Arch Dermatol Res (2007) 298:413–420
DOI 10.1007/s00403-006-0713-x

REVIEW

Influence of pH on wound-healing: a new perspective for wound-therapy?

Lars Alexander Schneider · Andreas Korber · Stephan Grabbe · Joachim Dissemond

Received: 21 July 2006 / Accepted: 23 September 2006 / Published online: 8 November 2006

Abstract Wound healing is a complex regeneration process, which is characterised by intercalating degradation and re-assembly of connective tissue and epidermal layer. The pH value within the wound-milieu influences indirectly and directly all biochemical reactions taking place in this process of healing. Interestingly it is so far a neglected parameter for the overall outcome. For more than three decades the common assumption amongst physicians was that a low pH value, such as it is found on normal skin, is favourable for wound healing. However, investigations have shown that in fact some healing processes such as the take-rate of skin-grafts require an alkaline milieu. The matter is thus much more complicated than it was assumed. This review article summarises the existing literature dealing with the topic of pH value within the wound-milieu, its influence on wound healing and critically discusses the currently existing data in this field. The conclusion to be drawn at present is that the wound pH indeed proves to be a potent influential factor for the healing process and that different pH ranges are required for certain distinct phases of wound healing. Further systematic data needs to be collected for a better understanding of the pH requirements under specific circumstances. This is important as it will help to develop new pH targeted therapeutic strategies.

Keywords Wound healing · Chronic wounds · Wound-therapy · PH value · Skin-grafts · Wound-milieu

L. A. Schneider
Department of Dermatology, Venerology and Allergology, University School of Medicine, Maienweg 12, Ulm 89081, Germany

A. Korber · S. Grabbe · J. Dissemond (✉)
Department of Dermatology, Venerology and Allergology, University School of Medicine, Hufelandstraße 55, Essen 45122, Germany
e-mail: joachimdissemond@hotmail.com

Introduction

Wounds can be compared with a "large biological building site", where degradation of dead tissue intercalates with the assembly of new structures of extracellular matrix and the covering lining of epithelium. In order to complete this regeneration process successfully the wound is metabolically very active. This involves biochemical reactions for which the pH value is a very important factor.

The pH value expresses the negative logarithmic scale for the effective concentration of H^+-ions in solution ($pH = -\log[H^+]$), i.e. in the interstitial milieu of wounds. It ranges from 0 to 14 thus defining H^+-ion concentrations of 10^0–10^{-14} mol/l. Chemical reactions require each a certain optimum pH value and the latter is modified by endogenous and exogenous factors, like for example the ambient temperature [1]. In summary the pH value is a key determinant for the metabolism during wound healing and thus also an important parameter for therapeutic interventions in wound-care.

pH value of normal skin

Under normal circumstances an acidic milieu is found on the skin surface which has been described first by

Hesus et al. in 1892 [12] and was later on confirmed again by Schade and Marchionini in 1928 [29] This acidic milieu varies depending on the anatomical location and age of the person between a pH of 4–6 and has always been seen as an important aspect of the skin's barrier function. This pH milieu also seems to be important for the resistance against external chemicals [3, 24]. Sex-specific differences in pH milieu between men and women could not be found so far [38]. The physiological pH value results from amino acids, fatty acids and others produced and secreted by the keratinocyte layer and the skin appendages, which provide a local shift in the natural lactate–bicarbonate buffer system of the body towards an acidic milieu.

pH values and microorganisms on the skin

The skin's acidic milieu is disturbed in wounds, where underlying tissue with the body's internal pH milieu of 7.4 becomes exposed. Most relevant human-pathogenic bacteria need pH values above 6 and their growth is inhibited by a lower pH value [21, 23, 30, 32]. The same applies to candida albicans yeast, another increasingly important pathogenic microorganism, as higher pH values promote an overgrowth with candida species on the skin [27]. In this context a study by Stüettgen and Schaefer showed that the pH milieu of normal skin becomes more alkaline by bacterial colonisation [31].

Restoring the natural acidic milieu on the skin can thus effectively help to reduce the microbial load on the body surface even if they are multiresistant to antibiotics. An interventional clinical study supported this view by showing that topical application of acidic ointments in diabetics and stroke patients significantly reduced their bacterial load on the skin surface [15]. It is interesting and somewhat seems paradox, that essential bacterial enzymes like most of the staphylococci-derived proteases are diminished in their activity by an alkaline milieu, whereas the pH on normal skin promotes greater protease activity [8]. Enterotoxin C2 from Staphylococci (SEC2) for example changes its three-dimensional protein structure and with it the activity depending on the pH value of the surrounding milieu [14]. Many wounds, especially chronic leg ulcers are often colonised by intestinal, oral and resident dermal microorganisms. However, whether a bacterial colonisation is per se a factor for delayed wound healing has so far not been conclusively answered [16]. But it can be unfavourable for the healing process, as for *Staphylococcus aureus*, one of the most common contaminating bacteria found in wounds it has been shown that its presence delays the healing of chronic wounds [11]. Therefore it is a generally accepted concept in clinical practice that one should aim to reduce bacterial colonisation of wounds by appropriate therapeutic measures. The body's innate defence seems to pursue the same strategy, as in wounds that are invaded by neutrophils to combat bacteria, clinically seen as pus in the wound, the pH value shifts towards acidic milieu. However, a causal relationship between the measured pH values and the degree of bacterial contamination or the species of contaminating bacteria within the wound has not been established so far [15]. Another aspect in this context is that changing the pH value can affect the effectiveness of antibiotics in infected wounds. In vitro observations have shown for example that the toxicity of a new glycopeptide antibiotic (Oritavancin, LY333328) towards vancomycin resistant *Enterobacter* species (*E. faecium*) decreases significantly in an acidic milieu with a pH value of 6.4 compared to pH values of 7.4 and 8.4 [22]. For the aminoglycoside gentamycin, still important for gram negative soft tissue infections, it is just the same. Its activity also strongly increases in an alkaline milieu as a pH value of 7.8 results in a 90-fold higher biological efficacy compared to pH 5.5. In contrast for some other antibiotics, such as chloramphenicol, clindamycin and most of the β-lactam antibiotics it has been shown that they are not inactivated in an acidic milieu.

Therapeutic interventions changing the wound pH milieu could help to eliminate bacterial contamination and might therefore tackle one potential co-factor for the delayed wound healing process. However, the question of whether or not and under which certain circumstances a bacterial colonisation is actually unfavourable for the natural healing process has to be answered more precisely by means of future research in this field.

pH milieu influences the proteolytic activity in chronic wounds

In chronic wounds the physiological balance between tissue degradation and tissue reassembly is lost and catabolic processes predominate. This explains the plethora of proteolytic enzymes found in the milieu of chronic wounds. As long as the wound remains the inflammatory phase, the catabolic enzymes remain active in the tissue. When the healing eventually progresses and inflammation subsides, the physiological balance slowly returns and protease activity diminishes. In this context a study by Trengove et al. demonstrated that activity of matrix-metalloproteases (MMPs)

decreases consistently in venous leg ulcer patients as they progress from non-healing to healing [33]. In addition, the authors found that the physiological opponent of MMPs, the tissue inhibitor of MMP (e.g. TIMP-1) raises to about tenfold the normal level in healing wounds [2]. To take this further Greener et al. investigated the pH dependency of certain proteases like cathepsin-G, elastase, plasmin and MMP-2 that are relevant for matrix degradation and re-assembly in chronic wounds. A total of 19 secretion samples from patients with chronic wounds were collected. The samples demonstrated a pH value of 7.5–8.9. Half of the measured samples were in the pH range of 8.1to 8.3. This is very interesting as the pH optimum for MMP-2, plasmin and elastase is 8.0. A shift of the wound pH value down to 6.0 would entail a 40–90% decrease of activity of these enzymes and imply a profound impact on the biochemistry of proteolytic activity at this stage [9, 10]. These effects may induce a benefit for wound healing, but that is speculative at this point and would have to be backed up by appropriate further investigations.

pH milieu in wounds depends on time course and wound-stage

During the healing of acute wounds a temporary physiological acidosis is observed, which results from several contributing factors. Important in this context is the generation of organic acids, e.g. lactic acid and the increased demand for O_2 during the healing process combined with a stasis of tissue perfusion increasing the local pCO_2 in wounds [13, 15, 25]. The production of lactic acid is linked with the increase in glycolysis during the phase of increased collagen production during the healing process, which reaches its physiological maximum on day 20 [15, 16]. Another facultative contribution to the acidic milieu comes from pus within the wound [15].

This physiological acidosis might be beneficial for the healing process, as an in vitro model with human dermal fibroblasts for experimental acute wounds showed a significant decrease in cell migration and DNA synthesis following an increase of the pH milieu. The authors conclude in their publication that an acidic milieu is more beneficial for the investigated parameters related to wound healing [17]. Apart from that also other processes, which are important for wound healing, such as proliferation of fibroblasts, are induced by an acidosis [19]. Another argument for the long standing hypothesis that a quick restoration of a normal acidic skin milieu is good for wound healing comes from the physiology of oxygen supply to the tissue [18, 20, 36]. The rationale behind this is that besides inhibiting microbial colonisation, a low pH value also leads to the so-called Bohr-effect, i.e. an increase of the amount of available oxygen for cells [13, 18]. The Bohr-effect, which was first described by the Danish physiologist Christian Bohr in 1904, results from a decreased binding capacity of haemoglobin under conditions of decreased pH and/or increased CO_2 levels in tissues. This leads to a release of oxygen normally still bound to haemoglobin. Due to this effect the available tissue concentration of oxygen at the wound edge, i.e. the frontier of migrating epithelium, increases, which would be beneficial for healing [20].

In contrast to acute wounds, time course analysis of pH value in chronic venous leg ulcers and pressure sores has shown that the wound-milieu in these wounds remains shifted to an alkaline milieu for most of the time except for the re-epithelisation phase, where it becomes acidic again [7, 28]. In a clinical investigation enrolling 50 patients with chronic leg ulcers the mean pH value measured was 7.7 (±0.3 SD), with a total range measured of 7.3–8.9 [36]. Another study with 15 patients found values in the same range, i.e. 7.5–7.9. Interestingly, the adjacent normal skin on the lower limbs 10 cm away from the ulcer demonstrated pH values of 6.2–6.6 [7]. Thus the pH value in chronic wounds is alkaline and the ulcers are surrounded by a zone of adjacent skin with a disturbed acidic milieu, i.e. barrier function. The same authors conducted measurements of pH milieu in 8 patients with chronic pressure sores on their legs in different healing stages where they found a mean pH value of 5.7 (±0.5 SD) in stage I wounds, whereas the corresponding values for stage II and stage III wounds were higher, i.e. 6.9 (±1 SD), respectively 7.6 (±0.2 SD). Thus there is a clear difference in pH milieu between early and later stage chronic pressure sores, with one exemption. If the wound became re-epithelialised during stage II, the pH values dropped to 6.0 (±0.5 SD) thus the values of normal skin surface [17].

In another clinical study by Tsukada et al. serial measurements of three patients with a chronic venous leg ulcer revealed an average pH value of 6.1 (±1.3 SD) in stage II ulcers and 7.5 (±0.4 SD) in stage III ulcers. These results confirm again that the milieu in stage III chronic wounds is much more alkaline than in earlier stages of wound healing. Finally they measured pH values in different areas of epitheliating wounds in four patients. Measurements in the centre of the wound gave the highest pH values on average 7.6 (±0.6 SD), whereas those on the epitheliated wound borders showed physiological pH values of 5.9 (±0.4 SD)

like normal skin [34]. Unfortunately the manuscript neither contains details about the measuring procedure itself nor about the exact clinical criteria, according to which the patients' wounds were classified.

pH milieu changes after wound debridement

The influence of the pH milieu on wound healing has gained attention in wound-bed-preparation [20, 26]. Pus, necrotic tissue, and serum crusts are clinical indicators of lower pH milieu. Such wounds had a mean pH value of 6.1 (±0.6 SD). After a surgical debridement of chronic wounds covered with necrotic tissue the pH milieu increases immediately from an average of 5.7–8.4 [34]. The same happens, if crusts on a wound are removed by means of a hydrocolloid dressing. Thus any sort of wound debridement seems to result in a pH value shift towards an alkaline milieu. This raises interest in the context of biosurgical debridement of wounds. Biosurgery has proven to be beneficial and is achieved by putting larvae of lucilia sericata flies onto the wound. This intervention is also accompanied by a shift of the pH value into the alkaline range. The reason for this shift is not clear yet. It has been discussed that the larvae secret multiple substances like e.g. phenyl acetate, phenyl-acet aldehyde, allantoin, urea, ammonium-ions and calcium-carbonate and digest the fibrinous wound secretions. On the background of therapeutic success with this strategy it is now speculated, whether the shift of pH milieu might actually be one reason for the observed benefit of biosurgery [6]. However, convincing arguments for this assumption have yet to be presented.

Another method of wound-bed-preparation in chronic wounds is the proteolytic debridement. Table 1 lists the enzymes, which have been used in such preparations. These data were recruited from the national formulary, additional information gained from scientific articles and from pharmaceutical companies. As many of the enzymes are only efficiently active within a restricted pH range it becomes clear that one should know the pH value of the wound-milieu in order to check prior to use, whether the preparation to be chosen can be effective at all under the given conditions.

Table 1 Biochemical characteristics of a variety of enzymes used in preparations for enzymatic wound debridement

DNAse
Activity pH 4.5–5.5 (fibrinolysis)
Activity pH 7.0–8.0 (DNA lysis)
Fibrinolysin
Activity pH 7.0–8.0
Kollagenase
pH optimum 6.0–8.0
Krill-enzyme
pH optimum above 7.5
Papain
Activity pH 3.0–12.9
pH optimum 7.0
Plasmin
pH optimum 7.0
Streptodornase
pH optimum pH 7.5
Streptokinase
Activity pH 7.3–7.6
Sutilain
pH optimum 6.0–6.8
Trypsin
pH optimum 7.0

Modern wound care therapy modifies the wound pH value

The use of hydrocolloid dressings does not change the pH milieu of normal skin [34]. However, if modern wound-dressings are used on chronic wounds, the pH values in the wound-milieu can be modified in various ways. Our own investigations with 39 patients with chronic wounds and a total of 247 pH measurements could show that individual pH values in such wounds vary from person to person with a total range of 5.4–8.6 (Fig. 1). We further found in both, acute and chronic wounds treated by modern standards of wound care, a mean pH about 7.4. A time course analysis of wound pH milieu in selected individual patients over 12 months revealed that the pH values over this period of time could vary by 1.73 units [6]. Particularly the kind of dressing applied to the wound itself affects the pH value underneath it. Wound secretions of chronic wounds under non-permeable dressings demonstrated a more acidic milieu than secretions of wounds, where a permeable dressing is used. The acidic secretions of such wounds treated with occlusive synthetic dressings showed in further in vitro investigations a capacity to inhibit bacterial growth on the one hand and promote fibroblast growth on the other [35]. Wilson et al. investigated this potential benefit of an acidic pH achieved by special dressings further in a prospective clinical analysis with 36 patients suffering from a chronic venous leg ulcer. These patients were randomised into two groups. Group 1 was treated twice weekly with an un-buffered emulsion of pH value 7.3, whereas group 2 was treated with a buffered phosphate solution of pH value 6.0. Readout criterion was the spatial spreading of epithelium on the wound surface. In group 2 that received the buffered pH value 6.0 emulsion the epithelium spreaded

Fig. 1 Measuring the wound pH value in a chronic wound with an customised flat glass-membrane-probe

22.6 mm/day (±15.2 SD), whereas in group 1 treated with 7.3 pH value emulsion only a reduced spreading of 3.3 mm/day (±7.4 SD) was measured. The authors further noticed that all ulcers in group 2 healed completely, whereas 11% (2/18) of the ulcers in group 1 did not heal [36]. In another open prospective clinical study 20 patients with chronic venous ulcer were treated for 24 weeks with a multi-layer dressing. The pH value initially had a median of 7.4 and decreased to 6.6 at the end of the investigation in those patients that improved under therapy. In addition to this an inverse correlation between pH value and available oxygen supply in the wound was found, which in principle supports the above mentioned Bohr-effect [25]. In summary a targeted titration of the wound pH towards an acidic milieu appears to support the self-healing process of the wound.

pH milieu influences the take-rate of skin-grafts

Many wounds do not heal by themselves and need skin-graft transplantations. Until now only very few investigations have been carried that investigated the relationship between wound pH milieu and the take-rate of skin-grafts. Furthermore, the few studies that were performed in this field are very heterogeneous in measurement techniques, patients recruited and grafts used for transplantation. Despite this fact, however, they all hint into the same direction. An investigation by Glinz et al. with 36 patients reports again a range of pH values of 6.9–9.4 in the wound-milieu. In 64% of patients the maximum pH value was 8.2. The authors further state in this article that under a local therapy regime with cotton gauze soaked in 0.9% saline solution the optimum pH range for the highest take-rate of 90% achieved was 7.4–8.2 [15]. Unfortunately, the article lacks many important details, such as the transplantation take-rate in the other pH ranges and clinical data of the enrolled patients. Furthermore the authors used several skin replacement strategies in parallel within this study involving mesh-graft and full thickness skin-grafts without differentiating between them. A second study in this field by Sayegh et al. first correlates the take-rate of skin transplants in wounded rats with the pH range within the wound. At a pH value of 6.6 a 0–30% take-rate, at a pH value 6.8 a 50–100% take and at a pH value 7.0 a 87–100% take was noted. The animal data was then compared to the take-rates of skin transplants in humans. The authors recruited 25 patients with 2nd and 3rd degree burns for this part of the study. At a pH milieu of 6.4 overall 20% of skin-grafts were successful, at a pH value of 6.6–35%, at pH value 6.8–66% at pH value 7.0–77% and at pH value 7.2–90%. Thus their finding in rats could be confirmed in humans with burn wounds. To look at other types of wounds the authors then recruited 18 patients with different types of ulcers. As before, below a cut-off pH value of 7.4 no graft was taken, whereas in the cases where the actual pH milieu was above this cut-off 100% of skin-grafts were taken [16]. These findings are supported further by another investigation by Ye et al., who also looked at the take-rate of skin-graft in patients with acute and chronic wounds of different origin. In a total of 90 patients no case was noted, where a skin-graft was successful in wounds with a pH value below 7.0, whereas as before, 99% of skin-grafts were taken in wounds with a pH value of 7.4 and higher [37].

In summary all studies performed support the view that a skin transplant heals best on a chronic wound if the pH value is above 7.4. Important aspects of the different studies in this field are summarised in Table 2.

Conclusion

Looking at the various aspects in which the pH value can influence wound healing it clearly proves to be a potent influential factor for the final outcome. Interestingly, so far only few investigations have been performed in this field. The results from currently available data can be summarised as follows:

- physiological milieu of the skin is acidic, which supports the natural barrier function and helps to counteract microbial colonisation;
- chronic wounds and infected wounds with a high bacterial load characterised by a pH above 7.3;
- acute wounds, wounds with pus or necrotic tissue and chronic wounds that progress in their healing process show an acidic pH;
- pH value in wounds is a dynamic factor that can change rapidly with therapeutic interventions;

Table 2 Take-rates of skin transplants in different studies compared with wound pH values

Author	Species	Wound type	*n*	Successful grafting	
				pH	Take-rate (%)
Sayegh	Rat	Arteficial	15	6.6	0–30
				6.8	50–100
				7.0	87–100
				7.2	100
Sayegh	Human	Burn	25	6.4	20
				6.6	35
				6.8	66
				7.0	77
				7.2	90
Sayegh	Human	Ulcers	18	<7.4	0
				>7.4	100
Ye	Human	Ulcers	90	6.8–7.0	0
				7.0–7.2	6
				7.2–7.4	47
				7.4–7.6	91.4
				>7.4	99

- wound debridement increases the pH value;
- successful skin-grafting needs a wound-bed with pH values above 7.3.

Therefore, the pH value in wounds seems to be influenced by many different endogenous and exogenous factors. Figure 2 summarises the current available data for typical acute and chronic wounds (Fig. 2). Investigations looking at various aspects of wound healing support the old general view, that an acidic pH in the wound supports most aspects of the natural healing process. Such a pH milieu suppresses bacterial growth, reduces proteolytic activity, enhances fibroblast growth in vitro, leads to more oxygen supply and is an indicator of successful self-healing of chronic wounds. In contrast to that, biosurgery is characterised by a shift towards an alkaline pH. Furthermore many chronic wounds will not heal by themselves despite all modern wound care dressing strategies. In these cases deliberated surgical intervention is inevitable and one of the key aspects of that is skin-grafting. In this field all data available so far clearly shows that a successful skin-graft needs an alkaline wound milieu.

In total there are only few investigations in this field on the influence of the pH milieu in wound healing so far. But from what is known it becomes clear that future investigations aiming at a targeted modification of the wound pH milieu might be a very promising novel approach in wound care. To illustrate this with

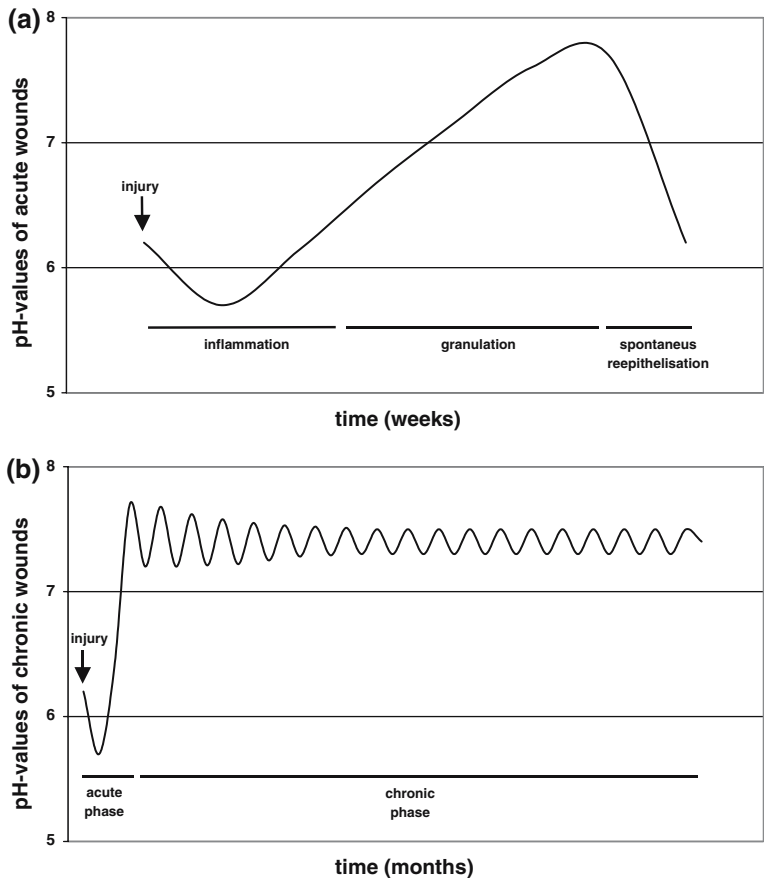

Fig. 2 **a** Course of pH milieu in acute wounds. **b** Course of pH milieu in chronic wounds

another example, the raising clinical problem of multiresistant bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA) can be taken. Those bacteria are very difficult to tackle and a treatment approach with a shift of the wound pH milieu might be a new strategy to eliminate them from wounds [4, 5]. Thus as the basis for further expansion of our knowledge in this field routine pH measurements should be considered as a first step. The measurement procedure is simple, fast and can therefore also be performed in an outpatient clinic. The industry has already provided first new products, which allow influencing directly the wound pH value. Thus, the so far neglected parameter pH milieu might together with other clinical data from the patients' records provide in the future the basis for some therapeutically decisions.

References

1. Braun-Falco O, Korting HC (1986) Der normale pH-Wert der menschlichen Haut. Hautarzt 37:126–129
2. Bullen EC, Logaker MT, Updike DL, Benton R, Ladin D, Hou Z, Howard EW (1995) Tissue inhibitor of metalloproteinases-1 is decreased and activated gelatinases are increased in chronic wounds. Invest Dermatol 104:236–240
3. Dikstein S, Zlotogorski A (1994) Measurement of skin pH. Acta Derm Venereol Suppl 185:18–20
4. Dissemond J, Koppermann M, Esser S, Schultewolter T, Goos M, Wagner SN (2002) Therapie eines Methicillin resistenten Staphylokokkus aureus (MRSA) im Rahmen der Behandlung eines chronischen Ulcus mit sterilen Fliegenmaden. Hautarzt 9:608–612
5. Dissemond J, Körber A, Lehnen M, Grabbe S (2005) Methicillin resistenter *Staphylococcus aureus* (MRSA) in chronischen wunden: therapeutische optionen und perspektiven. J Dtsch Dermatol Ges 3:256–262
6. Dissemond J, Witthoff M, Brauns TC, Haberer D, Goos M (2003) Untersuchungen zum pH-Wert des Milieus chronischer Wunden im Rahmen einer modernen Wundtherapie. Hautarzt 54:959–965
7. Glibbery A, Mani R (1992) pH in leg ulcers. Int J Microcirc Clin Exp 11:S109
8. Glinz W (1971) pH-Mesungen des Granulationsgewebes vor freier Hauttransplantation. Zentralbl Phlebol 10:105–113
9. Greener B, Hughes AA, Bannister NP (2005) The effect of pH on proteolytic activity in chronic wound fluids and methods for determination. Poster Z079 2nd WUWHS Congress, Paris
10. Greener B, Hughes AA, Bannister NP, Douglass J (2005) Proteases and pH in chronic wounds. J Wound Care 14:59–61
11. Halbert AR, Stacey MC, Rohr JB, Jopp-McKay A (1992) The effect of bacterial colonization on venous ulcer healing. Australas J Dermatol 33:75–80
12. Hesus E (1892) Die Reaktion des Schweißes beim gesunden Menschen. Monatsschr Prakt Dermatol 343:400–401
13. Hunt TK, Twoney P, Zederfeldt B, Dunphy JE (1967) Respiratory gas tension and pH in healing wounds. Am J Surg 114:302–307
14. Kumaran D, Eswaramoorthy S, Furey W, Sax M, Swaminathan S (2001) Structure of staphylococcal enterotoxin C2 at various pH levels. Acta Crystallogr D Biol Crystallogr 57:1270–1275
15. Kurabayashi H, Tamura K, Machida I, Kubota K (2002) Inhibiting bacteria and skin pH in hemiplegia: effects of washing hands with acidic mineral water. Am J Phys Med Rehabil 81:40–46
16. Lampiaho K, Kulonen E (1967) Metabolic phases during the development of granulation tissue. Biochem J 105:333–341
17. Lengheden A, Jansson L (1995) pH effects on experimental wound healing of human fibroblasts in vitro. Eur J Oral Sci 103:148–155
18. Leveen HH, Falk G, Borek B, Diaz C, Lynfield Y, Wynkoop BJ, Mabunda GA, Rubricius JL, Christoudias GC (1973) Chemical acidification of wounds. An adjuvant to healing and the unfavorable action of alkalinity and ammonia. Ann Surg 178:745–753
19. Liu Y, Kalen A, Risto O, Wahlstrom O (2002) Fibroblast proliferation due to exposure to a platelet concentrate in vitro is pH dependent. Wound Repair Regen 10:336–340
20. Mani RA (2000) Is wound bed preparation assessably noninvasively? In: Cherry G, Harding KG, Ryan TJ (eds) International congress and symposium series No. 250, wound bed preparation. Royal Society of Medicine Press, London, pp 23–28
21. Marchionini A, Schmidt R (1938) Säuremantel der Haut und Bakterienabwehr. Klin Wochenschr 54:461–467
22. Mercier RC, Stumpo C, Rybak MJ (2002) Effect of growth phase and pH on the in vitro activity of a new glycopeptide, oritavancin (LY333328), against *Staphylococcus aureus* and *Enterococcus faecium*. J Antimicrob Chemother 50:19–24
23. O'Meara S, Cullum N, Majid M, Sheldon T (2000) Systemic review of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. Health Technol Assess 4:1–237
24. Rippke F, Schreiner V, Schwanitz HJ (2002) The acidic milieu of the horny layer: new findings on the physiology and pathophysiology of skin pH. Am J Clin Dermatol 3:261–272
25. Roberts G, Hammad L, Collins C, Shearman C, Mani R (2002) Some effects of sustained compression on ulcerated tissues. Angiology 53:451–456
26. Romanelli M (2003) Objective assessment during wound bed preparation. In: Falanga V (ed) New concepts in wound bed preparation. Springer, Berlin Heidelberg New York, pp 23–34
27. Runeman B, Faergemann J, Larko O (2000) Experimental *Candida albicans* lesions in healthy humans: dependence on skin pH. Acta Derm Venereol 80:421–424
28. Sayegh N, Dawson J, Bloom N, Stahl W (1988) Wound pH as a predictor of skin graft survival. Curr Surg 45:23–24
29. Schade H, Marchionini A (1928) Der Säuremantel der Haut. Klin Wochenschr 7:12–24
30. Stewart CM, Cole MB, Legan JD, Slade L, Vandeven MH, Schaffner DW (2002) *Staphylococcus aureus* growth boundaries: moving towards mechanistic predictive models based on solute-specific effects. Appl Environ Microbiol 68:1864–1871
31. Stüttgen G, Schaefer H (1974) Die Hautoberfläche. In: Stüttgen G, Schaefer H (eds) Funktionelle Dermatologie. Springer, Berlin Heidelberg New York, pp 184–190
32. Thomas LV, Wimpenny JW, Davis JG (1993) Effect of three preservatives on the growth of *Bacillus cereus*, Vero cytotoxigenic *Escherichia coli* and *Staphylococcus aureus*, on plates with gradients of pH and sodium chloride concentration. Int J Food Microbiol 17:289–301
33. Trengove NJ, Stacey MC, MacAuley S, Benett N, Gibson J, Burslem F, Murphy G, Schultz G (1999) Analysis of the acute

and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen 7:442–452
34. Tsukada K, Tokunaga K, Iwama T, Mishima Y (1992) The pH changes of pressure ulcers related to the healing process of wounds. Wounds 4:16–20
35. Varghese MC, Balin AK, Carter DM, Caldwell D (1986) Local environment of chronic wounds under synthetic dressings. Arch Dermatol 122:52–57
36. Wilson IAI, Henry M, Quill RD, Byrne PJ (1979) The pH of varicose ulcer surfaces and its relationship to healing. VASA 8:339–342
37. Ye RC (1957) The relationship of pH of the granulation tissue and take of the skin graft. Plast Reconstr Surg 19:213–217
38. Zlotogorski A (1987) Distribution of skin surface pH on the forehead and cheek of adults. Arch Dermatol Res 279:398–401