# The role of pH modulation in wound bed preparation

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**ARTICLE POINTS**

1 The TIME concept, used to determine barriers to healing in the diabetic foot, will direct clinicians to the dominant factors that may prevent wound progression.

2 Some wounds fail to epithelialise despite best practice in wound care.

3 As chronic wounds are linked to highly destructive protease levels, a major advance would be to control this environment by use of a pH modulator in an attempt to emulate a wound in an acute phase of healing.

4 Cadesorb (Smith & Nephew Healthcare, Hull) has yet to be used extensively in diabetic foot lesions but may provide a useful adjuvant to wound care.

**KEY WORDS**
- **Epithelialisation**
- **Proteases**
- **pH modulation**
- **Wound bed preparation**

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## Introduction

**Failure or delay in wound healing in diabetes mellitus is commonly associated with coexisting peripheral vascular disease, polyneuropathy and a multiplicity of factors that can interact to lead to the development of a chronic wound (Edmonds et al, 2004). Recent research into non-healing wounds has led to a growing recognition that biochemical and cellular abnormalities may play a role in the deficit of granulating wounds to re-epithelialise (Lobmann et al, 2002). The aim of this article is to explore the use of a pH modulator in the treatment of diabetic foot ulcers.**

In vivo studies examining wound fluid from both acute and chronic wounds suggest that proteolytic activity, in particular that by matrix metalloproteinases (MMPs), appears to be elevated in diabetic and other chronic wounds (Lobmann et al, 2002; Trengrove et al, 1999; Rogers et al, 1995). In normal tissue and repair, the function of these enzymes is controlled to some degree by tissue inhibitors of metalloproteinases (TIMPs), which appear to have a reduced expression in chronic wound fluid (Yager and Nwomeh, 1999). Unabated activity of MMPs in wound healing delays the deposition of the extracellular matrix, depletes growth factor and cytokine expression, and effectively results in deficient cell migration and wound contraction seen in chronic and diabetic wounds (Goodson and Hunt, 1986; Yue et al, 1986; Spanheimer, 1988).

Modulation of proteases is an integral part of wound bed preparation and current methods to attempt to achieve this include thorough debridement, wound irrigation and topical antimicrobials (Falanga, 2003). It has been demonstrated that an additional method of MMP control is adjustment of the wound pH (Greener et al, 2005; Schultz et al, 2005).

## Background

Wound bed preparation provides a structured, holistic approach to wound assessment (Schultz et al, 2003), which takes into account patient issues, underlying comorbidity problems and wound bed management. Once patient issues regarding quality of life are addressed (Ashford et al, 2000) and underlying comorbidity issues such as glycaemic control achieved, the wound bed can be focused upon. The concept of 'TIME' has been previously considered as a method of focusing on the wound bed and identifying dominant factors which result in barriers to healing (Schultz et al, 2003). TIME stands for:

- non viable **T**issue
- presence of **I**nfection or **I**nflammation
- **M**oisture imbalance and
- failure of **E**dges or **E**pithelialisation to take place.

Epithelialisation is 'the process in which the germinal layer of the epidermis [...] migrates across the granulation tissue to form a new layer of epidermal cells' (Dodds and Hayes, 2004). In order for successful epithelialisation to take place it is essential that the issues around T, I, and M are addressed. To ensure this process takes place in a timely fashion there must be a blood supply to provide oxygen and nutrients to the wound bed. In the neuroischaemic foot, revascularisation may be a major challenge (Edmonds et al, 2004).

Edmonds et al (2004) state that in the neuropathic diabetic foot lesion, it is often important to ensure that the ulcers are 'saucerised', with removal of callus, dried exudate, necrosis and cellular debris in order to overcome 'E'. If, however, this takes place, all other issues are addressed, and the wound margins continue to fail to epithelialise, then additional factors should be considered.

There is an increasing realisation of

**PAGE POINTS**

1 The role of the proteases is to degrade bacteria and allow rapid neutrophil ingress, followed by a return to low protease levels allowing remodeling of the extracellular matrix.

2 A protease's activity is strongly dependant on the pH of its surroundings (Schultz et al, 2005).

3 Open wounds tend to have a neutral or alkaline pH, predominantly in the range of 6.5–8.5 (Dissemond et al, 2003).

4 One strategy to promote healing in chronic wounds may be to decrease the proteolytic activity to the normal levels observed in acute wounds (post-48 hours) by use of a pH modulator.

the factors which are responsible for the inhibitory activity observed in chronic wound fluid (Schultz et al, 2003). Over-exertion of proteolytic enzymes has been posited as one mechanism through which the chronic wound environment inhibits cell proliferation. Various studies have explored the association between decreasing wound surface pH and wound healing (Schultz et al, 2005). For the purposes of this article, the potential benefits of a pH-modulating ointment will be considered for use in instances when, despite 'conventional' diabetic foot management, the wound continues to fail to epithelialise.

## Action of pH on MMP activity

pH is a measure of the acidity or alkalinity of an aqueous solution (on a scale of 0–14). Skin surface has an acidic pH of around 5, whereas the body's internal environment maintains a near-neutral pH of 7.

MMPs are not noted in normal, healthy resting tissue. However, some, if not all, MMPs are expressed in response to injury (Parks, 1999). MMPs are responsible for the degradation of components of the extracellular matrix. These play an important role in acute wound healing. The level and duration of their expression is tightly controlled by tissue inhibitors of metalloproteinases (TIMPs; Trengrove et al, 1999).

A protease's activity is strongly dependent on the pH of its surroundings (Schultz et al, 2005). Open wounds tend to have a neutral or alkaline pH, predominantly in the range of 6.5–8.5 (Dissemond et al, 2003). Since chronic wounds can be described as having permanently elevated protease levels resulting in a prolonged inflammatory state, one strategy to promote healing may be to decrease the proteolytic activity to the normal levels observed in acute wounds (post-48 hours) by use of a pH modulator. A weakly acidic environment may promote healing in open wounds by inhibiting the action of proteases (Leveen et al, 1973).

Lowering wound pH to around 5 dramatically slows down the activity of harmful proteases that can break down the newly formed matrix and also cause prolonged inflammation (Greener et al, 2005). Lowering the pH from 8 to 4 can reduce protease activity by 80% (Schultz et al, 2005). Greener et al (2005) stated that: 'wound pH must be greater than 4 for healing activity to take place and less than 7 to avoid degradation of the newly formed matrix.'

They demonstrated that the pH-dependent activity profiles of four proteases important in wound healing (cathepsin G, elastase, plasmin, MMP-2) showed peak enzyme levels, where the protein is broken down more rapidly than at other pH values (*Figure 1*). The group of proteases observed in the study had a similar mechanism of action and revealed similar pH profiles when levels of degradation of a gelatin film were examined using laser imaging and staining.

The evidence for the role of pH in diabetic foot wound healing is limited as most of the studies have examined chronic wound fluid from burn or varicose wounds in both human and murine models. Tsukada et al (1992) examined the effect of pH in chronic ulcers. Their study showed that the pH of chronic ulcers reflected the stage of the ulcer: the more advanced the stage, the higher the wound pH. The pH of non-epithelialised wounds was found to be similar to that of Stage III pressure ulcers (pH 7.5), while the pH of newly formed epithelium at wound edges was similar to that of normal skin (around pH 5.9).

In a more recent study, Dissemond et al (2004) measured 247 pH values in 39 patients with chronic wounds of mixed aetiologies, one of whom had diabetes, over a 12-month period at an outpatient clinic. Their results concur with those of Tsukada et al (1992), whereby the pH range of protease levels was a dynamic factor throughout the healing process. However, Dissemond et al (2003) did not attribute any significance of wound healing stage to pH level.

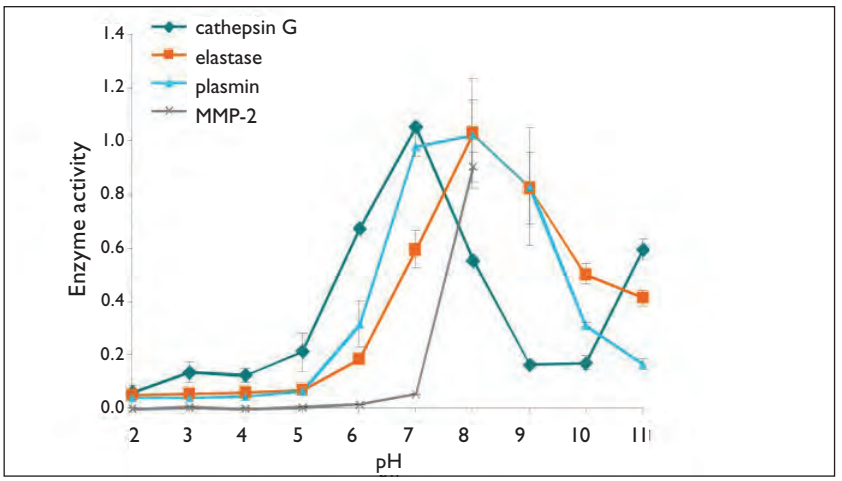


*Figure 1. Protease modulation by pH.*

## Modulating pH by use of a topical ointment

Protease modulation is a means of reducing protease activity, but it must not damage the extracellular matrix we are attempting to protect. In the wound bed, this matrix is predominantly collagen-based (Edmonds et al, 2004). Leveen et al (1973) showed that prolonged topical acidification of wound surfaces promoted epithelialisation by increasing the availability of cellular oxygen at the wound bed; alkalinisation hindered this process and delayed wound closure. This study also concluded that acidification was found to increase the $pO_2$ of surfacce wounds by a shift in the oxyhaemoglobin dissociation curve (the Bohr effect; Leveen et al, 1973).

Cadesorb (Smith & Nephew Healthcare, Hull) is the proprietary name of a pH-modulating ointment which, according to its manufacturer, can reduce protease activity. It consists of a matrix of cross-linked carboxylated starch beads in a PEG/PPG (polyethylene glycol and polypropylene glycol) carrier. The cross-linked starch beads modulate the pH of the local environment without any adverse effects on healing tissue. The ointment may be applied directly to the granulating wound bed with a secondary foam dressing of choice. The product will work as long as it is in contact with the wound bed with no residual effects once irrigated from the wound at dressing change.

According to the manufacturer, it should not be used on wounds which require debridement (T), topical antimicrobials (I), or have excess exudate (M), since these barriers to healing should have been addressed in the first instance. There should, therefore, be no need for topical antimicrobials or additional interactive dressings.

This may provide a cost effective method of controlling the wound environment of the chronic wound when used appropriately.

## Conclusion

The application of TIME to determine barriers to healing in the diabetic foot will direct the clinician to the dominant factors that may prevent wound progression. Some wounds fail to epithelialise despite best practice in wound care. As chronic wounds are linked to highly destructive protease levels, a major advance would be to control this environment by use of a pH modulator in an attempt to emulate a wound in an acute phase of healing. Cadesorb has yet to be used extensively in diabetic foot lesions but may provide a useful adjuvant to wound care. ■


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