease.
Source: Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur J Vasc Endovasc Surg 2006, with permission.(28)

When tobacco use was more prevalent, atherosclerotic disease primarily affected the ilio-femoral segments. However, with the decline in tobacco use and the increasing prevalence of diabetes mellitus, the crural (tibial) segments are now more frequently affected. Observational studies note the disease pattern in diabetes tends to be diffuse, calcific and highly complex in small calibre vessels which are more difficult to treat. (29, 30)

Traditionally, the gold standard imaging modality for identifying the location and degree of stenosis or occlusion was catheter angiography (digital subtraction angiography). However, computed tomography angiography (CTA) has been widely adopted as a comparable non-invasive alternative with technological improvements in imaging quality and acquisition time allowing for 2-dimensional (2D) and 3-dimensional (3D) reconstructions. CTA has reduced sensitivity (95%) and specificity (91%) in imaging the infra-popliteal segment in comparison to the aortoiliac and femoro-popliteal segments.(31) Duplex ultrasonography may also be considered as the first line investigation for PAD as it is inexpensive, there is no radiation exposure or administration of contrast agents.(32) However, its use depends on availability and the treating physicians confidence due to inter-operator variability. It is also difficult to evaluate the heavily calcified vessels associated with diabetes in PAD with ultrasound and CTA.(32) For diabetic foot disease, diagnostic catheter angiography is largely performed to quantify PAD, particularly on the infra-popliteal segment, and then endovascular intervention can be performed during the same procedure.

Revascularisation for PAD was once limited to open surgery. However, technological advancements in endovascular revascularisation have been rapid with guidelines and recommendations are regularly required to be updated with the latest endovascular therapies to guide contemporary practice.(33) Also, as a consequence of the multi-comorbid state in many patients with diabetes, patients requiring management of peripheral vascular disease and diabetic foot infection are medically complex and are at high risk of complications from both an anaesthetic and surgical perspective. Therefore, a less invasive 'endovascular' approach is often preferred.

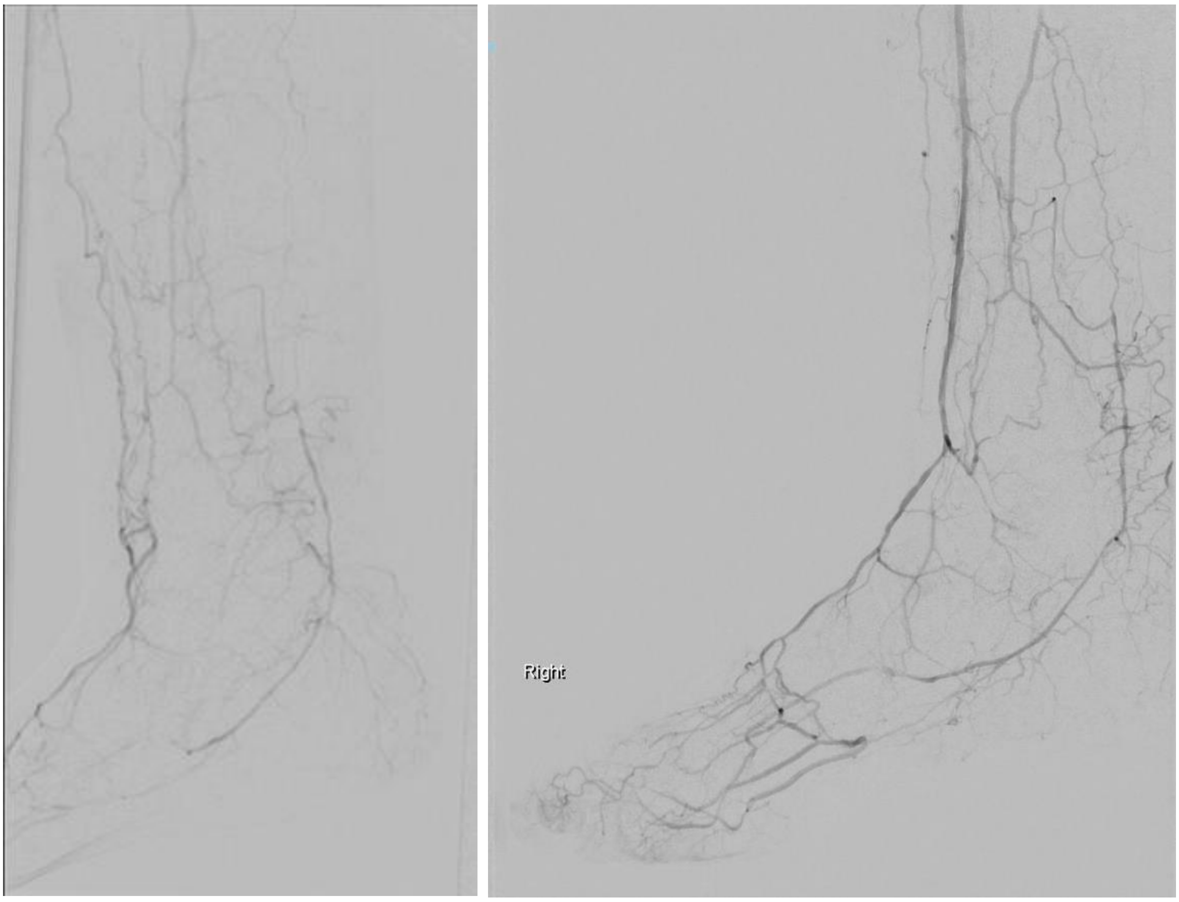

Figure 1.5. Pre- (left) and post-intervention angiogram with distal anterior tibial artery angioplasty improving contrast flow to the pedal arch and digital arteries.

Subject provided consent for the use of these images.

The definition of technology is two-fold with the more recognisable definition being machinery and equipment developed from the application of scientific knowledge. The second definition is the application of scientific knowledge for practical purposes. The need for new terminology and guidelines is essential to reflect the significant advances in PAD pathophysiology and to optimise treatment which is a technological development.

1.3. Technologies in wound assessment

Regular objective assessment of diabetic foot wounds is essential for early identification of indolent or deteriorating wounds so that intervention can be performed. This is particularly important in the diabetic foot ulcer population where patients' ability to self-monitor may be difficult due to the location of the wound on the foot which is often over the plantar region. Patients with advanced diabetic retinopathy may not be able to see their feet at all.

One of the key areas for monitoring wound healing is the wound area. A wound area reduction by >50% at 4 weeks is a predictor of complete healing at 3 months.(34, 35) This acts a pivotal time point for evaluating wounds which are not responding to their current wound care regime and may need further intervention. This is a concept widely adopted by consensus and guideline groups, including the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine.(36, 37) Sheehan et. al, demonstrated that if a wound fails to achieve this wound area reduction, that only 9% of wounds heal by 12 weeks.(35)

Use of a disposable ruler is the most common technique for wound measurement as it is quick, cheap and readily available. However, there is often significant interobserver error as the axis selected for length and width is subjective.(38) Physical tracing of wound perimeter using acetate paper with pre-printed 1 cm^2 squares allows manual calculation of the area of the wound. Visitrak (Smith & Nephew Wound Management, Inc., Largo, FL) is a planimetry device where the tracing is re-drawn onto a tablet device which automatically calculates the surface area. These techniques require physical contact of the wound with the devices which carries a risk of infection and discomfort for the patient. Islands of epithelium may also develop within the wound bed which cannot be captured in the measurement leading to further inaccuracies.(39)

Sequential photos of the wound at each wound review collated into the patient’s medical records provides an overall picture of the progress of the wound. However, the angle, lighting, and distance of the photo from the wound can misrepresent the wound state.

Technological developments have been focused on developing integrated measurement tools with photography for a non-contact approach. 2D devices use a scaling marker to be placed next to the wound with the size of the wound calculated relative to the marker of known dimensions, but inaccuracies may occur due to parallax.(40) 3D devices (e.g., WoundVue camera ((LBT Innovations Limited, Adelaide, Aust)) use laser structured light techniques, laser scanning and stereophotogrammetry to create 3D reconstructions and wound measurements including depth and volume.(41-43)

Figure 1.6. The WoundVue Camera: a 3D camera for diabetic foot ulcer wound measurement using the laser structured light technique (LBT Innovations Limited, Adelaide, Australia developed with the Australian Institute for Machine Learning, University of Adelaide)

However, all these technologies require specialised software and equipment which can be bulky, expensive and relatively inaccessible for use in the clinical environment. To make this technology more accessible for the clinical setting, the NDKare phone (Nucleus Dynamics Pty Ltd, Singapore, Singapore) has been developed to address these issues.

1.4. Technologies in wound management

To achieve wound healing, the other main facets of diabetic foot management as recommended by the IWGDF need to be optimised (i.e., treatment of infection, revascularisation when required and offloading of wound), otherwise topical management of the wound will likely fail.(44)

In principle, wound dressings are created to facilitate the ideal moist wound healing environment.(45) The decision for the most appropriate dressing is based on clinical evaluation of the wound bed tissue, the presence of infection, amount of exudate and location of the wound on the foot.

Of additional consideration in the diabetic foot ulcer population, the dressings need to be conformable to the foot shape and enclosure within a shoe, able to withstand shear stress forces and allow for dressing changes frequently and easily to monitor for infection.(46) Antimicrobial dressings are often used in these patients for the prevention of infection which also may manage the associated increased exudate. There are numerous dressings which each having specific properties as listed in the following table.

Dressing type	**Advantages**	**Disadvantages**
Low adherent	Simple Hypoallergenic Inexpensive	Minimal absorbency
Hydocolloid	Absorbent May be left for days Aids autolysis	May be unsuitable for infected wounds May cause maceration
Hydrogels	Absorbent Aids autolysis	May be unsuitable for infected wounds May cause maceration

Foams	Thermal insulation Good absorbency Conforms to contours	May adhere to wound
Alginates	Highly absorbent Bacteriostatic Haemostatic Good for cavities	May adhere to wound
Iodinated products	Antiseptic Moderately absorbent	Iodine allergy Discolours wound
Silver impregnated	Antiseptic Absorbent	Cost

Table 1.1. Classes of dressings for diabetic foot infections
Modified from J. R. Hilton, D. T. Williams, B. Beuker, D. R. Miller, K. G. Harding, Wound Dressings in Diabetic Foot Disease, Clinical Infectious Diseases, Volume 39, Issue Supplement_2, August 2004.(47)

Use of negative pressure wound therapy (NPWT) is a weak recommendation by the IWGDF for reduction in wound size in addition to best standard of care and to promote post-surgical wound healing in DFU.(6) Similar recommendations have been made by the Wound Healing Society of the United States for the management of diabetic foot wounds. (48) NPWT has been demonstrated to increase the rate of wound healing and achieving wound closure in comparison to conventional dressings in diabetic foot ulcers and potentially decreases the risk of amputation.(49) NPWT causes three-dimension stress known as ‘macro-strain’ with centripetal force with macrodeformation, microdeformation and decreased oedema with increased cellular proliferation, angiogenesis and decreased infection.(50) Wounds larger in diameter (>10cm) and depth have more significant wound contraction with a better response to macrodeformation.(51)

Despite optimal topical therapy, complex diabetes-related foot wounds remain very difficult to heal. These are wounds with exposure of deep structures such bone, tendon, joint or fascia where the wound bed inherently does not have adequate blood supply and it is difficult for granulation tissue to develop over these areas. This often develops in patients following debridement or local amputation for diabetic foot infection which may result in extensive soft tissue loss. In addition, the structural integrity of the underlying tissue becomes compromised with bone exposure with potential osteomyelitis, desiccation of tendons with impaired function and mobility. This places the wound at high risk of infection and sepsis with complex diabetic foot ulcers approximately at 11-fold risk of forefoot or major limb amputation than granulating ulcers.(52, 53)

Guidelines for standardisation of the use of NPWT in DFU have not be updated since the Tucson Expert Consensus Conference on V.A.C. Therapy first updated their 'Guidelines regarding negative wound therapy (NPWT) in the diabetic foot' in 2006.(54) As a result, the Tissue Repair of Burns and Trauma Committee and the Cross-Straits Medicine Exchange Association has published a consensus document in 2021 which recommends that wounds with exposed bone and/or should undergo skin flap coverage instead of NPWT due to the limited ability for granulation tissue formation.(55) Soft tissue reconstructive operations such as tissue expansion, local flaps, distant flaps or free flaps can be performed to preserve foot function and facilitate quicker healing with increased tissue coverage. Suitability for flap coverage needs to be carefully evaluated based on the wound type and patient factors. Diabetic foot wounds are prone to infection despite initial appearances of macroscopically healthy tissue and an infected wound base may cause failure of flaps. Patent target tibial arteries are required for free flap surgery, but the significant degree of atherosclerosis in the tibial arteries in diabetes limits patient suitability for free flap surgery.

The anatomical location of the ulcer on the foot needs to be considered and flaps may be bulky and may not be able to replicate the physiological function of the tissue, e.g., thick fibrous connective tissue on the plantar aspect of the foot which needs to be able to withstand weightbearing pressure.(56) Reconstructive surgery procedures are complex and tend to be prolonged, so patient fitness for surgery including cardiopulmonary function needs to be adequately assessed given patients are often co-morbid.(57)

To achieve wound healing over these areas, dermal substitutes have been developed which include Integra (Integra Life Sciences Corp., Plainsboro, NJ), AlloPatch Pliable (MTF Biologics, Edison, NJ) and DermACELL (Stryker, Kalamazoo, MI). These products integrate into the wound bed and allow the infiltration of fibroblasts, growth factors and promote angiogenesis. Functionally, dermal substitutes act as a scaffold for organised collagen to develop with perfusion of the wound to allow granulation tissue to develop over difficult to heal areas.(58) The use of dermal substitutes has largely been in burns, plastics and reconstructive surgery realm where there is destruction of the dermis with limited autologous tissue for soft tissue reconstruction due to the often large extent of injury.(59, 60) Dermal substitutes would be ideal for complex diabetic foot ulcers with a more robust wound bed potentially decreasing the risk of repeat shear and pressure injuries to healed wounds. However, their use has not been widely adopted in the management of diabetic foot wounds because of the risk of infection with biological templates such as Integra (Integra Life Sciences Corp., Plainsboro, NJ), and the high costs. As an inexpensive, synthetic alternative, the biodegrable temporising matrix (BTM) (PolyNovo Biomaterials Pty Ltd, Port Melbourne, Victoria, Australia) has been developed with its use mainly adopted in the burns, plastics and reconstructive surgery. However, these features make it also an appealing option for use in DFU which is has not yet been explored.

1.5 Aims

1.5.1 Clinical significance

Validate new technologies in the assessment and management of diabetic foot ulcers and wounds for use in clinical practice to improve treatment outcomes.

The aims of this research are:

1. To evaluate the efficacy of using BTM in the reconstruction of complex diabetic foot wounds.

2. To use the NDKare phone application to assess its accuracy and practicality for diabetic foot ulcer wound size assessment

3. To critically evaluate the historical classification and management of chronic limb ischaemia and critical limb ischaemia with the development of the latest GVG guidelines

CHAPTER 2

USE OF BIODEGRADABLE TEMPORISING MATRIX (BTM) IN THE RECONSTRUCTION OF DIABETIC FOOT WOUNDS: A PILOT STUDY

Beatrice Kuang, Guilherme Pena, Prue Cowled, Robert Fitridge, John Greenwood, Marcus Wagstaff, Joseph Dawson

(In Submission)

Statement of Authorship

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Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	A pilot study conducted evaluating the use of BTM to reconstruct complex diabetic foot wounds with exposed tendon, fascia, joint, bone, or chronic ulcers at high shear stress locations. These wounds have a very high rate of infection and risk of limb loss. BTM is capable of healing uninfected, non-ischaemic diabetic foot wounds with exposed deep structures and chronic wounds subject to high shear stress. The re-ulceration and infection rates were relatively low for this high-risk population. BTM may offer promise as an alternative to free flaps. We have submitted it to the journal Scars, Burns and Healing.

Principal Author

Name of Principal Author (Candidate)	Beatrice Kuang		
Contribution to the Paper	Data collection, data analysis, writing – original draft, writing – review & editing		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/01/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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ABSTRACT

Introduction

Complex diabetes-related foot wounds are at high risk of infection and subsequent major amputation unless healed expediently. Biodegradable Temporising Matrix (BTM) is a synthetic matrix that facilitates the organisation of the extracellular matrix, resulting in a neodermis layer over these difficult-to-heal areas. The aim of this study was to evaluate the efficacy of using BTM in the reconstruction of challenging diabetic foot wounds.

Methods

18 patients with complex diabetic foot wounds (exposed tendon, fascia, joint, bone), or chronic ulcers at high shear stress locations had BTM applied. Indications for BTM application were high shear stress location (66.6%), exposed bone (16.6%), exposed fascia (5.6%), exposed tendon (5.6%) and chronic non-healing wound (5.6%). The time to complete healing, infection rate and incidence of subsequent wound breakdown was analysed.

Discussion

14 of 18 patients completed the BTM treatment regime with all these patients achieving complete wound healing at a median time of 15.5 weeks. The 4 remaining patients had BTM removed early and withdrawn from the study due to residual

osteomyelitis, development of acute bypass graft occlusion or due to the COVID-19 pandemic. The rate of infection and re-ulceration were both 14.3%.

Conclusion

This is the first prospective cohort pilot study evaluating the use of BTM for complex diabetic foot wounds. BTM demonstrates potential in healing uninfected, non-ischaemic diabetic foot wounds with exposed deep structures and chronic wounds subject to high shear stress. The re-ulceration and infection rates were relatively low for this high-risk population. BTM may also offer promise as an alternative to free flaps.

Registered on the Australian New Zealand Clinical Trials Registry (ACTRN12618000608268p)

https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374903

INTRODUCTION

Over the last four decades, the prevalence of diabetes and its complications, including foot disease, have significantly increased worldwide.(61) An estimated 360 million people will have diabetes by 2030, in stark contrast to the 30 million people with diabetes in 1985.(62, 63) Approximately 25% of patients with diabetes develop a foot ulcer in their lifetime. (64) Diabetes-related foot ulcers (DFU) are the most common reason for hospitalisation in patients with diabetes, with more than 50% of DFUs becoming infected.(65) Due to the underlying multifactorial barriers to achieving healing in the diabetic foot, an estimated 25% of DFUs remain unhealed at 1 year.(66-68) Our group recently found that diabetes was implicated in 79% of minor amputations and 61% of major amputations performed in Australia and New Zealand between 2010 and 2015.(69) DFU substantially impacts an individual's quality of life with emotional and physical distress combined with economic loss, particularly in patients with chronic DFUs and those who progress to minor and major limb amputations.(70, 71)

For complex diabetes-related foot wounds such as those with exposed tendon, fascia, joint or bone, healing can often be difficult to achieve over these structures. These wounds often develop following extensive debridement for diabetes-related foot infection. Once these structures are exposed, their structural integrity and functionality (e.g., desiccation of tendons) degrades and they become a potential nidus for infection (bone exposed for osteomyelitis) with high risk of rapid spread (e.g., ascending via tendon sheaths). As a result, complex DFUs are 11 times more likely to progress to midfoot or major limb amputation than fully granulated ulcers.(72) Moreover, some patients may be too high risk for anaesthetic or may refuse major limb amputation, and these wounds may persist as chronic wounds. Split skin grafts (SSG) are generally contraindicated for tissue coverage over exposed tendon, joint and bone and also over ulcers exposed to major shear stress or weight-bearing. Free flaps are an option for closure of these wounds, but in complex DFUs in patients with significant comorbidities and those with tibial artery disease, a simpler solution would be advantageous.(73, 74)

Chronic DFUs and wounds exposed to high shear stress and recurrent breakdown are also at risk of becoming infected. In diabetes, abnormal extracellular matrix (ECM) remodelling in wound healing occurs secondary to the formation of advanced glycation end products (AGEs).(75) This results in increased ECM degradation, production of non-soluble fibrils and a poorly-organised, yet 'mature', ECM network contributing to chronic wound formation.(76) Obtaining tissue coverage over these wounds is essential to decrease the risk of these complications. Split skin graft application is often performed to obtain tissue coverage over large wound areas. However, split skin grafts can result in failure of the graft to take and/or may have the tendency to re-ulcerate due to a disorganised wound bed and abnormal biomechanical foot pressure.(77)

Dermal regenerative templates have been used in DFU soft tissue replacement since 1994.(78) Examples of dermal regenerative templates include Integra (Integra Life Sciences Corp., Plainsboro, NJ), AlloPatch Pliable (MTF Biologics, Edison, NJ) and DermACELL (Stryker, Kalamazoo, MI). These templates act as structural support for ECM maturation with cellular response modulation and promote revascularisation and cell regeneration.(79) Some templates also provide a physical barrier for wound tissue coverage and prevent evaporative water loss.(80) They increase the rate of healing in patients with uninfected, non-ischaemic DFUs, as well as reconstructing complex diabetes-related foot wounds.(78, 81-83) However, the use of acellular dermal matrices is limited in clinical practice due to the relatively high costs of the products.(84) In addition, there is a theoretical increased risk of infection, given the biological composition of these collagen-based dermal matrices.(85) For these reasons there has been an increased interest in the development of inexpensive, synthetic dermal matrices which do not confer the same risk of infection.(86)

Innovation

NovoSorb® Biodegradable Temporising Matrix **(**BTM) (PolyNovo Biomaterials Pty Ltd, Port Melbourne, Victoria, Australia) has been created to address the need for a synthetic dermal matrix for wound reconstruction in surgery. BTM consists of a biodegradable wound-facing foam bonded to a non-biodegradable transparent sealing membrane (Figure 2.1). The foam is placed onto the wound where it begins integrating at 2-3 weeks with full integration at approximately 6 weeks into the wound bed. At full integration, the sealing membrane is removed (delamination). The foam hydrolyses and is fully reabsorbed over approximately 18 months.

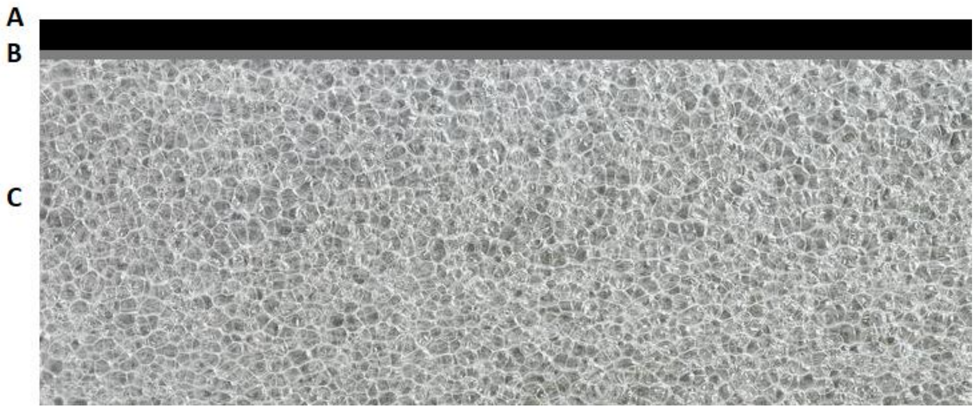

Figure 2.1. Illustration of BTM Structure.

A) Sealing membrane: temporary, non-biodegradable layer sealing the wound, reducing moisture loss and acting as a barrier to external pathogens.
B) Adhesive bonding layer between sealing membrane and foam
C) NovoSorb® foam: 2mm open cell matrix acts as a scaffold for infiltration of cellular materials for reconstruction of the dermis.
The synthetic structure is relatively inexpensive and does not confer the same risk of infection as the biological dermal matrix counterpart.

Clinical Problem Addressed

BTM was first clinically utilised in 2012 in burns surgery due to its ability to provide temporary wound closure, prevent wound contraction, integrate to prove structural integrity to the dermis and improve cosmesis compared to split skin graft alone.(86) Subsequently it has been demonstrated to be effective at reconstructing complex burn injuries.(87, 88) Its use has extended to plastic surgery for free flap harvest donor sites, soft tissue trauma injuries and following extensive debridement for necrotising fasciitis.(89-93) Following necrotising fasciitis debridement, the wound remains at risk of residual recurrent infection. However, several case series have demonstrated the maintenance of BTM's structural integrity and the ability for underlying infection to be expressed through perforations within the material for these cases. (92, 93) Often diabetic foot wounds are debrided for infection which can be extensive and may similarly pose a significant risk of residual or recurrent infection.

To date, there have been no studies evaluating the use of BTM in diabetic foot wounds. The aim of this study was to evaluate the efficacy of using BTM in the reconstruction of complex diabetic foot wounds, chronic DFUs and wounds subject to high shear stress.

MATERIALS AND METHODS

Patients

A prospective pilot study was conducted with ethics approval from Central Adelaide Local Health Network Human Research Ethics Committee (HREC/18/CALHN/468) and registered with the Australian and New Zealand Clinical Trial Registry (Registration No. ACTRN12618000608268p). Documented written informed consent was obtained from all participants.

Patients with diabetic foot wounds were enrolled from multidisciplinary diabetic foot clinics at the Royal Adelaide Hospital, Queen Elizabeth Hospital and Lyell McEwin Hospital, or whilst they were admitted under the Vascular Surgery unit at the Royal Adelaide Hospital. Patients were recruited from June 2019 to December 2020.

The inclusion criteria for this study were adult diabetic patients with complex deep wounds (i.e., with exposed tendon, muscle, fascia, joint or bone exposed), chronic non-healing ulcers and wounds deemed at risk of not healing due to high shear stress. The exclusion criteria were arterial insufficiency (absent pedal pulses, or toe pressures <30 mmHg), active local wound infection, or evidence of osteomyelitis on imaging tests, and the inability to attend regular outpatient clinics (e.g. patients living in rural and remote locations).

Patient demographics, wound characteristics, wound WIfI score(94) and peri- and post-operative details were collected prospectively. The main outcome in this study was to determine if wound healing closure could be achieved with BTM. The time to achieve wound healing, subsequent wound breakdown following healing and wound infection were considered secondary outcomes.

Eighteen patients were recruited according to the treating physician's assessment and treated with BTM during the study period. Four patients were subsequently withdrawn from the study: two patients were found to have residual osteomyelitis with an unsalvageable limb, one patient's infra-inguinal bypass occluded with subsequent arterial insufficiency and another patient declined to continue participation in the trial due to the COVID-19 pandemic. Fourteen patients were thus included in this study.

Surgical Technique

For all patients, a pre-operative bacterial swab culture was obtained from the wound site. All BTM applications were performed in an operating theatre with an anaesthetist present. They performed a regional ankle block with the anaesthetic type and dosage determined by the patient's co-morbidities, weight and degree of pre-existing peripheral neuropathy. A single dose of intravenous antibiotic based on microbial sensitivities was given prior to application of BTM. If no bacteria were grown, Cephazolin was given as per hospital protocol. The wound bed was scrubbed with a Medisponge® impregnated with chlorhexidine, followed by povidone-iodine for surgical site preparation.

The wound edge was sharply debrided using a standard surgical blade and the wound bed was lightly debrided using a metal ruler. In cases with visible bone in the wound bed, a drill was used to canulate into the medulla in order to provide an angiogenic marrow source for subsequent granulation tissue development. The wound was irrigated with povidone-iodine solution. BTM is supplied fenestrated, but additional perforations were made were made to the BTM to allow for easier drainage should a haematoma or fluid collection develop post-operatively. BTM was inset into the wound defect under slight tension using quilting staples or sutures to the wound edges to maximise adherence to the wound bed. For large flat wounds, Acticoat® (Smith and Nephew, Hull, UK) was used, Aquacel Ag® (ConvaTec, Princeton, NJ, USA) was used for wounds with moderate exudate, and negative pressure wound therapy (Vacuum Assisted Closure (VAC (KCI, San Antonio, TX, USA)) at 75 mmHg for wounds with high exudate. A 7-day course of oral antibiotics was given post-operatively based on the pre-operative bacterial swab. Patients were non-weightbearing on the operated limb for 5 days to optimise BTM adherence to the wound bed, the wound was reviewed for adequate integration of BTM and patients were subsequently discharged if deemed suitable. To accommodate the appropriate weight-bearing status, orthotic and podiatric input was sought early for suitable footwear to minimise the pressure loading and shear stress over the BTM site.

Dressings were changed by community nursing staff two or three times weekly based on their wound bed characteristics and clinical judgement, and reviews were performed weekly in the vascular outpatient clinic. Cotton-tipped applicators were rolled gently over the BTM towards the fenestrations at each review to remove any fluid that had collected between the BTM and wound bed surface in order to promote BTM integration. BTM integration and vascularisation was assessed by the observation of the development of a red-salmon colour of the BTM and capillary refill on digital pressure.

Delamination occurred once the BTM foam was integrated. If integration failed to occur by 6 weeks, the BTM remained *in situ* for a further 1-3 weeks to allow further time for integration. In the vascular outpatient clinic, the staples were removed and the plastic sealing membrane of BTM was peeled off using forceps. The wound bed was refreshed using a curette to remove any fibrin and biofilm. Depending on the size and depth of the wound, patients were selected to commence either: a suitable conventional dressing regime for smaller wounds until the wound fully healed, or a split skin graft for larger wound deficits. Similar to the secondary dressings for BTM, either Acticoat® or Aquacel Ag® were used for the conventional dressings. Split skin grafts proceeded as an elective procedure 2 weeks following BTM delamination. The skin grafts were harvested at 0.010” – 0.012” thickness using a Zimmer dermatome (Zimmer Surgical, Inc, Dover, OH) meshed at 1:1.5, and dressed with Jelonet (Smith and Nephew, Hull, UK) or with negative pressure wound therapy. Skin grafts were assessed for take at Day 5 post-operatively.

Management of Wound Infections

Infection at the BTM site was defined by the Society of Vascular Surgery's Wound, Ischemia, and foot Infection (WIfI) classification system.(94) Mild infection was defined by the presence of at least 2 of the following symptoms: local swelling/induration, erythema 0.5-2 cm around the ulcer, local tenderness/pain, local warmth or purulent discharge. Moderate infection was the presence of local infection (as described in mild infection) with erythema >2cm, or involving deeper structures (e.g., osteomyelitis, abscess, fasciitis) with no evidence of systemic inflammatory response. Initial antibiotic therapy was based on pre-operative wound swabs and was appropriately guided by subsequent wound culture and sensitivity results. Mild infection was managed with a course of oral antibiotics. Moderate infection was managed with intravenous antibiotics followed by oral antibiotics once the infection had clinically improved.

RESULTS

This pilot study included 18 patients with a median age of 56 years old (range 31-86 years old) and 16 were male (Table 2.1). All patients had type II diabetes, with a median HbA1c of 9.5% (range 7.2-13.4%). One patient had stage 4 chronic kidney disease (CKD) on peritoneal dialysis.

Subject number	Age	Sex	T2DM HbA1c (%)	CKD	Smoking status	Pedal pulse present	Toe pressure (mmHg)	WIfI Score
1	39	M	7.5	No	Never	Yes		1 0 0
2	59	M	8.5	No	Ex-smoker	Yes		2 0 0

3	86	M	9.4	No	Never	Yes	80	1 0 0
4	31	M	11.4	No	Never	Yes		3 0 0
5	51	M	13.4	No	Current smoker	Yes	90	1 0 1
6	76	M	7.2	No	Ex-smoker	Yes		2 0 0
7	50	F	10.6	No	Current	Yes		2 0 0
8	60	M	12.2	No	Current	No	48	3 0 0
9	49	M	9.4	No	Current	Yes		2 0 0
10	65	M	13.3	No	Ex-smoker	Yes	90	1 0 0
11	62	M	9.5	No	Current	Yes		1 0 0
12	49	M	8.8	Yes on HD	Ex-smoker	Yes		1 0 0
13	53	M	8.3	No	Never	Yes		2 0 0
14	32	M	11.8	No	Ex-smoker	Yes		1 0 0
Withdrawn Patients								
15	75	M	11	No	Never	No	66	3 0 0
16	43	M	11	No	Ex-smoker	Yes	86	1 0 0
17	72	M	7	No	Ex-smoker	Yes	32	2 2 0
18	74	F	5.6	No	Ex-smoker	Yes		3 0 0

Table 2.1. Patient Demographics

Initially 18 patients were recruited for the study and had BTM applied, but 4 patients were subsequently excluded with their BTM delaminated and removed earlier than study protocol. Two patients were discovered to have underlying osteomyelitis with the limb unable to be salvaged with both patients progressing to a below knee amputation. One patient developed an occluded infra-inguinal arterial bypass with arterial insufficiency whilst BTM was in situ. The patient had their BTM delaminated, underwent revascularisation procedures and subsequent ray amputation. One patient declined to continue participation in the trial due to the COVID-19 pandemic with the policy of their residential aged care facility mandating a period of quarantine following attendance at a hospital outpatient clinic.

The majority of wound defects resulted from diabetic foot infection debridement (77.8%) and amputations (16.7%) with one case of a chronic non-healing ulcer (5.5%) (Table 2). The decision to use BTM was based on the treating surgeon's preference with the indications for BTM being (i) areas at risk for high shear stress and breakdown (66.6%), (ii) exposed bone (16.6%), (iii) exposed tendon (5.6%), (iv) exposed dorsal fascia (Figure 2.2) (5.6%) and (v) chronic non-healing wounds with tendon on view (5.6%). One third of cases (33.3%) involved exposed fascia, tendon and bone, where direct split skin grafting was inappropriate. For the 14 patients who completed BTM treatment and were not excluded from the study, the BTM sealing membrane remained *in situ* on the wound bed site for a median time of 6 weeks (range 2.5-9 weeks).

a)

b)

c)

d)

Figure 2.2. Subject 2: A 59-year old male with the dorsal fascia with underlying tendon on view following debridement for a diabetic foot infection (a) Initial appearance of the wound following debridement, (b) appearance of the BTM at 7 weeks *in situ*, (c) following BTM delamination at the same review review and left to heal by secondary intention with conventional dressings, and (d) 6 months post BTM delamination.

Subject number	Wound location	Exposed tissue	Indication for BTM	BTM in-situ duration (weeks)	Wound infection
1	4th & 5th toe amputation site	Granulation tissue	Shear stress area	7	No
2	Dorsal midfoot debridement site	Dorsal fascia of the foot	Exposed fascia	7	No
3	Plantar midfoot abscess debridement site	Granulation tissue	Shear stress area	5	No
4	Lateral malleolus debridement site	Lateral malleolus	Exposed bone	9	No
5	Dorsal forefoot debridement site	Granulation tissue	Shear stress area	2.5	No
6	Lateral malleolus chronic non-healing ulcer	Peroneal retinaculum	Chronic non-healing	5	No
7	Plantar midfoot debridement site	Plantar fascia	Exposed fascia	5	No
8	Lateral mid-hindfoot debridement site	Granulation tissue	Shear stress area	7	No

9	Guillotine forefoot amputation site	Granulation tissue	Shear stress area	2.5	Yes (day 14 post op) – moderate, requiring BTM delamination
10	Forefoot amputation stump	Granulation tissue	Shear stress area	6	Yes (day 14 post op) – mild, treated with oral antibiotics
11	3rd, 4th, 5th toe ray amputation	Granulation tissue	Shear stress area	6	No
12	5th toe ray amputation site	Granulation tissue	Shear stress area	6	No
13	1st toe ray amputation site	Granulation tissue	Shear stress area	6	No
14	4th & 5th toe ray amputation site	Granulation tissue	Shear stress area	7	No
			Withdrawn Patients		
15	Heel	Calcaneum	Exposed bone	5	Yes
16	Lateral mid-forefoot debridement site	Granulation tissue	Shear stress	3.5	Yes

17	5th toe ray amputation and debridement	4th metatarsal head	Exposed bone	5	No
18	Dorsal midfoot debridement site	Granulation tissue	Shear stress area	5.5	No

Table 2.2. Wound bed characteristics and BTM details

All of the patients who completed BTM treatment achieved complete wound healing, with a median duration of 15.5 weeks (range 8-41 weeks) post BTM application, with 85.7% of patients remaining healed with no subsequent wound breakdown by the end of their follow-up period.

a) b)

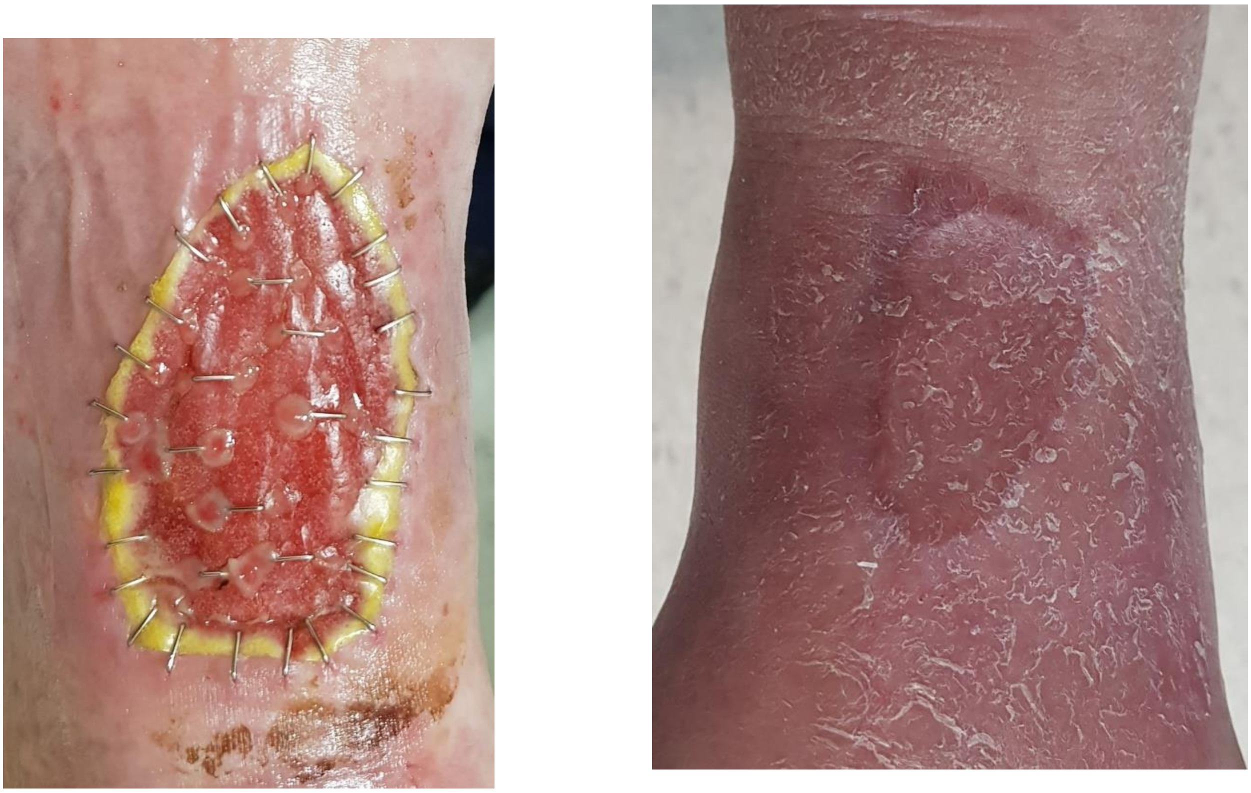

Figure 2.3. Subject 5: a) A 51-year old male with BTM *in situ* for 2.5 weeks on the dorsum of the foot. Where staples penetrate the BTM, granulation has extended through. The rapid growth of granulation tissue reflected accelerated BTM integration and prompted early delamination. b) 12 weeks post BTM delamination and 9 weeks post SSG application.

Deviations from the planned delamination time included Subject 5 (Figure 2.3) and 9 (Figure 2.4) who both had delamination at 2.5 weeks: the former because the BTM had fully integrated with granulations extending through the perforations in the BTM, indicating it was ready for split skin graft and healed without event. The latter was due to a moderate wound infection with high exudate causing non-adherence of the BTM. BTM remained *in situ* for 9 weeks for Subject 4 (Figure 2.5) due to a very large and complex wound deficit, which required more time for granulation tissue to develop. 21.4% of patients proceeded to split skin graft application and 78.6% continued with conventional dressings (Table 2.3).

Subject number	Post BTM wound management	Wound healing achieved	Time to achieve healing (weeks) post BTM application	Subsequent wound breakdown	Length of follow up (months)
1	Conventional dressings	Yes	41	Yes – 6 ½ months	18
2	Conventional dressings	Yes	12	No	17
3	Conventional dressings	Yes	17	Yes – 11 months	16
4	Split skin graft	Yes	21	No	15
5	Split skin graft	Yes	8	No	14
6	Conventional dressings	Yes	16	No	13

7	Conventional dressings	Yes	11	No	13
8	Split skin graft	Yes	13	No	13
9	Conventional dressings	Yes	17	No	12
10	Conventional dressings	Yes	16	No	9
11	Conventional dressings	Yes	13	No	9
12	Conventional dressings	Yes	15	No	8
13	Split skin graft	Yes	10	No	7
14	Conventional dressings	Yes	16	No	3

Table 2.3. BTM Results

Subject 1 was noted to have a significantly delayed healing (achieved at 41 weeks) and subsequent wound breakdown occurring 6 ½ months later, which was attributed to the individual's non-compliance with offloading, footwear and wound management. Subject 2 had a Charcot's arthropathy involving with tarsometatarsal joints with midfoot collapse; while the BTM was able to heal the drained abscess and debridement site, the wound re-ulcerated 11 months later at the same site. This was secondary to the ongoing weightbearing bony prominence from the biomechanical deformity despite offloading with orthotics.

Subject 9 & 10 developed BTM wound site infections, which both developed 14 days post BTM application. Subject 9 developed a moderate infection with a pre-operative wound swab demonstrating methicillin-resistant *Staphylococcus aureus* (MRSA). The patient was treated with 4 days of IV vancomycin and regular wound toilet with a Medisponge® impregnated with chlorhexidine and betadine irrigation. Following this treatment, the infection improved with resolution of the erythema, but the BTM was no longer adherent against the wound bed. The BTM was deemed not salvageable and it was removed in its entirety. The patient completed a 10-day course of oral amoxicillin/clavulanic acid as subsequent wound swab culture grew methicillin-susceptible *Staphylococcus aureus* (MSSA). Wound healing was achieved by secondary intention. Subject 10 developed a mild infection and completed a 10-day course of oral amoxicillin/clavulanic acid and 14 day course of oral ciprofloxacin targeting a wound swab culture demonstrating a mixed growth of coliforms and *Pseudomonas* species. The infection resolved and the BTM remained *in situ* and progressed to integration.

a)

b)

c) d)

Figure 2.4. Subject 9: A 49-year old male who had a guillotine forefoot amputation for diabetic foot infection sepsis control. (a) Prior to BTM application, (b) 14 days following BTM application, moderate infection developed with erythema extending >2cm from the wound margin treated which was managed with intravenous antibiotics and dressings, and (c) following 4 days of treatment the BTM become completely non-adherent to the wound bed. (d) The infection has resolved and the wound healed with conventional dressings.

Subject 8 healed his wound 3 months following BTM application. 4 months later, he developed a new ulcer on his foot due to the biomechanical changes in his foot from his original mid-hindfoot debridement procedure. MRI established metatarsal osteomyelitis with abscess formation and the patient proceeded with a BKA.

DISCUSSION

Due to the complex pathogenesis of diabetic foot ulcers, they are prone to chronicity, wound breakdown and severe infections that can lead to exposure of deeper structures following debridement. This may result in wound beds which are less robust, ungraftable with direct split skin graft or cause significant contour abnormalities.

We have demonstrated the use of BTM in 18 patients, with 14 patients completing BTM treatment of whom all achieved healing of their diabetic foot wounds. Patients with diabetic foot wounds have variable presentations and co-morbidities contributing to the development of their disease, and our patients in the study reflected this with variable glycaemic control, wound location and wound bed tissue composition.

Patients with extensive tissue loss and exposure of deep structures such as tendon and bone were successfully reconstructed and achieved wound closure. However, subsequently, 14.3% of subjects did develop re-ulceration at a later time point. Subject 4 had a lateral malleolus ulcer with tendons and ligaments on view (Figure 2.5) and was thus at very high risk of infection and major limb amputation.Free flap repair was an option, but BTM offered a good alternative as it is a relatively quick and easy procedure with simple postoperative care. Free flaps require longer anaesthetic time which is undesirable in the very comorbid and sick patient. They can also be bulky, making footwear application difficult, even after multiple revisions for thinning, and are contraindicated when significant tibial artery disease is present, whereas BTM offers durable cover with a better contour. BTM would be of particular benefit for rural hospitals, services without access to plastic surgery services or patients in whom free flap construction would be contra-indicated.

a)

b)

c)

d)

e)

Figure 5. Subject 4: A 31-year old male required extensive debridement over the lateral aspect of his ankle for a diabetic foot infection. (a) The lateral malleolus with the tendinous insertions and ligaments on view, (b) BTM was secured using staples surrounding the lateral malleolus, (c) BTM insitu for 9 weeks pre-delamination, and (d) post-delamination, and (e) the result 10 weeks following SSG application.

The infection rate in this limited sized cohort was relatively low at 14.3%. Jia et. al., found that patients presenting with non-infected diabetic foot ulcers, the incidence of subsequent diabetic foot infection was 40.1%.(95) Moreover, patients with deep diabetic foot ulcers were more likely to develop infections.(96) However, our observed low rate of infection was likely significantly impacted by the antibiotics given in the perioperative period for BTM application and frequent wound care and clinic review. For mild infections, we found BTM could remain *in situ* by expressing infected fluid out through the fenestrations in addition to standard wound infection management. High exudate can cause disruption of the integration of BTM with the wound bed. Potentially if more aggressive exudate management and dressing changes had occurred for Subject 9, it is possible that the BTM may have been salvagable.

Two of the patients (14.3%) re-ulcerated at the BTM site due to non-compliance with offloading and high biomechanical stress as discussed earlier. Pre-clinical trials examining BTM implanted into porcine models have demonstrated that the neodermis is principally composed of fibroblasts, keratinocytes, and blood vessels.(86) As a result, the BTM scaffolding is designed to promote shear force resistance and offers wound stability.(86, 97) Although there was a relatively low re-ulceration rate in this study, it was unclear if this theoretical advantage of BTM translated into increased robustness of the wound bed. In wounds which healed by secondary intention after BTM delamination, we observed that the wounds epithelised at a relatively quick rate: for example, Subject 2's wound initially had dorsal fascia on view, with BTM *in situ* for 7 weeks, then 5 weeks following BTM delamination the wound had healed.

Limitations

This pilot study is constrained by a number of limitations. In addition to the small number of patients, the lack of a control group denies us the ability to compare BTM to standard care. Ideally, patients would be randomised to standard wound dressing care including NPWT or BTM. However, this is difficult to achieve due to the diverse wound profiles and patient co-morbidities in the diabetic foot ulcer population. Further studies examining the histological changes in the neodermis in patients with diabetic foot wounds would be useful to compare to the pre-clinical trial group. This would verify whether BTM increases the robustness of the wound bed and accelerates wound epithelisation in this patient population.

Eighteen patients were originally recruited to this study with the application of BTM and four patients were subsequently withdrawn. This reflects the challenges of real-world diabetic foot wound management. For digital and forefoot amputations, there needs to be a balance between removing macroscopically infected tissue but also maintaining a functional foot with the risk of leaving residual microscopic osteomyelitis. Up to 60% of patients have been found to have residual osteomyelitis based on culture and/or pathology from samples of clinically uninfected bone taken by the treating surgeon intraoperatively.(98) Revascularisation procedures for tissue loss due to chronic limb-threatening ischaemia are essential to achieve wound healing and for BTM integration. However, graft occlusion is a known complication with infra-inguinal bypass patency rates of 74-90% at 3 years.(99, 100)

The logistics of outpatient follow-up was a significant barrier to patient recruitment in our study. A large proportion of our patient cohort live in outer metropolitan or rural areas for which the distance, time and cost for them to attend weekly follow up at our metropolitan hospital made their involvement impractical. As we have become more proficient with the use of BTM in this study, it is feasible that we could commence follow-up of these patients via videoconferencing to avoid patient travel for regular review.

The COVID-19 pandemic undoubtedly has had a significant impact on the provision of healthcare worldwide. Within our study, there were multiple resultant limitations. As the designated COVID hospital of our state, vascular surgery patients were decanted to other hospitals with resultant difficulty in patient recruitment, hospital avoidance by patients for recruitment and follow up, reduced operating theatre availability and difficulty organising face-to-face outpatient clinic reviews with a shift towards telehealth which was suboptimal for our study follow up.

CONCLUSION

BTM is a good management adjunct to utilise for wound healing in a variety of diabetic foot wounds. It has been demonstrated to be a simple reconstructive option for diabetic foot wounds with exposed deep structures for patients who are at risk of limb loss in whom direct split skin grafting would not be suitable or durable. It has low rates of re-ulceration and infection. BTM may be salvagable despite infection. Following BTM application, wound healing can be achieved by either split skin grafting or by secondary intention based on the suitability of the wound.

CHAPTER 3

ASSESSMENT OF A SMARTPHONE-BASED APPLICATION FOR DIABETIC FOOT ULCER MEASUREMENT

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Statement of Authorship

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Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/01/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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ORIGINAL RESEARCH-CLINICAL SCIENCE

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Assessment of a smartphone-based application for diabetic foot ulcer measurement

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Abstract

The accurate measurement of diabetic foot ulcer (DFU) wound size is essential as the rate of wound healing is a significant prognostic indicator of the likelihood of complete wound healing. Mobile phone photography is often used for surveillance and to aid in telemedicine consultations. However, there remains no accurate and objective measurement of wound size integrated into these photos. The NDKare mobile phone application has been developed to address this need and our study evaluates its accuracy and practicality for DFU wound size assessment. The NDKare mobile phone application was evaluated for its accuracy in two- (2D) and three-dimensional (3D) wound measurement. One hundred and fifteen diabetic foot wounds were assessed for wound surface area, depth and volume accuracy in comparison to Visitrak and the WoundVue camera. Thirty five wounds had two assessors with different mobiles phones utilizing both applications to assess the reproducibility of the measurements. The 2D surface area measurements by NDKare showed excellent concordance with Visitrak and WoundVue measurements (ICC: 0.991 [95% CI: 0.988, 0.993]) and between different users (ICC: 0.98 [95% CI: 0.96, 0.99)]. The 3D NDKare measurements had good agreement for depth and fair agreement for volume with the WoundVue camera. The NDKare phone application can consistently and accurately obtain 2D measurements of diabetic foot wounds with mobile phone photography. This is a quick and readily accessible tool which can be integrated into comprehensive diabetic wound care.

KEYWORDS
chronic wounds, diabetes, devices

1 | INTRODUCTION

The incidence of diabetic foot ulceration (DFU) continues to rise due to the increasing prevalence of diabetes mellitus and broadening life expectancy of these patients. The estimated worldwide prevalence of foot ulceration amongst diabetics is 1.7–6.3%.[1,2] An estimated 25% of patients with diabetes will develop foot ulceration during their lifetime.[3] Due to biomechanical changes, neuropathy, peripheral vascular disease and an immunocompromised state, wound healing is often slow and difficult to manage. Despite the high costs of DFU care, which accounts for up to 33% of all diabetes-related healthcare costs, approximately 25% of DFU remain unhealed at 1 year.[4,5] More than 50% of DFUs become infected and approximately 28% of these patients progress to an amputation.[3,6] The overall prognosis for DFU patients is very poor with 5% mortality within the first 12 months and 42% mortality within 5 years.[7]

1.1 | Clinical problem addressed

Best practice dictates that DFU management is coordinated in a multidisciplinary diabetic foot service involving evidence-based wound dressings, offloading, vascular and endocrine assessment and infection control.[8] At each review, the objective documentation of a reproducible assessment of wounds should include the key components of photography and wound measurements.[8] Accurate assessment is required in order to monitor wounds over time and allow for early identification of deterioration or indolence. Failure to achieve >50% reduction in wound area by 4 weeks for a DFU has been associated with a significantly decreased probability of healing.[9,10] The Wound Healing Society advises to consider such ulcers as refractory to the current treatment plan and that the management plan and/or etiology should be re-evaluated.[11]

The current techniques for wound assessment in clinical practice remain rudimentary and cumbersome. The most common technique is measurement by a disposable ruler which is quick and inexpensive. However, the measurement is subjective to the reference points for length and width selected by the individual, with overestimation in wound area size by up to 44%.[12,13] In comparison to acetate and digital planimetry, ruler-based measurements are unreliable and their use in clinical practice has been discouraged.[14,15] Planimetery measures the perimeter of the wound with good wound surface area accuracy.[15] However, it requires contact tracing of the wound which can be painful and time intensive.[16,17] Digital planimetry, a non-contact form of planimetry uses digital photographs and computer software to obtain two dimensional measurements.[18] However, this requires specialized computer software which is relatively labour intensive in order to obtain the measurements.[19]

A decrease in wound depth is the first stage of wound healing, followed by circumference reduction.[20] The inSight (eKare Inc., Fairfax, VA), Silhouette (Aranz, Christchurch, NZ) and WoundVue (LBT Innovations Limited, Adelaide, Australia) cameras are examples of three-dimensional (3D) wound cameras which provide accurate measurements with good inter-rater reliability.[21,22] However, 3D cameras can be prohibitively expensive for non-specialist clinics, may be bulky, and as a result are more often used in research rather than the clinical environment.

The NDKare application, available on mobile phone platforms, performs wound photography with integrated measurement software providing measurements of DFU to attempt to addresses the issues with current measurement techniques. The aim of this study was to assess the accuracy of the 2D and 3D wound measurements in comparison to the Visitrak planimetry system (Smith & Nephew Wound Management, Inc., Largo, FL) and the WoundVue 3D camera. The inter-rater measurement accuracy between different users of NDKare was also assessed.

2 | METHODS

Ethics approval was granted from Central Adelaide Local Health Network Human Research. Ethics Committee and documented informed consent was obtained from all participants.

Patients with DFU were enrolled from multidisciplinary diabetic foot clinics at the Royal Adelaide Hospital, Queen Elizabeth Hospital and Lyell McEwin Hospital, or whilst they were admitted under the Vascular Surgery unit at the Royal Adelaide Hospital. Patients were recruited from May 2019 to October 2019. A clinician and a research officer undertook a formal training session on the NDKare phone application provided by LBT Innovations prior to patient recruitment.

NDKare is a software application available on mobile phones developed by Nucleus Dynamics Pty Ltd (Singapore, Singapore). To measure a wound, an adhesive marking sticker is placed adjacent to the wound which acts as a scale for wound size. Within the application, a rectangular box will appear, and the wound and marker should be contained within these boundaries for calibration. This guides the recommended distance for photography between the wound and the phone camera. The in-built flashlight for the photo can be activated within the program for standardized lighting. A photograph is taken at a perpendicular angle to the wound (Figure 1).

The software automatically distinguishes the pixels that constitute the ulcerative area, from normal tissue. The user may finesse the wound boundary outline on the phone if required, by zooming in on the wound in the app and manually tracing the wound edge using their finger. From this, the 2D measurements including length, width, area and perimeter are generated (Figure 2). For serial wound imaging, a "ghost image" of the previous image of the wound will appear which will guide a consistent angle and distance for image capture. A

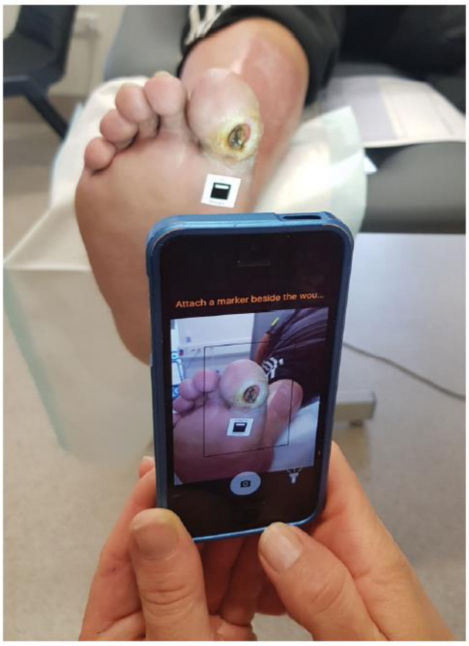
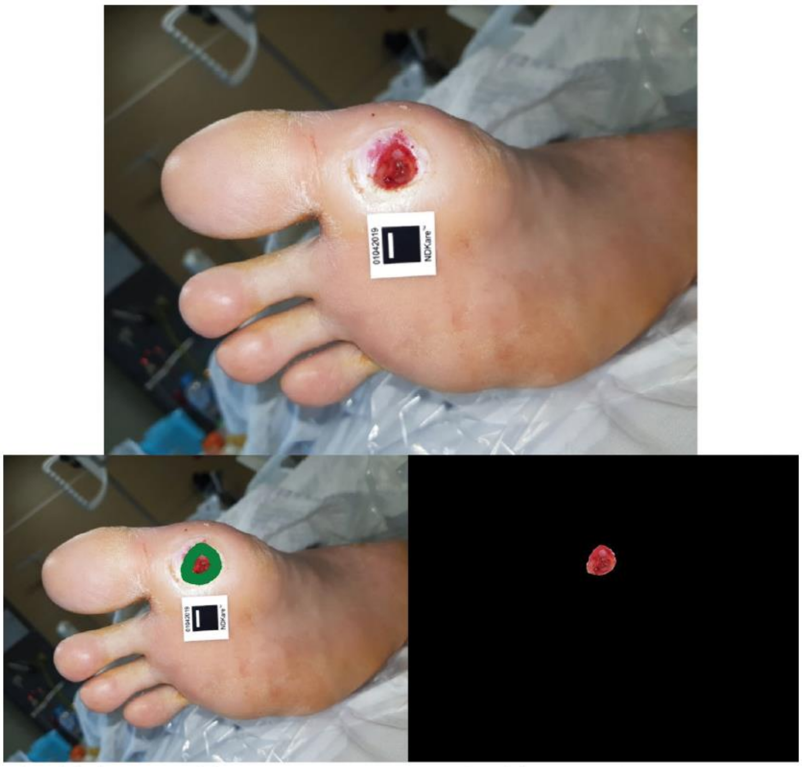


FIGURE 1 NDKare application. The marking sticker is placed in the same plane of the wound for orientation and size reference, then photo taken at a perpendicular angle to the wound



Length (cm)	1.3	Granulation (%)	99.6
Width (cm)	1.2	Slough (%)	0
Perimeter (cm)	4.9	Bone (%)	0.2
Area (cm²)	1.1	Necrosis (%)	0.2

FIGURE 2 NDKare wound assessment. The top panel is the photographed image of the wound, bottom left panel is the generated 2D metric measurements and the bottom right panel is the wound bed composition analysis

timeline of each patient's wounds with photographs and measurements is generated to allow for monitoring wound progression over time.

NDKare also requires a 20 s video panning over the wound to generate a 3D model of the wound utilizing the concept of "structure from motion" (Figure 3). This video is segmented into a smooth sequence of images of the wound taken from different vantage points. Image processing algorithms identify a small set of highly distinguishable pixels in the image set called "keypoints". As keypoints are distinct, an image processing algorithm can match corresponding keypoints across multiple images. Triangulating these yields a "sparse 3D reconstruction" of the wound. More sophisticated algorithms attempt to substantially increase the set of corresponding points beyond the initial set of matched keypoints, and triangulating the expanded set of matched points results in a "dense" 3D point cloud. To facilitate the computation of various metric properties of the wound, such as its depth and volume, the 3D point cloud is converted into a smooth 3D "surface reconstruction". Finally, the pixel colors of the wound are combined for "surface texturing" which is mapped onto a 3D model.[23] From the mobile phone, this video is directly uploaded onto an online Health Insurance Portability and Accountability Act (HIPAA) compliant cloud dashboard. HIPAA has established the standard for the protection of sensitive patient data with security measures required for physical and network data. On the dashboard, a total of eight points are made outlining the wound, the maximal depth and the marking sticker to generate the 3D measurements of depth and volume.

One hundred and fifteen wounds were assessed using the NDKare application by a single clinician (B.K.). During the same wound review, Visitrak and WoundVue camera measurements of the wound were also obtained. The Visitrak planimetry system was used as the traditional gold standard for the 2D measurements. Our group has previously demonstrated the validity of the WoundVue camera as a 3D measurement device for diabetic foot wounds.[22] We aimed to assess if the 2D measurements on the NDKare application were comparable to the Visitrak and WoundVue camera, and if the NDKare application 3D measurements were consistent with the WoundVue camera. Subsequently, the clinician (B.K.) using a Samsung Galaxy S8+ smartphone (Version 9, Seoul, KR, Samsung Electronics Co. Ltd.) and research officer (R.B.) using an Apple iPhone 5 (Version 10.3.4, Cupertino, CA, Apple Inc.) used the NDKare application to measure the same wound for a total of 35 2D and wound measurements for inter-

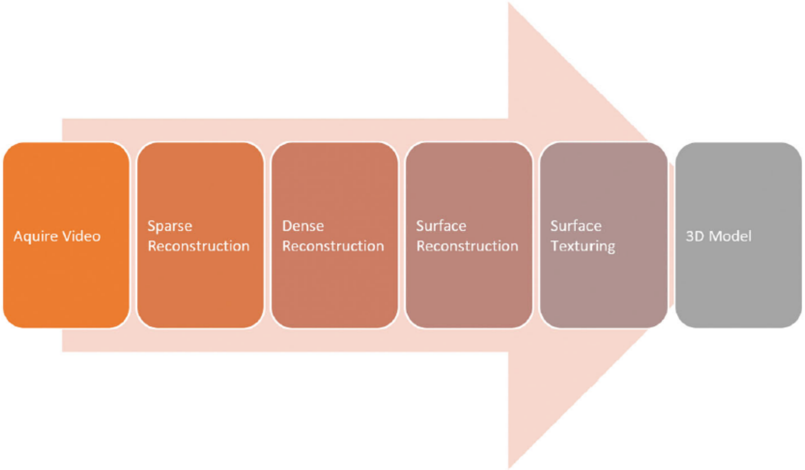


FIGURE 3 Structure from motion pipeline. NDKare 3D reconstruction software processing for converting the video of the wound to the 3D model [Color figure can be viewed at wileyonlinelibrary.com]

rater reliability. The research officer had limited time availability, and as a result was only able to measure 35 of the 115 wounds which had been assessed by the clinician.

2.1 | Statistical Analysis

Intraclass correlation coefficient (ICC) estimates and 95% confidence intervals (CIs) were calculated. Cicchetti's guidelines for interpretation of ICC inter-rater agreement measures were used with ICC values ≥0.75 indicating excellent agreement, 0.60–0.74 as good agreement and 0.40–0.59 as fair agreement.[24]

A two-way mixed-effect model with consistency of agreement statistical model was used for comparison of NDKare, Visitrak and WoundVue measurements, and between different users for inter-rater reliability.

All statistical analysis was performed using Stata Statistical Software (Release 15.1, College Station, TX: StataCorp LP).

3 | RESULTS

One hundred and fifteen diabetic foot wounds were assessed using the NDKare application, Visitrak and WoundVue camera for 2D and 3D measurements. Wounds included in this study were digital ulcers (49.6%), forefoot ulcers (19.1%), toe amputation sites (10.4%), midfoot ulcers (7.8%), heel ulcers (5.2%), multiple digit ulcers (4.3%), malleolar wounds (2.6%) and a forefoot guillotine amputation (0.9%). Diabetic foot wounds measuring <10 cm^2 comprised 80.9% of the cohort, 10.4% of wounds measured 10.1–19.9 cm^2 and 8.7% of wounds 20–66 cm^2. The median wound surface area measurement was 2.91 cm^2 (IQR 1.05–8.53). The median maximum depth and volume of the wounds was 0.25 cm^2 (IQR 0.04–0.86) and 1.15 cm^3 (IQR 0.07–10.13), respectively.

There was excellent inter-rater reliability between all three measurement devices for surface area (ICC: 0.99 [95% CI: 0.99, 0.99]). For maximum depth there was good agreement (ICC: 0.70 [95% CI: 0.56, 0.79]) and fair agreement for volume (ICC: 0.51 [95% CI: 0.29, 0.67]) between the WoundVue camera and NDKare application measurements.

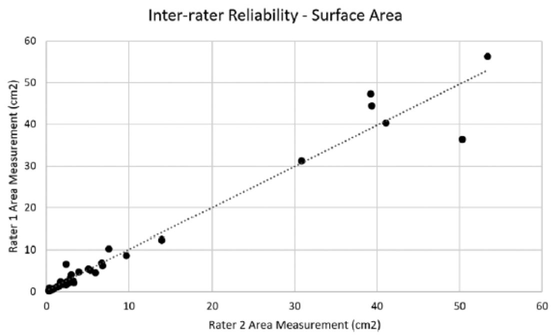


FIGURE 4 The inter-rater reliability of the NDKare application surface area measurements between two different users and smartphones

Thirty five diabetic foot wounds were assessed by two different assessors using the NDKare on different mobile phone devices for the 2D and 3D measurements. There was excellent inter-rater reliability for surface area (ICC: 0.98 [95% CI: 0.96, 0.99)]. For maximum depth there was good agreement (ICC: 0.63 [95% CI: 0.27, 0.81]) and good agreement for volume (ICC: 0.64 [95% CI: 0.28, 0.82]) (Figure 4).

4 | DISCUSSION

Over the last 20 years, the use of mobile devices has significantly increased due to a reduction in price and increase in processing and memory capabilities. Due to the widespread availability of smartphones, the subjective use of mobile phone images for telemedicine and serial wound imaging has become a frequent addition to modern wound care management. Whilst this is an improvement on wound descriptions and diagrams, we know that objective measurements of wounds are essential in order to be able to direct patient care. The

NDKare application utilizes the pre-existing smartphone camera hardware and the NDKare image processing and interpretation software to generate the 2D and 3D wound measurements. This design allows the NDKare system to be accessible to anyone owning a smartphone without the need for specialized equipment.

From our results, the NDKare system accurately measures the surface area of diabetic foot wounds in comparison to the gold standard Visitrak and recently validated WoundVue camera. Two different smartphone platforms (Samsung Galaxy S8+ and Apple iPhone 5) were used to compare the accuracy and reproducibility of the NDKare application. These phones have different cameras, flash, color and video processing software. In addition to these variables, two different users used each phone. Despite these multiple variables, our results highlights that different users with different smartphones can use this software and still obtain similar results. Although the clinician and research officer have varying levels of wound care experience, there were no noted significant differences in the use of the NDKare system to take wound photos. This is likely attributable to the same training session both individuals attended, but it may also reflect the ease of use of the NDKare interface.

The availability of a point-of-care, accurate, reproducible and readily available software to measure the surface area of the wound and photographically monitor a wound is a useful adjunct to aid clinical assessment in the multidisciplinary foot clinic.[25]

This benefit may extend to patient use as many already use mobile phone photos to inspect and monitor their ulcers. Phone applications which can provide detailed objective wound measurement data have been shown to increase patient's trust in health provider's assessment and may increase patient motivation during the wound healing process.[26] In addition, the "ghost images" may help patients with accuracy of wound image capture as they may be elderly or have visual impairment secondary to diabetes.[27]

For patients living in remote areas who are unable to attend multidisciplinary foot clinics, the Australian National Evidence-Based Guidelines for the Prevention, Identification and Management of Foot Complications in Diabetes recommends utilizing remote expert consultation with digital imaging. A randomized controlled trial showed this resulted in a reduction in ulcer size each week and a reduction in amputation rates in comparison to local physician care with digital imaging.[28] A recent study found that standard digital images taken on an iPhone as the sole diagnostic modality for assessing DFU has been shown to have limited validity and reliability in assessment. The authors recommended that systems needed to be developed with better diagnostic accuracy.[29] Using this software, photos of the wound and measurements can be uploaded remotely onto the cloud-based system via the mobile phone for availability to health care professionals to aid telemedicine consultation.

The NDKare system adapts similar technical principals as digital planimetry, with two key factors that affect the area measurement accuracy of their device. Firstly, the marker must lie on the same plane as the wound, and secondly, the angle of the camera should be perpendicular to the wound and marker.[30] Figure 4 demonstrates that at larger wound sizes, there was increased discrepancy in wound surface area measurements between different raters. For small wounds is it generally easier to identify the correct wound plane and perpendicular angle. However, for large wounds, the correct plane can be difficult to identify with loss of normal foot contours, varying depth and determining a perpendicular camera angle is also less straightforward. On reviewing our raw data, the most significant outlier from the trendline in Figure 4 was a large guillotine forefoot amputation with varying depth. There was no epithelised tissue on which to place the marking sticker, so the marking sticker was placed on paper adjacent to the wound held by the other rater. It is highly likely there is a degree of human error in maintaining the marking sticker in the same plane between raters' photo capture that has resulted in the large difference in surface area measurement. This was a limitation that was recognized at the time of the photo capture, however, we deemed it suitable to include as we were unsure if an accurate measurement would still be captured despite our potential human error.

As mobile phone camera technology and image quality continues to develop rapidly, the ability to accurately obtain 3D wound measurements may become feasible. Pre-existing 3D wound cameras have specialized hardware and software which use the concepts of stereophotogrammetry, laser and structured light scanning.[31] These techniques require bulky hardware with multiple cameras or lasers to image or scan the wound simultaneously at different angles. Although the NDKare application does not accurately obtain depth and volume measurements, there is already interest amongst mobile phone companies in the development of depth estimation hardware. Apple acquired PrimeSense, the company which developed the Microsoft Kinect structured light sensor in 2013.[32] Using this technology, Apple has subsequently developed the iPad Pro which has an in-built rear 3D camera and the iPhone X and later models which have the TrueDepth front-facing 3D camera.[33,34] The TrueDepth application programming interface (API) for depth data is available to iOS devices running iOS 11 or later.[35] Intel has also developed RealSense, which aims to integrate depth sensors into their mobile phones.[36]

A limitation of our study is that the feasibility of the diabetic foot ulcer patient population to use the NDKare application for self-monitoring was not evaluated. A participatory healthcare approach has been shown to increase patient engagement with an improvement in the shared decision-making process. There is the potential to decrease medical errors and increase staff adherence to optimal treatment practices, particularly for chronic diseases.[37] However, the adoption and consistent use of this technology needs to be assessed. Depending on the location of the wound, some patients will not be able to take photos of the wound and will require a carer to take the photos for them. Future studies examining the impact on patient self-care, compliance and limitations to patient utilization would be useful to evaluate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ABSTRACT

Objective

The accurate measurement of diabetic foot ulcer (DFU) wound size is essential as the rate of wound healing is a significant prognostic indicator of the likelihood of complete wound healing. Mobile phone photography is often used for surveillance and to aid in telemedicine consultations. However, there remains no accurate and objective measurement of wound size integrated into these photos. The NDKare™ mobile phone application has been developed to address this need and our study evaluates its accuracy and practicality for DFU wound size assessment.

Approach

The NDKare™ mobile phone application was evaluated for its accuracy in two- (2D) and three-dimensional (3D) wound measurement. 115 diabetic foot wounds were assessed for wound surface area, depth and volume accuracy in comparison to Visitrak™ and the WoundVue™ camera. 35 wounds had two assessors with different mobiles phones utilising both applications to assess the reproducibility of the measurements.

Results

The 2D surface area measurements by NDKare™ showed excellent concordance with Visitrak™ and WoundVue™ measurements (ICC: 0.991 [95% CI: 0.988, 0.993])

and between different users (ICC: 0.98 [95% CI: 0.96, 0.99)]. The 3D NDKare^{TM} measurements had good agreement for depth and fair agreement for volume with the WoundVue^{TM} camera.

Conclusion

The NDKare^{TM} phone application can consistently and accurately obtain 2D measurements of diabetic foot wounds with mobile phone photography. This is a quick and readily accessible tool which can be integrated into comprehensive diabetic wound care.

INTRODUCTION

The incidence of diabetic foot ulceration (DFU) continues to rise due to the increasing prevalence of diabetes mellitus and broadening life expectancy of these patients. The estimated worldwide prevalence of foot ulceration amongst diabetics is 1.7% to 6.3%.(10, 101) An estimated 25% of patients with diabetes will develop foot ulceration during their lifetime.(64) Due to biomechanical changes, neuropathy, peripheral vascular disease and an immunocompromised state, wound healing is often slow and difficult to manage. Despite the high costs of DFU care, which accounts for up to 33% of all diabetes-related healthcare costs, approximately 25% of DFU remain unhealed at 1 year.(102, 103) More than 50% of DFUs become infected and approximately 28% of these patients progress to an amputation.(64, 65) The overall prognosis for DFU patients is very poor with 5% mortality within the first 12 months and 42% mortality within 5 years.(104)

Clinical Problem Addressed

Best practice dictates that DFU management is coordinated in a multidisciplinary diabetic foot service involving evidence-based wound dressings, offloading, vascular and endocrine assessment and infection control.(105) At each review, the objective documentation of a reproducible assessment of wounds should include the key components of photography and wound measurements.(105) Accurate assessment is required in order to monitor wounds over time and allow for early identification of deterioration or indolence. Failure to achieve >50% reduction in wound area by four weeks for a DFU has been associated with a significantly decreased probability of healing.(106, 107) The Wound Healing Society advises to consider such ulcers as refractory to the current treatment plan and that the management plan and/or aetiology should be re-evaluated.(108)

The current techniques for wound assessment in clinical practice remain rudimentary and cumbersome. The most common technique is measurement by a disposable ruler which is quick and inexpensive. However, the measurement is subjective to the reference points for length and width selected by the individual, with overestimation in wound area size by up to 44%.(108, 109) In comparison to acetate and digital planimetry, ruler-based measurements are unreliable and their use in clinical practice has been discouraged.(110, 111) Planimetery measures the perimeter of the wound with good wound surface area accuracy.(111) However, it requires contact tracing of the wound which can be painful and time intensive.(43, 112) Digital planimetry, a non-contact form of planimetry uses digital photographs and computer software to obtain two dimensional measurements.(113) However, this requires specialised computer software which is relatively labour intensive in order to obtain the measurements.(114)

A decrease in wound depth is the first stage of wound healing, followed by circumference reduction.(115) The inSight® (eKare Inc., Fairfax, VA, USA), Silhouette® (Aranz, Christchurch, NZ) and WoundVue™ (LBT Innovations Limited, Adelaide, Australia) cameras are examples of three-dimensional (3D) wound cameras which provide accurate measurements with good inter-rater reliability.(42,

116) However, 3D cameras can be prohibitively expensive for non-specialist clinics, may be bulky, and as a result are more often used in research rather than the clinical environment.

The NDKare™ application, available on mobile phone platforms, performs wound photography with integrated measurement software providing measurements of DFU to attempt to addresses the issues with current measurement techniques. The aim of this study was to assess the accuracy of the 2D and 3D wound measurements in comparison to the Visitrak™ planimetry system (Smith & Nephew Wound Management, Inc., Largo, FL, USA) and the WoundVue™ 3D camera. The inter-rater measurement accuracy between different users of NDKare™ was also assessed.

METHODS

Ethics approval was granted from Central Adelaide Local Health Network Human Research Ethics Committee and documented informed consent was obtained from all participants.

Patients with DFU were enrolled from multidisciplinary diabetic foot clinics at the Royal Adelaide Hospital, Queen Elizabeth Hospital and Lyell McEwin Hospital, or whilst they were admitted under the Vascular Surgery unit at the Royal Adelaide Hospital. Patients were recruited from May 2019 to October 2019. A clinician and a research officer undertook a formal training session on the NDKare^{TM} phone application provided by LBT Innovations prior to patient recruitment.

NDKare^{TM} is a software application available on mobile phones developed by Nucleus Dynamics Pty Ltd (Singapore, Singapore). To measure a wound, an adhesive marking sticker is placed adjacent to the wound which acts as a scale for wound size. Within the application, a rectangular box will appear, and the wound and marker should be contained within these boundaries for calibration. This guides the recommended distance for photography between the wound and the phone camera. The in-built flashlight for the photo can be activated within the program for standardised lighting. A photograph is taken at a perpendicular angle to the wound (Figure 3.1).

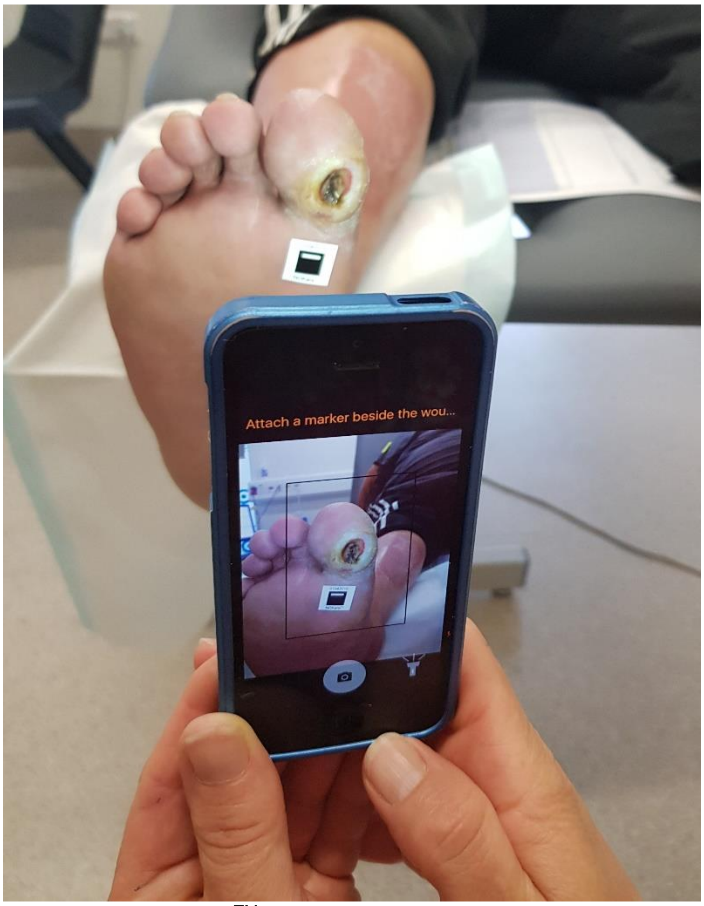
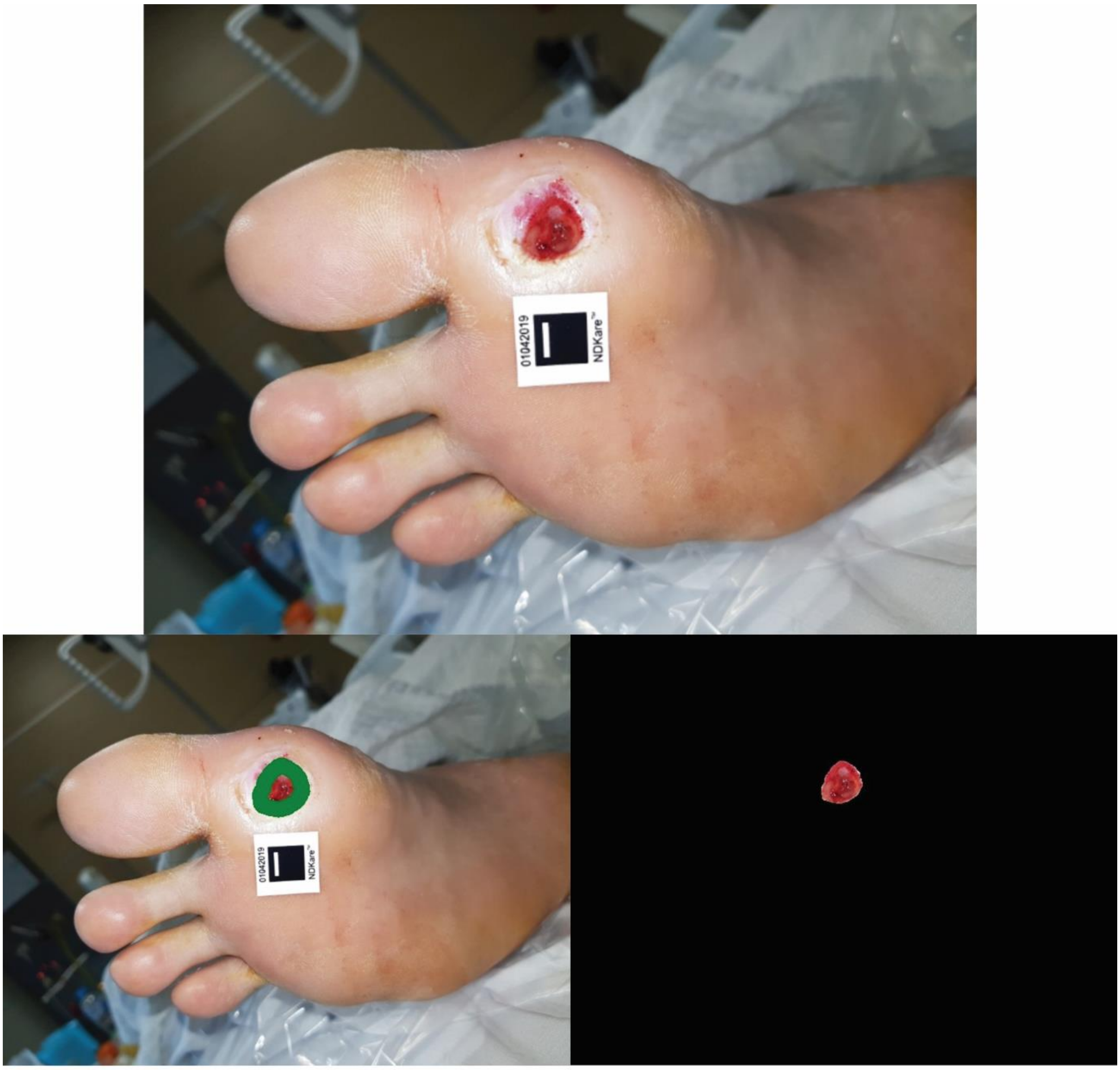


Figure 3.1. NDKare^{TM} application. The marking sticker is placed in the same plane of the wound for orientation and size reference, then photo taken at a perpendicular angle to the wound.

The software automatically distinguishes the pixels that constitute the ulcerative area, from normal tissue. The user may finesse the wound boundary outline on the phone if required, by zooming in on the wound in the app and manually tracing the wound edge using their finger. From this, the 2D measurements including length, width, area and perimeter are generated (Figure 3.2). For serial wound imaging, a ‘ghost image’ of the previous image of the wound will appear which will guide a consistent angle and distance for image capture. A timeline of each patient’s wounds with photographs and measurements is generated to allow for monitoring wound progression over time.



Length (cm)	1.3	Granulation (%)	99.6
Width (cm)	1.2	Slough (%)	0
Perimeter (cm)	4.9	Bone (%)	0.2
Area (cm²)	1.1	Necrosis (%)	0.2

Figure 3.2: NDKare^{TM} wound assessment. The top panel is the photographed image of the wound, bottom left panel is the generated 2D metric measurements and the bottom right panel is the wound bed composition analysis.

NDKare also requires a 20 second video panning over the wound to generate a 3D model of the wound utilising the concept of ‘structure from motion’ (Figure 3.3). This video is segmented into a smooth sequence of images of the wound taken from different vantage points. Image processing algorithms identify a small set of highly distinguishable pixels in the image set called ‘keypoints’. As keypoints are distinct, an image processing algorithm can match corresponding keypoints across multiple images. Triangulating these yields a ‘sparse 3D reconstruction’ of the wound. More sophisticated algorithms attempt to substantially increase the set of corresponding points beyond the initial set of matched keypoints and triangulating the expanded set of matched points results in a ‘dense’ 3D point cloud. To facilitate the computation of various metric properties of the wound, such as its depth and volume, the 3D point cloud is converted into a smooth 3D ‘surface reconstruction’. Finally, the pixel colours of the wound are combined for ‘surface texturing’ which is mapped onto a 3D model.(117) From the mobile phone, this video is directly uploaded onto an online Health Insurance Portability and Accountability Act (HIPAA) compliant cloud dashboard. HIPAA has established the standard for the protection of sensitive patient data with security measures required for physical and network data. On the dashboard, a total of 8 points are made outlining the wound, the maximal depth and the marking sticker to generate the 3D measurements of depth and volume.

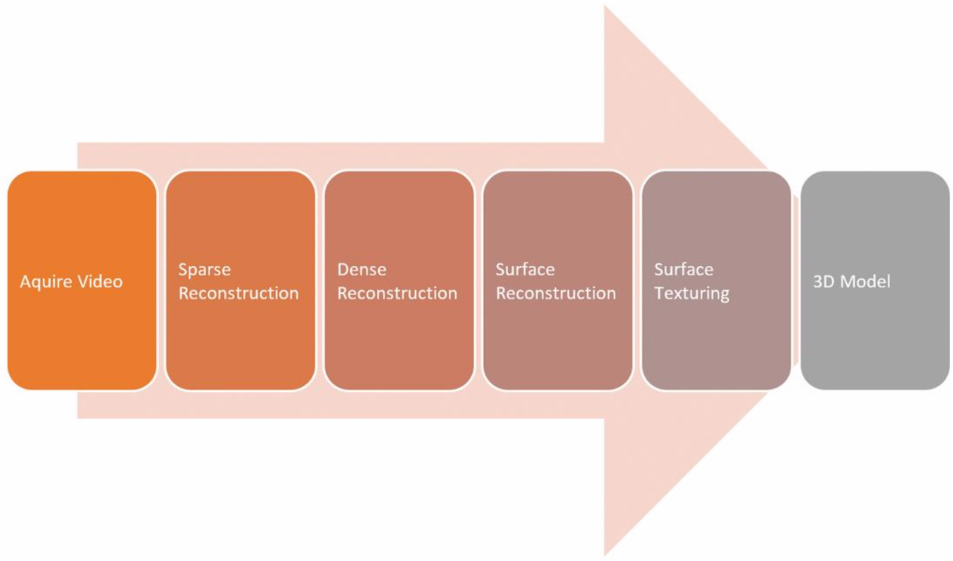


Figure 3.3.: Structure from motion pipeline. NDKare™ 3D reconstruction software processing for converting the video of the wound to the 3D model.

115 wounds were assessed using the NDKare™ application by a single clinician (B.K.). During the same wound review, Visitrak™ and WoundVue™ camera measurements of the wound were also obtained. The Visitrak™ planimetry system was used as the traditional gold standard for the 2D measurements. Our group has previously demonstrated the validity of the WoundVue™ camera as a 3D measurement device for diabetic foot wounds.(116) We aimed to assess if the 2D measurements on the NDKare™ application were comparable to the Visitrak™ and WoundVue™ camera, and if the NDKare™ application 3D measurements were consistent with the WoundVue™ camera. Subsequently, the clinician (B.K.) using a Samsung Galaxy® S8+ smartphone (Version 9, Seoul, KR, Samsung Electronics Co. Ltd.) and research officer (R.B.) using an Apple iPhone® 5 (Version 10.3.4, Cupertino, CA, Apple Inc.) used the NDKare™ application to measure the same wound for a total of 35 2D and wound measurements for inter-rater reliability. The

research officer had limited time availability, and as a result was only able to measure 35 of the 115 wounds which had been assessed by the clinician.

Statistical Analysis

Intraclass correlation coefficient (ICC) estimates and 95% confidence intervals (CIs) were calculated. Cicchetti's guidelines for interpretation of ICC inter-rater agreement measures were used with ICC values ≥0.75 indicating excellent agreement, 0.60-0.74 as good agreement and 0.40-0.59 as fair agreement.(118)

A two-way mixed-effect model with consistency of agreement statistical model was used for comparison of NDKare™, Visitrak™ and WoundVue™ measurements, and between different users for inter-rater reliability.

All statistical analysis was performed using Stata Statistical Software (Release 15.1, College Station, TX: StataCorp LP).

RESULTS

115 diabetic foot wounds were assessed using the NDKare™ application, Visitrak™ and WoundVue™ camera for 2D and 3D measurements. Wounds included in this study were digital ulcers (49.6%), forefoot ulcers (19.1%), toe amputation sites (10.4%), midfoot ulcers (7.8%), heel ulcers (5.2%), multiple digit ulcers (4.3%), malleolar wounds (2.6%) and a forefoot guillotine amputation (0.9%). Diabetic foot wounds measuring <10cm^2 comprised 80.9% of the cohort, 10.4% of wounds

measured 10.1-19.9cm^2 and 8.7% of wounds 20-66cm^2. The median wound surface area measurement was 2.91 cm^2 (IQR: 1.05 to 8.53). The median maximum depth and volume of the wounds was 0.25 cm^2 (IQR: 0.04-0.86) and 1.15 cm^3 (IQR: 0.07-10.13) respectively.

There was excellent inter-rater reliability between all three measurement devices for surface area (ICC: 0.99 [95% CI: 0.99, 0.99]). For maximum depth there was good agreement (ICC: 0.70 [95% CI: 0.56, 0.79]) and fair agreement for volume (ICC: 0.51 [95% CI: 0.29, 0.67]) between the WoundVue^{TM} camera and NDKare^{TM} application measurements.

35 diabetic foot wounds were assessed by two different assessors using the NDKare^{TM} on different mobile phone devices for the 2D and 3D measurements. There was excellent inter-rater reliability for surface area (ICC: 0.98 [95% CI: 0.96, 0.99)]. For maximum depth there was good agreement (ICC: 0.63 [95% CI: 0.27, 0.81]) and good agreement for volume (ICC: 0.64 [95% CI: 0.28, 0.82]) (Figure 3.4).

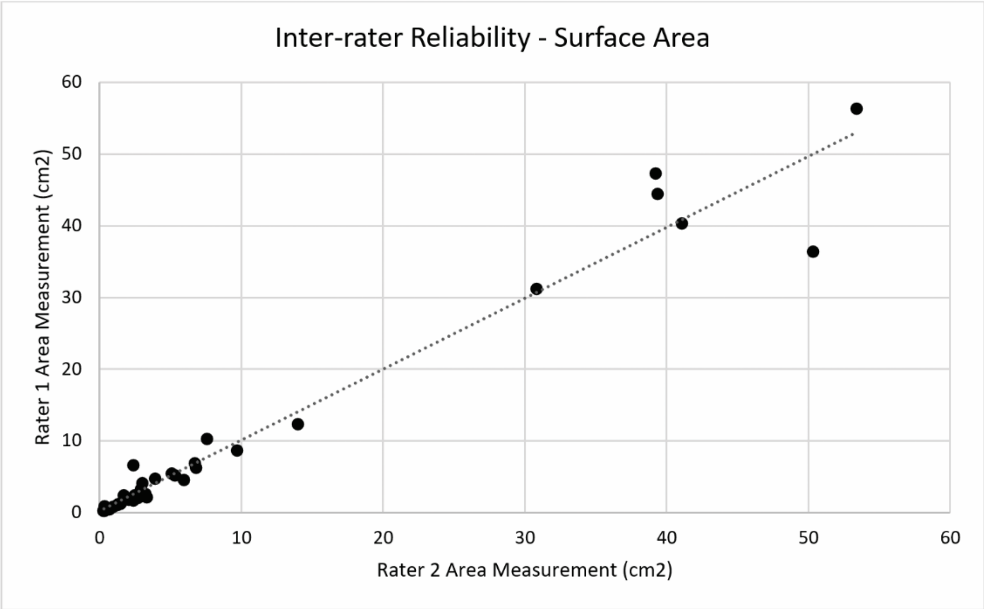


Figure 3.4.: The inter-rater reliability of the NDKare^{TM} application surface area measurements between two different users and smartphones.

DISCUSSION

Over the last 20 years, the use of mobile devices has significantly increased due to a reduction in price and increase in processing and memory capabilities. Due to the widespread availability of smartphones, the subjective use of mobile phone images for telemedicine and serial wound imaging has become a frequent addition to modern wound care management. Whilst this is an improvement on wound descriptions and diagrams, we know that objective measurements of wounds are essential in order to be able to direct patient care. The NDKare^{TM} application utilises the pre-existing smartphone camera hardware and the NDKare^{TM} image processing and interpretation software to generate the 2D and 3D wound measurements. This design allows the NDKare^{TM} system to be accessible to anyone owning a smartphone without the need for specialised equipment.

From our results, the NDKare™ system accurately measures the surface area of diabetic foot wounds in comparison to the gold standard Visitrak™ and recently validated WoundVue™ camera. Two different smartphone platforms (Samsung Galaxy® S8+ and Apple iPhone® 5) were used to compare the accuracy and reproducibility of the NDKare™ application. These phones have different cameras, flash, colour and video processing software. In addition to these variables, two different users used each phone. Despite these multiple variables, our results highlights that different users with different smartphones can use this software and still obtain similar results. Although the clinician and research officer have varying levels of wound care experience, there were no noted significant differences in the use of the NDKare™ system to take wound photos. This is likely attributable to the same training session both individuals attended, but it may also reflect the ease of use of the NDKare™ interface.

The availability of a point-of-care, accurate, reproducible and readily available software to measure the surface area of the wound and photographically monitor a wound is a useful adjunct to aid clinical assessment in the multidisciplinary foot clinic.(119)

This benefit may extend to patient use as many already use mobile phone photos to inspect and monitor their ulcers. Phone applications which can provide detailed objective wound measurement data have been shown to increase patient's trust in health provider's assessment and may increase patient motivation during the wound healing process.(120) In addition, the “ghost images” may help patients with accuracy of wound image capture as they may be elderly or have visual impairment secondary to diabetes.(121)

For patients living in remote areas who are unable to attend multidisciplinary foot clinics, the Australian National Evidence-Based Guidelines for the Prevention, Identification and Management of Foot Complications in Diabetes recommends utilising remote expert consultation with digital imaging. A randomised controlled trial showed this resulted in a reduction in ulcer size each week and a reduction in amputation rates in comparison to local physician care with digital imaging.(122) A recent study found that standard digital images taken on an iPhone® as the sole diagnostic modality for assessing DFU has been shown to have limited validity and reliability in assessment. The authors recommended that systems needed to be developed with better diagnostic accuracy.(123) Using this software, photos of the wound and measurements can be uploaded remotely onto the cloud-based system via the mobile phone for availability to health care professionals to aid telemedicine consultation.

The NDKare™ system adapts similar technical principals as digital planimetry, with two key factors that affect the area measurement accuracy of their device. Firstly, the marker must lie on the same plane as the wound, and secondly, the angle of the camera should be perpendicular to the wound and marker.(124) Figure 4 demonstrates that at larger wound sizes, there was increased discrepancy in wound surface area measurements between different raters. For small wounds is it generally easier to identify the correct wound plane and perpendicular angle. However, for large wounds, the correct plane can be difficult to identify with loss of normal foot contours, varying depth and determining a perpendicular camera angle is also less straightforward. On reviewing our raw data, the most significant outlier from the trendline in Figure 4 was a large guillotine forefoot amputation with varying depth. There was no epithelised tissue on which to place the marking sticker, so the marking sticker was placed on paper adjacent to the wound held by the other rater. It is highly likely there is a degree of human error in maintaining the marking sticker in the same plane between raters' photo capture that has resulted in the large difference in surface area measurement. This was a limitation that was recognised at the time of the photo capture, however, we deemed it suitable to include as we were unsure if an accurate measurement would still be captured despite our potential human error.

As mobile phone camera technology and image quality continues to develop rapidly, the ability to accurately obtain 3D wound measurements may become feasible. Pre-existing 3D wound cameras have specialised hardware and software which use the concepts of stereophotogrammetry, laser and structured light scanning.(125) These techniques require bulky hardware with multiple cameras or lasers to image or scan the wound simultaneously at different angles. Although the NDKare™ application does not accurately obtain depth and volume measurements, there is already interest amongst mobile phone companies in the development of depth estimation hardware. Apple® acquired PrimeSense®, the company which developed the

Microsoft Kinect® structured light sensor in 2013.(126) Using this technology, Apple® has subsequently developed the iPad Pro® which has an in-built rear 3D camera and the iPhone® X and later models which have the TrueDepth® front-facing 3D camera.(127, 128) The TrueDepth® application programming interface (API) for depth data is available to iOS devices running iOS™ 11 or later.(129) Intel® has also developed RealSense™, which aims to integrate depth sensors into their mobile phones.(130)

A limitation of our study is that the feasibility of the diabetic foot ulcer patient population to use the NDKare™ application for self-monitoring was not evaluated. A participatory healthcare approach has been shown to increase patient engagement with an improvement in the shared decision-making process. There is the potential to decrease medical errors and increase staff adherence to optimal treatment practices, particularly for chronic diseases.(131) However, the adoption and consistent use of this technology needs to be assessed. Depending on the location of the wound, some patients will not be able to take photos of the wound and will require a carer to take the photos for them. Future studies examining the impact on patient self-care, compliance and limitations to patient utilisation would be useful to evaluate.

CHAPTER 4

THE GLASS IS HALF FULL – TRANSITIONING FROM TASC TO GLASS IN THE MANAGEMENT OF CHRONIC LIMB-THREATENING ISCHAEMIA

Beatrice Kuang, Robert Fitridge, Michael Conte, Joseph Dawson

(Manuscript)

Statement of Authorship

Title of Paper	The Glass is Half Full – Transitioning from TASC to GLASS in the Management of Chronic Limb-Threatening Ischaemia
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☑ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Commentary/Perspectives paper evaluating the evolution of anatomical based classification systems for peripheral arterial disease and highlights the deficiencies of using TASC II to guide contemporary practice. An overview of the Global Vascular Guideline's new GLASS concept is provided with examples of use in clinical practice to guide clinicians in identifying optimal revascularisation strategies.

Principal Author

Name of Principal Author (Candidate)	Beatrice Kuang		
Contribution to the Paper	Data collection, data analysis, writing – original draft, writing – review & editing		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/01/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Robert Fitridge		
Contribution to the Paper	Contributed to design of GLASS staging system Reviewed and revised manuscript % 10%		
Signature		Date	10/11/20

Name of Co-Author	Michael S. Conte		
Contribution to the Paper	Review and editing of drafts		
Signature		Date	28/12/20

Name of Co-Author	Joseph Dawson		
Contribution to the Paper	Provided important input in planning of the research, supervised development of work, helped to evaluate and edit the manuscript.		
Signature		Date	29/01/2022

INTRODUCTION

Critical limb ischaemia (CLI) was first defined in 1982 by the Working Party of the International Vascular Symposium, and did not specifically include patients with diabetes. (132) Since its inception the definition has been applied broadly to a widely heterogenous group of patients, hindering the development of robust, evidence-based recommendations for the assessment and management of CLI. In recognition of the paucity of evidence to guide the management of this challenging disease, the Global Vascular Guideline (GVG) working group was formed, comprising of a steering committee from the three major global vascular surgical societies: the European Society for Vascular Surgery (ESVS), the Society for Vascular Surgery (SVS) and the World Federation of Vascular Societies (WFVS) and international experts from all relevant specialties. The GVG has introduced new terminology and concepts reflective of the contemporary cohort of patients affected by peripheral arterial disease (PAD). The term chronic limb-threatening ischaemia (CLTI) is preferred over CLI and describes peripheral vascular disease (PAD), represented by the presence of objectively documented atherosclerotic PAD, in combination with rest pain with confirmatory haemodynamic studies, gangrene or tissue loss for >2 weeks duration.(133)

The clearly defined concept of CLTI has allowed the development of a new anatomical classification system for PAD, within an evidence-based revascularisation framework. The Global Limb Anatomic Staging System (GLASS) has been proposed by the GVG to guide clinical decision-making in the management of CLTI whilst also providing a framework for evidence-based revascularisation into the future.

ANATOMICAL CLASSIFICATION SYSTEMS FOR PERIPHERAL ARTERIAL DISEASE

Over the last 70 years, numerous classification systems have been developed to aid the evaluation of PAD, each with their own strengths and weaknesses (Table 4.1). Only half of the most common classification systems of PAD incorporate anatomical features.

Classification	Year developed	Direct treatment	Diabetes specific	Pros	Cons
CLINICAL CLASSIFICATION SYSTEMS					
Fontaine	1954	Yes	No	Historically proven; easy to apply to patient	No objective criteria
Rutherford	1986 1997 (revised)	Yes	No	Historically proven, quickly apply to patient, objective	Classically should not be applied in diabetes, no consideration of wounds
American Medical Association (AMA)	2008	No	No	Good for use in disability, reflects state of the patient's global health	Not intended to direct treatment, mixed arterial and venous categories
WIfI	2014	Yes	Yes	Robust to account for several factors in foot pathology	No anatomical assessment
ANATOMICAL CLASSIFICATION SYSTEMS					
Bollinger	1975	No	No	Categorical variable can be used in research, allows for documentation of change in follow-up	No basis on symptoms, applies poorly to diabetes
Graziani	2007	No	Yes	Application in diabetes	Does not address aortoiliac disease, does not direct therapy
TASC II	2007	Yes	No	Defined disease process, used in several research studies	Treatment recommendations not widely accepted and may need updating
Angiosome	1987 2014 (renewed interest)	Yes	No	May help optimise revascularisation strategy	Needs further validation
GLASS	2019	Yes	Yes	May guide optimal revascularisation strategy, predictive of patency.	New and not validated in many research studies

Table 4.1. Comparison of clinical and anatomical classification systems for chronic peripheral vascular disease (modified from Hardman et al. (134))

An anatomical based classification for PAD was first introduced by Vogelberg (135) in 1975, with the lower limb circulation divided into pelvic, thigh and calf vessels, with grading of atherosclerotic disease severity. This was refined by Bollinger et al. (136) in 1981 with defined arterial segments, an assessment of the degree of stenosis caused by a lesion, and the length of diseased segments. Since these classification systems were developed, the prevalence of diabetes has dramatically risen, with the number of adults with diabetes almost quadrupling since 1980 to 422 million currently affected worldwide. (137) During this time it became apparent that the pattern of disease in patients with diabetes was significantly different from non-diabetics, with a predilection to distal tibial disease. Graziani (138) noted that 74% of diabetic patients with tissue loss had tibial disease, and these tibial vessels had long length disease (>10cm) and more occlusions compared to stenoses. Graziani's morphological categorisation was introduced to address this change in disease distribution; it identified the number of tibial vessels, the degree and number of stenoses and occlusions in the tibial vessels and combined this with femoropopliteal disease.

In the same year as Graziani's observations, the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (TASC II) was published, and despite not having a tibial classification system, was widely adopted to become one of the most common PAD classification systems used to characterise patient populations and guide clinical practice.(139) TASC II built on the foundations of the original TASC I document published seven years prior which provided an important early attempt to systematically describe arterial lesions. The principal changes to TASC II reflected an increasing endovascular practice with its classification system developed to guide clinical decision making for an optimal endovascular or open revascularisation plan largely based on the anatomical distribution of disease. For aorto-iliac and femoral-popliteal disease, endovascular treatment was recommended for type A lesions which were the least complex and open surgery for the most complex type D lesions. For type B lesions, an ‘endovascular first’ approach was generally preferred and for type C lesions, open revascularisation was generally considered optimal.

THE NEED FOR A NEW CLASSIFICATION SYSTEM

Since its publication thirteen years ago, TASC II has received significant criticisms and concerns. Despite this, it has become ubiquitous in the reporting and management of PAD. In the year of its release Pedrini published an editorial critiquing TASC II and questioning whether it was a *“suitable document for specialists?”.* (140) He quoted mistakes, inaccuracies and a lack of information, citing old references, lack of evidence and conflicting recommendations. It was suggested that the division of aorto-iliac and femoral-popliteal disease into separate treatment algorithms did not account for the complex, multi-level disease commonly seen in clinical practice. In particular, there was a notable absence of any classification for infra-popliteal arterial disease, despite the exponential increase in prevalence of diabetes and its association with occlusive disease in these vessels.(28) Schillinger et al. (141) noted that indications for revascularisation were not discussed with a paucity of evidence-based recommendations and Kukkonen et al. (142) declared the *“grading of lesions confusing and cumbersome”* due to a lack of clear definition of crucial terms, including ‘stenoses’. Furthermore they discovered several lesion types that were impossible to grade, with TASC II not accounting for multi-level disease.(141, 142) In a study of experienced vascular interventionalists grading 200 angiograms according to TASC II, there was total agreement in only 7% of cases. Even after open discussion of the more challenging cases, agreement only reached 54%. For the interobserver agreement in the assignment of TASC II classification, the kappa score was 0.44, where a kappa score of <0.4 describes an unreliable test (143).

Despite the clear recommendations that TASC II C and D lesions should be managed by predominantly operative intervention, numerous studies have subsequently demonstrated that aorto-iliac and femoral-popliteal disease TASC II C and D lesions can be successfully treated by endovascular intervention.(144-147)

Following these criticisms the TASC IIb document was published in 2015 providing an update of endovascular and surgical revascularisation and a much needed infra-popliteal classification. (148) There were also recommendations for increased endovascular management as more complex anatomies were reclassified accordingly. The TASC IIb document was originally planned to be an updated consensus for revascularisation management for PAD and to act as an intermediate until the publication of TASC III. However, this was probably too little too late with ongoing concerns regarding insufficient emphasis on evidence with a reliance on ‘expert opinion’, over-representation by non-vascular surgeons, concerns over potential conflict of interest, and a dominance of North American and European contributors. For these reasons the Society for Vascular Surgery (SVS), the European Society for Vascular Surgery (ESVS) and World Federation of Vascular Societies (WFVS) withdrew from future TASC III document contributions and joined forces to develop the Global Vascular Guidelines.(149)

Despite the numerous criticisms of TASC II, it was an extensive document covering a wide range of topics relevant to PAD, of which the revascularisation section comprised only 1 of 7 chapters. Moreover, only two-thirds of a page in the 63-page document was devoted specifically to endovascular treatment of infra-inguinal disease. Therefore for all its flaws it should not be forgotten that TASC accomplished numerous important achievements for the management of PAD including forming the first consensus document, the creation of a classification system, and highlighting the importance of medical management of PAD in primary care.

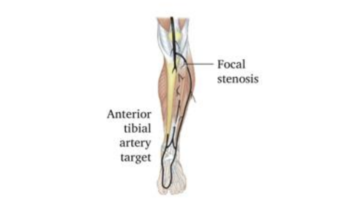
Regarding Pedrini’s original question, *“is it a suitable document for specialists?”,* this was actually addressed at the time by the TASC II authors. They clarified that *“TASC is a comparatively short document, mainly for non-specialists… therefore, technical details for specialists are discussed in lesser detail”.* This statement may have been in direct response to the controversy that the document created at the time, or may have been the genuine goal of the document from the outset. However, it is now evident that TASC II does not adequately describe or represent modern vascular practice and the new Global Vascular Guidelines (150) represent a new era of patient-focussed revascularisation, catering for the changes in PAD distribution with the increased prevalence of diabetes. The GLASS anatomical staging system represents a departure from individual and segment focused systems to a more wholistic approach taking into account the whole limb and the patient’s quality of life, whilst integrating the complexity faced to achieve limb revascularisation.

THE GLASS ANATOMICAL STAGING SYSTEM

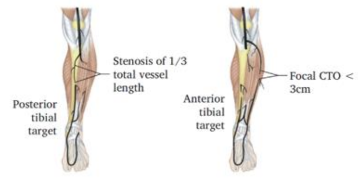
In the quest for evidence-based revascularisation (EBR), the GVG suggests utilising the PLAN concept; a 3-step integrated approach focussing on the factors which are clinically relevant to achieving patient-focused revascularisation. PLAN sequentially evaluates **P**atient risk, **L**imb severity, and **AN**atomic pattern of disease. Patient risk is estimated based on an assessment of peri-operarative mortality risk and life-expectancy, determining whether the patient should undergo revascularisation or be treated with conservative measures. Limb threat is assessed by the Wound, Ischaemia, and foot Infection (WIfI) classification system developed by the SVS which stratifies amputation risk based on wound extent, degree of ischemia, and presence and severity of foot infection. (151) The anatomical pattern and severity of disease is described by the new GLASS classification.

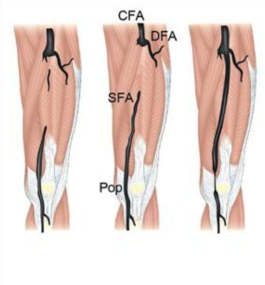
The approach to CLTI by GLASS classification is profoundly different compared to TASC. Revascularisation of the whole of the limb is addressed, rather than discrete lesions at single levels, which has been correlated with poorer revascularisation outcomes. The basis of GLASS is to define an arterial path that provides in-line flow to the foot, based on the recognition that clinical success, particularly with tissue loss, nearly always relies on this. GLASS introduces two novel concepts, the Target Arterial Path and estimated Limb-Based Patency.

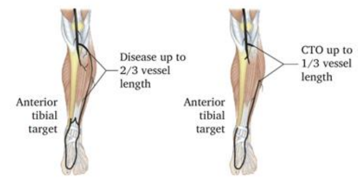
<table>
<tr><th colspan="2">Femoral-popliteal Segment</th><th colspan="2">Infra-popliteal Segment</th></tr>
<tr><td colspan="2">Grade 0
Mild or no significant (<50%) disease</td><td colspan="2">Grade 0
Mild or no significant disease in the primary target artery path</td></tr>
<tr><td>Grade 1
• Total length SFA disease <1/3 (<10 cm)
• May include single focal CTO (< 5 cm) but not flush occlusion
• Popliteal artery with mild or no significant disease</td><td>

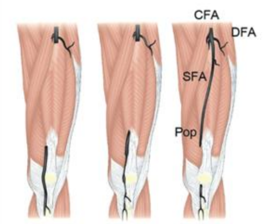

</td><td>Grade 1
Focal stenosis of tibial artery <3cm</td><td>


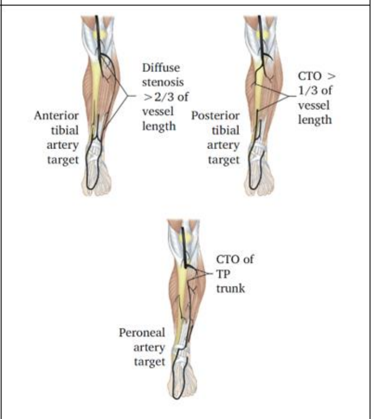
</td></tr>
<tr><td>Grade 2
• Total length SFA disease 1/3-2/3 (10-20 cm)
• May include CTO totalling <1/3 (10 cm) but not flush occlusion
• Focal popliteal artery stenosis <2 cm, not involving trifurcation</td><td>

</td><td>Grade 2
• Stenosis involving 1/3 total vessel length
• May include focal CTO (<3 cm)
• Not including TP trunk or tibial vessel origin</td><td>


</td></tr>
<tr><td>Grade 3
• Total length SFA disease >2/3 (>20 cm) length
• May include any flush occlusion <20 cm or non-flush CTO 10-20 cm long
• Short popliteal stenosis 2-5 cm, not involving trifurcation</td><td>


</td><td>Grade 3
• Disease up to 2/3 vessel length
• CTO up to 1/3 length (may include tibial vessel origin but not tibioperoneal trunk)</td><td>


</td></tr>
<tr><td>Grade 4
• Total length SFA occlusion >20 cm
• Popliteal disease >5 cm or extending into trifurcation
• Any popliteal CTO</td><td>


</td><td>Grade 4
• Diffuse stenosis >2/3 total vessel length
• CTO >1/3 vessel length (may include vessel origin)
• Any CTO of tibioperoneal trunk if AT is not the target artery</td><td>


</td></tr>
</table>

Figure 1. Global Limb Anatomic Staging System (GLASS) classification of femoral-popliteal (FP) and infra-popliteal (IP) disease (modified from Conte et al. (150))

The Target Arterial Path (TAP) is determined by the interventionalist as the optimal arterial path to restore in-line flow to the ankle and foot based on angiographic imaging. The least diseased infra-popliteal artery is usually selected, but angiosome-based revascularisation may be chosen in the setting of tissue-loss. GLASS estimates the chances of endovascular success based on the individual grading of the combined femoral-popliteal (FP) and infra-popliteal (IP) segments on a scale of 0 to 4 (Figure 4.1). If there is severe calcification based on subjective assessment in either of the segments, an additional ‘1’ is added to the score for that segment. These combined grades lead to an overall GLASS score. The current evidence surrounding the revascularisation of infra-malleolar (IM) arteries remains scarce. In order to account for this, GLASS includes the option of a pedal modifier to describe the arteries crossing the ankle and the pedal arch: P0: target artery crosses ankle into foot, with intact pedal arch; P1: Target artery crosses ankle into foot, absent or severely diseased pedal arch; P2: no target artery crossing ankle into foot. Whilst this is not currently included within the overall limb stage it allows future evidence-based research to guide these interventions.

FP Grade	IP Grade				
	0	1	2	3	4
4	III	III	III	III	III
3	II	II	II	III	III
2	I	II	II	II	III
1	I	I	II	II	III
0	N/A	I	I	II	III

Table 2. Global Limb Anatomic Staging System (GLASS) stage assignment based on combined Femoro-Popliteal (FP) and Infra-Popliteal (IP) grades

The grading of the FP and IP segments is then stratified into a GLASS stage using a consensus-based matrix (Table 4.2). The assignment of GLASS stages were based on a recent systematic review of revascularisation outcomes in CLTI (152). GLASS stages are classified as low (stage I), intermediate (stage II) and high (stage III) complexity disease which correlates with likely immediate technical failure (ITF) and 1-year LBP following endovascular intervention (153): Stage 1 (low complexity): ITF <10% and >70% 12-month LBP; Stage 2 (intermediate complexity): ITF 10-20% and 50-70% 12-month LBP; Stage 3 (high complexity): ITF >20% or <50% 12-month LBP. Once the GLASS stage has been calculated this can be integrated into the overall PLAN framework to provide guidance regarding evidence-based revascularisation (Figure 4.2).

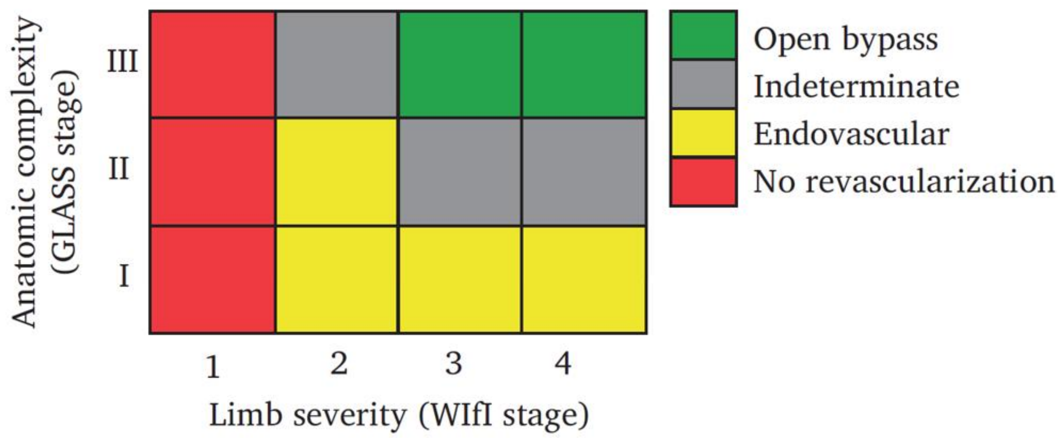


Figure 4.2. The Global Limb Anatomic Staging System (GLASS) preferred initial revascularisation strategy for infra-inguinal disease in average-risk patients with suitable autologous vein conduit available for bypass.

Source: Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. European Journal of Vascular and Endovascular Surgery, 2019, with permission.(24)

In order to achieve a balance between disease complexity and everyday utility, GLASS has included several pragmatic assumptions. Firstly, it is primarily an endovascular tool as it is recognised that the factors determining success in open bypass surgery (inflow-conduit-outflow) are intrinsically different to endovascular outcomes. Secondly, the focus is on infra-inguinal disease, with the assumption that proximal disease will have been treated prior to, or at the time of, infra-inguinal intervention with resultant good inflow into the infra-inguinal segment. This was because it was felt that the pre-existing TASC classification and recommendations for proximal disease treatment are associated good long-term results; namely an endovascular first approach for aorto-iliac disease, endarterectomy for common femoral artery disease with the optimisation of durable in-line flow for profunda femoris disease. (133)

Limb-Based Patency (LBP) describes the maintenance of in-line flow throughout the entirety of the TAP from groin to ankle, allowing a direct comparison of long-term anatomical patency rates and outcomes amongst revascularisation strategies in CLTI. Loss of LBP can be described by anatomical or haemodynamic criteria. Anatomic failure describes occlusion, critical stenosis, or requirement for reintervention affecting any portion of the TAP. Haemodynamic failure describes a significant drop in ABI (≥0.15) or TBI (≥0.10), or identification of ≥50% stenosis in the TAP, in the presence of recurrent or unresolved clinical symptoms (e.g, rest pain, indolent or deterioration of tissue loss).

GLASS IN CLINICAL PRACTICE

A large retrospective study by Ferraresi et. al., identified the demographics of patients undergoing endovascular procedures for CLTI and their associated GLASS classification.(154) Patients were predominantly stratified into the lowest and highest FP, IP and GLASS stages, with few in the intermediate severity group. Many patients had an absent or severely diseased pedal arch, highlighting the importance of the infra-malleolar modifier.

Early validation studies have examined the use of GLASS in the real-world setting. An increased GLASS stage was associated with higher rates of reintervention, major amputation and restenosis at 1-year and 5-year follow up, ITF and lower amputation free survival.(155-157) High GLASS IP grade was not identified as a prognostic indicator of the 1-year wound healing rate, but high IP calcification severity was significantly associated with delayed wound healing.(158)

SVS IPG PHONE APPLICATION

See examples (Figures 4.3, 4.4, 4.5)

GLASS and WIfI calculators have been integrated into the SVS iPG phone application which is freely available for download on app stores for increased accessibility in clinical practice. Based on the description of an individual's FP and IP segment disease, the app can calculate an individual's GLASS grade and their subsequent predicted outcomes for ITF and 1-year LBP.

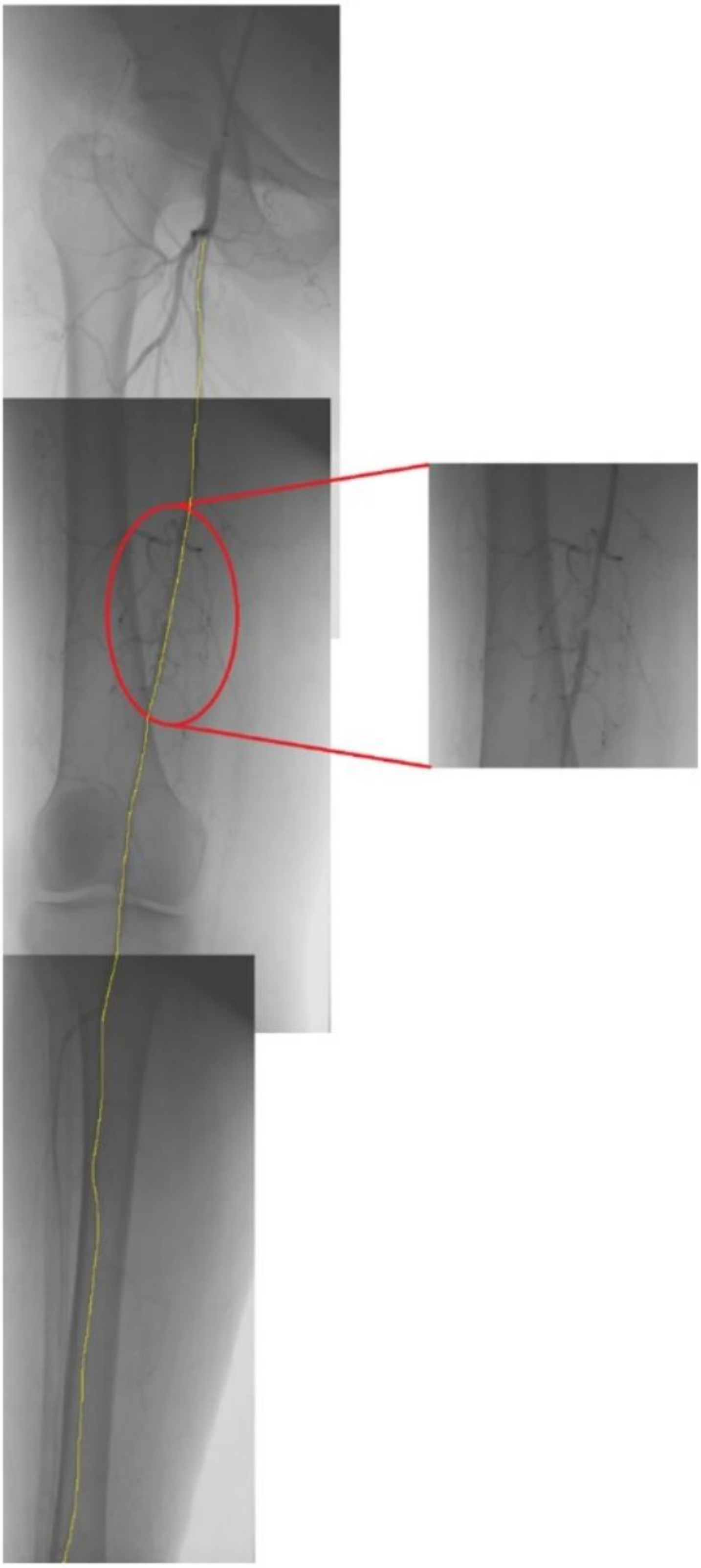


Figure 4.3. GLASS Stage I. The target arterial path (TAP) is outlined in yellow via peroneal the artery. Femoro-popliteal (FP) grade is 1 (total length SFA disease <1/3 (<10cm) with a single focal CTO <5cm). Infra-popliteal (IP) grade is 0.
Subject provided consent for the use of these images.

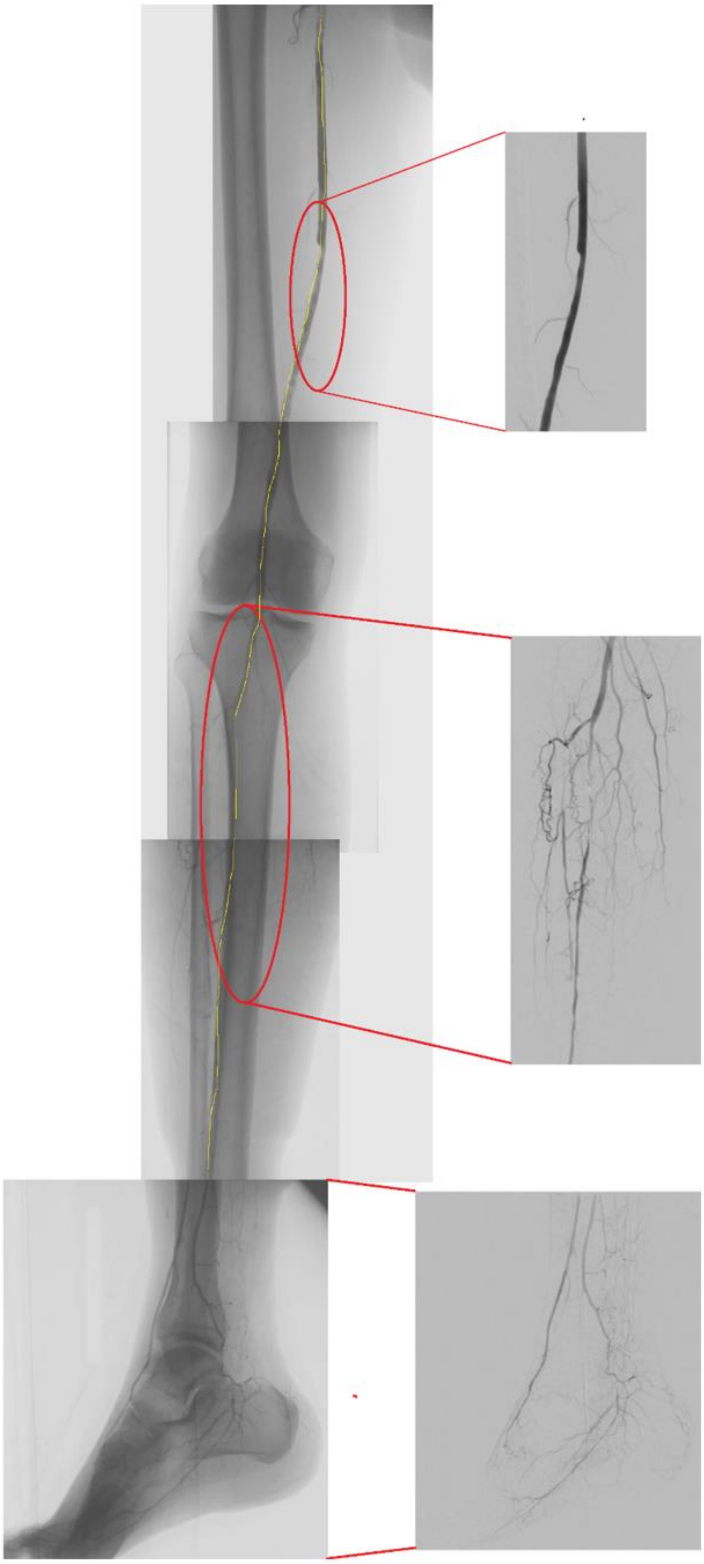


Figure 4.4. GLASS Stage II. The target arterial path (TAP) is outlined in yellow via the peroneal artery. Femoro-popliteal (FP) grade is 1 (Total length SFA disease <1/3). Infra-popliteal (IP) grade is 3 (CTO up to 1/3 length). In this example the infra-malleolar grade is P1 (target artery crosses ankle into foot; severely diseased/absent pedal arch).
Subject provided consent for the use of these images.

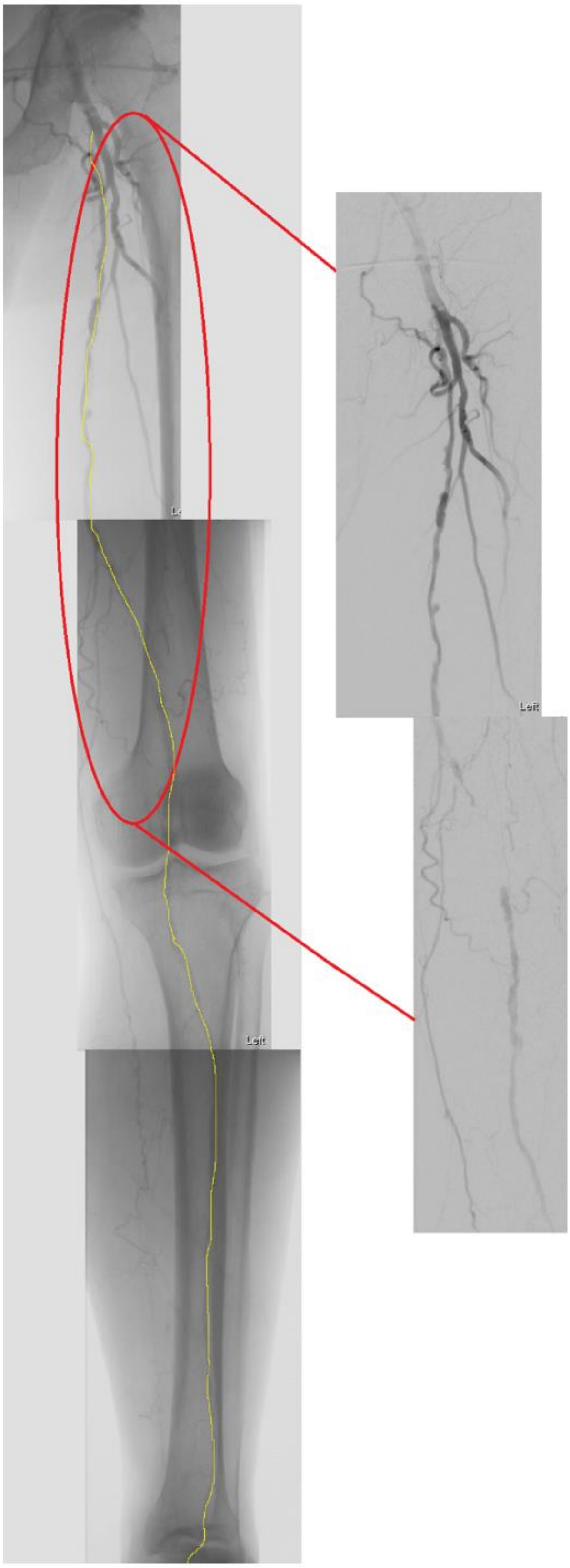


Figure 4.5. GLASS Stage III. The target arterial path (TAP) is outlined in yellow via the peroneal artery. Femoro-popliteal (FP) grade is 4 (length of SFA disease is >20 cm and heavily calcified). Infra-popliteal (IP) grade is 0.
Subject provided consent for the use of these images.

CONCLUSION

GLASS provides an updated classification system for the assessment and management of CLTI reflective of the distribution of disease in modern PAD and the advancements in endovascular technology. Whilst the TASC documents were pivotal in the evolution of PAD classification and management, their numerous limitations resulted in reduced applicability in modern practice. GLASS provides a patient and limb-centred approach and a framework to establish evidence-based practice in an evolving field. The GVG acknowledges that whilst GLASS is based on a recent systematic review for outcomes in CLTI, the new grading system needs prospective validation in its application in clinical practice and for research worldwide. It is expected to undergo revisions with improvements in technology and emerging research as outcomes continue to be reported.

SUMMARY AND FUTURE DIRECTIONS

As the rate of diabetes continues to increase with an aging population and as the obesity epidemic progresses, it would be reasonable to assume that the prevalence of diabetic foot disease will trend accordingly. Society continues to rapidly adopt technological developments in all facets of life, this also extends to the advancements in diabetic foot disease management.

Chapter 2 evaluates a new dermal template for complex diabetic foot wounds at high risk of limb loss without expedient healing which is essential but difficult to achieve in the management of diabetic foot disease.

Within society, mobile phones have become ubiquitous in daily working life with increased and rapid accessibility of information. The increasing use of electronic medical health records has lended itself to the digitisation of wound care assessment with inclusion of photography. Advances within this technology is the focus of chapter 3 with the goal of making it more accessible for clinicians and patients in rural and remote populations.

The most notable advancements in technology has been the developments in endovascular intervention for PAD in the last two decades.(159) It is widely acknowledged that the adoption of endovascular technologies has outpaced the ability for high quality prospective research to occur. Chapter 4 evaluates not only the progression of endovascular technology but also the historical definitions and classifications of chronic limb ischaemia. Contemporary definitions and anatomical classification of lower limb arterial disease is essential for the evaluation and future management of chronic limb-threatening ischaemia. This will ensure consistent contemporary reporting of outcomes and be essential for assessment of endovascular technologies.

This thesis examines the use of these technologies with Chapter 2 and 3 highlighting the significant benefits they have demonstrated in the clinical trials.

Aim 1

To evaluate the efficacy of using BTM in the reconstruction of complex diabetic foot wounds.

BTM was applied to complex diabetic foot wounds (exposed tendon, fascia joint or bone) or chronic ulcers, non-healing ulcers or wounds in areas of high shear stress. We examined the feasibility of the use of BTM in the clinical setting with the patients excluded or withdrawn from the study reflecting the real-world limitations in the treatment of complex DFU with residual osteomyelitis, progressive PAD and the impact of the COVID-19 pandemic. As a pilot trial, we have detailed a protocol and methodology for the application of BTM in the DFU population which differs from the plastics and burns populations due to the nature of the wound bed and depth.

We have found that BTM was able to achieve complete wound healing in all the patients in our study with significant potential benefit for the management of these wounds. These patients would normally be managed with a prolonged course of conventional dressings which may fail or require reconstructive surgery (e.g. free flap reconstruction) for which their medical co-morbidities and distal arterial disease may limited their suitability.

The deviations from protocol for planned delamination time provided an excellent learning opportunity from a pilot study perspective. 6 weeks for BTM integration into the wound bed is only an estimation, rather it is more beneficial to evaluate the clinical status of BTM with the development of granulation within the BTM foam which may warrant shortening or prolonging the planned delamination time.

Despite infection being a significant concern in diabetic foot wounds, with BTM, the infection rate was relatively low, this is particularly promising as biological dermal templates may be avoided by some treating medical practitioners due to the theoretical increased risk of infection. If infection develops, the wound and BTM may be salvaged with early identification and intervention to maintain BTM adherence to the wound bed.

Based on the porcine models, BTM may increase the robustness of the wound bed to prevent re-ulceration. Whilst there was a low re-ulceration rate noted in the study, without a control group and longer follow-up for comparison it remains unclear if this approach definitively reduces re-ulceration rates.

Aim 2

To use the NDKare phone application to assess its accuracy and practicality for diabetic foot ulcer wound size assessment

The NDKare phone application adapted phone software to obtain accurate 2D measurements of diabetic foot wounds when in comparison to the WoundVue Camera and Visitrak which are validated wound measurement tools. However, the

3D measurements using this technique were not accurate in comparison to the WoundVue Camera which is largely attributed to the specialised hardware within dedicated 3D cameras which is currently not available in smartphones.

In terms of practicality, different users with different smartphones were able to use the application with no statistically significant difference in measurement results.

Aim 3

To critically evaluate the historical classification and management of chronic limb ischaemia/critical limb ischaemia with the development of the latest GVG guidelines

The definition of chronic limb ischaemia and critical limb ischaemia were incorrectly adapted for use in patients with diabetes which has a different pathogenesis and natural history to smoking-related arterial occlusive disease. Superseding the TransAtlantic Inter-Society Consensus classification system for peripheral arterial disease, the Global Vascular Guidelines developed the Global Anatomic Staging System and the term chronic limb-threatening ischaemia for the modern approach to evaluating peripheral arterial disease and the endovascular treatment options by incorporating the target arterial path and limb-based patency concepts.

Future directions

Patients with diabetes often have PAD affecting the pedal arteries in addition to more proximal vessels. As endovascular technology improves, interventionalists are increasingly considering if pedal artery intervention should be performed for limb salvage in CLTI.(33) This is reflected in the GLASS classification with the inclusion of a pedal modifier score, but this is optional and not included in the overall limb stage. Pedal angioplasty has been demonstrated to improve wound healing and shorten healing time, but it has not been shown to improve limb salvage or amputation-free survival.(160, 161) As this is an area of ongoing research, the inclusion of a pedal modifier will allow for standardised reporting of future evidence based research.

The COVID-19 pandemic has demonstrated the ability to shift towards a telemedicine format for the provision of healthcare services. The use of the NDKare phone application could be adaptable to the rural and remote populations for liaising with high-risk foot services. Central Adelaide Local Health Network Vascular and Endovascular Surgery unit is developing a telehealth software package utilising augmented reality (AR) technology to "see through the eyes" of rural health workers in their assessment, triaging, and treatment of foot and lower limb wounds, and to allow training of local health workers. Aims of this project includes developing 2D and 3D wound measurement tools with holograms to visually aligns and compare the wound over time. Whilst the NDKare application incorporated a wound bed classification analysis, it was not formally evaluated in our study as it appeared to identify tissue type based on colour alone and it was inaccurate on clinical review by the treating medical practitioners. However, as a large-scale study, the AR study aims to design a wound annotation tool to train machine learning to automatically label the tissue composition.

Whilst BTM theoretically requires a vascularised wound bed to integrate, there is emerging interest for the feasibility in ischaemic diabetic foot wounds. The dermal matrix itself with facilitates cellular response modulation and promotes revascularisation.(79) Exploration of its use in other wounds such as small chronic wounds <1cm^2 which also place the limb at risk of loss could also be explored in future.

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