Local management of diabetic foot ulcers with a polyabsorbent TLC-NOSF dressings — a real-life pilot study in real life from Kuwait

Authors (clockwise from top left): *Naser Alhumaidi, Mariam Alessa, Abdul Aziz Alshahe and Emilio Galea*

Chronic wounds are an international and regional concern affecting many patients, demanding substantial resources from healthcare systems. Managing patients with these wounds is costly in terms of time and resources required, not forgetting the detrimental impact on the quality of life of these individuals. Moreover, diabetic foot problems are very common throughout the world, and their recurrence is high. In 2016, the World Health Organization (WHO, 2022) reported that 14.7% of the population of Kuwait are suffering from diabetes, with very high percentages of overweight, obese and inactive individuals. It is inevitable that many of these individuals suffer and/or will suffer in the future from diabetes-related foot ulcers and complications, and the management of these wounds is complex. The authors reviewed the evidence behind a local treatment indicated for chronic wounds and specific in neuropathic diabetic foot ulcers. In view of the high level of evidence regarding this local treatment, a pilot study was conducted in 2021 to analyse the feasibility of a larger-scale observational study. The article highlights the results of the initial pilot and discusses the feasibility of conducting further research to justify implementation of technology lipido-colloid nano-oligosaccharide factor (TLC-NOSF) dressings in the local management of patients with diabetic foot ulcers in Kuwait.

Naser Alhumaidi *is Senior Specialist in General Surgery, Head of Diabetic Foot Unit Department of Surgery, Farwaniya Hospital, Kuwait;* ***Mariam Alessa*** *is Diabetes Specialist Podiatrist, Diabetic Foot Unit Department of Surgery, Farwaniya Hospital, Kuwait;* ***Abdul Aziz Alshaheen*** *is General Practitioner Surgery, Diabetic Foot Unit Department of Surgery, Farwaniya Hospital, Kuwait;* ***Emilio Galea*** *is International Medical Director, Urgo Medical*

Wound chronicity was probably first mentioned in literature in 1953 in reference to wounds that were difficult to heal or did not follow a normal healing process (Greeley, 1953). Terminology used includes hard-to-heal wounds, difficult to heal wounds, non-healing wounds and complex wounds (Kyaw et al, 2017). However, most papers do not provide a clear cut-off duration to define the chronicity of wounds (Kyaw et al, 2017).

Chronic wounds, including, lower-limb ulcers, diabetic foot ulcers (DFUs) and pressure injuries (PIs), present features of chronicity from the onset, while other wounds may initially start as acute, like burns, traumatic or postoperative wounds, and become chronic or hard to heal after weeks of stagnation, either due to the patient's general condition or inappropriate global management or local care (Atkin et al, 2019). These wounds "start by either direct trauma to tissue already compromised by underlying pathology or by breakdown of tissue under unbroken skin" and are "characterised by a physiological barrier to recovery before the breach in the skin appears, an underlying pathophysiology, chronic inflammation and a mostly unpredictable healing trajectory" (Atkin et al, 2019).

It is estimated that the prevalence of chronic wounds is between 1% and 2% in developed countries with the most prevalent wounds being venous leg ulcers (VLUs), pressure injuries and DFUs in people aged over 60, where some of the wounds may not heal completely for a year or more (Atkin et al, 2019).

Diabetes is a systemic disease that has been recently described as having reached epidemic

proportions in modern society (Ferreira, 2020). Trophic disorders and infections are common complications in the feet of patients with advanced stages of the disease and are the main cause of amputation of the lower limb in those patients with diabetes (Ferreira, 2020). Diabetic foot complications lead to severe medical, social and economic consequences for the patients, while also posing a substantial public health problem (Piaggesi and Apelqvist, 2017). The threat of ulceration and amputation is higher in people suffering from diabetes compared to people without diabetes, and it is estimated that, somewhere in the world, every 20 seconds, an amputation is performed on an individual living with diabetes (Adiewere et al, 2018).

Foot ulceration is a common morbidity among diabetic complications as it is estimated that, annually, foot ulcers develop in 9.1 million to 26.1 million people with diabetes worldwide (International Diabetes Federation, 2015). More than 5% of people with diabetes have a history of foot ulceration and the cumulative lifetime incidence may be as high as 25% (Piaggesi and Apelqvist, 2017), while Armstrong et al (2017) suggest that between 19% and 34% of people with diabetes are likely to be affected by foot ulceration.

Clinicians involved in wound care traditionally have relied on habit, expert opinion and available product and treatment information (Cowan and Stechmiller, 2009). However, it is stated that wound management research improves patient care and clinical outcomes by standardising assessment, planning and implementation of treatment (World Union of Wound Healing Societies, 2020). It is generally agreed that relevant, good standard scientific evidence should be used to influence practice to help clinicians provide the best and most appropriate care for patients (Woodbury and Kuhnke, 2014). The implementation of evidence-based wound care concurs with better clinical outcomes for the patients and cost savings for the care systems and payers (Pacella et al, 2018).

Why TLC-NOSF dressings in the management of chronic wounds?

Recommendations on the appropriate treatment and care of people with specific diseases and conditions, should be based on the best available evidence, aiming to improve the quality of healthcare (Garbi, 2021). Two such guidelines were published in 2019 considering the management of DFUs. The International Working Group for Diabetic Foot (IWGDF) consider the use of technology lipido-colloid nano-oligosaccharide factor dressings (TLC-NOSF) in non-infected, neuroischaemic DFUs in order to enhance the wound-healing process (Rayman et al, 2019).

In addition, the National Institute for Health and Care Excellence (NICE) states that "evidence supports the case for adopting UrgoStart dressings to treat diabetic foot ulcers and venous leg ulcers in the NHS, because they are associated with increased wound healing compared with non-interactive dressings. UrgoStart dressings should therefore be considered as an option for people with diabetic foot ulcers or venous leg ulcers after any modifiable factors such as infection have been treated" (NICE, 2019).

Furthermore, in a recent systematic review, the authors concluded that: "All the evidence provided suggest that these dressings provide clinicians with an evidence-based option for the management of chronic wounds; that the TLC-NOSF dressings are beneficial in promoting the healing process, reducing healing times, enhancing patients' health-related quality of life, and in allowing a more cost-effective procedure (Nair et al, 2021).

The potassium salt of sulfated oligosaccharides in the TLC-NOSF dressing has been shown to provide biological activities, including, reduction of matrix metalloproteases (MMPs), interaction with growth factors and restoring biological functions, thus promoting wound repair and shortening time to wound healing (Volkin et al, 1993; White et al, 2015). It has also been demonstrated that, when treating neuroischaemic DFUs with a TLC-NOSF dressing, transcutaneous oxygen pressure is improved (Lázaro-Martínez et al, 2020).

The aforementioned systematic review by Nair et al (2021) lists 21 publications of different levels, ranging from double-blind randomised controlled trials (RCT) to case reports, involving over 12,000 patients (Nair et al, 2021). Of main note are the RCTs, including the WHAT (Wound Healing Active Treatment) RCT, involving 117 patients presenting with VLUs, 27 centres which established superior wound area reduction (P=0.006) and better healing rates (P=0.029) with TLC-NOSF dressing compared with another MMP-inhibitor dressing (Collagen – oxidised regenerated cellulose) (Schmutz et al, 2008). The 'Challenge' study was conducted with 187 patients from 45 centres with venous leg ulcers, showed significant improvements in early wound area reduction (P=0.002) and in patients' quality of life with TLC-NOSF dressings compared with non-interactive dressings

(Meaume et al, 2012; 2017). The European double-blind RCT 'Explorer' study, performed in patients presenting with neuro-ischaemic DFUs and involving 240 patients from 43 centres, demonstrated a significantly higher wound closure rate (P=0.002) and a shorter time-to-closure (P=0.029) were achieved with the TLC-NOSF dressing in comparison to a non-interactive dressing (Edmonds et al, 2018; Lázaro-Martínez et al, 2019).

Lázaro-Martínez et al (2019) go further to suggest that "treating DFUs with TLC-NOSF dressing and good SoC (standard of care) results in higher wound closure rates than with a neutral dressing and the same good standard of care, whatever the duration and the location of the treated wounds. However, the earlier the TLC-NOSF dressing is initiated in DFU treatment, the greater the benefits". Moreover, reduced healing times for leg ulcers, pressure injuries and DFUs treated with the TLC-NOSF dressings were described in current practice (real-life studies) from pooled analysis of the data from eight observational studies involving 10,220 patients (Münter et al, 2017).

New wound dressings are now presented, formed of a pad of poly-absorbent fibres coated with the TLC-NOSF healing matrix. The introduction of the poly-absorbent fibres can be used in the management of wounds both in the granulation stage of wound healing, as well as wounds at the debridement stage (Sigal et al, 2019). The clinical efficacy and safety profile of this new modality was demonstrated in two interventional, prospective, single-arm clinical trials (Sigal et al, 2019). The results from these two clinical studies showed that the investigated dressings are an effective, safe and simple treatment for the local management of chronic wounds at the different stages of healing and leading wound closure (Sigal et al, 2019).

A prospective, multicentre, observational study involving 1,140 patients in 130 centres with chronic wounds of various aetiologies were managed with the investigated polyabsorbent TLC-NOSF dressing, was conducted in Germany (Dissemond et al, 2020). After a mean duration of 56±34 days, by the final visit, 48.5% of wounds have healed and 44.8% improved. Similar results were reported notwithstanding of wound aetiology or proportions of sloughy and granulation tissue when the treatment with polyabsorbent TLC-NOSF dressings was initiated.

In view of the above results, the authors' intention was to investigate the performance of the polyabsorbent TLC-NOSF dressings in patients with DFUs from Kuwait.

Design, results and assessment

This pilot open-label, mono-centric (Diabetic Foot Center, Farwaniya Hospital, Kuwait), single arm, non-interventional observational study, was conducted between February and October 2021. Patients were followed up in an outpatient setting for a maximum duration of 18 weeks (or until healing). Patients presenting with a DFU at the 'sloughy' or granulating stage were included, while DFUs presenting with active infection were not included in the evaluation. The primary endpoint was to assess the overall improvement of DFU following management with the poly-absorbent fibre TLC-NOSF dressing (UrgoStart Plus®, Urgo), with the secondary objective was to assess overall performance of the dressing (from the clinicians' and patients' point of view).

Decisions regarding diagnosis and therapy were made by the clinic staff and their usual therapeutic procedure was not influenced by the study. Clinical best practices were implemented according to the protocols of the Center. The Center Staff could discontinue the use of the evaluated dressing and any patient's participation in the study at any point of the observation.

The relevant demographic information and medical history, as well as the following information were recorded at the initial visit: DFU diagnosed as neuropathic, ischaemic, neuro-ischaemic; offloading; wound location; presence of multiple wounds (in case of patients presenting with multiple eligible wounds, the wound considered by the team as the most suitable was selected for the study); wound recurrence and duration.

Demographic information and relevant medical history of the patients, wound characteristics (aetiology, wound duration, wound area, wound bed tissue and exudate level), previous and current wound treatment were recorded at the initial visit. Informed consent was also completed in the initial visit. Wound characteristics, wound healing progression and the occurrence of adverse events were assessed during the interim visits, performed on a regular basis. Outcomes related to the final assessment visit included treatment evaluation and healing progression in wound area reduction

A total of nine patients were recruited but two patients did not complete the evaluation (one dropped out and one experienced a wound infection). The remaining seven participants were all male aged 61.8 ± 8.893 (51 to 76). All patients had diabetes mellitus type 2. One patient had a previous kidney transplant and three patients

had lower-limb ischaemia. Three of the patients were utilising offloading devices. *Figure 1* describes the wound types.

Only one patient had more than one wound. Duration of the wounds varied from 14 days to 180 days (55.428 ± 1.96). All patients were previously being managed by silver antimicrobial dressing apart from one for whom Omega-3 dressing was applied. Patients underwent debridement (sharp = 4, mechanical/autolytic = 3) before starting the treatment. The patients were followed up between February and March 2021. Dressing changes were mostly conducted every 3 days. Initial wound area ranged from 4.5 cm^2 to 195 cm^2 *[Figure 2]*, with a mean = 42.4 cm^2, as compared to the final visit where the mean was 6.92 cm^2 *[Figure 3]*. All the wounds decreased in wound area, with five of the wounds (71.4%) completely healed. *Figure 4* portrays the images of each wound at the initial, intermediate and final visits.

Discussion

The authors embarked on this pilot study on a limited cohort of patients to investigate the efficacy of the TLC-NOSF treatment range in

Figure 1. Wound type.

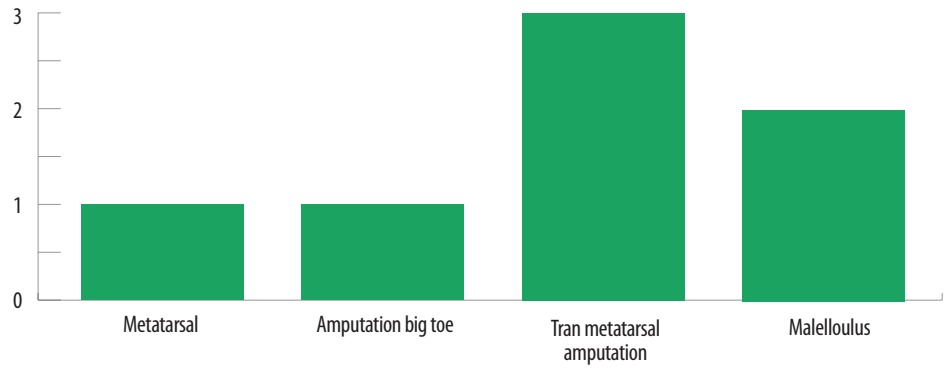


Figure 2. Wound area reduction per patient.

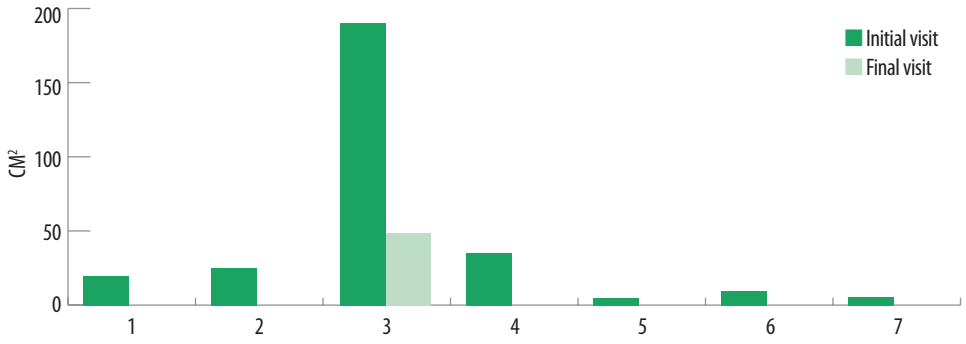


Figure 4. Wound area regretion (mean).

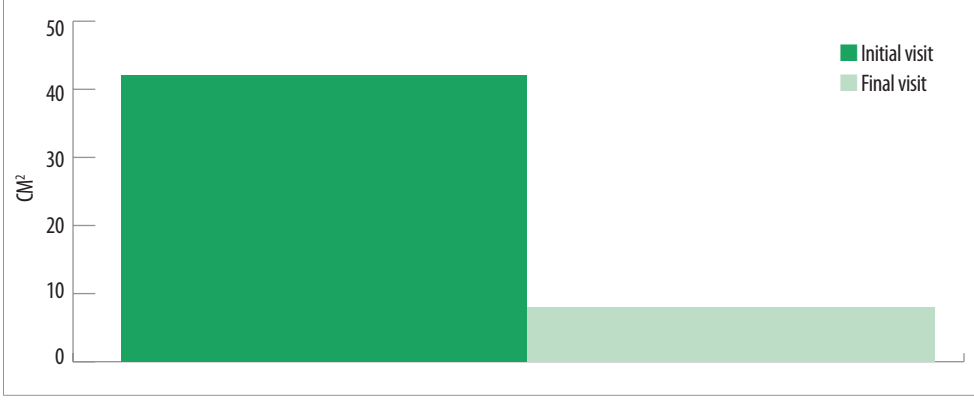
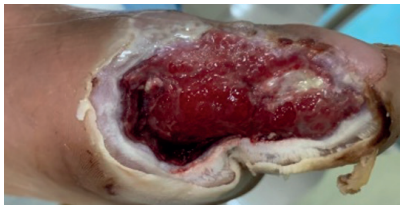
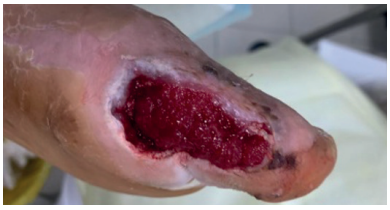
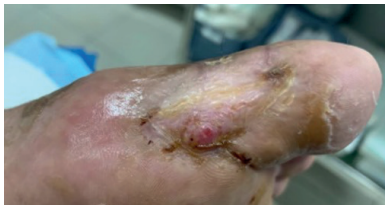
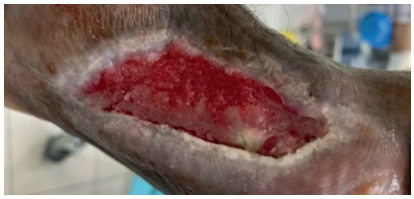
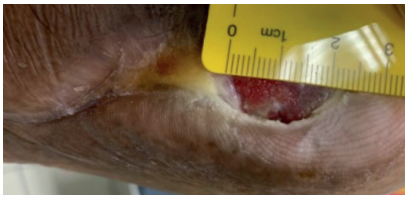
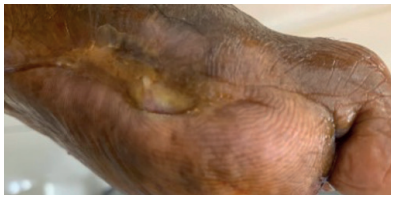
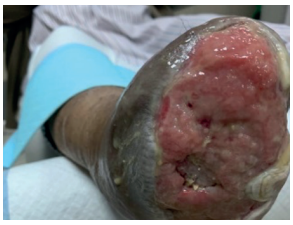
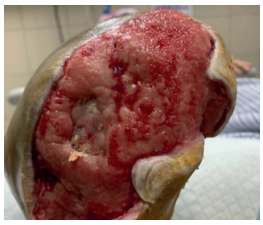
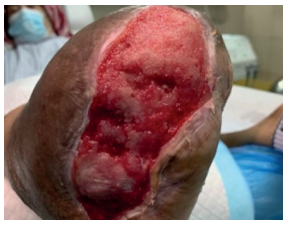
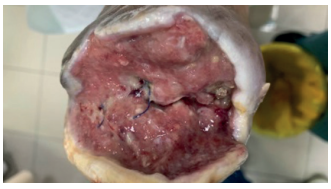
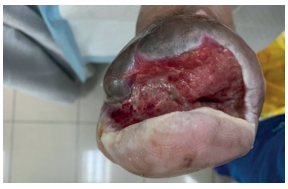
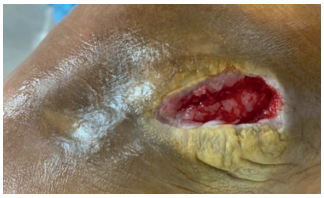
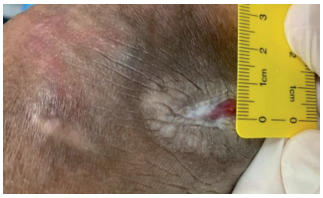
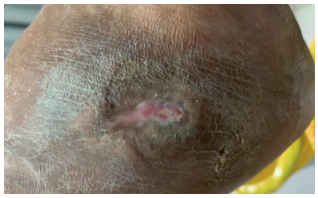
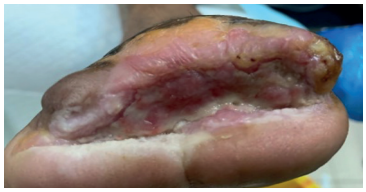
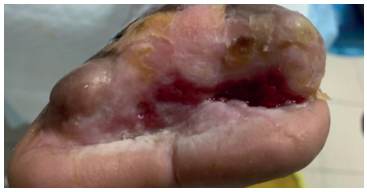
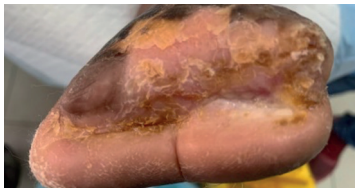
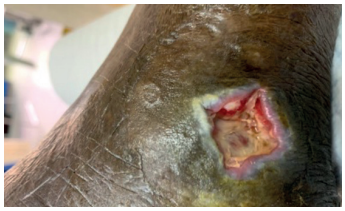
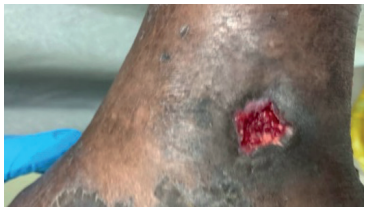
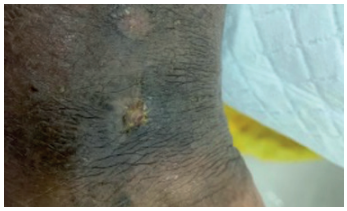


Fig 4: the patient wounds at the initial visit, intermediate visit and final visit.

Initial visit	Intermediate Visit	Final Visit
 24th February	 21st April	 9th May
 9th February	 20th April	 11th May
 4th March	 25th May	 27th July
 14th February	 10th March	 25th April
 15th April	 24th April	 10th May
 21st March	 22nd April	 9th May
 14th February	 18th March	 16th May

advance of the planned project of a larger scale observational study. The decision to trial the polyabsorbent TLC-NOSF dressing in DFU patients from Kuwait was to evaluate if the results similar to those obtained in Germany (Dissemond et al, 2020) would be achieved. The German real-life observational study included 1,140 patients, with chronic wounds of various aetiologies (leg ulcers, diabetic foot ulcers, pressure ulcers, etc), which were treated with the investigated dressings in 130 centres, for a mean duration of 56±34 days.

By the final visit, 48.5% of wounds had healed and 44.8% had improved. The result of the evaluation was encouraging with the documented good results. These results will prompt further and more in-depth evaluation. Lessons learnt was that, in order to conduct a larger scale trial, the set-up, collection of data and analyses of the results need to be conducted in a better, more systematic manner. In the pursuing proposed study, the clinicians will gather data in a more uniform and professional manner by employing the services of a contract research organisation (CRO) to assist in the planning, setup, and day-to-day execution and management and analyses of the clinical data, in order to be able to present the study in the proficient manner expected.

Conclusion

Pilot studies are referred to as small scale scale versions, or a trial run, in preparation for a major study as pre-testing or trying out of a particular research intervention, mainly to assess the feasibility and likelihood of success (Van Teijlingen and Hundley, 2001). Copious evidence is available regarding the management of chronic wounds with the TLC-NOSF treatment range, which, however, was mainly conducted in Europe. "Replicability refers to a different team arriving at the same results using the original author's artifacts" (NASEM, 2019). In view of this, the authors decided to do an initial evaluation of the TLC-NOSF treatment range in DFU patients from Kuwait. The initial results were very encouraging to conduct further investigations.

It was noted, however, that it might be beneficial if the trial might be conducted using a protocol that includes an antimicrobial and desloughing dressing prior to initialising the TLC-NOSF dressings — it is suggested that infections occur in up to 58% of patients presenting with a new foot ulcer (Del Core et al, 2018). A real-life observational study was conducted by a German team headed by Dissemond (2020) including 2,270 patients with acute and chronic wounds of various aetiologies that were treated with a poly-absorbent silver dressing with technology lipido-colloid with silver ions, TLC-Ag (UrgoClean Ag®, Urgo) dressing for a mean duration of 22±13 days. All clinical signs of local infection and the diagnosed wound infections were substantially reduced at 2 weeks after the treatment initiation, while all wound infection parameters continued to reduce until the last visit. The suggested new protocol will include the procedure of utilisation of this antimicrobial dressing to remove any overt or covert infection prior to starting the TLC-NOSF treatment. WME

Conflict of interest

There was no conflict of interest.

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