The role of matrix metalloproteinases in diabetic wound healing: a case study

Pedro Miguel Dias dos Santos, Carla Manuela Pereira Menezes, Pedro Sérgio Aleman Gageiro Carvalho and Maria Rosário Roque Andrade Almeida

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Article points

1. In diabetic ulcers there is an excess of matrix metalloproteinases (MMPs) and a decrease of the tissue inhibitors of MMPs.
2. Sucrose-octasulfate is a modulator of MMPs.
3. Consider a sucrose-octasulfate impregnated dressing in non-infected, neuro-ischaemic diabetic ulcers that fail to heal despite optimal clinical care.
4. In this case, complete healing was achieved after 10 weeks of a sucrose-octasulfate dressing.

Key words

- Chronic ulcer
- Diabetic foot ulcer
- Matrix metalloproteinase
- Wound healing

Authors

Pedro Miguel Dias dos Santos is General Surgery Resident, Centro Hospitalar do Oeste, Torres Vedras, Portugal; Carla Manuela Pereira Menezes is Head of Diabetic Foot Unit and General Surgeon, Centro Hospitalar do Oeste, Torres Vedras, Portugal; Pedro Sérgio Aleman Gageiro Carvalho is General Surgeon, Centro Hospitalar do Oeste, Torres Vedras, Portugal; Maria Rosário Roque Andrade Almeida is Head of General Surgery Department, General Surgeon, Centro Hospitalar do Oeste, Torres Vedras, Portugal

A patient was referred for a general surgery appointment due to two chronic diabetic foot ulcers. After unsuccessful standard treatment, both ulcers were successfully treated using a dressing containing sucrose octasulfate for 10 weeks, a modulator of matrix metalloproteinases. This clinical case supports the use of sucrose octasulfate dressing as a local treatment and in addition to the patients' treatment regimens for neuroischaemic diabetic foot ulcers, as recommended by the International Working Group on the Diabetic Foot. The successful management of chronic wounds is still a complex issue and it is always necessary to use a multidisciplinary approach.

Complications of diabetes that affect the lower extremities are a complex, perennial and costly problem in clinical practice and are responsible for require more home health care, have more emergency department visits and can subsequently lead to more hospitalisations than in matched population controls (Armstrong et al, 2017; Singer et al, 2017). There are multiple and variable causes but without a single treatment that will assist in all cases. In this article, we will discuss the matrix metalloproteinases (MMPs) that are involved in chronic non-healing wounds to explicitly highlight their importance in dictating the healing trajectory.

Chronic lower-limb ulcers

The leg ulcer is a syndrome characterised by circumscribed or irregular loss of the epidermis or dermis, reaching subcutaneous tissue and underlying tissues, which affects the extremities of the lower limbs (Frade et al, 2005).

Chronic ulcers of the lower limbs are defined as a wound that does not heal within 6 weeks, despite adequate treatment (Afonso et al, 2013). Causes of chronic ulcers are multifactorial and include vascular diseases, neuropathic (usually diabetic), trauma, vasculitis, lymphoedema, chronic infectious disease or osteomyelitis, rheumatoid arthritis, sickle cell anaemia and cutaneous tumours, among others (Afonso et al, 2013). Vascular aetiology predominates, with venous hypertension being responsible for 60–70% of ulcers, while arterial insufficiency or mixed arteriovenous disease cause 10–25% of ulcers (Afonso et al, 2013; Singer et al, 2017). In approximately 3.5% of patients, the cause of the ulcer is not identified. (Afonso et al, 2013).

Diabetic foot ulcers

There is a 25% likelihood that patients with diabetes will develop a foot ulcer. (Khan et al, 2020). About 20% of those with moderate to severe infection will require some degree of amputation (Armstrong et al, 2017; Khan et al, 2020). Indeed, diabetes is the leading cause of non-traumatic lower extremity amputations (Khan et al, 2020). Mortality after diabetes-related amputation exceeds 70% at 5 years for all patients with diabetes (Armstrong et al, 2017).

Aetiologies of diabetic foot ulcers (DFU) are multifactorial and encompass repetitive stress over an area that is subject to high vertical or shear stress in patients with peripheral neuropathy and atherosclerotic peripheral arterial disease (Armstrong et al, 2017; Singer et al, 2017).

"Diabetic foot syndrome" involves others pathological conditions, like Charcot's neuroarthropathy, osteomyelitis and, finally and potentially preventable, amputation. Thus, due to

the natural history of diabetes and its associated morbidity and mortality, it has been referred to as a true "silent pandemic".

Barriers in the wound healing process

Wound healing is a complex mechanism, with multiple processes orchestrating harmoniously for restoration of structure and function of the tissue (Ayuk et al, 2016). However, there are some factors that impair the healing process and cause chronicity, including slough, debris, exudate, biofilm, impaired angiogenesis and elevated levels of MMPs (Galea and Khatib, 2020). In DFU, factors associated with poor healing include advanced end organ disease (congestive heart failure, peripheral artery disease, or end-stage kidney disease requiring renal-replacement therapy) and the inability to walk independently (Armstrong et al, 2017).

Treatment

General principles for the management of lower-extremity ulcers include the following.

Wound debridement involves the removal of devitalised tissue and reduces bacterial burden. Careful, surgical debridement down to viable bleeding tissue, is the most rapid method. Autolytic dressings and enzymatic agents may also be considered (Singer et al, 2017).

Wound dressings that promote an appropriate level of moisture at the wound–dressing interface, be impermeable to microorganisms and protect the ulcer from further injury and shear stress should be used (Alexiadou and Doupis, 2012; Singer et al, 2017). There are also dressings are available that contain antiseptic agents such as silver nanoparticles (Singer et al, 2017).

Infection control is critical in chronic ulcers. Of all lower-extremity ulcers, DFU are the most prone to infection (Singer et al, 2017). Diagnosis of infection is made clinically. Microbiology findings support and direct antibiotic therapy. IV antibiotics should be considered in patients with clinically evidence of systemic infection, with local infection that is worsening or not responding to oral antibiotic agents or clinically significant coexisting immunocompromising conditions.

Treatment of underlying conditions such as diabetes and, not least, lifestyle changes (e.g. smoking cessation and dietary modifications) should also be implemented (Singer et al, 2017). There are specific therapies based on the type of ulcer.

Neuropathic ulcers

Offloading pressure plays a vital role and its value is increasing in the prevention and management of ulcers, especially neuropathic ulcers (Singer et al, 2017). Patients must receive ongoing professional foot care with careful inspection of their footwear. In some cases, they should be referred to a foot specialist to consider correction of any bone abnormalities (Singer et al, 2017). The most effective method of offloading, which is also considered to be the gold standard, is the nonremovable total-contact cast (Alexiadou and Doupis, 2012).

Venous ulcers

Compression therapy is strongly recommended for venous leg ulcers (Singer et al, 2017). Graded pressure is applied from the toes to the knees and should include the heel, with more pressure applied distally. The recommended compression pressures for the treatment of venous leg ulcers with varicose veins, the post-thrombotic syndrome, or lymphoedema are between 30 and 40 mmHg (Singer et al, 2017). In severe cases, an ankle–brachial index (ABI) < 0.5, compression should not be used because it may further reduce arterial flow (Singer et al, 2017).

Arterial ulcers

The most effective approach to get faster healing of arterial ulcers is to restore local blood flow by revascularisation procedures, including endovascular therapies or surgical bypass techniques (Singer et al, 2017).

MMPs in healing

Other methods have also been suggested to be beneficial as add-on therapies, such as using modulators of MMPs.

The process of wound healing requires the degradation of the extracellular matrix (ECM) to be controlled (Ayuk et al, 2016). MMPs are key players in all phases of wound healing. They

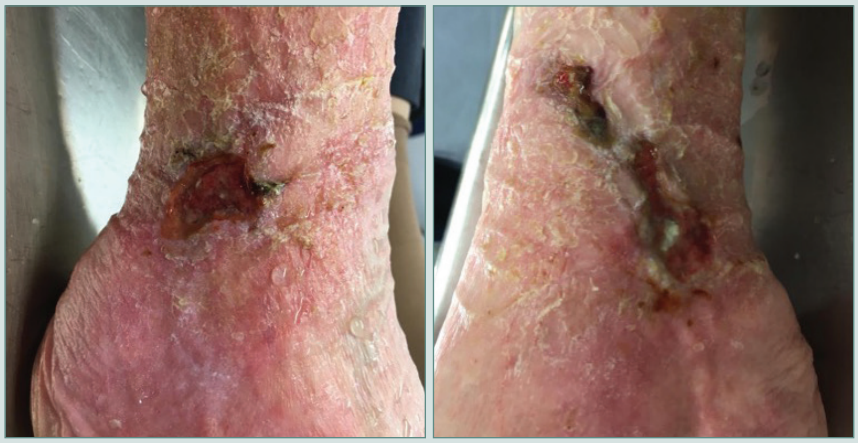

Figure 1: Ulcers on the external malleolus (left) and internal malleolus (right) at presentation.

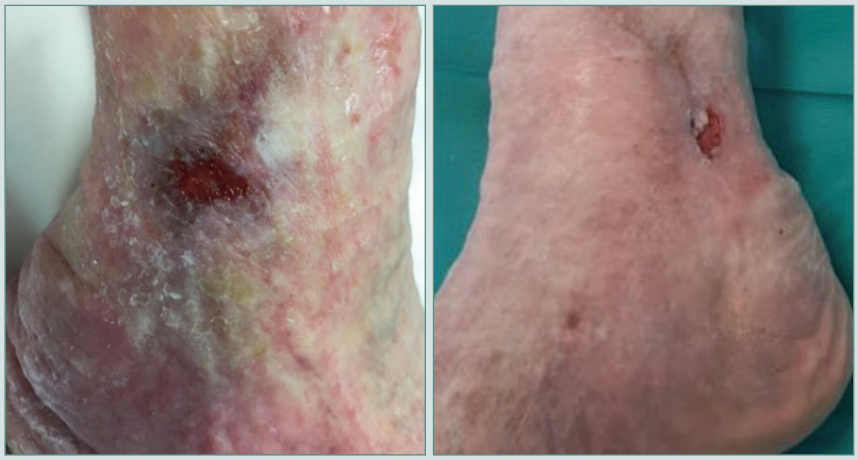

Figure 2: Ulcers on the external malleolus (left) and internal malleolus (right) 4 weeks after change to a dressing containing sucrose octasulfate, a modulator of MMPs.

remove damaged proteins and temporary ECM during the inflammatory phase, break down the capillary basement membrane for angiogenesis and cell migration in the proliferation phase, and contract and remodel tissue in the remodelling phase (Muller et al, 2008; Ayuk et al, 2016). The overwhelming increase in gelatinases (MMP-2 and MMP-9) and collagenases (MMP-1 and MMP- 8) are a factor that particularly contributes to delayed wound healing (Muller et al, 2008; Ayuk et al, 2016). The imbalance of these matrix proteins and their inhibitors is associated with abnormal wound healing, a familiar problem seen in people with diabetes (Muller et al, 2008; Ayuk et al, 2016).

Case study

A 78-year-old female patient was referred for a general surgery appointment due to two diabetic foot ulcers of 2 months' duration. She had arterial hypertension and long-standing diabetes (HbA_{1c} 7.4%) with associated peripheral neuropathy. The patient denied any history of trauma or intermittent claudication.

At presentation, she had varicose veins on the right lower limb and a bi-maleolar ulcer on the right leg consisting of a superficial ulcer on the external malleolus, measuring approximately 2.5 × 2.0 cm, and a second superficial ulcer on the internal malleolus, approximately 5.0 × 1.5 cm (*Figure 1*). Both ulcers were exudative, sloughy and malodorous, with signs of localised infection (local warmth, erythema and tenderness). The femoral and popliteal pulses were palpable bilaterally. Distal pulses on the right leg were absent, with an ABI of 1.1, probably caused by the glycation of blood vessels and the presence of slight calcification of the vessels.

Arterial Doppler ultrasound revealed the permeability of the femoral and popliteal segments bilaterally, flows with three-phase pattern and preserved velocities. On the right, monophasic distal flow was observed with reduction of the systolic peak. Venous Doppler ultrasound revealed the permeability of the deep venous system with normal return flow. There was insufficiency of the right saphenous-femoral confluence, with truncular avalvulation of the internal saphenous vein. According to the Edmonds classification (1987), the diagnosis of neuroischaemic diabetic foot was made.

The diagnosis of successive reinfections was made clinically and supported by microbiological findings. Accordingly, targeted antibiotic therapy was prescribed, complemented with a wound debridement, compression therapy, leg elevation, offloading of pressure, application of different dressings, including topical antimicrobials, more specifically ionic silver and, not least, a tight glycaemic control.

Over the 9-month period after initiation of standard treatment, there was evident improvement of percentage slough in the ulcers bed and the signs of infection were resolved. However, the ulcers had stagnated in size. At this point, a sucrose octasulfate impregnated dressing was initiated. Sucrose octasulfate is a modulator of MMPs.

Healthy granulation tissue developed and the wound area reduced significantly at each dressing change over the following 4 weeks (*Figure 2*).

There was an evident progression and the ulcers had completely closed 10 weeks after the initiation of sucrose octasulfate dressing (*Figure 3*).

Conclusion

Given the fact that MMPs have been shown to be overexpressed in most pathologies, including diabetes, they have been accepted as potential targets for new therapeutics (Muller et al, 2008; Ayuk et al, 2016). A great deal of research is underway in identifying specific drug inhibitors.

In the case study described, the addition of sucrose octasulfate dressing, an MMPs modulator, to the patient's treatment regimens contributed to healing the ulcers. The International Working Group on the Diabetic Foot recommends consider the use of the sucrose octasulfate impregnated dressing in non-infected, neuroischaemic diabetic foot ulcers that are difficult to heal despite best standard of care (Edmonds et al, 2018; Schaper et al, 2019; Galea and Khatib, 2020)

The successful management of chronic wounds is still a complex issue and needs to be addressed more precisely. It is necessary to utilise a multidisciplinary approach involving healthcare professionals and researchers in the development of new technologies to heal chronic wounds more successfully and prevent amputations. ■

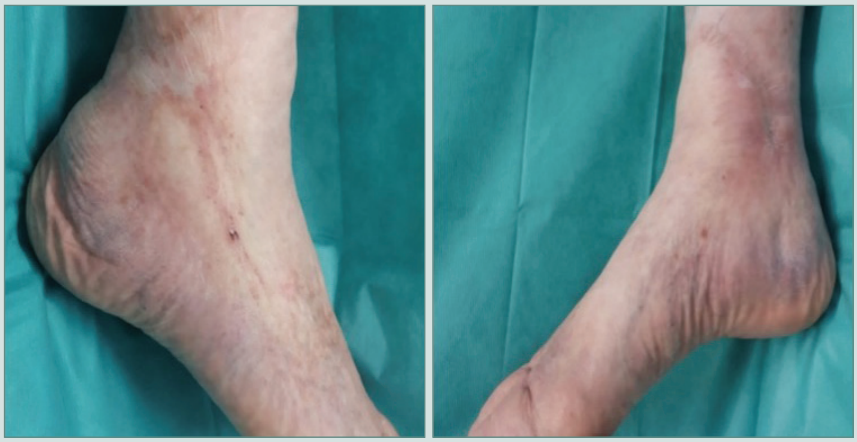

Figure 3: Complete healing 10 weeks after sucrose-octasulfate dressing was initiated.

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The new CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. What is the minimum duration (in weeks) beyond which a lower limb ulcer is defined as chronic? Select ONE option only.

   A. 4
   B. 6
   C. 8
   D. 10
   E. 12

2. According to Alfonso et al (2013), which one of the following anaemia's is most likely to cause a chronic lower leg ulcer? Select ONE option only.

   A. Folate deficiency
   B. Iron deficiency
   C. Normochromic normocytic
   D. Sickle cell
   E. Vitamin B12 deficiency

3. Which is the commonest vascular cause of chronic lower leg ulcers? Select ONE option only.

   A. Arterial insufficiency
   B. Lymphoedema
   C. Mixed arteriovenous
   D. Vasculitic
   E. Venous hypertension

4. According to Khan et al (2020), what percentage of people with diabetes will likely develop a foot ulcer? Select ONE option only.

   A. 10
   B. 25
   C. 33
   D. 50
   E. 66

5. According to Armstrong et al (2017), what is the approximate mortality (%) at five years after diabetes-related amputation? Select ONE option only.

   A. 10%
   B. 30%
   C. 50%
   D. 70%
   E. 90%

6. According to Singer et al (2017), which lower-extremity ulcer is most prone to infection? Select ONE option only.

   A. Arterial
   B. Diabetic foot
   C. Mixed arterio-venous
   D. Traumatic
   E. Venous hypertension

7. A 79-year-old woman with type 2 diabetes has a mixed arterio-venous chronic lower limb ulcer.

   Which one of the following Doppler ABPI measurements is a contraindication to treatment with compression therapy? Select ONE option only.

	Lower-limb systolic BP (mmHg)	Upper-limb systolic BP (mmHg)
A.	60	140
B.	80	130
C.	100	110
D.	120	90
E.	140	70

8. A 49-year-old man with type 2 diabetes has a chronic left lower leg neuropathic, non-infected foot ulcer.

   Which is the single most appropriate management? Select ONE option only

   A. Autolytic dressings
   B. Compression therapy
   C. Non-removable total contact cast
   D. Sucrose-octasulfate impregnated dressings
   E. Surgical debridement

9. Which single one of the following matrix metalloproteinases (MMPs) is a gelatinase involved in delayed wound healing? Select ONE option only

   A. MMP-1
   B. MMP-2
   C. MMP-3
   D. MMP-4
   E. MMP-5

10. According to the International Working Group on the Diabetic Foot, for which one of the following people with type 2 diabetes is it most appropriate to trial a sucrose-octasulfate impregnated dressings? Select ONE option only.

    A. A 41-year-old man with a traumatic leg ulcer
    B. A 52-year-old woman with a non-infected neuro-ischaemic leg ulcer
    C. A 59-year-old man with a chronic arterial leg ulcer
    D. A 64-year-old woman with a chronic venous hypertension leg ulcer
    E. A 70-year-old man with a DFU and underlying osteomyelitis