A breakthrough in the management of neuro-ischaemic diabetic foot ulcers

A growing proportion of diabetic foot ulcers are being diagnosed as neuro-ischaemic. Management of this type of wound is complex, requiring prompt referral, debridement where indicated, appropriate footwear, offloading, dressings and the treatment of infection. Until recently, no drug or device had been demonstrated to effectively treat neuro-ischaemic foot ulcers. The discovery that matrix metalloproteinases are involved has led to the identification and study of nano oligosaccharide factor, which shows promise in treating this challenging condition.

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Chronic wounds are not only a burden to healthcare systems but significantly reduce patients' quality of life and often lead to serious events, such as limb amputations and sometimes even premature death (Järbrink et al, 2017). Diabetic foot ulcers (DFUs) score high in the incidence of chronic wounds; the annual population-based incidence of DFUs ranges from 1.0% to 4.1%, with a lifetime incidence that may be as high as 25% globally (van Dieren et al, 2010). DFUs can been categorised as neuropathic, ischaemic or neuroischaemic (Yost, 2010) *[Table 1]*. The prevalence of neuroischaemic ulcers has increased since the 1990s, from approximately 33% to >50% of DFUs (Limperopoulou et al, 2005). Over half of DFUs in high-income countries are diagnosed as neuroischaemic, mostly as a result of more accurate and frequent vascular assessment to detect peripheral arterial disease (Schaper et al, 2016). While both can occur separately, current evidence suggests that neuropathic and ischaemic problems occur simultaneously (Limperopoulou et al, 2005).

DFUs are a result of multifactorial and simultaneous contributing factors. The main causes are peripheral neuropathy and ischaemia from peripheral vascular disease (Pendsey, 2010). Neuroischaemia is the combination of the effects of neuropathy and ischaemia. Both micro- and macrovascular dysfunctions impair perfusion. Motor and sensory components of the nervous system are affected, leading to damage of the intrinsic foot muscles and an imbalance in the flexion and extension of the foot (Pendsey, 2010). This leads to anatomic deformities, expediting abnormal bony prominences and pressure points that are precursors to ulcers. Autonomic neuropathy is "a cause of altered blood flow regulation with an opening of arteriovenous shunts and precapillary sphincter malfunction, which decreases nutritive blood flow and manifests as warm, dry skin, increasing the likelihood of skin breakdown" (Lepäntalo et al, 2011). Dry skin makes the feet susceptible to fissures. In addition to this, atherosclerosis usually occurs prematurely in patients with diabetes. Commonly, the more distal vessels below the trifurcation, such as the peroneal, anterior and posterior tibial arteries, are involved (Pendsey, 2010). Loss of sensation through damage to the sensory nerves compounds the problem as trauma goes undetected (Pendsey, 2010).

Neuroischaemia predominately leads to the development of ulcers on the margins of the foot, toes and dorsum of the foot rather than at pressure sites from poorly fitting shoes (Dalla et al, 2015). These ulcers may be surrounded by a thin glassy callus halo (Edmonds et al, 2008). Ulcers in the interdigital spaces are a consequence of tight shoes, while planter ulcers are mostly associated with trauma (Edmonds et al, 2008).

Management of neuroischaemic DFUs

Management of this type of wound is quite complex and involves prompt referral, debridement (where indicated), appropriate footwear and offloading, dressings and treatment of infection (Ndip and Jude, 2009). Referral to a vascular specialist is essential

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Table 1. Categories of diabetic foot ulcer (Yost, 2010)	
Type	**Percentage**
Neuro-ischaemic	50
Neuropathic	35
Ischaemic	15

for assessment and revascularisation where possible. It has been suggested that even in critical limb ischaemia, amputation should not be done without consultation with a vascular surgeon (Lepäntalo et al, 2000). Although the role of the vascular surgeon is pivotal in the management of ischaemic foot ulcers, the importance of a multidisciplinary team approach cannot be overemphasised (El Sakka et al, 2006). The five cornerstones of the management of the diabetic foot, according to the International Working Group on the Diabetic Foot, are (Schaper et al, 2016):

- Identification of the at-risk foot
- Regular inspection and examination of the at-risk foot
- Education of the patient, their family and healthcare providers
- Routine wearing of appropriate footwear
- Treatment of pre-ulcerative signs.

The proper management of the neuroischaemic foot is crucial. If a foot is misdiagnosed and managed as being neuropathic without further tests to confirm or rule out ischaemia, there could be serious, avoidable consequences such as limb loss (Schaper et al, 2016). Although neuroischaemic ulcers are the most common DFUs, until recently, no studies have assessed the superiority of any device in a cohort of patients with only neuroischaemic ulcers (Armstrong et al, 2011) and no device or drug has demonstrated efficacy in neuroischaemic DFU treatment (Rafetto, 2017).

Nano-oligosaccharide factor: a breakthrough

In recent years, the complexity of neuroischaemic ulcers has been explored in greater detail and issues such as fibroblast dysfunction, neovascularisation and high matrix metalloproteinase (MMP) levels have been identified as prolonging the inflammatory process and delaying healing (Edmonds et al, 2008; Dinh et al, 2012). MMPs belong to a family of zinc-containing endopeptidases. They are calcium-dependent, capable of degrading and remodelling the proteins that form the extracellular matrix, and carry out different biological and physiological functions. MMPs are regulated by specific endogenous tissue inhibitors of metalloproteinases (TIMPs), hormones, growth factors and cytokines (Ren et al, 2014). Therapies directed at modulating MMPs may therefore be promising in healing ulcers.

Selection of the best treatments for neuroischaemic DFUs needs to be based on high-level clinical evidence (Edmonds et al, 2017). Using a local therapy to modulate MMPs in chronic wounds with a vascular component could therefore be useful in the management of neuroischaemic ulcers if it has produced promising findings in purely neuropathic DFUs (Richard et al, 2012). Sucrose octasulfate protects fibroblast growth factor and induces dermal fibroblast and keratinocyte proliferation in quiescent cultures (Burch and McMillan, 1991; Desai et al, 1995). In view of this, experiments were conducted to identify how this molecule could be used in the management of skin ulcers. Nano-oligosaccharide factor (NOSF) is an innovative compound derived from the chemical oligosaccharide family that has demonstrated MMP-inhibiting properties and clinical efficacy. It promotes healing in leg ulcers, pressure ulcers, DFUs and recurring wounds (White et al, 2015).

In vitro studies using a dermal equivalent model have shown that technology lipido-colloid (TLC)-NOSF significantly reduces the activity of some MMPs, such as gelatinases (MMP2 and MMP9) and collagenases (MMP1 and MMP8) (Coulomb et al, 2008a and b; Couty et al, 2009) that are involved in the chronicity of DFUs (Lobmann et al, 2002; 2006; Liu et al, 2009). TLC-NOSF stimulates the proliferation of fibroblasts, favouring wound healing and stimulating the formation of extracellular matrix by increasing collagen synthesis and hyaluronic acid synthesis *in vitro* (Bernard et al, 2005; 2007).

The main evidence supporting NOSF comes from two trials. The Wound Healing Active Treatment (WHAT) randomised, open-label controlled trial was conducted in 27 centres in the UK and France. Patients with leg ulcers of venous or mixed origin were given 12 weeks of treatment with TLC-NOSF or collagen/oxidised regenerated cellulose (CORC) (Bohbot, 2010). Both patient populations had similar characteristics and leg ulcers at baseline. The TLC-NOSF dressing reduced wound surface area by 54.4% compared to 13.0% with the CORC dressing during the 12-week period (P=0.0286). The healing rates were 5.5 mm^2/day with TLC-NOSF and 1.5 mm^2/day with CORC (P=0.029). TLC-NOSF also reduced the size more wounds by >40%: 56.1% versus 35.0% with CORC (P=0.022). In addition to this, TLC-NOSF was found to have a better safety profile than CORC. The Challenge Study was a controlled, randomised phase 3 multicentre double-blind clinical trial carried out in 45 centres in France. Ninety-three patients were randomised to UrgoStart®, which contains a TLC-NOSF layer, and 94 to neutral foam dressing (Meaume et al, 2017). After 8 weeks of treatment,

Table 2. Results of the Explorer study (Edmonds et al, 2017)			
Grade	**TLC plus NOSF**	**TLC only**	***P*-value**
Wound closure, *n* (%)	60 patients (48%)	34 patients (30%)	18 percentage points difference, 95% CI 5–30; adjusted odds ratio 2.60, 95% CI 1.43–4.73; *P*=0.002
ITT analysis; Time to closure (in days) by week 20 – Kaplan Meier analysis	180 (range: 163–198)	120 (range: 110–129)	TLC-NOSF shortened the mean time to closure by 60 days compared to an advanced neutral dressing (*P*=0.029)

there was a significantly greater reduction in wound surface area with UrgoStart than the foam dressing (58.3% versus 31.6%, respectively; *P*=0.0021). Wound surface area reduction during this period was 6.13 cm^2 with UrgoStart versus 3.26 cm^2 with the foam dressing (*P*=0.0038). The healing rate was 10.83 mm^2 per day with UrgoStart and 5.15 mm^2 per day with the foam dressing (*P*=0.0056). At the end of the trial, a significantly greater percentage of patients who had received UrgoStart had wounds whose area was >40% smaller than at baseline (65.6% for UrgoStart versus 39.4% for the foam dressing; *P*=0.0003) (Meaume et al, 2017).

Quality of life issues were discussed in a Challenge Study follow-up publication. The EuroQol 5D-5L quality of life questionnaire was completed by the patients at baseline and at week 8 using a three-level visual analogue scale analysing five dimensions:

- Mobility
- Autonomy
- Activity
- Pain/discomfort
- Anxiety/depression.

Patients reported less pain and discomfort (*P*=0.022) as well as less anxiety and depression (*P*=0.037) with TLC-NOSF treatment (Meaume et al, 2017).

Pooled data from eight observational studies from France and Germany were analysed to extrapolate these randomised controlled trial results to daily practice (Münter et al, 2017). The authors assessed time to complete wound closure and time to 50% reduction in pressure ulcer scale for healing score using the Kaplan–Meier model (estimation of average time to closure) and subgroup analysis (depending on the Margolis severity score). The studies included a total of 10,220 patients with various wounds – 77.3% had leg ulcers, 12.8% had DFUs and 9.9% had pressure ulcers. The overall closure rate was 30.8% and the average time to complete closure was 111 days with UrgoStart compared to 210 days with other treatments. The time to closure was shorter if UrgoStart was used as first-line rather than second-line treatment) (Münter et al, 2017).

UrgoStart in neuroischaemic DFUs

It was decided to conduct a pilot open-label trial of UrgoStart following the positive results from other trials. The prospective multicentre, non-controlled trial included adults with a grade 1A (Texas classification) uninfected neuropathic foot ulcer 1–15 cm^2 in size with a duration of 1–24 months (mean 6.7±5.2 months). The primary endpoint was relative reduction in wound surface area (%). The results showed an 82% median surface reduction by week 12. Ten patients' DFUs (31.3%) had healed during this period (Richard et al, 2012). It was therefore concluded that the TLC-NOSF matrix (UrgoStart Contact) could be an interesting adjunct in the therapeutic treatment of these chronic wounds.

This clinical trial was the precursor to the biggest study undertaken with the TLC-NOSF: the sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer) study, which included 240 patients with neuroischaemic DFUs managed with TLC® Contact layer wound dressing with or without NOSF (Edmonds et al, 2017). The double-blind trial was conducted in five countries (France, Germany, Italy, Spain and the UK) across 43 hospital centres with specialised diabetic foot clinics using a multidisciplinary approach. The results were extremely positive *[Table 2]*. Interestingly, in the NOSF group, 65% (46/71) of 'younger' wounds (duration <6 months) closed compared to just 25% (14/55) of older wounds (≥6 months). This suggests that earlier adaption of UrgoStart provides better results. The sucrose octasulfate dressing was found to be effective, safe and easy to implement. These results support the use of this dressing in the treatment of neuroischaemic DFUs in addition to a good standard of care. Reactions to the Explorer RCT have been very promising, where it was suggested that: "the results are certainly more encouraging than findings for most interventions that have been reported to date" (Tucker, 2018).

Conclusion

There has been a paradigm shift from the belief that neuropathy is the main problem with diabetic feet. There is a growing consensus that ischaemic and/or neuroischaemic ulceration is increasing. The Explorer study is the first to

demonstrate the effectiveness of a treatment for this condition. Results support the use of NOSF dressing in the management of neuroischaemic DFUs in addition to a good standard of care. DFJME

References

Armstrong DG, Cohen K, Courric S et al (2011) Diabetic foot ulcers and vascular insufficiency: our population has changed, but our methods have not. *J Diabetes Sci Technol* 5(6): 1591–95

Bernard FX, Barrault C, Juchaux F et al (2005) Stimulation of the proliferation of human dermal fibroblasts in vitro by a lipidocolloid dressing. *J Wound Care* 14(5): 215–20

Bernard FX, Juchaux F, Laurensou C (2007) Effets d'un pansement lipidocolloïde sur la production de matrice extracellulaire par des fibroblastes dermiques humains in vitro. *JPC* X11(58): 9–11

Bohbot S (2010) Management of venous leg ulcers with two active wound dressings. Protocol of a randomized clinical trial. *Journal of WOCN* 37(3): S57

Burch RM, McMillan BA (1991) Sucralfate induces proliferation of dermal fibroblasts and keratinocytes in culture and granulation tissue formation in full-thickness skin wounds. *Agents Actions* 34(1–2): 229–31

Coulomb B, Couty L, Fournier B et al (2008a) A NOSF (nano-oligasaccharide factor) lipido-colloid dressing inhibits MMPs in an in vitro dermal equivalent model. *Wound Repair Regen* 16(6): A74

Coulomb B, Couty L, Fournier B et al (2008b) Evaluation of a matrix impregnated with NOSF in an in vitro dermal reconstruction model. *Journal Plaies Cicatrisations* 13: 54–7 [article in French]

Couty L, Fournier B, Laurensou C et al (2009) A NOSF (nano-oligosaccharide factor) lipido-colloid dressing stimulates MMPs/TIMPs complexes formation leading to MMPs inhibition in an in vitro dermal equivalent model. *Wound Repair Regen* 17(4): A6

Dalla Paola L, Carone A, Vasilache L Pattavina M (2015) Overview on diabetic foot: a dangerous, but still orphan, disease. *Eur Heart J Suppl* 17(suppl_A): A64–8

Desai UR, Vlahov IR, Pervin A, Linhardt RJ (1995) Conformational analysis of sucrose octasulfate by high resolution nuclear magnetic resonance spectroscopy. *Carbohydr Res* 275(2): 391–401

Dinh T, Tecilazich F, Kafanas A et al (2012) Mechanisms involved in the development and healing of diabetic foot ulceration. *Diabetes* 61(11): 2937–47

Edmonds M, Lázaro-Martínez JL, Alfayate-Garcí JM et al (2017) Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* pii: S2213-8587(17)30438-2 [epub ahead of print]

Edmonds ME, Foster AV, Sanders L (2008) *A Practical Manual of Diabetic Foot Care.* 2nd edn. Blackwell, Oxford. Available at: http://bit.ly/2FfZCYv (accessed 20 February 2018)

El Sakka K, Fassiadis N, Gambhir RP et al (2006) An integrated care pathway to save the critically ischaemic diabetic foot. *Int J Clin Pract* 60(6): 667–9

Järbrink K, Ni G, Sönnergren H, Schmidtchen A et al (2017) The humanistic and economic burden of chronic wounds: a protocol for a systematic review. *Syst Rev* 6(1): 15

Lepäntalo M, Biancari F, Tukiainen E (2000) Never amputate without consultation of a vascular surgeon. *Diabetes Metab Res Rev* 16(Suppl 1): S27–32

Lepäntalo M, Apelqvist J, Setacci C et al (2011) Chapter V: diabetic foot. *Eur J Vasc Endovasc Surg* 42(Suppl 2): S60–74

Limperopoulou D, Bates M, Petrova NL, ME E (2005) The epidemic of neuroischaemic foot. Diabetic Foot Study Group, Chalkidiki

Liu Y, Min D, Bolton T et al (2009) Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers. *Diabetes Care* 32(1): 117–9

Lobmann R, Ambrosch A, Schultz G et al (2002) Expression of matrix-metalloproteinases and inhibitors in the wounds of diabetic and non-diabetic patients. *Diabetologia* 45(7): 1011–6

Lobmann R, Zemlin C, Motzkau M et al (2006) Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. *J Diabetes Complications* 20(5): 329–35

Meaume S, Dompmartin A, Lok C et al; CHALLENGE Study Group (2017) Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomised controlled trial. *J Wound Care* 26(7): 368–79

Münter KC, Meaume S, Augustin M et al (2017) The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. *J Wound Care* 26(Suppl 2): S4–15

Ndip A, Jude EB (2009) Emerging evidence for neuroischemic diabetic foot ulcers: model of care and how to adapt practice. *Int J Low Extrem Wounds* 8(2): 82–94

Overall CM, Lopez-Otin C (2002) Strategies for MMP inhibition in cancer: Innovations for the post-trial era. *Nat Rev Cancer* 2(9): 657–72

Pendsey SP (2010) Understanding diabetic foot. *Int J Diabetes Dev Ctries* 30(2): 75–9

Raffetto JD (2014) Which dressings reduce inflammation and improve venous leg ulcer healing. *Phlebology* 29(1 Suppl): S157–64

Ren Y, Gu G, Yao M, Driver VR (2014) Role of matrix metalloproteinases in chronic wound healing: diagnostic and therapeutic implications. *Chin Med J (Engl)* 127(8): 1572–81

Richard JL, Martini J, Faraill MB (2012) Management of diabetic foot ulcers with a TLC-NOSF wound dressing. *J Wound Care* 21(3): 142–7

Schaper NC, van Netten JJ, Apelqvist J et al; International Working Group on the Diabetic Foot (2016) Prevention and management of foot problems in diabetes: a summary guidance for daily practice 2015 based on the IWGDF Guidance Documents. *Diabetes Metab Res Rev* 32(Suppl 1): S7–15

Tucker ME (2018) *Dressing Hastens Neuroischemic Diabetic Foot Ulcer Healing.* Available at: www.medscape.com/viewarticle/890826 (accessed 20 February 2018)

van Dieren S, Beulens JW, van der Schouw YT et al (2010) The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil* 17(Suppl 1): S3–8

White R, Cowan T, Glover D (2015) *Supporting Evidence-Based Practice: A Clinical Review of TLC Healing Matrix.* Available at: http://bit.ly/2sHLVyU (accessed 20 February 2018)

Yost ML (2010) *According to THE SAGE GROUP a Significant Number of Diabetic Foot Ulcer Patients Also Suffer from Peripheral Artery Disease (PAD).* Available at: http://bit.ly/2sHTPln (accessed 20 February 2018)