Evaluation of NOSF in neuropathic diabetic foot ulcers

'Lower limb amputation has a devastating effect on patients and their families as well as being costly to the NHS'

Diabetes mellitus is a metabolic disorder of multiple aetiology, which results from defects in insulin secretion, insulin action or both (World Health Organization [WHO], 1998).

The number of patients with diabetes is increasing year upon year (*Table 1*). Diagnosed prevalence doubled between 1994 and 2003 in the UK and in England was forecast to be 5.05% by 2010 (Diabetes UK, 2006; 2007).

Foot complications are common in diabetes. Diabetic neuropathies affect up to 50% of people with diabetes, but the exact prevalence of those who have diabetic peripheral neuropathy is difficult to estimate due to the wide variability of clinical tools used (Tapp and Shaw, 2009). The National Institute of Health and Clinical Excellence (NICE, 2004) suggest that the prevalence of diabetic peripheral neuropathy is 20–40%.

Hirsch et al (2001) state that when using the ankle-brachial index (ABI), the prevalence of peripheral arterial disease (PAD) in people with diabetes who were aged over 40 was 20% — the prevalence rose to 29% in those aged over 50.

Neuropathy and PAD are secondary to hyperglycaemia and adverse arterial risk factors (such as smoking, hypertension and dyslipidaemia). Around 5% of people with diabetes may develop a foot ulcer at any time and amputation rates are around 0.5% per year.

Where neuropathy and ischaemia lead to ulceration (especially with poor glucose control), the foot can become infected, often with polymicrobial invasion, and amputation is possible if the infection is not managed appropriately (NICE, 2004).

AMPUTATION

Every year in the UK, approximately 5000 people with diabetes will undergo some degree of amputation and up to 70% of people die within five years of having an amputation as a result of diabetes (Diabetes UK, 2007).

Lower limb amputation has a devastating effect on patients and their families as well as being costly to the NHS. Therefore, it is important to look at the

Table 1
UK diabetes prevalance — 2006 to 2007 (Powell, 2009)

Country	*Prevalence*		*Number of people*	
	2006[1]	*2007*[2]	*2006*[1]	*2007*[2]
England	*3.6%*	*3.7%*	*1,891,000*	*1,961,976*
Northern Ireland	*3.06%*	*3.14%*	*55,000*	*56,924*
Scotland	*3.4%*	*3.52%*	*165,000*	*171,513*
Wales	*4.1%*	*4.21%*	*127,000*	*131,119*
UK average prevalence	*3.54%*	*3.66%*		
UK total diagnosed			*2,238,000*	*2,321,532*

[1]2006 UK Diabetes prevalence based on Quality and Outcomes Framework (QOF) data (Diabetes UK, 2006)
[2]2007 UK Diabetes prevalence based on QOF data (Diabetes UK, 2007)

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MARTIN TURNS
Lead Podiatrist in Diabetes, Diabetes Centre, Royal Sussex County Hospital, Brighton

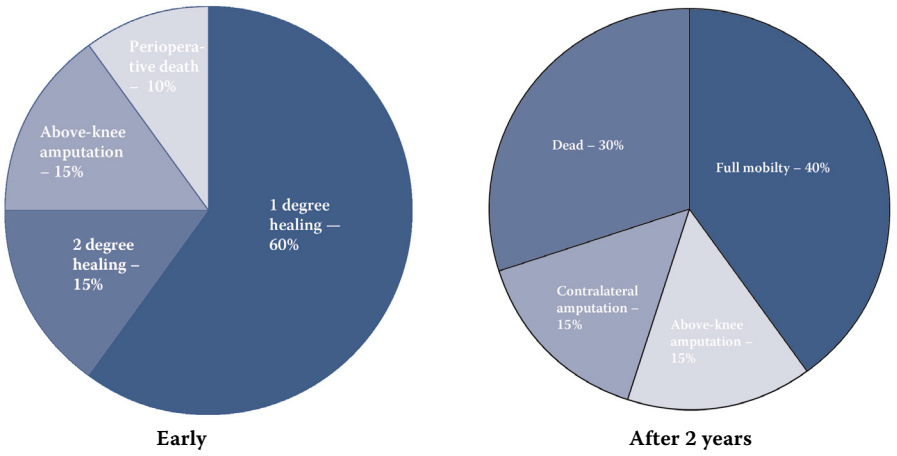

Figure 1. Fate of the patient with below-knee amputation (Norgren et al, 2007)

factors that may predispose people to lower extremity amputation.

Predictive factors for amputation

The American Society for Microbiology and the Infectious Diseases Society of America (ASM/IDSA, 2008) report on 78 patients admitted to hospital due to acute diabetic foot infection and who were retrospectively analysed to determine the predictive factors for amputation.

Patients who had an amputation (n=52) had a high incidence of prior foot lesions and the investigators established a 20-times higher rate of amputation for limbs with Wagner ulcer grade 4–5.

An earlier prospective study by Adler et al (1999) shows that peripheral sensory neuropathy, peripheral vascular disease, foot ulcers (particularly if they appear on the same side as the eventual lower extremity amputation), former amputation, and treatment with insulin, are all independent risk factors for lower extremity amputation in patients with diabetes.

It is evident, therefore, that previous foot ulcers and/or more serious foot ulcers are predictors of lower limb amputations.

Clinicians are thereby confronted with two main issues:

- How to heal ulcers quickly so that the risk of non-healing or deterioration is reduced
- How to increase the likelihood that healing will occur in chronic wounds.

CHRONIC WOUNDS

A chronic wound is a wound that has not healed for 4–6 weeks (Chadwick and Acton, 2009). Falanga (2005) describes several pathogenic abnormalities that could contribute to failure to heal, ranging from disease-specific intrinsic flaws in blood supply, angiogenesis and matrix turnover, to extrinsic factors such as infection and continued trauma (*Table 2*).

There are many factors contributing to chronicity and despite the use of evidence-based wound management, some wounds fail to heal. There are a number of published studies that look at the healing rates of neuropathic ulcers. Margolis et al (1999) suggest that mean healing at 12 and 20 weeks was 24.2% and 30.9% respectively. Marston et al (2003) reported healing at 12 weeks in only 18.3% of control subjects. It is, therefore, clear that many wounds are at risk of becoming chronic, leading to long-term complications such as osteomyelitis and lower extremity amputations.

Liu et al (2009) and Lobmann et al (2002) suggest that increased concentrations of matrix metalloproteinases (MMPs) are found in chronic wounds and may be a cause of slow or non-healing wounds. The MMP family of proteases are zinc-dependent endopeptidases that can degrade extracellular matrix (ECM) components, thereby impeding wound tissue regeneration.

MMPs are produced by several different types of cells in the skin, including

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Table 2
Factors that contribute to chronicity

Patient-specific factors	*Wound-specific factors*
Underlying disease	*High levels of exudate*
Age, immobility, poor nutrition	*Location of wound*
Concurrent drug therapies	*Depth or size*
Poor concordance	*Duration of wound*
Circulatory disorders	*Recurrence*

fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils.

In normal wound healing, MMPs seem to be involved in various processes. In the first phase of wound repair, MMPs participate in the removal of devitalised tissue. During the repair phase, MMP activities are necessary for angiogenesis, for contraction of the wound matrix, for migration of fibroblasts, and for keratinocyte migration and epithelialisation. During the final phase of wound healing, MMPs participate in the remodelling of newly synthesised connective tissue. MMPs are, therefore, necessary for normal wound healing and tissue repair (Lobmann et al, 2002). However, MMP activity is specifically inhibited by the tissue inhibitors of metalloproteinases (TIMPs) (Lobmann et al, 2002).

Lobmann et al (2002) assessed the role of proteases inhibitors (TIMPS) in diabetic foot ulcers. They compared concentrations of five separate MMPs and TIMP-2 in chronic diabetic foot ulcer biopsies with the concentrations in the traumatic wound biopsies of people without diabetes. They found that there were significant differences in the concentrations of MMPs and TIMP-2 in biopsies from diabetic foot ulcers compared with non-diabetic trauma wounds. Specifically, the average concentration of MMP-1 was increased 65-fold ($p<0.001$) in biopsies of the chronic diabetic foot ulcers compared with the average concentration measured in biopsies of the traumatic wounds.

Similarly, the average concentration of pro-MMP-2 in chronic diabetic ulcers was increased threefold ($p=0.041$) compared with traumatic injuries; the average concentration of active MMP-2 in diabetic ulcers was increased sixfold ($p=0.033$); the average concentration of MMP-8 was increased twofold ($p<0.002$); and the average concentration of MMP-9 was increased 14-fold ($p=0.027$).

In contrast to increased concentrations of MMP in diabetic wounds, the concentrations of TIMP-2 were lower ($p<0.007$) in the chronic diabetic foot ulcers than in the non-diabetic traumatic wounds.

Therefore, it could be suggested that if the MMP/TIMP balance can be altered, this could lead to an improvement in healing rates for some patients.

URGOSTART® CONTACT PROTEASE INHIBITOR

One dressing designed to address the MMP/TIMP imbalance in the favour of healing, is the protease inhibitor UrgoStart Contact (Urgo Medical).

UrgoStart Contact is a contact layer with technology lipido-colloid (TLC), which promotes a moist environment, provides pain-free dressing changes and stimulates fibroblast proliferation in conjunction with nano-oligosaccharide factor (NOSF). NOSF aims to promote wound closure through inhibition of matrix metalloproteinase (MMP) activity.

NOSF is incorporated within the TLC lipido-colloid gel and locally released in the wound.

A dressing impregnated with NOSF was recently evaluated in an unpublished double-blind randomised controlled trial, which demonstrated that it heals twice as fast as a neutral dressing. In the trial, 187 venous leg ulcers patients aged 18 years and older were randomised and treated with either the foam dressing UrgoStart (impregnated with NOSF), or the neutral foam dressing UrgoCell® TLC (without NOSF). Each dressing was evaluated by

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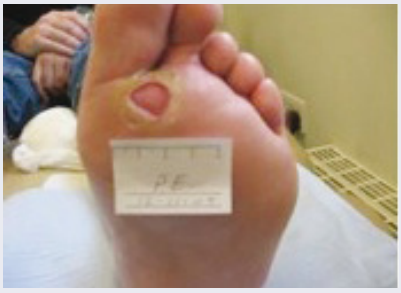

Figure 2: Case Study 1: Diabetic foot ulcer prior to management with Urgostart Contact.

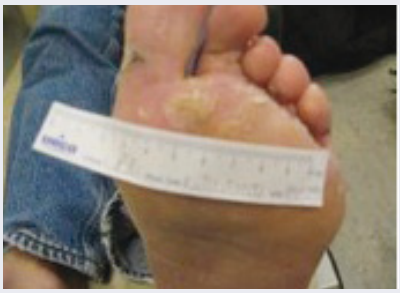

Figure 3: Case Study 1: Diabetic foot ulcer fully healed following management with Urgostart Contact.

the investigating physician every two weeks until the eighth week of treatment. Results indicated that after eight weeks, a greater wound surface area reduction (in relative and absolute values) was noted in the NOSF group, and was highly significant (p=0.0038) versus the control group (Meaume, 2011).

CASE STUDIES

The following two case studies are based on patients with diabetic foot wounds who attended a secondary care outpatient diabetes centre and were successfully managed with UrgoStart Contact.

Case study 1

The first case features a 51-year-old single male patient with type 2 diabetes, which was diagnosed in 2008. He was taking a range of medication, including metformin, gliclazide and simvastatin.

The assessment in the outpatient diabetes centre was carried out by the author in December 2008. It indicated palpable dorsalis pedis, posterior tibial and biphasic foot pulses in both feet.

A sensory neurological assessment also indicated numbness, reduced 10g monofilament sensation and reduced vibration sensation in both feet. The patient had background retinopathy in both eyes and a history of other microvascular problems.

He had previously been seen by the author at the podiatry clinic in December, 2008, when he had multiple ulcers to the right first, left fifth and left fourth interdigital area, which had developed shortly after his diagnosis of diabetes.

Fortunately these ulcers healed without any complications. On 4 December, 2008, his glycated haemoglobin (HbA1c) was very high at 12%.

On 15 January, 2009 he presented to the podiatry clinic in the diabetes centre, with a right heel ulcer and a left foot third toe ulcer. There was no evidence of any infection at either site and both ulcers were healed by 26 February, 2009 after the patient had been issued with a Aircast® boot.

When the ulcer had healed he stopped using the Aircast boot and used his shoes, which were deemed appropriate. However, on 9 November, 2009 he attended the podiatry clinic after a recent A&E investigation into a left foot plantar ulcer (*Figure 2*). He was prescribed penicillin and flucloxacillin by the A&E staff and the ulcer was debrided, swabbed and redressed with an antimicrobial dressing. The swab indicated that there was no significant bacterial growth.

On 6 November, 2009 the patient had been given a blood test. His HbA1c was 6.1% with a C-reactive protein level of under 5mg/l, which is normal. C-reactive protein is an inflammatory marker and could indicate infection.

Performance of UrgoStart Contact

On 16 November, 2009 the antimicrobial dressing was discontinued and a simple non-adherent dressing was applied at the podiatry clinic diabetes centre. On 26 November, 2009 the wound measured 1.5 x 1.5cm (2.25cm^2). The surrounding skin exhibited diffuse callus but there was no maceration and the tissue was 100% granulating. The wound was redressed with UrgoStart Contact as the primary dressing, as chosen by the author. This was chosen due to the risk of delayed healing. A non-adherent dressing, felt pad and bandage were also used.

This dressing regimen continued until healing occurred on 7 December, 2009 (*Figure 3*).

At each review the dressing changes were painless and the patient stated he was very happy with the use of UrgoStart Contact due to the speed of healing. From the clinician's perspective, the dressing was easy to use and could be removed without any evidence of trauma to the wound bed.

A-Aircast boot was issued to the patient, but throughout the period of UrgoStart use he admits to not wearing it while he was mobilising. The patient was reviewed on 19 January, 2010 and the healed area remained intact.

The use of UrgoStart Contact improved the healing time compared to conventional dressings in this patient with a diabetic foot ulcer, despite the fact that the recommended Aircast pressure relief boot was not worn throughout the treatment period.

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Case study 2

This case study focuses on a 75-year-old man with type 2 diabetes, which he had developed 10 years previously. His medical history included insomnia and depression. He was also taking a wide range of medication, including enalapril, gliclazide, amlodipine, amitriptyline, metformin, ferrous sulphate, paracetamol and co-dydramol.

He was initially admitted to hospital on 25 June, 2009 after being sent to A&E by his GP following a walking holiday. He had developed a blister on the plantar aspect of his right first toe. It was noted in A&E that the skin was black and coming away and that there was redness and tracking up his right leg. There was also an ulcer between the first and second toes. Initial assessment also indicated a necrotic ulcer on the right foot, which was blistered and black.

The patient was admitted for vascular review, X-ray of the foot and intravenous (IV) antibiotics. He was also placed on nil by mouth with IV fluids. His foot was elevated and an urgent duplex was arranged. The duplex showed an absence of significant arterial disease.

He was seen the following day by the vascular specialist registrar who noted the presence of pre-gangrenous changes to his first and second toes and along the second and first metatarsal bones. On 6 July, 2009 the patient underwent amputation and debridement of the right first toe to control the sepsis.

Following this, arterial wave forms shown by the Duplex scan did not indicate any arterial disease on the right leg, with sharp triphasic flow patterns noted throughout the posterior tibial artery and the anterior tibial artery proximal to the malleolus. The ABPI on the right leg was estimated at 1.1. Similarly, there was also no arterial disease noted on the left leg and sharp triphasic flow patterns were noted through the posterior tibial artery. The ABPI on the left leg was estimated at 1.2.

On 12 July, 2009 the patient underwent further surgery for revision of right hallux and second toe amputation and debridement. Negative pressure was applied to the wound on 15 July. On 3 August the vascular consultant decided to discontinue the negative pressure dressing and a Hydrofiber® (ConvaTec) dressing was applied. On 7 August, 2009, the negative pressure dressing was restarted and on 17 August, 2009 the patient was discharged home with a portable negative pressure dressing in situ.

On 26 August the patient was readmitted as his right foot/leg was swollen and emitting an offensive discharge. The third and fourth toes also appeared dusky and pre-gangrenous. Therefore, on 2 September the patient underwent a right transmetatarsal amputation and on 14 September he was discharged home with another Hydrofiber dressing applied to the wound. An Aircast boot was also worn following discharge from hospital to reduce excessive pressures on the wound when mobilising.

Outpatient review

On 18 September, 2009 the patient received his first outpatient podiatry review and it was arranged that he would be seen weekly in the podiatry clinic and twice-weekly by the community nurses. An antimicrobial dressing was used on the wound at this visit.

The patient was reviewed again by the vascular surgeon on 14 October, 2009 in the outpatient department.

The wound was healing and elevation which had been requested by the vascular surgeon to reduce oedema in the lower limb, was reinforced. He also received follow-up in the podiatry clinic.

Performance of UrgoStart Contact

On 9 October, 2009, the author made a clinical decision that any indication of foot infection had gone. Thus, the antimicrobial dressing was stopped and UrgoStart Contact was commenced. On 16 October, 2009 the wound measured 10.5cm at its longest point and 3.5cm at its widest point. UrgoStart Contact was applied with a foam secondary dressing and premier pad, which is a simple absorbent pad, and secured in place with a bandage.
The surrounding skin was very slightly macerated and there was slough present, especially on the dorsal aspect. This was debrided at each clinic review.

At a review on 27 November, the wound had deteriorated as the patient had been walking too much and he was advised to rest. By the 29 January, 2010 the wound

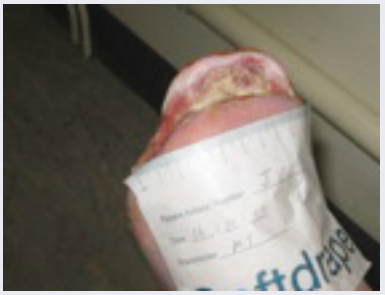

Figure 4: Case Study 2: Diabetic foot wound prior to management by Urgostart Contact.

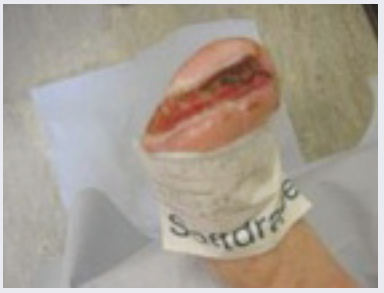

Figure 5: Case study 2: Different view of diabetic foot wound prior to management by Urgostart Contact.

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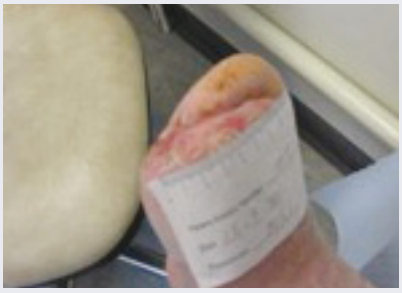

Figure 6: Case study 2: Diabetic foot wound healed in the dorsal aspect following management by Urgostart Contact.

'Ischaemic wounds can lead to lower limb amputation due to the complexities of diabetic foot disease, particularly the presence of infection'

(which now only affected the plantar aspect of the foot) deteriorated further, due to the patient walking on it again, and he was advised to rest it further.

By 5 February the wound had improved significantly as the patient had been resting more and it now only measured 1.5 x 1.2cm.

On 26 February the wound measured 1.5 x 1cm (1.5cm^2 — a reduction of 95%). The UrgoStart Contact was discontinued and the patient was considered for total contact casting. Total contact casting is a form of pressure offloading. This was used to offload the planter aspect of the foot where pressures when walking are highest.

The UrgoStart Contact dressing changes had been painless at each review and the patient stated that he was very happy with both this and the speed of healing (*Figures 4–6*).

From the clinician's perspective, the dressing was easy to use and could be removed without any evidence of trauma to the wound bed. The patient's care had been shared with the community nursing team and there was no negative feedback regarding UrgoStart Contact.

DISCUSSION

Both case studies feature neuropathic patients who have good lower limb arterial blood flow and there is an expectancy these wounds will heal. However, it is the speed of healing that is interesting, as well as the fact that these wounds were progressed from a non/slow-healing state into a healed state.

Of particular interest is the fact that Case Study 1 healed without the use of adequate pressure relief (the patient was non-compliant with the use of an Aircast boot). Pressure relief is an integral part of wound healing (NICE, 2004) and this factor alone could have been the cause of non-healing. Since the wound healed despite pressure relief not being adequate, this would indicate that, in this case, Urgostart Contact dressing was effective.

UrgoStart Contact can be used effectively in the management of neuropathic diabetic foot wounds, however, the author has not been involved in case studies that demonstrate its effectiveness on diabetic neuroischaemic wounds.

Ischaemic wounds can lead to lower limb amputation due to the complexities of diabetic foot disease, particularly the presence of infection (Lipsky et al, 2004; NICE, 2004). PAD jeopardises the viability of soft tissues and bone, and facilitates the spread of infection by impeding the penetration of leukocytes and antibiotics to the infected sites (Kosinski and Lipsky, 2010).

Further evidence for the effectiveness of UrgoStart Contact is available in a recent open-label, uncontrolled, non-blinded pilot study featuring 34 patients with diabetic foot ulcers (mean diabetes duration — 17 years). An open-label trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered. After treatment with UrgoStart Contact, the patients' wound area decreased by an average of 63%. Complete healing was observed in 10 patients after a mean treatment time of 8.8 (±3) weeks (Richard, 2010).

CONCLUSION

Healing diabetic foot wounds is a complex process and the basic mechanisms of wound healing in diabetes need to be understood further to develop innovative treatment strategies (Lobbman et al, 2002).

UrgoStart Contact allows clinicians to address factors that may cause chronicity. It can be used in wounds that have been present for more than 4–6 weeks or if rapid healing is required.

The wound must be closely monitored and the dressing changed if there is no improvement in wound size (although to achieve optimum benefit UrgoStart Contact must be used for 4–5 weeks minimum). However, as these case studies have shown it can be used effectively to heal neuropathic diabetic foot wounds. WUK

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