Diabetic foot ulcer management with TLC-NOSF (Technology Lipido-colloid Nano-oligosaccharide Factor) wound dressings

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Diabetes and its associated complications is one of the biggest burdens that healthcare providers face. Diabetic foot ulcers (DFUs) are difficult-to-heal wounds resulting from the diabetes-related pathogenic abnormalities. Statistics from China are high, with the largest global prevalence of people with diabetes, and the local expenditure for this disease is second only to the US (Zhang et al, 2021). Moreover, 20% to 33% of costs related to diabetes mellitus are used for treatments of the diabetic foot (Chun et al, 2019). International and Chinese national guidelines broadly agree on the standard of care for the management of diabetic foot ulcers and it is very well understood that evidence-based holistic management, including local wound dressings, can improve healing outcomes. The clinical cases portrayed are aimed at describing the attainment of the implementation of Technology-Lipido-Colloid Nano-Oligosaccharide Factor dressing (TLC-NOSF). The TLC-NOSF dressing has been included in recent recommendations by the International Working Group on the Diabetic Foot (IWGDF) 2019 Guidelines and the National Institute for Health and Care Excellence (NICE, UK) and was the focus of a recently published systematic review highlighting the robust evidence behind this technology.

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Diabetes in the adult population has been increasing at alarming rates globally, where numbers have quadrupled from 1980 to 2014 (Zhou et al, 2016). China has the largest number of patients with diabetes in the world, where it is estimated that there are over 116 million people now living with the condition, which equates to 10.9% of the adult population (International Diabetes Federation, 2019). Advanced ageing of the human population is another contributor, as diabetes tends to affect older individuals (Khan et al 2020), with a high percentage of Americans aged 65 and older, equating to 26.8%, or 14.3 million seniors (American Diabetes Association, 2020).

The weighted prevalence of diabetes in China diagnosed by the World Health Organization criteria is on the increase, from 9.7% in 2007 to 11.2% in 2010, according to a study in 2017 (Li et al, 2020). The expenditure is also alarming, with China spending an estimated USD109.0bn on the management and treatment of diabetes and its complications in 2019, second only in expenditure terms to the US (Zhang et al, 2021).

The global prevalence of diabetic foot shows an average of 6.4% (Zhang et al, 2020). The annual incidence of DFUs in people with diabetes is suggested to range from 2% to 5%, with the lifetime risk ranging from 15% to 20% (Chun et al, 2019). Interestingly, about 20% to 33% of costs related to diabetes mellitus are used for the treatment of diabetic foot (Chun et al, 2019). The annual incidence of DFUs in China is suggested to be 8.1%, with a 5.1% amputation rate among patients with diabetes, while the fatality rate among these patients is 14.4% (Jiang et al, 2015). The average cost of hospitalisation for DFUs is CNY17,183 and the average length of stay is 18 days (Zhang et al, 2021).

DFU is considered one of the leading causes of hospitalisation in people with diabetes, where estimates state that approximately

20% of hospital admissions among patients with diabetes mellitus are the result of DFUs (Yazdanpanah et al, 2015). DFU may be a precursor to infection, gangrene, amputation and even death, if appropriate care is not implemented (Snyder and Hanft, 2009). The rate of lower-limb amputation in people with diabetes mellitus is reported to be 15 times higher than people without diabetes and approximately 50%–70% of all lower-limb amputations are due to DFUs (Leone et al, 2012).

Statistics presented by D-Foot International Organisation are alarming: 1 in 11 adults has diabetes; every 20 seconds, a limb is lost worldwide due to diabetes; one in seven people with diabetes will develop a foot ulcer; and up to 85% of all lower-limb amputations related to diabetes mellitus are preceded by a foot ulcer (D-Foot International, 2020).

DFU management

Numerous papers, guidelines and protocols have been published over the years. One such publication by the American Podiatric Medical Association and the Society for Vascular Medicine suggests that DFU management and prevention should include: prevention of ulceration, offloading, diagnosis of diabetic foot osteomyelitis, local wound care and re-vascularisation (Hingorani et al, 2016).

Other scientific societies and medical associations regularly review their guidelines and recommendations, taking in current clinical evidence, and there seems to be a general consensus regarding the five key elements of standard of care for DFU: offloading; metabolic control/holistic management; assessment of infection; assessment of perfusion/ischaemia; and evidence-based local wound care (Bullen et al, 2020). This outline follows the recommendation of the International Working Group on the Diabetic Foot (IWGDF) 2019 guidelines (Schaper et al, 2020), which highlights the importance of the following: prevention of foot ulcers; offloading foot ulcers; diagnosis, prognosis, and management of peripheral artery disease (PAD); diagnosis and treatment of foot infection; interventions to enhance healing of foot ulcers; and classification of diabetic foot ulcer (Schaper et al, 2020).

Chinese guidelines based on domestic and foreign guidelines, combined with the clinical experience and research results of Chinese specialists, were published in 2020, highlighting 50 recommendations, which include: evaluation and diagnosis of diabetic foot disease; performing a comprehensive medical evaluation; assessment and diagnosis of diabetic foot infections; assessment and diagnosis of PAD; assessment and diagnosis of peripheral neuropathy; classification and grading of diabetic foot ulceration; preoperative risk stratification; formation of a multidisciplinary limb protection team; management of blood glucose, blood pressure and lipids in people with diabetic foot; the treatment of atherosclerosis in diabetes foot disease; debridement and bone reconstruction; principles and methods of wound healing; offloading; protection of high-risk foot and prevention of ulcer recurrence; risk assessment and stratification of diabetic foot disease; and diabetic foot health education (Wang et al, 2020).

Although most clinicians worldwide are aware of the high level of evidence supporting the beneficial therapeutic effect of offloading and the inclusion of recommendations for offloading in all guidelines, effective pressure offloading is not commonly used in many wound care settings (Bus, 2012). In China, this may be attributed to the lack of podiatry hospital departments, lack of knowledge and poor availability of tools for effective debridement and offloading tissue repair (Xu and Ran, 2016).

Local wound management of the DFU

Modern dressings are mainly based on the moist healing environment theory and have numerous advantages compared with traditional dressings (Vowden and Vowden, 2017). Different dressings have different characteristics and may be targeted at different pathological types of wounds as these also have their own characteristics (Shi et al, 2020).

Wound bed preparation (WBP) is a structured approach to wound healing, which includes: treating the cause; patient-centered concerns; determining the patient's ability to heal; local wound care: monitoring wound history and clinical examination; debriding wounds with adequate pain control when appropriate; assessing and treating wounds for infection/inflammation; initiating moisture management; evaluating the rate of healing; and considering edge effect (Sibbald et al, 2021). The edge effect suggests therapies for stalled but healable wounds, which need to stimulate healing and be cost-effective (Sibbald et al, 20201).

In DFUs, it has been stated that the global healing rate is 24% after 12 weeks and 33% after 20 weeks of standard treatment, which relates to approximately 70% of DFUs remaining unhealed

after 20 weeks of standard treatment (Margolis et al, 2000). In a recently published post-hoc analysis of a double-blind study regarding the management of neuroischaemic DFUs, it was shown that a timely implementation of a robust standard of care will increase healing rates, independent of the size and location of the ulcer (Lázaro-Martínez et al, 2019).

While hyperglycaemia induces the majority of the micro- and macro-vascular complications associated with people with diabetes, it also increases matrix metalloproteinases (MMP) activity and there are significantly higher levels of MMP in patients with metabolic syndrome as compared with normal individuals (Ayuk et al, 2016). Reducing the levels of MMPs could optimise chronic wound healing, and therapies that are directed at reducing these levels may have promising outcomes in ulcer healing (Lázaro-Martínez et al, 2016).

Nano-oligosaccharide factor (sucrose octasulfate dressing based on technology lipido-colloid, TLC-NOSF)

The TLC-NOSF wound contact layer or healing matrix (UrgoStart®), when in contact with wound exudate, forms a gel that soaks up wound exudate and decreases levels of MMPs. The TLC-NOSF wound contact layer or healing matrix is stated to decrease MMP levels on the wound surface, thus promoting wound repair and shortening time to wound healing (Lázaro-Martínez et al, 2016) and has also been shown that transcutaneous oxygen pressure is improved when treating neuroischaemic DFUs with a TLC-NOSF dressing (White et al, 2015).

In a recently published systematic review (Nair et al, 2021), the authors documented finding "a total of 21 publications of different levels, ranging from double-blind randomised control trials to case reports, involving over 12,000 patients". The authors highlighted that the evidence includes double-blind randomised control trials (RCTs), and the post hoc analyses of RCTs regarding the use of the TLC-NOSF dressing not only assessed the efficacy of the dressing in reducing healing time and improving financial benefits, but also established the positive effects of the dressing on patients' health-related quality of life and economic benefits.

Moreover, recent guidelines published by the IWGDF (Schapper et al, 2020) and the National Institute for Health and Care Excellence (NICE, 2019) recommends the use of the TLC-NOSF dressing in different chronic wounds. The outcome of wound healing was well documented in a real-life observational study in 1,140 patients with different aetiologies (Dissemond et al, 2020), including DFUs, where 48.5% of wounds had healed and 44.8% had improved, regardless of wound aetiology or proportions of sloughy and granulation tissue at the start of treatment. Interestingly, Lázaro-Martínez et al (2019) concluded in their post-hoc analyses of the Explorer RCT (Edmonds et al, 2018) that "the earlier the TLC-NOSF dressing is initiated in DFU treatment, the greater the benefits".

The following cases were conducted in different hospital clinics in China. The clinicians opted to evaluate TLC-NOSF dressings in view of the strong evidence behind this local treatment suggesting reduced healing time in relation to DFUs.

Case 1 — Dr. Zhong Long, Executive Vice Director, Wound Healing Centre, Peking University 3rd Hospital, Beijing, China

An 82-year-old male with a 19-year-old history of type 2 diabetes mellitus, who had been on insulin long term and had been a smoker of

Case 1 – Dr. Zhong Long, Executive Vice Director, Wound Healing Centre, Peking University 3rd Hospital, Beijing, China.

Figure 1a – on presentation (March 2, 2021).

Figure 1b – (March 8, 2021) after two dressing changes.

Figure 1c – (March 15, 2021) after four dressing changes.

many years, presented with a 3-month history of swelling and pain after walking. Patient also reported decreased sensation and numbness in the foot with limited mobility.

He self-referred to the hospital on March 2, 2021 because of an ulcer on the plantar aspect of his right foot, which had been present for 1 month without any management. The DFU *[Figure 1a]* measured 2.7 cm x 0.7 cm with minimal exudate and no signs of local infection. Routine wound hygiene was carried out and TLC-NOSF contact layer applied. Dressing was kept *in situ* with sterile gauze bandaging. Dressings were changed every 3 days thereafter. By March 8, the wound had decreased in size to 2.5cm x 0.5cm *[Figure 1b]*. Dressing changes continued as previous, every 3 days. The wound was healed by March 15 *[Figure 1c]*, after four dressing changes.

Case 2 – Dr. Zhong Long, Executive Vice Director, Wound Healing Centre, Peking University 3rd Hospital, Beijing, China

A 63-year-old male with a 20-year history of type 2 diabetes mellitus, who was on insulin long term, hypertension for 20 years, a history of tuberculosis and had been a smoker for many years, self-referred on March 11, 2021 with ulceration on the lateral aspect of his right foot. The ulcer was not being managed up to this point. He previously had a left lower-extremity artery bypass surgery, left deep femoral vein and carotid artery dissections.

On presentation, the foot was cold and dry, and the patient was complaining of foot numbness. The DFU *[Figure 2a]* measured 1.2 cm x 0.8 cm with minimal exudate and no signs of local infection. Routine wound hygiene was carried out and TLC-NOSF foam border was applied. Dressings were thereafter changed every 3 days. By March 15, the wound had decreased in size to 0.5 cm x 0.4 cm *[Figure 2b]*. Dressing changes continued as previously every three days. The wound was closed by March 29 *[Figure 2c]*, after 3 weeks of treatment duration.

Case 3 – Dr. Wang Jun, Endocrinology Department, Shaoxing People's Hospital, Shaoxing ; Dr. Zhu Shijun, Vascular Surgery Department, The Second Affiliated Hospital of Zhejiang University, Hangzhou, China

This case centred on a 60-year-old male with history of primary hypertension, prostatic hyperplasia, renal calculi, renal cysts, abnormal liver function and low T3 (triiodothyronine) syndrome. He was diagnosed 13 years ago with type 2 diabetes mellitus accompanied with ensuing peripheral neuropathy, peripheral vascular disease and retinopathy.

The patient presented on the April 13, 2020 with an 8.0 cm x 4.0 cm ulcer on the lateral aspect of the left dorsum, with some surrounding eschar and gangrene of the left toe with signs of infection.

He was admitted for holistic management, including glucose management, systemic antibiotics and anticoagulation treatments. On April 16, 2020, amputation fourth and fifth phalanges, bone cement placement and vacuum sealing drainage suction was performed under general anaesthesia. Postoperatively, continuous negative pressure suction was continued. The patient was discharged and was followed by outpatient wound dressing changes.

By May 16, the wound measured 9.0 cm x 6.0 cm x 2.0 cm depth. Granulation tissue was present but progress was slow *[Figure 3a]*. Wound hygiene was performed and TLC-NOSF foam

Case 2 – Dr. Zhong Long, Executive Vice Director, Wound Healing Centre, Peking University 3rd Hospital, Beijing, China.

Figure 2a – on presentation (March 11, 2021).

Figure 2b – (March 15, 2021).

Figure 2c – (March 29, 2021).

Case 3 – Dr. Wang Jun, Endocrinology Department, Shaoxing People's Hospital, Shaoxing ; Dr. Zhu Shijun, Vascular Surgery Department, The Second Affiliated Hospital of Zhejiang University, Hangzhou, China.

Figure 3a – wound on presentation (May 16) before starting TLC-NOSF local treatment.

Figure 3b – after five dressing changes (May 25) wound bed appears healthier.

Figure 3c – after a further five dressing changed (June 5) healthy granulation tissue is covering all wound bed.

Figure 3d – further progress noted with another 3 dressing changes (June 12).

Figure 3e – By August 12, the wound size was considerably reduce and regime changed to TLC-NOSF contact layer.

Figure 3f – wound completely healed by September 23.

dressing was applied topically. The dressing was changed on alternate days. By May 25 (five dressing changes), the size of the wound was decreased slightly to 8.7 cm x width 5.6 cm x 1.2cm depth, but the wound bed appeared healthier *[Figure 3b]*. By June 5, the wound bed showed healthy granulation and the wound size was decreased to 8.5 cm x 5.5 cm x 0.5 cm depth *[Figure 3c]*. By June 12, the wound was showing good progress and good reduction of wound size (8.0 cm × 5.5 cm × 0.4 cm depth) *[Figure 3d]* and the decision was taken to reduce the dressing changes to twice weekly. By August 12, the wound was greatly reduced (3.0 cm x 2.0 cm) and the dressing was changed to TLC-NOSF contact layer *[Figure 3e]*. Wound was completely healed by September 23 *[Figure 3f]*.

Case 4 – Dr. Jiang Dong, Endocrinology Department, Jun Xie Hospital, Nanjing, China

An 84-year-old male with a history of long-standing type 2 diabetes on insulin, also suffering from hypertension and atherosclerotic coronary disease, was admitted with a traumatic wound on his left heel *[Figure 4a]*. The wound had been present for 2 months and was self-managed. Initial radiological investigations revealed emphysema and inflammation in both lungs. Foot X-ray did not show any abnormalities in the foot, while ultrasound showed mild stenosis

Case 4 – Dr. Jiang Dong, Endocrinology Department, Jun Xie Hospital, Nanjing, China.

Figure 4a – on presentation (May 9).

Figure 4b – after initial debridement and first dressing application.

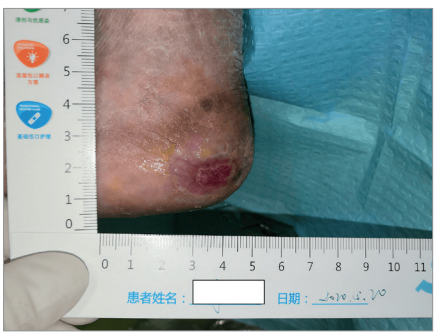

Figure 4c – Wound after five dressing changes (May 20).

of the left dorsalis pedis artery, bilateral external iliac arteries, left femoral artery, left popliteal artery and vascular sclerosis of the left anterior tibial artery. Ankle brachial pressure index of the left foot was 0.70.

Sharp debridement was performed and TLC-NOSF contact layer applied *[Figure 4b]*. The dressings were changed every 2 days. By May 20 (five dressing changes), the wound size had progressed considerably and epithelial migration was present *[Figure 4c]*.

Apart for the wound care provided, general information and education regarding managing his diabetes and lifestyle was provided by the multidisciplinary team, including metabolic control, appropriate well-balanced diet and foot care. It was suggested that initially there should be no weight-bearing on the foot and he was provided with suggestions and awareness regarding special shoes for people with diabetes to protect both feet.

Case 5 – Dr. Fan Xinzhao and Meng Jianfu, Endocrinology Department, Nanfang Hospital Affiliated to Southern Medical University, Guangzhou, China

A 46-year-old female presented with a sprain of the left foot. The patient had diabetes mellitus for 5 years and sprained her left foot a week ago, causing redness, pain and elevated temperature without any skin breakdown. She went to the local hospital where an X-ray of the left foot was taken, which did not show any obvious fractures or joint dislocation. Three days later, after washing the left foot with hot water, a blood blister of about 3 cm in diameter and a yellow blister of about 4 cm in diameter appeared on the dorsal surface of the forefoot where she self-referred to Nanfang Hospital, China, on September 11, 2020 *[Figure 5a]*. An MRI report revealed diffuse soft tissue swelling and inflammation of the left foot. Incision and drainage was conducted to reduce wound tension and remove necrotic tissues, control the infection and prevent further expansion of the infection and decompression to avoid secondary injury due to pressure *[Figure 5b]*.

Consultations were sent for metabolic control, enhancement of nutrition and also to offer psychological counselling to provide encouragement and support to patient. TLC-Ag (UrgoTul Ag®/Silver, Urgo) was initially applied to manage the local infection — the dressing was changed every 3 days. After two dressing changes (September 18), signs of local infection subsided and TLC-NOSF foam dressing was applied *[Figure 5c]*. The dressing was changed every two days. By October 9, the wound was showing signs of healthy granulation *[Figure 5d]* and dressing were thereafter changed every 7 days. Wound continued to reduce in size and by October 30, the wound was reduced to 0.2 cm x 0.2 cm *[Figure 5e]* and complete wound closure was achieved by the November 6 *[Figure 5f]*.

Discussion

The lifetime risk of a person suffering from diabetes of having a foot ulcer is very high. DFUs are a foremost health problem worldwide, which not only causes significant economic burdens but also

Case 5 – Dr. Fan Xinzhao Meng Jianfu, Endocrinology Department, Nanfang Hospital Affiliated to Southern Medical University, Guangzhou, China.

Figure 5a – foot on referral (September 11, 2020).

Figure 5b – After incision and drainage.

Figure 5c – after two dressing changes with TLC-Ag (September 18).

Figure 5d – October 9.

Figure 5e – October 30.

Figure 5f – November 6.

Disclaimer:
Zhong Long, Wang Jun, Zhu Shijun, Jiang Dong and Fan Xinzhao have no conflicts of interest to declare. Emilio Galea is employed by Urgo Medical as the International Medical Director for Australasia, Middle East and South Africa. TLC-NOSF Dressing (UrgoStart) is a patented product (Laboratoires Urgo, Chenôve, France).

affect both the patient and the society as a whole. Regardless of the cause of the DFU, correct diagnosis and prompt evidence-based treatment are essential in the management of these ulcers. Wound healing is a complex process, which is more complicated in people with diabetes. Holistic management of these patients is necessary and recent studies, such as the Explorer RCT (Edmonds et al, 2018) and endorsements by the recommendations of the IWGDF (Schaper et al, 2019) and NICE (2019), have highlighted the importance of local wound management in DFU.

The cases portrayed in this paper represent a cohort of patients suffering from DFUs, managed under real-life conditions in China. The results, after the application of TLC-NOSF, represent a rapid improvement in the wound-healing process through wound surface area reduction. The results of these clinical cases are in line with the findings of the results of other publications cited in the aforementioned systematic review (Nair et al, 2021), corroborating that TLC-NOSF provides a real clinical benefit for the management of chronic wounds and can be considered as an option for the management of such chronic wounds when used as part of evidence-based standard of wound care. WINT

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