Transformational healing solutions: improving patients’ lives

Declaration of interest
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Web: www.markallengroup.com
Tel: +44 (0)20 7501 6726 Email: anthony.kerr@markallengroup.com

Publishing Director: Anthony Kerr
Editor, Journal of Wound Care: Rachel Webb
Supplement Editor: Vicqui Stuart-Jones
Associate Publisher, Medical Education: Tracy Cowan
Designer: Jenny Watson
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PROLOGUE: TRANSFORMATIONAL HEALING SOLUTIONS

In recent years, the provision of wound care for patients has dramatically improved through the development of new therapeutic options, allowing for a wide range of wound care therapy choices. In June 2014, an educational International Surgical Wound Forum (ISWF) was held to present current options in wound care to a multidisciplinary group of healthcare providers. Topics included negative pressure wound therapy with instillation and dwell time (NPWTi-d), surgical incision management (SIM), use of NPWT in the management of the open abdomen, epidermal skin harvesting, and advanced wound dressings. This supplement provides in-depth discussion of some of the topics covered at the 2014 ISWF.

Declaration of interest
KH presented as a faculty member during the 2014 International Surgical Wound Forum (ISWF), an annual educational event sponsored by KCI, an Acelity company. He is the guest editor for this educational supplement based on faculty presentations from the ISWF 2014. Acelity provided editorial assistance.

Key words: negative pressure wound therapy; instillation therapy; surgical incision management; epidermal skin harvesting; wound dressings

From the early age of medicine to today, treating patients with wounds continues to be a difficult field for healthcare providers. Numerous factors, including patient lifestyle, comorbidities, and the wound environment itself, all serve to alter the healing process and potentially result in the development of chronic, difficult-to-heal wounds. These wounds significantly affect patients, causing social and financial burden; however, patients are not the only ones challenged by chronic non-healing wounds. The health-care system has to deal with the increase of health-care professional input, hospitalisations, and diagnostic screening and testing, which all contribute to the rising cost of health care.

Advances in technology and medicine have also lead to advances in wound care, moving the field forward. The discovery of antibiotics and the development of the tulle gras and film dressings offered an important stepping stone for those treating patients with wounds. These early discoveries led to the development of modern wound dressings with anti-microbial properties, hydrocolloids, hydrogels, alginates, and biological dressings.

Additionally, the advent of new technology has paved the way for the development of negative pressure wound therapy (NPWT). Commercialised in the late 1990s, NPWT (V.A.C. Therapy, KCI, an Acelity company, San Antonio, TX, USA) utilised negative pressure to induce microstrain and macrostrain responses in the wound bed and to promote an environment favourable to healing. Since its launch, NPWT usage in acute and chronic wounds has steadily increased due to clinicians observing wound improvement in patients treated with this technology, which has led to new technologies for the use of negative pressure in wound healing. A commercialised system is now available that combines NPWT with intermittent instillation of a topical wound solution with a dwell time (NPWTi-d, V.A.C. VeraFlo Therapy, KCI, an Acelity company, San Antonio, TX, USA) for wounds that would benefit from controlled automated wound cleansing. For patients with an open abdomen, a negative pressure system specifically designed for use as a temporary abdominal closure method with a visceral protective layer (ABThera Active Abdominal Therapy, KCI, an Acelity company, San Antonio, TX, USA) has also been developed. Finally, because these NPWT systems have benefitted patients who have open wounds, a surgical incision management system (SIM; Prevena Incision...
Management System, KCI, an Acelity company, San Antonio, TX, USA) has been designed specifically for use over closed incisions.

With the options for wound care treatments rapidly expanding, an international educational event (International Surgical Wound Forum, ISWF) was held in Edinburgh, Scotland (UK) to promote discussion among health-care professionals from all over the world regarding new transformation healing solutions for wound care. This supplement serves to review some of these new technologies (e.g., NPWTi-d and SIM) as well as recent information on using epidermal grafts as an alternative to traditional autologous grafts for wound healing.

In order to understand where the fields of medicine and wound healing are heading, it is important to know the history and how innovation drives advancement. A review of innovations in wound care is presented that connects innovation in medicine with advancement of wound care.

Complex wounds often require more health-care provider visits, placing a burden not only on patients but also on the health-care system. While NPWT has been shown to promote a wound environment favourable to healing, some complex wounds would benefit from the delivery of topical wound solutions. A comparison between NPWT and NPWTi-d is presented along with a description of real-world NPWTi-d applications.

Surgical incisions present a distinct set of complications separate from open wounds. The risk of developing complications, such as infection and wound breakdown, is often increased in patients with multiple comorbidities. Here, a review of the literature relevant to NPWT over incisions is presented, together with case studies demonstrating its use in high-risk patients.

In recent years, an alternative method has become available for clinicians to undertake skin grafting. Harvesting of the epidermal layer of the skin has now been simplified with the use of an epidermal harvesting system (CelluTome Epidermal Harvesting System; KCI, an Acelity company, San Antonio, TX, USA). In some cases, these epidermal skin grafts may be used in place of traditional skin grafting over wounds when only the epidermal layer is needed. An article reviewing this new procedure is presented along with case studies.

Innovation has facilitated the development of many different options of wound dressings. Health-care professionals can now choose the dressing based on the requirements of the wound environment in order to promote healing. In the case of diabetic foot ulcers, a number of factors contribute to the wound environment to inhibit wound healing. A review of general and local factors contributing to non-healing diabetic foot ulcers and options for wound management through advanced wound dressings is presented.

This supplement seeks to inform health-care professionals of new transformational healing solutions available for wound care. It combines real-world applications with expert opinions on the use of various NPWT technologies and advanced wound dressings in the care and treatment of patients with complex wounds. It also provides an update on a number of recent innovations in wound healing that all practising clinicians should find of relevance. Wound healing is an expanding field of health care and much is being achieved by continued innovation that is beneficial for patients.

REFERENCES


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Innovation in medicine requires unique partnerships between academic research, biotech or pharmaceutical companies, and health-care providers. While innovation in medicine has greatly increased over the past 100 years, innovation in wound care has been slow, despite the fact that chronic wounds are a global health challenge where there is a need for technical, process and social innovation. While novel partnerships between research and the health-care system have been created, we still have much to learn about wound care and the wound-healing processes.

Declaration of interest
KH presented as a faculty member during the 2014 International Surgical Wound Forum (ISWF), an annual educational event sponsored by KCI, an Acelity company. He is the guest editor for this educational supplement based on faculty presentations from the ISWF 2014. Acelity provided editorial assistance.

Key words: wound healing, innovation, chronic wounds

Innovation has been described as the successful improvement of techniques, methods, or equipment and embodies a combination or synthesis of knowledge to create new products, processes, or services. It is a multi-staged process whereby organisations advance, compete, and differentiate themselves successfully in the marketplace. The Austrian economist and political scientist, Joseph Schumpeter (1883–1950), argued that innovation comes about through new combinations made by an entrepreneur, resulting in a new product, a new process, the opening of a new market, a new way of organising a business and new sources of supply.1 Today, such advancement involves the capacity to adapt quickly by adopting new innovations such as products, processes, strategies and organisation. Traditionally, the focus has been on new products or processes; but more recently new business models have come into focus, with a particular interest in the way a value is delivered and profits are secured. For example, clinical innovation broadly consists of technological innovation and service through focus and strategic partnerships, process innovation through innovative facilities, and social innovation through meeting the changing needs of culture (Fig 1).

Drivers for innovation for academic, business and clinical sectors are largely based on financial pressures to reduce costs, increase efficiency and to do more with less. Thus, there is increased competition, shorter product life cycles, greater focus on meeting changing customer needs, and stricter regulation. Industry and community needs for sustainable development comprise the increasing demand for accountability and demographic, social, and market changes, the rising customer expectations regarding service and quality, the changing economy, and the greater availability of potentially useful technologies.

Translational science and innovation
Translational research is defined as ‘the acceleration of advances in research towards societal benefit,’ which is the process of taking scientific research from the laboratory to the patients’ bedside.2 The Severnside Alliance for Translational Research (SARTRE) was created in 2009 between the universities of Cardiff and Bristol to combine and accelerate their efforts in translational research.

Keith Harding CBE, FRCP, FRCP, FLSW, Dean of Clinical Innovation, Head of Wound Healing Research Unit (WHRU), School of Medicine, Cardiff University, Cardiff, UK
Email: HardingKG@cardiff.ac.uk

FIG 1. The four pillars of clinical innovation
research and to provide a focal point for interactions with external partners, such as bio-pharmaceutical companies. SARTRE’s aim is to build capacity and align translational research programmes through regular networking meetings and targeted research. SARTRE is supported by the Welsh Office of Research and Development and by the Medical Research Council, with a goal to work to create a leading translational research hub in the south west of England and South Wales.

A real world example of translational science and innovation is the Wound Healing Research Unit (WHRU), first developed as an outpatient wound clinic in 1972 to evaluate the management of surgical wounds. The WHRU, created within the Department of Surgery at the School of Medicine, University of Wales College of Medicine (UWCM), employs individuals from multi-professional backgrounds and provides a unique, comprehensive approach to improve health-care delivery to patients with chronic wounds (such as leg ulcers, pressure sores, diabetic foot ulcers) and patients with problems healing acute/surgical wounds. The WHRU has produced 1574 publications (1975–2013), created and runs the first Masters-level course on wound healing and tissue repair, and secured 45 grants and £15 million funding for teaching. The WHRU has undertaken 198 clinical studies, forged links with 56 companies, and obtained £20 million to undertake research studies.

Recently, the WHRU has collaborated with the Welsh Government to establish an all-Wales approach for wounds called the Welsh Wound Innovation Centre (WWIC) (Fig 2). This new innovative partnership seeks to standardise the approach and economic strategy for the wound healing sector and includes involvement from all
the different stakeholder groups, such as institutions, government, the NHS, company networks and bodies in other countries.

Innovation in medicine and wound management

During 1900–1940, most wounds were treated with gauze dressings, a practice that had not changed since Egyptian times. However, during this time huge advances were being made in medicine, including the introduction of insulin for diabetes (1922) and the discovery of penicillin (1928) with the first antibiotics coming into circulation in 1932. The following three decades (1950–1970) saw the first advancements in wound dressing, such as the development of tulle gras (1950) and the theory of moist wound healing with the first film dressings coming onto the market in 1971. This period also saw a number of medical enhancements with the introduction of prescriptions for depression (1951), diuretics for high blood pressure (1958), the first anti-rejection medicines for organ transplants (1968), and the first biotech products (synthetic human insulin) in 1978. During the 1980s to 2000, a plethora of different wound dressings, including the first antimicrobials, came onto the market, beginning with hydrocolloid dressings in 1983 and the introduction of biological dressings in 1995. During this period, the first monoclonal antibody treatment (1986) and the first treatments for HIV/AIDS (1987) were introduced. However, the 21st century has perhaps seen the greatest advancements, particularly in wound management, with the proliferation and controversy of more active dressings (e.g. antimicrobials and biologicals), which were arguably quickly adopted but rapidly misused. The development of many copycat advanced products and the launch of the first wound diagnostics also occurred. Yet, this era has seen little new innovation.

Wound care outcomes and costs

Wound care is becoming an increasing complex clinical practice, especially in light of a growing need for innovative wound care treatments. In England, wound prevalence and cost data were collected to estimate the cost of wound care. A total of 2300 wounds (1.44 per patient) were investigated in 1644 patients. The majority (74.1%) of these wounds were treated in the community by district nurses, 21.2% were treated in hospital, and 4.8% were treated in residential or hospice care. More than one in four hospital inpatients (26.8%) had a wound. The median duration was 6–12 weeks; however, 24% had their wound for 6 months or more. Additionally, almost 16% of patients had remained unhealed for a year or longer and one in eight wounds (12.8%) were reported as showing signs of infection. The estimated cost of wound care was £15 million to £18 million (£2.5 million to £3.1 million per 100,000 population) with the equivalent of 88.5 full-time nurses and up to 87 hospital beds. In this study, the most important determinant of cost was wound complications. Thus, effective and timely diagnosis, appropriate treatment, and active measures to prevent complications and wound-related hospitalisation are essential.

The burden of chronic wounds in the USA is similarly complex and costly. Sen et al. demonstrated that chronic wounds were estimated to affect 6.5 million patients. They calculated that an excess of US$25 billion is spent annually on treatment of chronic wounds, and the burden is rapidly growing due to increasing health-care costs, an ageing population, and a sharp rise in the incidence of diabetes and obesity worldwide. A marketing analysis reported that the annual wound care products market in the USA was projected to reach $15.3 billion by 2010. Forty million inpatient surgical procedures were performed in the USA in 2000, followed closely by 31.5 million outpatient surgeries. An additional burden of wound healing has been shown to be skin scarring, costing $12 billion annually. The immense economic and social impact of wounds calls for a higher level of attention and resources to understand biological mechanisms underlying cutaneous wound complications. In a 2012 study by Fife et al., electronic health records from 59 USA hospital-based outpatient wound centres in 18 states, for 5240 patients with 7099 wounds, were analysed for outcomes, patient and wound variables, and costs for facility and physician fees and procedures. The mean patient age was 61.7 years, 52.3% were male, 73.1% were Caucasian, and 52.6% were Medicare beneficiaries. The average wound surface area was 19.5cm². The mean number of serious co-morbid conditions per patient was 1.8, with the most common being diabetes (46.8%), obesity or being overweight (71.3%), and having cardiovascular or peripheral vascular disease (51.3%). During their episode of wound management or within four weeks of the last visit, 1.6% of patients died. In total, 65.8% of wounds healed; the average time to heal was 15 weeks with 10% of wounds taking 33 weeks or more to heal. Of wounds that healed, 50.8% did so with only the use of moist wound care and
Chronic cutaneous wounds also represent a major health-care burden in China. However, limited information exists regarding the epidemiologic changes associated with recent social and economic development. In a cross-sectional survey of 2513 patients who had undergone treatment of chronic cutaneous wounds from 17 hospitals between 2007 and 2008, wound prevalence was 1.7%. The patients’ ages ranged from 18 days to 96 years (median: 58 years). The leading causes of chronic cutaneous wounds were diabetes (31.3% men, 35.3% women) and trauma (26.4% men, 19.2% women). Manual workers (38.5% men, 29.3% women) and retirees (27.9% men, 23.5% women) accounted for over half the chronic cutaneous wound patients. Only 22.4% were treated with modern dressings or other novel technologies; however, 77.8% of patients received antibiotics. Treatment was paid for by patients (42.3%), social medical insurance (25.0%), commercial medical insurance (4.8%) and free medical care (27.9%). The large population and considerable financial burden mean that serious attention should be paid to the early detection, prevention and diagnosis of these wounds.

**Global estimates of the prevalence of diabetes**

Comorbidities often alter wound healing, resulting in increased risk for development of chronic non-healing wounds. As such, it is necessary to identify the prevalence of these comorbidities. Studies from 91 countries were evaluated to calculate age and sex-specific diabetes prevalence, which were applied to national population estimates, to determine national diabetes prevalence for all 216 countries for 2010 and 2030. The world prevalence of diabetes among adults (aged 20–79 years) was 6.4%; diabetes was calculated to be affecting 285 million adults in 2010 and predicted to increase to 7.7% and 439 million adults by 2030. Based on these data, the researchers predicted that between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries. These predictions indicate a growing burden of diabetes, particularly in developing countries.

The cost of wound care to the National Health Service (NHS) in the UK has been estimated between £2.3 billion and £3.1 billion a year. The economic burden of diabetic foot ulcer (DFU) complications in the UK accounts for 15–25% of the total health-care resources for diabetes. It is estimated that with basic diabetes management and care, up to 80% of all diabetic foot amputations can be prevented, although rates of recurrence of DFUs have been estimated to be greater than 50% over three years.

**Prevalence, annual incidence and cost of leg and pressure ulcers in Europe**

A systematic review of international prevalence studies of lower-limb ulceration in adult populations in Europe identified 22 studies. In the UK, it has been estimated that 70,000–190,000 patients with an open leg ulcer are receiving treatment at any time. In Europe, 84 million people over the age of 65 had leg ulcers in 2008. The prevalence of leg ulcers in adults was 0.12–0.32% (490,000–1.3 million), whereas the incidence of venous leg ulcers in adults aged over 65 was 1.16% (980,000). The cost per episode of wound care was estimated to be €2500–10,800 (£6650) with an indicative annual cost of €6.5 billion (for venous leg ulcers only).

Pressure ulcers (PUs) are a relatively common risk among hospital inpatients and residents in long-term care whose mobility is restricted. There are limited data on the incidence of hospital-acquired PUs in European hospitals, but point prevalence studies are more common. These studies generally suggest that between one in four and one in five acute hospital inpatients has a PU at any time. Few studies have quantified the costs associated with PUs in European hospitals. The cost of treating and preventing pressure ulceration in the UK across all care settings was estimated to be between £1.4 billion and £2.1 billion (£2.2–3.2 billion) in 2000, which was approximately 3–4% of the total health-care spend in that year.

**Prevalence of surgical site infection (SSI) in Europe**

Surgical site infections (SSIs) are the cause of 20% of all of health-care-associated infections (HCAs) and at least 5% of patients undergoing a surgical procedure develop a SSI; the majority are preventable, yet one third of all postoperative deaths are attributable, at least in part, to SSIs.

The European project, Hospitals in Europe Link for Infection Control through Surveillance (HELICS), was designed to reduce rates of nosocomial infection by sharing surveillance data collected in accordance with an agreed protocol. In 2004, 111,361 surgical procedures in the participating countries gave rise to 3365 SSIs, with a cumulative incidence of 3.02% within 30 days.
In England, national surveillance covering 149,745 surgical procedures (performed between 1997 and 2003) identified 5457 surgical infections (3.6% overall). Patients with surgical wound infection accounted for 3–4% of surgical procedures (300–400 patients). The attributable length of hospital stay amounted to 11 days per patient (3300–4400 bed days) and the attributable cost per episode was £5800 (£1.74–2.32 million).\(^9\) Posnett and Franks\(^9\) further stated that a typical hospital carrying out 13,500 at-risk operations annually can expect 525–650 SSIs, at a cost of £2 million and 5200 excess bed-days, with an estimated length of hospital stay increasing to nine days.\(^9\) Reducing the rate of infection by just 10% could release £200,000 and more than 500 bed-days.\(^9\)

**Underlying defects associated with wound healing—potential targets for innovation**

Optimal healing of a cutaneous wound requires a well-orchestrated integration of the complex biological and molecular events of cell migration and proliferation, and of extracellular matrix deposition and remodeling. Cellular responses to inflammatory mediators, growth factors, and cytokines, and to mechanical forces, must be appropriate and precise. However, this orderly progression of the healing process is impaired in chronic wounds. Several pathogenic abnormalities contribute to failure to heal (Fig 3). Yet, despite these obstacles, there is increasing cause for optimism in the treatment of chronic wounds. Enhanced understanding and correction of pathogenic factors, combined with stricter adherence to standards of care and with technological breakthroughs in biological agents, are giving new hope of tackling the problem of impaired healing.

**Management of wound healing—a potential target for innovation**

Impaired wound healing is the main factor in the presence of chronic wounds. Removal of devitalised tissue or debris, treatment of inflammation and/or infection, maintaining wound moisture balance, and the preparation of wound bed edges are the main components of wound management and can serve as new targets for innovation.\(^17\–19\) As such, the effective use of dressings and devices to manage the wound bed and jump-start wound healing are essential to ensure the optimal care of ulceration. However, although there is a wealth of literature on these subjects, there is less conclusive information, mainly due to the use of a variety of research designs and numerous ethical issues that impede investigation. Thus, many Cochrane reviews conclude that there is insufficient or limited evidence to direct practice. More recently, alternative outcomes other than healing that may improve a persons’ health-related quality of life (HRQoL), such as pain relief, odour control, and exudate management, are being considered.

**Review of current wound care dressings**

The most recent systematic review by Dunville et al.\(^20\) looked specifically at dressings for healing DFUs. Fifteen studies were included in the review and all reported the number of ulcers healed. There was evidence that hydrogel dressings were associated with significantly higher odds of ulcer healing than basic wound contact dressings (OR 3.10 [95% CI 1.51, 5.50]) and that foam dressings were also associated with higher odds of ulcer healing compared with basic wound contact dressings (OR 4.01 [95% CI 1.07, 10.7]).\(^20\) In the remaining five single study comparisons, there was no evidence of any difference between one dressing and another and, in general, estimates had large uncertainty due to low sample sizes.

**Medical devices for wound healing**

There are various treatment options that are currently utilised to aid wound healing, such as wound dressings, hyperbaric oxygen therapy, topical oxygen delivery, light therapy, warm-up therapies, electrical stimulation, and ultrasound, with various levels of evidence. The device that has gained the most attention is negative pressure wound therapy (NPWT). NPWT uses con-
trolled subatmospheric pressure to assist with wound healing. The basic modes of action include removal of infectious materials, promotion of perfusion and granulation tissue formation, and reduction of oedema. It was not until the early 1980s that research began to investigate the healing capabilities of wound drains and gauze under adhesive film dressing evacuated to -60 to -80mmHg. The economic impact of NPWT requires further evaluation to justify the increased cost of treatment against the overall benefit of shorter healing times.

Cochrane reviews of NPWT have suggested that there is insufficient quality research evidence for NPWT because the methodological quality of the trials is low, with high susceptibility to bias. Randomised clinical trials support the use of NPWT in certain wound types, but there are still some gaps between evidence-based data and excellent clinical results. Despite lack of data, overall clinical experience has been positive, and NPWT is in widespread use with its role in wound care expanding worldwide. Qualitative data have reported that NPWT can create an environment that promotes wound healing, potentially reducing the frequency of dressing change and hospital stay. Further research is needed to establish the relationship between negative pressure, perfusion, and the optimal pressure for wound healing. Where dramatic improvements in outcome have been observed (e.g. open abdomen), there are clearly ethical challenges in running comparative studies using less-beneficial treatments. Prospective, multicentre studies with a common protocol should be performed and are thus needed. In 2008 the first international consensus, best practice document on NPWT was produced by the World Union of Wound Healing Societies where it stated that NPWT can have a positive impact on a patient’s quality of life.

More recent studies have reported positive results for NPWT in combination with automated intermittent instillation of a topical wound solution with a dwell time (NPWTi-d). Adjunctive NPWTi-d, in addition to debridement and appropriate systemic antibiotics, has been successfully used for extremity and trunk wounds, acutely infected wounds, chronic lower leg and foot wounds, a variety of complex wounds (e.g., open fractures, pressure ulcers, and non-healing post-operative wounds), and open, contaminated, or infected wounds. In addition to the benefits of NPWT, such as drawing wound edges together, promoting perfusion and granulation tissue formation, and reducing oedema, the instillation of topical wound solutions cleanses the wound bed and allows for the removal of infectious materials, devitalised tissue, and slough.

**Skin grafts to assist wound closure**

Traditional autografts are split-thickness and full-thickness skin grafts and have long been used to achieve successful wound closure. However, the potential downsides of these grafts include cost, pain, difficult procedure, and donor-site complications. Other skin graft options include allografts, use of biologics or skin substitutes, and epidermal grafts. Interestingly, epidermal skin grafts are a viable alternative to traditional autografts when only the epidermal skin layer is needed. The harvesting procedure, which can be performed in an outpatient setting, results in minimal donor-site complications and does not require donor-site anaesthesia.

**Health-related quality of life (HRQoL)**

There is increasing recognition that HRQoL is a valuable outcome measure in wound care and should be included in reviews of new and existing therapies to ensure that importance is placed on the impact of health services on the patient experience. Providing health care within a socially supportive environment can increase patient well-being, contribute to positive health experiences, and may have a profound effect on how services are provided. The Cardiff Wound Impact Schedule (CWIS) was developed by the WHRU to address the disease-specific issues related to chronic wounds of the lower limb. The CWIS is able to discriminate between those with healed ulcers and active ulcers (p<0.01), has high internal consistency and the ability to discriminate between health states with good reproducibility. CWIS allows clinicians to identify items of patient concern, which can then be used to negotiate options of care most suited to individual patients.

**Conclusions**

Wounds offer many opportunities for innovation. Chronic wounds are a global health challenge where there is a need for technical, process, and social innovation.

The therapeutic armory currently consists of assessment and diagnostic tools, dressings, devices, drugs, surgery, and biologically based therapy with a robust evidence base. Academic and clinical credibility needs enhancing, and there is still much to learn about psychological processes and human behaviour.
### REFERENCES


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Complex wounds pose a considerable burden to patients and the health-care system. The development of negative pressure wound therapy (NPWT) has revolutionised the treatment of these wounds. NPWT helps create a favourable wound healing environment by removing infectious material, decreasing oedema and promoting perfusion and granulation tissue formation. Additionally, NPWT has been reported to help reduce time to wound closure and length of hospital stay. Modifications of this foundation of wound care have added intermittent instillation with a dwell time to NPWT (NPWT-i-d). This new system offers more comprehensive wound care through automated wound irrigation, allowing more control over the wound environment and the opportunity to deliver topical wound solutions directly to the affected tissues. A comparison between the two therapies, NPWT and NPWT-i-d, is described, and two real-world applications of NPWT-i-d are presented.

Declaration of interest
TW presented as a faculty member during the 2014 International Surgical Wound Forum (ISWF), an annual educational event sponsored by KCI, an Acelity company, held in 2014 in Edinburgh, Scotland. This article is part of a KCI-funded educational supplement based on 2014 ISWF faculty presentations about wound-care strategies using negative pressure wound therapy. Acelity assisted with the editorial review of the manuscript. TW also has a consultant agreement with KCI, an Acelity company.

Key words: negative pressure wound therapy with instillation, wound healing, dwell time, instillation therapy

The widespread use of negative pressure wound therapy (NPWT) has revolutionised the treatment of complex wounds. It helps create a favourable environment for wound healing through stimulating granulation tissue formation and perfusion, reduction in oedema, and removal of exudate and infectious material.1,2 NPWT effects may be due to the concept of macrostrain (contraction of the wound caused by contraction of the foam), and microstrain (stretch and straining of the cellular elements pulled into the foam), which has been reported to promote cellular proliferation.3-5 This review will focus on one form of NPWT (V.A.C. Therapy; KCI, an Acelity company, San Antonio, TX, USA) and its latest technology.

The systems
NPWT is a system composed of a hydrophobic open-cell reticulated foam dressing that is placed into the wound and then covered by a semi-occlusive drape. A hole cut in the drape allows attachment of suction tubing to the dressing. The other end of the tubing is connected to a microprocessor-controlled pump that creates negative pressure in a continuous or intermittent fashion. The tubing has pressure-sensing channels that allow for measurement of pressure at the wound surface to help with pressure regulation.

The latest form of NPWT technology, the V.A.C. Ultra Negative Pressure Wound Therapy System (KCI, an Acelity Company, San Antonio, TX, USA), is an integrated wound management system that can be used for both traditional...
NPWT and NPWT with automated intermittent instillation of topical wound solutions with a dwell time (NPWTi-d; V.A.C. VeraFlo Therapy, KCI, an Acelity company). NPWTi-d helps cleanse the wound by loosening contaminants, followed by the subsequent removal of these materials during the negative pressure phase. A significant improvement in this system is that the topical solution is delivered to the wound as a preset volume, compared with the gravity feed seen with the original system. A ‘fill assist tool’ also allows a clinician to determine visually an appropriate volume of topical wound solution to be instilled for the specific wound dressing.

Continuous versus intermittent instillation systems
In another commercially available instillation system (Svedman Wound Treatment System; Innovative Therapies Inc., Hunt Valley, MD), the topical wound solution is instilled while the negative pressure is being applied (continuous instillation). With this type of system, when negative pressure is applied, tunnels may remain collapsed and areas of undermining and the edges of crevices may be pulled together; thus, these areas inside the wound would be inaccessible to the instilled solution. Conversely, during an intermittent system, when negative pressure is paused during the instillation and dwell phases, the inside of tunnels, crevices and areas of undermining are allowed to open up and are accessible to the instilled solution. In a bench top agar-based anatomic wound model, the solution was demonstrated to access areas of tunneling in an intermittent instillation system (i.e. three 10-minute dwell times) while being inaccessible to the instilled solution. Conversely, during an intermittent system, when negative pressure is halted and areas of undermining and the edges of crevices may be pulled together; thus, these areas inside the wound would be inaccessible to the instilled solution.

NPWTi-d and non-infected wounds
There is in vitro evidence that instillation of normal saline alone may be more effective than traditional NPWT. In a non-infected full-thickness porcine wound model, instillation of normal saline every 6 hours resulted in wound fill with higher quality granulation tissue composed of increased collagen when compared with NPWT alone. The 43% increase in granulation tissue thickness after 7 days was statistically significant (p<0.05). It should be noted that the increased granulation tissue seen with NPWTi-d (an intermittent therapy with a dwell time) was subsequently shown in this model to be greater than simply using an intermittent therapy alone.

The findings from the porcine model have been supported by a recent human clinical study in which NPWTi-d with normal saline was used in 131 wounds of various aetiologies seen in 131 patients at three different centres in France. Saline was instilled for 20 or 30 seconds with a dwell time of 10 minutes, followed by -125mmHg continuous negative pressure for 4–12 hours. The results of this study were a 98% closure rate after an average of 13 days of treatment. The investigators also observed increased granulation tissue formation and reduced wound volume.

NPWTi-d and other wounds
A list of wounds that are appropriate for adjunctive NPWTi-d has been previously published. Typical wound types include: wounds with invasive infection, extensive contamination, stalled wounds, diabetic foot ulcers, and wounds with a very viscous exudate (Case study 1). NPWTi-d should not be used as the sole therapy for these wounds; it should be combined with a comprehensive programme that includes debridelements, if indicated, and when appropriate, use of systemic antibiotics.

NPWTi-d should not be used if topical solution will be instilled into the abdominal or thoracic cavities. Solutions should not be used if they will degrade the foam or other parts of the system. Since NPWTi-d is an intermittent mode, it should not be used in wounds where continuous negative pressure therapy is required, such as a bolster for skin grafts.

Solutions
In published guidelines, a greater than 80% consensus for three solutions was reached by an international 13-member group of NPWTi-d experts. Solutions that reached more than 80% agreement were Lavasept (polyhexanide 0.04%), Prontosan Wound Irrigation Solution (polyhexanide 0.1% + Betaine; B Braun, Inc., Bethlehem, PA, USA) and Microcyn/Dermacyn (hypochlorous acid; Oculus Innovative Sciences, Petaluma, CA, USA). However, many other solutions, such as saline and Dakin’s solution (quarter strength), have been reported to have been successfully used with the NPWTi-d system by physicians. Dilute lidocaine used in an NPWTi-d system has been demonstrated to be extremely effective in treating the pain that may be associated with NPWT. A greater than 70% decrease in pain medication requirements was seen by instilling very dilute lidocaine (approximately 5% of the maximal recommended dose of topical lidocaine) intermittently in an NPWTi-d system.
**Foams**

New reticulated open-cell foams (ROCF) have been developed specifically for use with NPWTi-d. The V.A.C. VeraFlo Dressing (ROCF-V; KCI, an Acelity company, San Antonio, TX) is a less hydrophobic dressing that has been demonstrated to have enhanced fluid distribution properties in a bench top model. The ROCF-V is also stronger than the standard ROCF dressing (V.A.C. GranuFoam Dressing; KCI, an Acelity company, San Antonio, TX, USA) under both tensile and tear loading. The use of the ROCF-V dressing has been shown to provide better granulation tissue formation in a non-infected porcine wound model after 7 days of NPWTi-d with saline compared with standard ROCF with NPWT. Additionally, the V.A.C. VeraFlo Cleanse Dressing (ROCF-VC; KCI, an Acelity company, San Antonio, TX, USA) is available with NPWTi-d and is composed of denser material than the ROCF-V dressing with a higher tensile strength. Due to its tubular shape and design, the ROCF-VC dressing is easily configured for a variety of wound geometries.

**Tubing sets**

The V.A.C. VeraFlo Therapy System has two options for the type of tubing setup that can be used in conjunction with the NPWTi-d (V.A.C. VeraT.R.A.C Pad or V.A.C. VeraT.R.A.C. Duo Tube Set, Fig 1). The new tubing setup incorporates both the instillation and negative pressure tubing connecting them so the fluid is delivered and removed through a single pad placed on the foam in the wound. If desired, the option does still remain to use a separate pad connecting the irrigation tubing to the wound along with separate suction tubing connecting the wound to the pump. The V.A.C. VeraT.R.A.C. Duo Tube Set may be more appropriate for larger or vertical wounds (Case study 2).

**Cost analysis**

In a pilot study, patients (n=15) receiving adjunctive NPWTi-d with silver nitrate instillation, along with debridement and systemic antibiotics, were compared with a retrospective control group of patients (n=15) who received standard moist wound care to treat infected wounds. The results showed there was a smaller number of treatment days, less time to clear a clinical infection, less time to wound closure, and less total days in the hospital for those patients who received NPWTi-d. All of these results were statistically significant (p<0.001). A retrospective study of 142 patients by Kim et al.

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**FIG 1** Tubing set options for use with NPWTi-d. V.A.C. VeraT.R.A.C Pad (a) and the V.A.C. VeraT.R.A.C. Duo Tube set (b) are shown.
Case studies

Case study 1

A 56-year-old man presented with a three-day history of abdominal pain. Work-up was consistent with a perforated viscus with free intraperitoneal air (Fig 2a). At the time of surgery, he was found to have a perforated duodenal ulcer, with the nasogastric (NG) tube coming out of the perforation (Fig 2b). The patient underwent surgery to appropriately treat his perforation. Postoperatively, he had a wound with a very viscous exudate not able to be removed completely by traditional NPWT (Fig 2c). The patient was switched to an NPWT-d system with normal saline instillation (10-minute soak time followed by 4 hours of NPWT) (Fig 2d). His wound quickly improved in appearance and became filled with healthy granulation tissue (Fig 2e). His wound went on to heal completely and was seen to be fully healthy and healed at an office visit 6 months later (Fig 2f).

FIG 2 Case study 1 wound presentation, treatment, and healing. Abdominal CAT scan showing free intraperitoneal air (a). Perforated duodenal ulcer with NG tube coming out of perforation (b). Postoperative wound with very viscous exudate (c). NPWT-d dressing in place (d). Improved wound after treatment with NPWT-d (e). Healed wound 6 months later (f).
Case study 2
A 76-year-old woman underwent elective surgery to repair a recurrent ventral hernia. The hernia repair was reinforced with an onlay polypropylene mesh. She was discharged from the hospital on the second postoperative day. The patient was readmitted on postoperative day 13 with hypotension, dehydration, and an elevated white blood count (14,600). An abdominal CT scan showed an air-fluid collection in the abdominal wall (Fig 3a). The patient originally underwent percutaneous drainage by an interventional radiologist, followed by an open operative incision and drainage with removal of the mesh. Cultures grew *Enterobacter cloacae*, *Staphylococcus epidermidis*, *Bacteroids fragilis*, and *Clostridia perfringens*. A bowel perforation or enterocutaneous fistula could not be demonstrated clinically. After the open incision and drainage (Fig 3b), ROCF-VC was placed in the wound (Fig 3c) before partial wound closure (Fig 3d). A duo irrigation/suction pad set up was used (Fig 3e). Microcyn was instilled with a soak time of 10 minutes followed by NPWT for 4 hours. The patient improved quickly clinically. The wound was clean at the first dressing change where the ROCF-VC was replaced in the wound (Fig 3f-h). On postoperative day 10, the wound had improved and was closed enough that placement of Penrose drains alone could be done (Fig 3i). The wound went on to heal uneventfully when seen in an outpatient visit 4 weeks postoperative (Fig 3j).

Future
Large controlled trials and continued experience with NPWTi-d on various wound types may help provide the answers to its most appropriate use and the preferred settings of this system. The real future of NPWTi-d may be the directed instillation of specific topical wound solutions to facilitate the major phases of wound healing.
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INCISIONAL NEGATIVE PRESSURE WOUND THERAPY FOR HIGH-RISK WOUNDS

With an ageing population and a growing number of people with obesity and/or undergoing advanced cancer therapies, there is an increasing risk of surgical site complications including surgical site infections (SSIs). Postoperative shifting of large mobilised tissue flaps, such as in abdominoplasties, remains a dreaded complication, particularly following massive weight loss. Besides negative implications for the patient, surgical site complications result in an economic burden due to prolonged and repeated wound treatments. Preventative tools to reduce SSIs are needed. In selected patients at high risk of SSI and/or wound breakdown, use of incisional NPWT has been shown to actively manage clean, closed surgical incisions. This article contains a review of scientific and clinical research relevant to incisional NPWT use over surgical incisions, with particular emphasis on the common problem of wound breakdown and SSI following body-contouring surgery in post-bariatric patients. Although there are a growing number of studies describing use of incisional NPWT in a variety of applications, including vascular, cardiac and orthopaedic, a literature search revealed few studies regarding incisional NPWT use post body-contouring surgery. In a clinical study of seroma formation, less seroma and haematoma formation was reported in post-bariatric patients who received incisional NPWT, versus the control, following body-contouring surgery. In another study of widely applied external NPWT wound dressings over the ventral and lateral trunk following post-bariatric abdominal dermolipectomy, results showed a significant reduction in exudate formation, earlier drain removal, and decreased length of hospitalisation, compared with conventional treatment. Additional controlled studies are needed to validate the clinical impact of incisional NPWT following body-contouring surgery, and to determine proper recommendations for its use.

Declaration of interest
REH served as a scientific advisor to KCI, an Acelity company, and presented as a faculty member during the 2014 International Surgical Wound Forum (ISWF), an annual educational event sponsored by KCI, an Acelity company. This article is part of a KCI-funded educational supplement based on 2014 ISWF faculty presentations. Acelity provided editorial assistance.

Key words: surgical incision management, negative pressure wound therapy, closed incision, topical negative pressure therapy, skin circulation, Prevena Therapy
Despite advances in surgical techniques, greater optimisation of systemic factors that may compromise wound healing, and systemic antibiotic prophylaxis, the problems of decreased microcirculation in wounded tissue and the formation of seroma in large wounds have still not been solved satisfactorily. Given the well-established positive clinical effects of negative pressure wound therapy (NPWT) on open and complicated wounds, the application of this technique over closed wound incisions has elicited interest in the scientific community. A growing body of evidence has reported positive benefits of NPWT over closed, clean incisions, particularly in high-risk patients with comorbidities, who are more likely to develop surgical site complications.

One unsolved surgical problem is the postoperative shifting of large mobilised tissue flaps, such as in abdominoplasties, especially when previous incisions have been performed in the abdominal area. Seroma or haematoma formation as well as longstanding pseudobursa formations have been frequently addressed as sequelae following body-contouring surgery. The complication rate of this surgical procedure has been reported to be even higher following massive weight loss. Complications, such as wound necrosis or delayed secondary healing, are also high following abdominal dermolipectomy after massive weight loss. In this context, ischaemia or inadequate micro-perfusion are known to be triggers of wound healing complications. Our group previously showed that the part of the abdominal fat typically resected during dermolipectomy has the lowest oxygen saturation ($\text{SaO}_2$) before surgery, and that previously well-oxygenated parts in the median line of the abdominal fat undergo a significant decrease in $\text{SaO}_2$ on mobilisation and subsequent suturing.

Based on positive experiences our group has observed at our clinic with conventional topical negative pressure wound therapy (NPWT) in chronic and acute wounds, we theorised that the physiological principles behind the success of NPWT may be applicable over closed wound incisions in order to protect the incision from external infectious sources. We have subsequently employed the use of NPWT over incisions of multiple wound types, including abdominoplasty incisions post bariatric surgery. Applying NPWT to a closed incision has been termed incisional NPWT. Dedicated surgical incision management systems (SIM) have been developed to help actively manage surgical incisions, and are increasingly commercially available worldwide. For the purposes of this paper, SIM refers to incisional NPWT as delivered by the Prevena Incisional Management System (KCI, an Acelity company, San Antonio, TX, USA).

In addition to clinical studies, we have performed scientific studies to determine the influence of NPWT on incisions as well as on underlying skin. Since limited data exist on the effect of NPWT on closed skin microcirculation and oxygen saturation, as well as haemoglobin content in the post-capillary phase, our scientific studies have focused on circulatory parameters to elucidate the physiological effects of incisional NPWT and to assure that no harmful forces are exerted on a closed surgical incision. The purpose of this article is to review scientific and clinical research relevant to SIM and incisional NPWT use over closed incisions and to highlight these findings with regard to the common problem of wound breakdown and SSI following body-contouring surgery in patients who have experienced weight loss. Case studies illustrating the use of incisional NPWT and SIM are also included.

**Methodology for literature search**

We conducted a PubMed search using the key terms ‘negative pressure incision management’, ‘negative pressure wound therapy’, ‘closed incision’, ‘topical negative pressure therapy’ and ‘skin circulation’. Relevant publications were screened and selected for review and comparison within this article.

**Mechanisms of action supported by scientific studies**

An increased understanding of the science behind incisional NPWT and its effects on wound and periwound tissue is essential to expand the use of incisional NPWT. Well-described mechanisms of action of incisional NPWT include protection of the incision site from external infectious sources and help in holding incision edges together. Incisional NPWT also removes fluids and infectious materials from the surgical site, which is especially important in critical anatomical locations. Other mechanisms of action, particularly at the cellular and molecular level, are less understood and the subject of ongoing research. The following is a brief description of relevant scientific research that has been performed on incisional NPWT.

**Microcirculatory blood flow and oxygen saturation**

Investigators at our facility have studied the mechanisms of influencing micro-perfusion...
under an incisional NPWT system in healthy human subjects. These initial tests were meant to help determine whether exerting NPWT on incisions and healthy skin could adversely affect the healing process. We applied the NPWT system to healthy subjects to measure skin circulation under NPWT using the O2C (‘oxygen to see’) device (LEA Medizintechnik GmbH, Giessen, Germany) with white light spectroscopy and combined laser Doppler flowmetry. An incisional NPWT dressing was applied over an O2C probe on abdominal skin (n=20), and then on the inner thigh (n=15). Results showed an increase in SaO2 and blood flow at all time intervals, compared with baseline on the abdomen as well as the thigh. However, these results are preliminary and have not yet been submitted for publication.

Findings of increased microcirculation and improved oxygen saturation levels may well explain why NPWT over closed incisions appears to improve wound healing. In an evaluation of peristernal perfusion after cardiac surgery via median sternotomy, Atkins et al. determined that incisional NPWT increased perfusion relative to controls (standard dressings) and compensated for reduced perfusion rendered by mammary artery harvesting in high-risk patients. Compared with standard care-treated incisions, SIM-treated incisions had significantly improved mechanical properties (strain energy density, peak strain) and a narrower scar/healed area in the deep dermis on day 40.

The clinical impact on seroma production after abdominoplasty in a small post-bariatric patient population has also been studied. Patients who received a wide NPWT dressing (n=13) after a dermolipectomy showed a significantly (p<0.001) lower rate of postoperative seroma drainage when compared with a control group (n=10) with conventional pressure garment dressings. In these patients, widely applied external NPWT wound dressings over the ventral and lateral trunk following post-bariatric abdominal dermolipectomy led to a significant reduction in exudate formation, earlier drain removal and thus decreased length of hospitalisation.

Review of clinical literature
Various papers from different fields have been published that highlight potential physiological and theoretical advantages as well as positive

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**FIG 1** Cross-sectional depiction of an incision closed with sutures without incisional NPWT applied (a). Application of SIM has been shown to decrease lateral tissue tension and increase incisional apposition (b). (Reprinted with permission from KCI, an Acelity company)
clinical findings of use of incisional NPWT in critically ill patients. Stannard et al. performed a prospective, randomised controlled trial of incisional negative pressure therapy to manage surgical incisions following blunt trauma. They determined the relative risk of developing an infection to be 1.9 times higher in control patients (n=119 with 122 fractures) than in patients treated with NPWT (n=130 with 141 fractures) (95% confidence interval: 1.03-3.55). A decreased incidence of wound dehiscence and total infections after high-risk fractures was reported in patients who received NPWT over closed surgical incisions. Stannard et al. concluded that NPWT should be considered for high-risk wounds after severe skeletal trauma. Case series have also demonstrated successful use of incisional NPWT after surgery on lower extremity and acetabular fractures, ventral hernia repair, and a high-grade soft tissue injury. Other studies note favourable outcomes with SIM over vascular surgery incisions and with incisional NPWT in reducing seroma or haematoma formation at flap donor sites.

In a prospective case-control study of eight vascular surgery patients who underwent vascular bypass procedures, where both femoral areas were incised to gain access to the femoral arteries, SIM was placed over closed incisions of one femoral area while a standard postoperative wound dressing was placed over the contralateral femoral area incision. No complications occurred in the SIM wounds, and three significant complications occurred in the control wounds. In this study, preliminary data suggested a potential reduction in wound complications using SIM over closed incisions, without an increase in haemorrhage, in high-risk patients with severe comorbidities undergoing vascular surgery.

Pachowsky et al. reported a significant reduction of seroma formation in SIM-treated closed surgical incisions versus standard dressing following total hip arthroplasty. The development of postoperative seromas is frequently encountered following total hip arthroplasty due to the large wound area. In their randomised 19-patient study, the authors observed a statistically significant difference (p=0.021) in average size of seroma formation in control wounds (n=10) of 5.08ml versus 1.97ml in the NPWT group (n=9) on day 10. The authors concluded that SIM over closed incisions decreased development of postoperative seromas in the wound and improved wound healing.

Similarly, in a porcine study evaluating the effect of closed incision management with NPWT on haematoma/seroma formation, application of incisional NPWT significantly decreased haematoma/seroma levels without fluid collection in the canister, which could be explained by increased lymph clearance that was detected during the study.

Following a retrospective chart review, Schmedes et al. reported their experience with NPWT applied to massive flap donor sites after latissimus dorsi or scapular free flap harvest. Major donor site complications occurred in 12% (n=5) of the 42 patients who received only conventional care over the donor site incision, as compared with a 6% (n=3) complication rate among 52 patients in the NPWT-treated incision group. The authors concluded that NPWT could be a safe technique in the management of massive scapular and latissimus dorsi free flap harvest sites, and that it could help to reduce associated major donor wound complications in free flap surgery.

Mark et al. retrospectively evaluated the efficacy of incisional negative pressure wound therapy when placed over clean, closed incisions following caesarean section in 63 obese (body mass index (BMI)>45kg/m²) patients. Five complications were reported in the control group (10.4%; 5/48) versus zero complications in the NPWT group (0%; 0/21) (p=0.15). Although the results were not significant, the authors suggested a potential decrease in wound complications in morbidly obese women treated with incisional NPWT following caesarean section.

In a prospective, randomised controlled clinical trial comparing incisional NPWT with standard dry dressings over surgical incisions in high-risk patients with multiple comorbidities, Masden et al. evaluated incisions in 81 patients for postoperative infection and dehiscence. A total of 6.8% (3/44) of the NPWT group and 13.5% (5/37) of the dry dressing group developed wound infection, but this was not statistically significant (p=0.046). Overall, 35% of the dry dressing group and 40% of the NPWT group had a wound infection, dehiscence, or both. These high rates of infection and/or dehiscence are similar to reported findings with wide NPWT application to the ventral trunk in post-bariatric patients undergoing dermolipectomy, whereby the risk for complications can be as high as...
41%.17,18 However, in the post-bariatric patient population that received incisional NPWT following abdominoplasty or dermolipectomy, incisional NPWT led to a significant reduction in exudate formation, enabled early drain removal, and decreased length of hospitalisation compared with the conventionally treated group.24

Case studies
The following are case descriptions of two patients at high risk of surgical site complications who received incisional NPWT or SIM over closed incisions following a surgical procedure for massive weight loss at our institution. Adult patients with clean, closed incisions that were deemed above-average risk for developing wound dehiscence or SSI received incisional NPWT or SIM over the incision post-abdominoplasty or dermolipectomy. Initially, we developed a customised wide abdominal dressing, with a skin-protecting drape to separate the polyurethane (PU) foam from skin contact, in order to fit properly over a large undermined surface. The idea was to exert local pressure to the subcutaneous wound area underneath the mobilised skin flaps in order to occlude dead space and at the same time approximate and reduce tension on the wound edges. When customisable dressings were commercially available with a skin-protecting textile interface between the foam and the underlying incision (Prevena Customizable Dressing, KCI, an Acclity company, San Antonio, TX, USA), we then applied either conventional NPWT (V.A.C. Therapy, KCI, an Acelity company, San Antonio, TX, USA) or SIM using the customisable dressing at -125mmHg for 5 days postoperatively. Drains were placed as usual and were inserted outside the incision and the wide incisional NPWT dressing, if applicable.

Case study 1
A multi-morbid 59-year-old female patient with coagulopathy and an increased risk for surgical site complications underwent abdominoplasty following significant weight loss (Fig 2a). The incision was primarily closed with resorbable intracutaneous sutures (Fig 2b). An adhesive drape was applied over the whole anterior trunk to protect skin from contact with the PU foam of the NPWT system, and a sterile compress was applied to protect umbilicus beneath the drape (Fig 2c). A wide PU NPWT dressing was applied over the anterior hemi-trunk to exert compression over all undermined wound surfaces and contracture of the incision edges beneath the dressing. Continuous negative pressure of -125mmHg was applied for 5 days (Fig 2d). The incision healed uneventfully. Fig 2e shows a good quality scar that seems premature at six weeks following surgery and incisional NPWT placement over abdominoplasty area.

Case study 2
A 53-year-old man with redundant skin following massive weight loss required mastectomy and reduction for treatment of post-bariatric gynecomastia (Fig 3a and 3b). A mastectomy was performed, as well as a superior lipectomy on the anterior abdomen, followed by free transplantation of the nipple-areola complex (Fig 3c). A dedicated, commercialised incisional NPWT system was applied intraoperatively (SIM; Prevena Therapy) over the closed incision and free nipple areola grafts that were protected with a wide gauze dressing to prevent adhesion (Fig 3d). Negative pressure was initiated at -125mmHg (Figure 3e). On postoperative day 5, on dressing removal, an imprint of the foam was visible along the incision, indicating good contact between the foam and the skin.

FIG 2 Multi-morbid 59-year-old female patient with coagulopathy and risk of surgical site complications prior to undergoing abdominoplasty (a). Closed incision following abdominoplasty (b) Adhesive incision drape applied over whole anterior trunk to protect skin from contact with the PU foam of NPWT system and sterile compress applied to protect umbilicus beneath drape (c). Wide NPWT dressing is applied, covering anterior hemi-trunk. Contraction of large foam area is visible with -125mmHg continuous negative pressure (d). Six weeks following the surgical procedure, the incision remains closed with scar tissue of good quality (e).
and incision line. The free nipple areola grafts showed excellent take, scar edges appeared smooth and approximated, and healing was visibly advanced (Fig 3f), compared with our experience using conventional dressings in other routine patients. At the 3-month follow-up, the scar was stable and clinically smooth and pliable, yet active (Fig 3g).

**FIG 3** Preoperative images of a 53-year-old patient with massive weight loss and redundant skin who will undergo mastectomy and reduction for treatment of post-bariatric gynecomastia (a,b). A mastectomy and superior lipectomy on the anterior abdomen were performed, followed by free transplantation of the nipple-areola complex (c). SIM using a customisable dressing was applied intraoperatively over the incision line and free nipple areola grafts (d). Subatmospheric pressure was initiated at -125mmHg (e). On postoperative day 5, the SIM dressing was removed. The free nipple areola grafts showed excellent take, scar edges appeared smooth, and healing was visibly advanced (f). Result at 3 months after post-bariatric gynecomastia treatment with anterior body lift and bilateral free nipple retransplantation—scar is stable and clinically smooth and pliable, yet active (g).
Discussion

It is increasingly understood that different wounds, much like the different people affected by them, need to be treated on an individual basis, as not all wounds heal without problems. A number of advanced dressings, including transparent films and hydrocolloids have, therefore, been developed since the mid-1980s to replace traditional gauze pads and non-adherent dressings as primary coverings for acute and chronic wounds. The use of hydrocolloids, gels, foams, alginates, tissue adhesives or wound-protective materials mainly aims at reducing the frequency of dressing changes from several times a day to several times a week. New approaches to aid wound healing, such as tissue engineering and regenerative medicine, are very promising, but are not yet available in many institutions for routine clinical use.

Meanwhile, traditional methods of primary incision closure as well as dressing cover over surgical incisions have not changed much over the last few decades. Methods of surgical incision or laceration closure include sutures, staples, tissue adhesives, paper tape, or combinations thereof. Dressings over incisions have traditionally included gauze or an adhesive transparent dressing. We believe that, just as the need for advanced wound dressings has been derived from complexities in closing difficult-to-heal wounds, there is a potential benefit of advanced dressings over closed incisions of patients who are more likely to develop SSI or wound breakdown. Commercially available incisional NPWT systems, such as SIM, are lightweight and easily portable, and have been designed to be customised for irregular or large incisions, offering potential patient comfort and mobility.

Given the ubiquitous shortage of money in today’s health-care systems, cost-effective means of reducing SSI rates are important and should be carefully considered for a larger clinical application. In several clinical studies, incisional NPWT and SIM have been associated with lower rates of overall wound complications, wound dehiscence and seroma formation, and SSI,9,12,29 dehiscence, and overall complications requiring surgical intervention11,39 in a variety of wound types and in morbidly obese patients. A post-bariatric patient population who received incisional NPWT following abdominal dermolipectomy experienced significantly reduced exudate formation, earlier drain removal, and decreased length of hospitalisation compared with the conventionally treated group.24 Reduced scar formation and improved mechanical properties of the incision have also been reported with use of incisional NPWT in porcine experimental wounds.25 Case studies presented in this paper demonstrate stable, clinically smooth and good-quality scar tissue following use of incisional NPWT.

Despite the fact that the exact mechanisms of incisional NPWT on incision healing are still a matter of research, evidence suggests it may be accomplished in part through an increase in tissue blood circulation. This micro-circulatory effect may particularly benefit high-risk patients who undergo body-contouring surgery following massive weight loss. Independent of any socio-economic considerations, this incision tool with such potential to reduce surgical site complications definitely requires further attention. Additional controlled studies should be carried out to validate the clinical impact of SIM/incisional NPWT and to determine best recommendations for its use.

Conclusion

The literature is generally favourable regarding the positive effects of incisional NPWT in reducing seroma formation,12,32,33 SSI,9,12,29 dehiscence,12,39 and/or overall complications requiring surgical intervention11,39 in a variety of wound types and in morbidly obese patients. A post-bariatric patient population who received incisional NPWT following abdominal dermolipectomy experienced significantly reduced exudate formation, earlier drain removal, and decreased length of hospitalisation compared with the conventionally treated group.24 Reduced scar formation and improved mechanical properties of the incision have also been reported with use of incisional NPWT in porcine experimental wounds.25 Case studies presented in this paper demonstrate stable, clinically smooth and good-quality scar tissue following use of incisional NPWT.

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USE OF EPIDERMAL GRAFTS IN WOUNDS: A REVIEW OF AN AUTOMATED EPIDERMAL HARVESTING SYSTEM

Chronic wounds continue to present a significant challenge to health-care providers across the globe. Unlike acute wounds, chronic wounds do not proceed through an orderly process of repair. In recent years, a number of wound healing treatments, such as dermal replacement scaffolds and negative pressure wound therapy, have promoted wound healing by stimulating the formation of granulation tissue. However, until recently there were few modalities designed to promote epithelialisation of a fully granulated wound. Split-thickness skin grafts (STSGs) have long been the gold standard for the management of acute wounds, but have not gained favour in the treatment of chronic wounds for several reasons: discomfort associated with the donor site, the creation of a second wound (donor site) in a patient with poor wound-healing potential, and a lack of documented efficacy for the procedure. Epidermal grafting does not have some of the limitations encountered with STSG; however, it has not gained wide acceptance, as previous harvesting techniques were cumbersome and time-consuming. A novel automated epidermal harvesting system, CelluTome Epidermal Harvesting System (KCI, an Acelity company, San Antonio, TX, USA), was commercially introduced in 2013. The system yields up to 128 epidermal micrografts that can be easily harvested at the bedside without anaesthesia and transferred to the recipient site. The harvesting technique and the use of epidermal grafts in wounds are reviewed here.

Declaration of interest
TES presented as a faculty member during the 2014 International Surgical Wound Forum (ISWF), an annual educational event sponsored by KCI, an Acelity company, held in 2014 in Edinburgh, Scotland. His article is part of a KCI-funded educational supplement based on faculty presentations at the 2014 ISWF session related to wound care strategies using epidermal micrografts. Acelity provided editorial assistance. TES is a consultant for KCI, an Acelity company.

Key words: epidermal grafting, chronic wounds, wound healing

Chronic wounds remain a significant challenge for wound care specialists. While acute wounds proceed through the normal stages of healing, chronic wounds generally do not follow an orderly process of regeneration and repair. The healing process can be lengthy, requiring frequent office visits and dressing changes.

Split-thickness skin grafts (STSGs), a mainstay in the reconstruction of acute wounds, have not been used extensively in the treatment of chronic ulcers. In the last decade, cellular- and tissue-based products (CTPs) largely superseded skin grafting for a number of reasons. First, STSG harvesting and placement must be performed under anaesthesia by a surgically trained specialist. Second, the donor site becomes a second wound, which may be painful and difficult to heal. Moreover, in certain locations, such as the plantar aspect of the foot, the coverage may not be durable.
Epidermal grafting utilises autologous skin without some of the limitations of STSG. Dermatologists first used epidermal grafting in 1964 and later for the treatment of hypopigmented lesions; however, epidermal grafting did not gain wide acceptance because the harvesting techniques were cumbersome and time-consuming. Despite the challenges of harvesting epidermal grafts, successful use has been reported in the treatment of burns and chronic wounds. In the majority of cases, suction blister epidermal grafting was employed. The suction apparatus raises the epidermal blisters and the epidermis is harvested using a free hand-blade technique.

Recently, an automated epidermal harvesting system (CelluTome Epidermal Harvesting System; KCI, an Acelity company, San Antonio, TX, USA) that applies negative pressure to harvest epidermal microdomes (Fig 1) was commercially introduced. Depending on the age of the patient and the thickness of the skin on the donor site, the harvesting time varies from 15 to 60 minutes; the average time is approximately 30 minutes. Once epidermal microdomes are ready, the epidermal grafts are transferred to adhesive film and applied to the wound or ulcer and secured in place using compression wraps, bolster dressings, or negative pressure wound therapy (NPWT). The harvesting technique and the use of epidermal grafts in wounds are reviewed here.

**Epidermal grafting procedure**

Epidermal grafting provides an approach in the treatment of acute and chronic wounds. The epidermal harvesting system enables physicians to harvest epidermal grafts conveniently and reliably while minimising donor site complications. The epidermal grafts can be used on wounds that have a clean granulating base that is free of non-viable tissue. The wound may be debrided prior to application of the epidermal graft if deemed appropriate by the treating physician.

The inner thigh is the preferred donor site; any hair on the inner thigh should be clipped and the skin prepared with 70% isopropyl alcohol. Betadine Solution (Purdue Products LP, Stamford, CT, USA) should be avoided as it results in the harvester adhering to the skin.

The harvester should be positioned on the donor site with the blue handle orientated in the upwards position and secured with the provided Velcro strap (Velcro USA Inc., Manchester, NH, USA; Fig 2). The physician should visually confirm complete contact with the skin and reposition if necessary. The vacuum head should then be fitted to the harvest site with tubing oriented up (Fig 3). Alternate corners of the vacuum head-harvester complex should be pressed to ensure a good seal.

Next, the ‘Start’ button should be pressed on the control unit. The system heats the skin to between 37°C and 41°C and applies 400–500mmHg of negative pressure. The vacuum head also provides illumination so that the site can be observed through the view window. The microdome preparation takes from 15 to 60 minutes; the preparation is complete when round epidermal microdomes form (Fig 1).

To collect the microdomes, the control unit is turned off and the vacuum is removed from the
vacuum head. The vacuum head is unlatched from the harvester by pressing the blue handle on either side. A dressing is then inserted into the harvester and pressed firmly against the microdomes. The choice of dressing can be left to the discretion of the physician—Tegaderm film dressing (3M Company, St. Paul, MN, USA) is recommended for wounds with low levels of drainage. If using the film dressing, it is suggested that the dressing be rubbed gently against microdomes. Next, holding the harvester in place, the blue handle is retracted upwards until a click is heard, and then the handle is slowly returned to the start position. The dressing is carefully removed from the harvester (Fig 4 and Fig 5) and transferred to the recipient site. The microdomes are secured in place by using compression wrapping, a bolster dressing, or with NPWT. The donor site can be treated with a film dressing (Fig 6).

**Use of epidermal grafts in wounds**

Initial epidermal harvesting techniques used syringe-induced blister formation to obtain epidermal grafts for use over various wound types, including diabetic foot ulcers,11 wounds with exposed bone due to rheumatic diseases,15 and chronic leg ulcers.12 Use of these types of harvested epidermal grafts has also been reported in separate case studies concerning a refractory toe ulcer13 and a big toe wound with exposed bone.14

As the automated epidermal harvesting system described here has only recently been commercially available, only a few studies have been published on the use of epidermal grafts harvested with this system. One of the first publications in 2013 described the use of epidermal grafts over a chronic venous leg ulcer (VLU) and a chronic diabetic foot ulcer (DFU).2 In these two patients, either the wound was not healing or it was a recurrent wound. At 17 days and 24 days post grafting, respectively, the VLU and DFU were completely closed.

The effectiveness of epidermal grafting using grafts obtained with the automated epidermal harvesting system was first shown in a case series from the Bernard Mevs hospital in Port-au-Prince, Haiti.16 Seven patients with chronic lower extremity wounds received epidermal grafts. In 4 weeks, the authors observed a decrease in wound size in six of seven patients and, in one patient with lymphatic filariasis, the wound came to complete closure. Donor sites showed complete healing without complications within 2–4 weeks following the epidermal harvesting.16 Based on this data, a randomised controlled trial evaluating epidermal grafting in VLUs has been initiated (http://clinicaltrials.gov/show/NCT02148302). This clinical trial has recently started recruiting patients and will primarily measure differences in time to heal between patients that receive epidermal grafting and standard care. Secondary outcome measures will include percentage of VLUs healed each week, cost-effectiveness of epidermal grafting, incidences of adverse events, correlation between healing rate and levels of protease in the wound, and differences in pain scores self-reported by study participants.

Epidermal grafts may also be a suitable option when the patient is unable to have an STSG. In
patients with pyoderma gangrenosum, a neutrophilic dermatosis characterised by chronic, recurrent skin ulcerations, skin grafting can be problematic as new or worsening ulcerations may develop following the STSG procedure due to skin breakdown related to trauma. Richmond et al utilised epidermal grafts in five patients with pyoderma gangrenosum to initiate healing in these chronic wounds. All patients received one application of epidermal grafts. One patient showed a 63% wound reduction one week following epidermal graft placement, and the wound was fully re-epithelialized at 7 weeks post grafting. One patient fully healed at 5 weeks following the graft procedure, while another healed by week 12. The remaining two patients showed wound reductions of 64% and 99% within 8 weeks. No adverse events or donor site complications were observed, and donor sites were completely healed by one week post-grafting.

More recently, Gabriel et al. presented their initial experience using the epidermal harvesting system to harvest epidermal grafts in a small four-patient case series. The wounds treated included heat burn to a radiated breast, scalp melanoma excision site, a chronic foot wound, and a wound resulting from the removal of a sacral tattoo. Patient comorbidities included diabetes, tobacco use, obesity, and peripheral vascular disease. All harvesting procedures were conducted in a doctor’s office setting without anaesthesia; minimal to no pain during the harvesting procedure was observed. At the end of the 2-month follow-up period, complete wound closure was observed in three of the four patients. The remaining patient, with a chronic foot wound present for 8 years, showed 50% re-epithelialisation and reduction of the wound size. At follow-up, this wound remained at 50% re-epithelialisation. All donor sites were healed with no complications.

A healthy human study reported on the viability, formation, cell type, and growth factor secretion capability of epidermal grafts that were harvested from 15 healthy study subjects using the automated epidermal harvesting system. The microdome formation and harvesting device was observed in three of the four patients. The remaining patient, with a chronic foot wound present for 8 years, showed 50% re-epithelialisation and reduction of the wound size. At follow-up, this wound remained at 50% re-epithelialisation. All donor sites were healed with no complications.

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Njoo, M.D., Westerhof, W.,
NON-HEALING FOOT ULCERS IN DIABETIC PATIENTS: GENERAL AND LOCAL INTERFERING CONDITIONS AND MANAGEMENT OPTIONS WITH ADVANCED WOUND DRESSINGS

Medical knowledge about wound management has improved as recent studies have investigated the healing process and its biochemical background. Despite this, foot ulcers remain an important clinical problem, often resulting in costly, prolonged treatment. A non-healing ulcer is also a strong risk factor for major amputation. Many factors can interfere with wound healing, including the patient’s general health status (i.e., nutritional condition indicated by albumin levels) or drugs such as steroids that can interfere with normal healing. Diabetic complications (i.e., renal insufficiency) may delay healing and account for higher amputation rates observed in diabetic patients under dialysis treatment. Wound environment (e.g., presence of neuropathy, ischaemia, and infection) may significantly influence healing by interfering with the physiological healing cascade and adding local release of factors that may worsen the wound. The timely and well-orchestrated release of factors regulating the healing process, observed in acute wounds, is impaired in non-healing wounds that are blocked in a chronic inflammatory phase without progressing to healing. This chronic phase is characterised by elevated protease activity (EPA) of metalloproteinases (MMPs) and serine proteases (e.g., human neutrophil elastase) that interfere with collagen synthesis, as well as growth factor release and action. EPA (mainly MMP 9, MMP-8 and elastase) and inflammatory factors present in the wound bed (such as IL-1, IL-6, and TNFα) account for the catabolic state of non-healing ulcers. The availability of wound dressings that modulate EPA has added new therapeutic options for treating non-healing ulcers. The literature confirms advantages obtained by reducing protease activity in the wound bed, with better outcomes achieved by using these dressings compared with traditional ones. New technologies also allow a physician to know the status of the wound bed environment, particularly EPA, in a clinical setting. These may be helpful in guiding a clinician’s options in treating very difficult-to-heal ulcers.

Declaration of Interest
LU presented as a faculty member during the 2014 International Surgical Wound Forum (ISWF), an annual educational event sponsored by KCI, an Acelity company. This article is part of a KCI-funded educational supplement based on 2014 ISWF faculty presentations. Acelity provided editorial assistance.

Key words: protease, metalloproteinase, human neutrophil elastase, elevated protease activity, non-healing wounds, chronic wounds
Even though the introduction of insulin therapy has eliminated ketoacidosis as a principal cause of death in diabetic patients, a longer lifespan combined with unsatisfactory metabolic control has been associated with an increased prevalence of major complications. Diabetic foot ulcers (DFUs) are a serious complication of diabetes, leading to disability and early mortality. It is estimated that 15% of diabetic patients will develop foot ulcers and 6% of them will require hospitalisation. DFUs are the most common cause of non-traumatic major amputation around the world and the most costly type of chronic wound. Despite the huge amount of research into the underlying pathogenesis of impaired diabetic wound healing and new advances in treatment, chronic DFUs still remain an unsolved problem. While acute wounds follow a well-orchestrated sequence of events and reactions through four sequential phases (haemostasis, inflammation, proliferation and remodelling), in chronic wounds this orderly sequence of events does not occur and ulcers stall in the inflammatory phase. This review describes general conditions, diabetes-related complications, and wound bed features that may interfere with the healing process. Alterations in a chronic wound’s microenvironment and therapeutic options to correct these imbalances are also presented.

Biochemical differences in the microenvironment of diabetic wounds
It is well known that there are several differences between wound healing in people with diabetes versus people without diabetes. DFUs are characterised by reduced growth factor production and decreased or impaired angiogenic response, macrophage function, collagen accumulation, and epidermal barrier function. The keratinocyte migration is inhibited because of the reduction and abnormal localisation of endothelial growth factor receptor and the migration and proliferation of fibroblasts are also reduced. Patients with diabetes also have fewer nerves in the epidermis and papillary dermis of their skin. Patients with diabetes also have fewer nerves in the epidermis and papillary dermis of their skin. When do we define an ulcer as ‘non-healing’?

In 1994 Lazarus et al. defined a chronic wound as one that fails to progress through a timely sequence of repair or one that proceeds through the wound healing process without restoring anatomic and functional results. A 50% reduction in wound area over time is a valid endpoint to assess healing status. Sheehan et al. defined a DFU as non-healing in the case of wound area reduction less than 53% after 4 weeks of standard care. As demonstrated in these studies, 50% wound area reduction over time can be used as a pivotal clinical decision point in the management of DFUs.

Can diabetic complications prevent the healing process?
Based on cause of ulceration, DFUs are usually classified as neuropathic (50%), ischaemic (20%), and neuroischaemic (30%), when both neuropathy and peripheral vascular disease appear simultaneously.

Diabetic neuropathy
Motor, sensory and autonomic fibres are implicated in the complex context of diabetic peripheral neuropathy. They cause foot deformity, leading to high-pressure areas; sensory loss, causing unnoticed traumas; and alteration of skin hydration with anhidrosis. These modifications increase the risk of ulceration. Neuropathy is not only a key factor in ulcer development but also affects its outcome. Denervated skin has been shown to exhibit delayed wound healing. The sensory loss impairs the protective mechanism of off-loading, and the relative risk of developing an ulcer in a high-pressure area is 4.7. The presence of hyperkeratosis in a high-pressure area increases the ulceration risk to 11. Moreover, neuropathy also has a direct effect on wound healing. Denervated wounds in a rat model showed lower macrophage and T-lymphocyte counts.

Peripheral arterial disease
Adequate wound tissue oxygenation is required for tissue repair. Wound tissue hypoxia derives from three factors principally: peripheral arterial disease, increased O₂ demand for healing processes, and generation of reactive oxygen species (ROS). Temporary mild hypoxia produces cellular adaptive response: increased glycolysis process and synthesis of the hypoxia-induced factor (HIF). It activates several genes such as angiogenic cytokines (vascular endothelial growth factors, VEGF) and erythropoietin. Prolonged ischaemia is detrimental, exaggerating these physiological events and causing reperfusion injury and the formation of ROS. Moreover, hyperglycaemia impairs the HIF-1α transactivation, resulting in decreased hypoxia-induced VEGF expression.
Hyperglycaemia

Hyperglycaemia and its related factors, such as advanced glycation end-products (AGEs), play an important role in the impaired wound healing of DFUs. AGEs interfere with the healing process either directly or indirectly through their role in the pathogenesis of diabetic neuropathy and angiopathy. The accumulation of AGEs in wound tissue and their interaction with specific receptors, such as receptors for advanced glycation end-product, are responsible for reduced neutrophil migration. In addition, AGEs raise oxidative stress and decrease the antioxidant defence system. Several studies report that AGEs both alter the interaction between cells and the extracellular matrix (ECM) and the amount of ECM constituent; AGEs also cause structural changes in collagen I.

General conditions that can interfere with the healing process

While the main factors associated with diabetes that can hamper the wound-healing process have been described, other conditions not strictly related to diabetes should be evaluated, including nutrition, smoking, drugs (steroids), immobility, and anaemia. Patient noncompliance in using prescribed offloading devices can also result in delayed wound healing.

Malnutrition

DFU patients present a poor nutritional status, when compared with non-DFU patients. Yekta et al. reported that body mass index (BMI) below 25kg/m² was significantly associated with lower limb amputation in diabetic patients. Zhang et al. identified nutritional status as a predictor for clinical outcome in DFUs.

Malnutrition prolongs the inflammatory phase of the healing process. It reduces the proliferation of fibroblasts and the synthesis of collagen. It increases the risk of developing infection, decreasing T-cell function, phagocytic activity, and complement and antibody levels. Proteins play the most important role during the entire healing process. The lack of proteins decreases the synthesis of collagen and the production of fibroblasts. Fatty acids are necessary to promote the inflammatory phase as they provide a substrate for eicosanoid synthesis. In addition to basic macronutrients, micronutrients are required (Table 1).

Uraemia

Chronic kidney disease is an independent risk factor for development of foot lesions in the diabetic population. Further, diabetes is known as the leading cause of end-stage renal disease (ESRD). Renal failure predicts non-healing of ischaemic and neuroischaemic foot lesions, and ESRD is reported to be a strong risk factor for both ulceration and amputation in diabetic patients. Recent papers observed an amputation rate of 22% to 44% in ESRD patients affected by ischaemic foot lesions. In this context the negative impact of uraemia in the wound healing process is well defined. Even if all mechanisms are not clear, this condition seems to depress cellular proliferation at wound edges and reduce fibroblast growth. Further it has been documented that wound strength and granulation tissue mass are impaired in diabetic uremic wounds.

Wound bed conditions: infection

Even if infection is not a stated point of the pathogenic triad for the development of DFUs (neuropathy, ischaemia, and trauma), it is an important cause of morbidity, hospitalisation, amputation, and impaired healing. Compared with other type of wounds, the incidence of infection in DFUs is higher. Bacteria themselves are able to promote an environment that delays the wound-healing process. Moreover, their growth is increased by stress and compressive forces and decreased function of macrophages and neutrophils has been reported. Bacteria stimulate protease production by the activation of the immune system. In addition, some species of bacteria are able to secrete proteases themselves. Moreover, bacteria may aggregate on a surface, within extracellular polymeric substances (EPSs), formed by proteins, lipid and polysaccharides. These microbial communities are defined as biofilm. In the biofilm, bacteria present an alternate phenotype, which determines tolerance to both systemic and topical antibiotics.

| TABLE 1 Role of micronutrients in wound healing |
|--------------------------|--------------------------|
| Methionine, cysteine     | Synthesis of collagen    |
| Arginine                 | Improved immune reaction |
| Ascorbic acid            | Collagen synthesis       |
|                         | Hydroxylation of proline and lysine |
|                         | Stabilisation of the triple structure of collagen |
| Zinc                     | Cofactor for enzymatic reaction to induce cell proliferation |
| Iron                     | Cofactor for collagen synthesis Transport of oxygen |

...
Wound bed microenvironment: the key role in non-healing ulcers

Wound healing is a dynamic and well-orchestrated process, regulated by biological and molecular events consisting of cell migration, cell proliferation and deposition of ECM. It comprises four overlapping phases: haemostasis, inflammation, proliferation and wound contraction.7,8 Complex interactions must occur between growth factors, cells and matrix components to complete each phase and to move sequentially to the next one. When an alteration of this fine regulation occurs, the wound stalls in the inflammatory phase and the healing does not occur.9,10 This is the difference that is identified in a chronic ulcer compared with an acute wound.

Usually, non-healing wounds share similar features,11,12,56,57 including:

- High levels of proteases (enzymes that act on proteins, cutting up protein molecules)58
- Elevated inflammatory markers
- Low growth factor activity
- Reduced cellular proliferation.

The major groups of proteases involved in the wound healing process are the matrix metalloproteinases (MMPs, mainly MMP-1, MMP-2, MMP-8, MMP-9) and the serine proteases (human neutrophil elastase, HNE).58 MMPs are a family of zinc endopeptidases capable of degrading all the ECM components (e.g., collagens, elastin and glycoproteins). HNE is an enzyme that acts on a wide range of proteins in the ECM and on inflammatory mediators. These proteases play a positive role in every phase of the healing process. They eliminate damaged proteins, facilitate cellular migration, remodel the granulation tissue and regulate the activity of some growth factors. When synthesized, MMPs are in an inactive form. They need to be activated by other proteases and by serine proteases such as HNE. Their activity is inhibited by molecules called tissue inhibitors of metalloproteinases (TIMPs).59 The balance between the level of proteases and their inhibitors is essential to allow a physiological healing process.

Several studies have documented the presence of elevated levels of various MMPs and decreased levels of TIMPs in chronic wounds.60-62 Lobman et al.63 found that activity of MMP-1, MMP-2, MMP-8, and MMP 9 were significantly higher and that the levels of TIMP-2 were lower in DFUs, compared with acute wounds of non-diabetic patients. Elevated protease activity (EPA) degrades proteins that are not their normal substrate: growth factors, receptors and ECM proteins. For example, elastase produced by human neutrophils severely affects ECM components, such as fibronectin.64

The degradation of fibronectin and other proteins prevents the migration and attachment of keratinocytes and destroys growth factors.64

The alteration of protease activity is not the only feature of the chronic wound bed environment. Alterations in many other proteins include decreased levels of intact fibronectin,65,66 increased fibronectin degradation products,65,66 loss of type II transforming growth factor-beta (TGF-β) receptors on fibroblasts,65,67 reduced levels of platelet-derived growth factor (PDGF),66,68 and down-regulation of keratins in epithelial cells.65,69 Keratinocytes at the wound edges tend to be hyperproliferative and non-migratory,69 while fibroblasts in the base of the wound become senescent.70,71

How can a clinician know when elevated protease activity is present?

It is important to correct the underlying biochemistry to allow the healing process. According to a recent study, EPA is associated with a 90% probability of non-healing without an appropriate intervention.72 Approximately 28% of non-healing wounds have EPA. Stremitzer et al.73 investigated several specialists to assess their evaluation of signs and symptoms related to chronic wounds. Study data showed heterogeneity among all groups and a wide range of results. As the choice of treatment by a specialist is based on the assessment of the wound, it is possible to choose inappropriate therapy. Some signs and symptoms (e.g., pain, swelling, colour or fibrin) have been described to alert the clinician to chronic inflammation and potentially EPA, but there have been no studies that support these observations.46 Moreover, not all wounds with delayed healing have EPA. Therefore, clinicians need to be able to identify which wounds have EPA in order to apply the appropriate treatment.

Several advanced techniques (e.g., gelatine zymography, ELISA (enzyme-linked immunosorbant assay), fluorimetric assays) are used to analyse levels, types and activities of MMPs and other proteases in wound fluid derived by wound biopsy.74 However, in some cases, laboratory evaluation protease levels is not feasible. Woundchek Protease Status (Woundchek Laboratories, Gargrave, North Yorkshire, UK) is a diagnostic test developed to evaluate inflammatory protease activity (e.g., MMP-9, MMP-8, elastase) in chronic wounds in a short period of time.

We recently used Woundchek Protease Status in a blinded dermal replacement study.75 While there were no failures in the group with low protease activity, the failure rate was 63.6% in the...
group with EPA. The diagnostic test was easy to use and provided results in 15 minutes. It might help clinicians decide which treatment would or would not be appropriate and when to start and stop treatment.

**How to read the protease test results**
Based on our experience, if the protease test highlights EPA in the examined wound, a clinician could consider applying dressings that might reduce protease activity in wound. The lesion should be re-evaluated after 2 or 4 weeks of treatment. If protease activity remains high, the clinician should exclude the presence of infection and eventually continue protease-modulating therapy. If protease levels are normal, the wound bed is in the best condition to allow a physiological healing process.

Fig 1 is suggested as a guide for clinicians, when an ulcer does not heal after correctable factors (e.g., vascular disease, neuropathy, infection, metabolic disorder) have been addressed.

**Dressing and devices that reduce EPA in the wound environment**
To allow wound healing, all factors that delay this process need to be treated: revascularisation in case of peripheral ischaemia, administration of offloading to remove ulcer pressure, and adequate debridement and antibiotic therapy in case of local infection. Once that standard care is applied, the evaluation of the wound bed in the treatment of chronic DFUs is a key passage. In relation to this consideration, the concept of ‘wound bed preparation’,76 which is defined as the systemic approach to study and correct the molecular environment of the wound bed, should be implemented.

**Debridement**
In addition to the management of exudates and bacterial proliferation, wound debridement is an essential phase of wound bed preparation. In chronic wounds, surgical debridement should remove all non-viable tissues, reducing wound contamination.77 Debridement reduces the dysfunctional cell population70,71 and may help to stimulate cytokines and growth factors to restore the physiological healing process,76 which is the concept of using debridement to convert a chronic wound in an acute wound.

**Collagen/oxidised regenerated cellulose dressing**
Many studies have focused on dressings that reduce protease levels.78-80 They absorb wound exudates and retain the proteases within the dressing structure. A collagen/oxidised regenerated cellulose (ORC) dressing is composed of a freeze-dried sponge prepared from bovine colla-
gen and ORC.\textsuperscript{78,79} Cullen et al.\textsuperscript{78,79} compared a collagen/ORC dressing (Promogran Protease Modulating Matrix, Systagenix, an Acelity company, Gargrave, UK) with standard treatment, gauze. In these two \textit{in vitro} studies the collagen/ORC dressing significantly reduced all proteases present in DFU wound fluid, including neutrophil-derived proteases, plasmin, and MMPs. The ORC bound and inactivated elastase and other serine proteases in the wound fluid, entrap ping them and reducing their activity, while the collagen component acted as a substrate for MMPs. Moreover, collagen/ORC dressings protected growth factors from proteolytic degradation.\textsuperscript{78,79}

In the 2002 multicentre randomised controlled trial (RCT) (n=276) comparing collagen/ORC (n=138) with saline-moistened gauze (n=138) for treatment of DFUs, Veves et al.\textsuperscript{81} reported that after 12 weeks of treatment, 51 (37\%) collagen/ORC-treated DFUs and 39 (28.3\%) gauze-treated DFUs achieved complete wound closure (p=0.12). In the subset of DFUs with duration of longer than 6 months, more collagen/ORC-treated DFUs achieved closure: 43/95 (45.3\%) vs 29/89 (32.6\%); p=0.056. In this initial RCT, the collagen/ORC dressing had similar efficacy and safety compared with saline-moistened gauze and trended toward significance in DFUs with less than 6-month duration.\textsuperscript{81} In the 2007 RCT by Lázaro-Martínez et al.,\textsuperscript{82} patients with neuro- pathic DFUs of greater than 6-week duration were randomised to either a collagen/ORC dressing or the ‘treatment specified in the standardised protocol for good wound care’. After 6 weeks, significantly more patients in the collagen/ORC group achieved healing than in the standard care group: 12/19 (63\%) vs 3/19 (15\%); p<0.03. The mean healing time for the collagen group was also significantly shorter: 23.3 ± 1.15 days vs 40.6 ± 1.15 days; p<0.01.\textsuperscript{82} While the preclinical studies indicate the potential mechanisms of action for collagen/ORC dressings, the RCTs demonstrate their efficacy and safety in patients with DFUs.

### Topical negative pressure therapy

Topical negative pressure (TNP) is a non-invasive therapy system (such as V.A.C. Therapy, KCI, an Acelity company, San Antonio, TX, USA) that applies controlled negative pressure to the wound bed.\textsuperscript{83} TNP promotes a moist wound environment, reduces oedema, removes healing inhibitors, increases blood flow, and stimulates granulation tissue formation. TNP also promotes an improved balance between healing and non-healing factors. Moues et al.\textsuperscript{84} described a significantly (p=0.02) lower ratio of MMP9/TIMP-1 and significantly (p=0.01) lower levels of pro MMP-9 in fluid from wounds treated with TNP, compared with those treated with conventional gauze therapy. Greene et al.\textsuperscript{85} observed a reduction of 15\% to 76\% in MMP-9/NGAL (neutrophil gelatinase-associated lipocalin), MMP-9, latent MMP-2 and active MMP-2 in fluid taken from chronic wounds of three patients treated with TNP therapy.

### Conclusion

Non-healing ulcers, especially those in diabetic patients, present an ongoing clinical challenge. This review identifies the main conditions that prevent the healing process and discusses the features of the wound environment, including the role of MMPs and serine proteases. EPA has been associated with non-healing wounds, and there are dressings (e.g., the collagen/ORC dressing) that are designed to help reduce EPA in the wound environment. There are no clinical signs related to EPA, and laboratory evaluations take time. We have used a protease status test that evaluates inflammatory protease activity in the wound environment in a short period of time and have suggested a guide that shows how this test may provide information to help a clinician decide which treatment is appropriate for a non-healing ulcer.

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