# The significance of surface pH in chronic wounds

Wound healing is a complex, multifaceted process which is influenced by both intrinsic and extrinsic factors. The pH of the wound can affect many factors including oxygen release, angiogenesis, protease activity, and bacterial toxicity. Chronic non-healing wounds have an elevated alkaline environment. Healing occurs more readily in an acid environment. Current wound bed assessment is dependent on subjective evaluation with few diagnostic instruments available or suited to routine practice. Monitoring surface pH may provide a method of 'measuring' the condition of the wound bed and ultimately aid in determining the wound's response to treatment.

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Chronic non-healing wounds, such as leg ulcers, which affect up to 2% of the population, continue to pose a treatment challenge to the clinician (Callam et al, 1985; Nelzen et al, 1996; O'Brien et al, 2000; Moffatt, 2004). Clinical assessment of the wound bed of these chronic wounds is predominantly based on subjective interpretation with little recourse to objective analysis. Monitoring surface pH may provide a method of 'measuring' the condition of the wound bed and ultimately aid in determining the wound's response to treatment. This paper will present a review of wound pH and the physiological effects on wound healing.

## What is pH?

Regulation of hydrogen ions ($H^+$) in the fluid compartments of the body is of critical importance to health. Even a slight change in concentration can result in an alteration in the rate of chemical reactions (Solomon et al, 1990). The pH notation is a measurement of $H^+$ concentration and is measured on a logarithmic scale in the range of 0–14 (Solomon et al, 1990). A pH of 7 represents neutral, a pH below 7 is acidic representing a higher hydrogen concentration, while a pH value above 7 is termed base or alkaline and represents a lower hydrogen concentration. Because a logarithmic scale is used for all pH measurements, actual acidity increases much faster than the numerical change in pH might seem to indicate (Ganong, 2001). A pH of 5, for example, is 10 times as acidic as a pH of 6, representing a ten-fold increase in $H^+$ concentrations (Solomon et al, 1990).

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The protein buffering system is the most plentiful buffering system in the blood and tissue cells and acts to stabilise pH (Solomon et al, 1990). Proteins are able to take hydrogen ions out of solution and bind them to their structure, thereby decreasing the hydrogen ion concentration of the solution and minimising pH changes (Solomon et al, 1990). Haemoglobin is one type of intracellular buffer. When oxyhaemoglobin releases oxygen, the reduced haemoglobin possesses a net negative charge that can bind hydrogen ions (Solomon et al, 1990).

## pH and wound healing

Normal wound healing is characterised by the successful completion of four distinct but overlapping phases —haemostasis, inflammation, proliferation, and remodelling. Altered or impaired wound healing, as seen in chronic wounds, is marked by interruption of this process. The literature records some studies of the affects of pH on cellular events in wound healing and the alteration in surface pH of wounds when topical preparations have been used.

The pH environment of chronic wounds has been recorded within the range of 7.15–8.9 (Wilson et al, 1979; Tsukada et al, 1992; Romanelli et al,

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1997). This variability is representative of both healing and non-healing wounds. Both acute and chronic wounds with an elevated alkaline pH have demonstrated lower rates of healing than wounds in which the pH is closer to neutral (Leveen et al, 1973; Roberts et al, 1997; Gethin and Cowman, 2006).

Importantly, as the wound progresses towards healing, the pH moves to neutral and then becomes acidic (Tsukada et al, 1992; Kaufman et al, 1985). This has been demonstrated in one study which mapped the pH of pressure ulcers according to depth and tissue type (Tsukada et al, 1992). In the latter study, stage 1 pressure ulcers had a pH similar to that of intact skin (range 5.4–5.6), while the pH of stage 2 ulcers was 6.9. This increased to 7.6 for stage 3 ulcers. Of note in the study by Tsukada et al, epithelialised wounds had a mean pH of 6.0 compared with a mean of 7.8 for wounds without epithelial tissue, which was shown to be statistically significant ($p< 0.001$) (Tsukada et al, 1992).

The authors concluded that pH is related to tissue type and not the grade of the wound. Indeed, the presence of necrotic tissue and devitalised tissue in the wound causes an increased metabolic load on the wound resulting in tissue hypoxia (Hunt and Beckert, 2005). These wounds have excessive breakdown of the extracellular matrix (ECM) and consequently the wound itself as this occurs more readily in an alkaline environment (Greener et al, 2005; Gethin and Cowman, 2006). There are many potentially contributing processes towards this.

One of the altered processes is that of protease activity. Matrix metalloproteinases (MMPs) are a family of more than 20 proteases that collectively can degrade most of the components of the ECM (Greener et al, 2005). Proteases are enzymes that have the ability to cleave proteins. This ability is referred to as the 'activity' of the proteases and is dependent on both the amount of proteases present and on the presence of inhibitors (Hoffman et al, 1999). Every protease shows peak enzyme activity at certain pH levels, where the protein is broken down more rapidly than at other pH values (Greener et al, 2005). For example, cathepsin G has peak activity at pH 7.0; elastase at 8.0; plasmin at 8.0, MMP-2 at 8.0 and neutrophil elastase at 8.3 (Greener et al, 2005). Proteases are not only produced by the wound itself but also as end-products by bacteria. Ammonia, which is liberated from urea by the enzyme urease, is also produced by bacteria and is toxic to wound tissue but importantly favours an alkaline rather than an acid environment (Leveen et al, 1973; Thomas, 1990). This is significant in the chronic wound which can harbour at least four different types of bacteria at any one time (Trengrove et al, 1996).

**In addition to the effects on protease activity and oxygen release, other effects of lowering the pH to a more acidic environment are to reduce the toxicity of bacterial end products such as ammonia, enhancing the destruction of abnormal collagen in the ulcer bed, promotion of angiogenesis, increased macrophage and fibroblast activity and control of enzyme activity.**

The pH environment also influences oxygen release to the tissues. Oxygen delivery to damaged tissue particularly in the chronic wound is dependent not only on perfusion but diffusion (Hunt and Beckert, 2005). A lowering of pH by 0.6 units releases almost 50% more oxygen and a five-fold increase in release of oxygen by a shift of 0.9 pH units (Leveen et al, 1973). Within the chronic wound this is important as the likelihood of healing is high if tissue oxygen tension ($pO_2$) is >40mmHg, but is unlikely at levels of <20mmHg (Hunt and Hopt, 1997). Indeed in chronic recurrent wounds such as venous leg ulcers, the skin and local vasculature become scarred and atrophic, resulting in permanent obstacles to the transport of oxygen (Hunt and Beckert, 2005). Therefore, any factor that could cause even a small change in the pH of the wound may appreciably alter the available supply of oxygen to the tissues (Leveen et al, 1973).

In addition to the effects on protease activity and oxygen release, other effects of lowering the pH to a more acidic environment are to reduce the toxicity of bacterial end products such as ammonia, enhancing the destruction of abnormal collagen in the ulcer bed, promotion of angiogenesis, increased macrophage and fibroblast activity and control of enzyme activity (Thomas, 1990; Romanelli et al, 1997; Molan, 2002; Brett, 2003; Greener et al, 2005).

## Wound dressings and wound pH

Efforts to decrease wound surface pH using topical agents have had varying degrees of efficacy. Acetic acid in 1% and 5% solutions has been widely used in an attempt to reduce the pH. However, acetic acid lowers pH for only one hour after which it returns to pre-treatment levels (Leveen et al, 1973). Efforts to manage the bacterial burden of the wound using acetic acid has also had limited and variable efficacy.

In a letter to the *Lancet*, Milner (1992) reported eradication of *Pseudomonas aeruginosa* from seven chronic and two acute wounds after 2–7 days with once-daily soaks of 5% acetic acid. A further study used a 1% solution of distilled acetic acid diluted with equal part sterile water for management of exit site infection in 38 patients receiving continuous ambulatory peritoneal dialysis (Leung et al, 2001). The authors reported eradication of *Pseudomonas aeruginosa* infection in 92% (n=37) of cases with no relapse (Leung et al, 2001).

However, a randomised controlled trial of acetic acid compared with hypochlorite showed that acetic acid had no effect on organisms other than *P. aeruginosa* and that other organisms

either replaced *P. aeruginosa* or were present throughout (Phillips et al, 1968). Limitations of using acetic acid are, therefore, the short duration of effect, the lack of poly-antimicrobial effect and additional concerns regarding quality and safety. Acetic acid is currently not available as a sterile agent licensed for use in wound management.

The permeability of dressings to carbon dioxide contributes to lowering pH (Thomas, 1990). Occlusion of the wound prevents the loss of carbon dioxide consequently preventing the wound from developing a respiratory alkalosis (Thomas, 1990). Recent studies of this effect have included the use of honey dressings to alter surface pH (Gethin and Cowman, 2006). The surface pH and wound size of chronic non-healing wounds was monitored in 20 wounds over a two-week period (Gethin and Cowman, 2006). This study reported that wounds having a pH of ≤7.6 showed a 30% reduction in wound size after two weeks. As the pH increased, the reduction in size decreased. In addition, those with a pH of 8.0 or higher increased in size. The use of honey which has a pH of 3.5 showed a statistically significant reduction in surface wound pH after treatment ($p = 0.001$) (Gethin and Cowman, 2006).

Romanelli et al (1997) demonstrated a reduction in surface pH of granulating leg ulcers after 48 and 72 hours using Allevyn foam dressings (Smith and Nephew, Hull) . In the latter study, pH values reduced from a mean of 8.2 $^{+}$/-1.5 to a mean of 6.2 $^{+}$/- 0.2 after 72 hours. Wound pH has also been shown to reduce when hydrocolloids have been used (Varghese et al, 1986). More recent additions to the range of dressings to alter pH include Cadesorb (Smith and Nephew) which is a pH-modulating topical agent.

## Measuring wound pH

Litmus paper is unsuited to monitoring wound surface pH primarily due to a lack of specificity. The most frequently used instrument is a glass top electrode attached to a meter (Roberts et al, 1997; Romanelli et al, 1997; Mani and Ross, 2000; Gethin and Cowman, 2006). When a probe is used it is first calibrated in pH 4 and 7 and/or 9 buffers. The probe is rinsed in deionised water and then placed flat against the wound for 30 seconds and the result is displayed on the meter. Readings are taken when the wound dressing has been removed as over-exposure of the wound to the atmosphere can invalidate the result due to a loss of carbon dioxide and the influence of heat or cold or drying of the wound surface. It is important to state that results obtained are of surface pH and not tissue pH. In addition, to aid interpretation of results the condition of the wound bed and the presence or absence of devitalised tissue should be noted at the time of the reading, as this will contribute to a holistic assessment.

**In the future it may be possible to use a combination of validated outcome measures such as wound size and wound pH to determine treatment efficacy at time points earlier than complete wound closure. The use of this information could help the clinician in making treatment decisions and ultimately a move towards a targeted therapeutic approach to wound management.**

## Implications for practice

The development of wound diagnostic instrumentation is still in its infancy. While sophisticated systems such as magnetic resonance imaging and video image analysis can aid specialist assessment these are not suited to the routine clinical setting. Assessment of the wound bed by the clinician is primarily based on subjective interpretation with few objective instruments suited or available for use in routine practice. Of the objective methods available, monitoring of wound size is easy to conduct and can aid objective evaluation and be used to predict healing (Plassmann, 1995; Tallman et al, 1997; Margolis et al, 2000; Gethin, 2006). In the future it may be possible to use a combination of validated outcome measures such as wound size and wound pH to determine treatment efficacy at time points earlier than complete wound closure. The use of this information could help the clinician in making treatment decisions and ultimately a move towards a targeted therapeutic approach to wound management. Further studies to explore this issue are required. The advantages to clinical practice should such methods be validated would be to reduce the dependence on subjective assessments, and move in the direction of objective evaluation.

## Conclusion

Wound healing is a complex physiological process which is impaired in the chronic wound. Factors which influence wound healing include the pH environment. Both acute and chronic wounds move to a neutral and then acidic state as healing occurs. Monitoring pH may aid in objective assessment of the wound bed and evaluation of treatment progress. WUK

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## Key Points

- Proteases are pH dependent. Many proteases are most active in an alkaline environment.
- Wound healing occurs as the wound pH moves to neutral and then acidic.
- Oxygen is released from oxyhaemoglobin more readily as the pH shifts from alkaline towards neutral.
- Monitoring of surface wound pH may aid objective wound bed assessment.

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