Oxygen, pH, Lactate, and Metabolism for Wound Treatment

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Over time, we have come to recognize a very complex network of physiological changes enabling wound healing. An immunological process allows the body to distinguish damaged cells and begin a cleaning mechanism by separating damaged proteins and cells with matrix metalloproteinases, a complement reaction, and free radicals. A wide variety of cell functions help to rebuild new tissue, dependent on energy provision and oxygen supply. Topically applied lactate can improve this.

wound chronic wound hypoxia acidosis alkalosis lactate neoangiogenesis ECM polylactide

1. Introduction

The prolonged healing of wounds remains an unresolved challenge in modern medicine. Although wounds exhibiting prolonged healing are primarily minor, they have a substantial social impact and influence the patient's social status, daily living, and professional outcomes. Las Heras et al. [1] estimated 40 million chronic wounds worldwide, and the global wound market is predicted to reach USD 27.8 billion in 2026. The reasons given are the growing prevalence of chronic and surgical wounds as well as burn wounds. Cost-driving components include the increasing use of advanced wound care products, often as first-line therapies, where the advantages of these products over conventional treatment are the driving forces in the market [2]. The advantages may range from greater patient comfort to easier usability. However, the effectiveness of many methods is still questionable, as there may be underlying conditions for the chronification of wounds. Diabetes, frailty, or vascular or immunological diseases even may affect burn wounds [3]. Chronicity in burn wounds is a neglected topic, but Saaiq reported the incidence of Majolins ulcers as between 0.77 and 2%, primarily deriving from the healing per second intention [4].

Furthermore, the mortality of patients with chronic wounds rivals that of cancer patients [1], and the projected outpatient costs range from USD 9.9 to 35.8 billion, as outpatient treatment is a favored modality [5]. In their paper "Publicly Reported Wound Healing Rates: The Fantasy and the Reality," Fife et al. reported real-world data from randomized controlled trials and from the US Wound Registry that are prone to several risk-stratified quality measures. The conclusion was that RCTs (Randomized Controlled Trials) and US Wound Registry data provided convincing evidence that most wounds did not heal at all, but providers reported online healing rates over healing times that could only be qualified as impossible [6]. Thus, the costs are rising, but the treatment success is stalling.

2. Wound Healing

The provisional matrix, composed of fibrin, plasma FN (fibronectin), vitronectin, and platelets, is in contact with migrating keratinocytes of the basal layer on the basal membrane [7]. Initially, migrating epidermal cells find their way between the fibrin clot and the collagen-rich dermis. Thus, the matrix enables cell migration and promotes proto-myofibroblast contraction.

The proliferative and regenerative phase is characterized by fibroblast migration, collagen synthesis, angiogenesis, granulation tissue formation, re-epithelialization, protrusions developing cell–cell junctions, adhesion by integrins, and traction to the substratum [8][9]. Different cytokines and growth factors such as PDGF, IGF-1, IL- 1β, IL-8, interferon-gamma (IFN-γ), SDF-1, and TNF-α are chemotactic for BMSCs (bone marrow-derived stem cells) and HFSCs (hair-follicle-derived stem cells). MSCs (mesenchymal stem cells) develop immunosuppressive and anti-inflammatory effects, remodel the ECM, and increase angiogenesis and cell differentiation.

The healing cycle is initiated by the activation of keratinocytes induced by the release of interleukin-1, upregulating the release of K6, K16, and K17 keratins, which might increase the viscoelastic properties and enable cell migration [10], making the keratinocytes contractile, and cause shrinkage of the provisional basement membrane. Activation starts within 24 h upon the change of the keratinocytes to an activated status. Interferon-γ from lymphocytes induces the expression of K17, enabling contractility [11]. According to Safferling et al. [12], keratinocytes move in a shield extension mechanism for a multilayered epithelium, where suprabasal cells never come into contact with the ECM. In the coordination and overlapping of proliferation and migration, epithelium extends and closes the wounds. Basal keratinocytes are deactivated, dermal–epidermal junctions reappear, and hemidesmosomes anchor.

Collagen maturation during the remodeling phase can take 6 to 24 months [13]. The initial collagen matrix comprises 30% collagen type 3, while intact tissue contains 10–20% collagen type 3 and 80–90% collagen 1 [14]. Collagenases and proteases degrade these early fibrils, and this process is paralleled by collagen deposition. Crosslinking mediated by lysyl oxidase increases the thickness and stiffness, and the ratio of collagen 1 and collagen 2 is nearly the same as that for intact connective tissue. Twenty-eight different collagens have been identified in vertebrates; collagens II, III, V, and XI are fibril-forming collagens, while collagen I is the prevalent form in fibrotic conditions. As an essential part of normal wound healing, shrinking is mediated by myofibroblasts, which are generated under the influence of TGF-β. The differentiation into myofibroblasts largely depends on LDH and lactic acid, seems to be pH-dependent, and can be inhibited by gossypol, which inhibits LDH activity [15].

3. Current Insights

3.1. MMPs and Biofilms

The literature on different approaches to improving wound healing was reviewed with an emphasis on the pH of the wound, oxygen saturation improvement, and improvement of the metabolic situation. However, the authors are

aware that, recently, components influencing wound healing such as MMPs and biofilms have increasingly been topics of research. The growing knowledge has brought about a better understanding of the immensely complex network of MMPs and TIMPs. Unfortunately, initial studies on the binding of the Zn^{++} necessary for enzyme action did not result in therapeutic applications [16]. Nevertheless, this and other approaches are expected to be evaluated in the future [17], although most research is devoted to cancer.

Interestingly and independently from MMPs and biofilms, papers from earlier years described success in treating chronic wounds. For example, clinical applications of acidic dressings [18][19][20][21] and the application of topical lactate [22][23][24][25], as well as measures to increase the local oxygen saturation, such as occlusive dressings or HBO treatment [1], resulted in shorter healing times. Fortunately, most of these methods remain feasible but became lost from the therapeutic toolbox. In this paper, several approaches were discussed.

3.2. Correcting the pH:

When evaluating the effect of acidic dressings, the main mechanism might be the conversion of a highly alkalotic pH in chronic wounds to a less alkalotic one, possibly reducing MMP activity [26], making the oxygen delivery to the wound higher than that in a strongly alkalotic one. The higher oxygen delivery and lactate result in increased vasculogenesis and enhance the bacterial killing capacity of leukocytes in a neutral environment. Chronic wounds are marked by excessive activity of MMPs breaking down the extracellular matrix. According to Trengove et al. and Schultz et al., protease activity decreases during healing. Therefore, decreasing the pH might curb protease hyperactivity and contribute to healing. Adjusting the pH from 8 to 4 was associated with an 80% reduction in protease activity [27][28]. According to their table, when reducing the pH from 8 to 7.5, the reduction in protease activity might be about 25%. It was shown that the application of nanocrystalline silver could reduce MMP-9 levels to a greater extent than silver nitrate [29].

pH levels in chronic wounds are dependent on the stage of the ulcers, as demonstrated by Dissemond et al. Venous ulcers of stage one showed an average of pH 5.7, stage two 6.9, and stage three 7.6. A correlation to the ulcer type could not be established [30]. pH in feet ulcers was inconstant, but was used to diagnose infections [11].

Vu et al. [1] described a device to predict wound healing based on pH measurements.

Nevertheless, it was shown that applying acidifying dressings can correct or at least reduce an alkalotic pH. However, the short duration of the pH adjustment, owing to the short acidity-neutralizing time, may limit the effects of dressings. However, even short-term pH drops may be effective in restoring the capability of fibroblasts and keratinocytes to proliferate and migrate and improve wound healing. Polymeric dressings with controlled degradation to active monomers had the most extended effects on pH [31]. The speed of degradation to the active form determines the concentration of the active component and the duration reservoir of the bioactive polymer. In addition, the composition of the polymers influences the kind of acidic anions released. The application of physiological $NaHCO_3$ can correct acidosis. The effect can be monitored easily with a pH probe or litmus paper.

Acidifying can be done by wet dressings soaked with acidic components like lactic acetic acid, citric acid, or others in a not cytotoxic solution [32][33] or polymeric membranes from the lactic acid [34], which has the advantage of a controlled release and antioxidant activity, where it is hypothesized that it might contribute to a reduced grafting rate in partial-thickness burns [35][34]. Controlling the pH before grafting might be highly relevant in healing per the second intention with delayed grafting and dermal templates used in a two-step procedure.

3.3. Improving Hypoxia and Lactate Accumulation

Local hypoxia is the consequence of a disturbed vascular network and reduced supply, the increased oxygen demand by the production of reactive oxygen species, and a high metabolic demand for tissue neogenesis as by increased cell division and increased extracellular matrix production [36]. Depending on the depth of a wound, the intradermal capillary plexus is damaged along with papillary arterioles and venules or the intradermal plexus [37]. Hypoxia is the most extensive in the center of the wound and shows a gradient from the margin to the center [38]. Hypoxia can be reduced by external oxygen or by increasing neovascularization, which can be used therapeutically. In addition, the body itself accumulates lactate, indicating increased metabolic demand and action in the inflammatory repair process, fueling the cells necessary to initiate revascularization [39].

Hypoxia increases lactate production and accumulation [10][12]. This lactate accumulation in and around cells lowers the pH, working against the alkalinity derived from the reduced O_2 partial pressure and CO_2 loss. Accumulation of lactate triggers the neovascularization [23][40][41]. Hypoxia by itself is not sufficient.

In addition, lactate levels from 5 to 10 mM induce a hypoxia-like response in fibroblasts and other cells dependent on and independent of HIF [42]. With the local vascular network disturbed and the local oxygen tension reduced but still not zero, VEGF increases and initiates angiogenesis and cell growth, and vascular ingrowth. The low oxygen tension stimulates collagen synthesis through TGF-β1 and procollagen [43] and supports the healing process.

With a better vascularization of the wound, the oxygen tension rises, the CO_2 loss is reduced, and healing is accelerated, by providing oxygen for the other metabolic needs as increased cell division, stabilizing of collagen, and extracellular matrix generation. Capillary sprouting takes place from Day 3 to Day 10 after injury [44]. It is initiated by growth factors binding to their receptors on endothelial cells and dissolving the basal lamina. Activated endothelia are enabled to proliferate and form sprouts. Integrins, as superficial adhesion molecules, help to organize the endothelial cells, which produce matrix metalloproteinases that lyse the surrounding tissue, facilitating endothelial progress. Hyperbaric oxygen is effective in this state in hypoxic wounds [5], possibly by increasing stem cells proliferation, which was found in polylactides as well [12][45]. The combination of both therapeutic approaches might be useful, but had not been described until now.

This process can be supported by topical lactate application.

However, as demonstrated by Trabold, additional topical and implanted lactate significantly increased VEGF and TGF-β levels. Rendl demonstrated the effectiveness of creams containing lactate with VEGF at 1.5 and 3% concentrations, while the effect was diminished at higher concentrations, indicating toxicity, with higher apoptosis

and cell death. The composition of the lactate–glycolide application as a powder with external and intraperitoneal application can control the release of the lactate [25]. Lactate from Matrigel induced angiogenesis in a dose-dependent manner. Lactate subcutaneously implanted as polymers induced an angiogenic response with increased vessel density; topically applied lactate as a lactide polymer improved telomerase activity and skin quality in human partial-thickness burn wounds. Lactate reduced systemic oxidative stress parameters and resulted in a shorter healing time under reduced oxidative stress. It also decreased IL-6 and TNF-α early and increased TGF-β for a limited period.

Thus, internal and external lactate can support wound healing by supplying energy to cells in fresh and chronic wounds [46] and act as an antioxidant, reducing oxidative stress, which increases MMP1 production in the presence of LPS and H_2O_2 [47]. Thus, we can learn from all these studies that topical lactate application improves wound healing and reduces oxidative stress systemically. However, the lactate effect must be stopped in time, to avoid stiffness and contracted scars being produced by myofibroblasts [48].

When there is granulation tissue, the wound can either heal spontaneously or need to be grafted. In spontaneous wound healing, the pH must be between 7.5 and 8.5 to enable cell proliferation and differentiation, and the closure of the wounds. An alkalotic pH can be improved by applying lactate using the most feasible method as a membrane.

If the wound must be grafted, the optimum take rate occurs between pH 6.8 and 7.2 or at pH ≥ 7.4.

The optimum pH for enabling bacterial killing by leukocytes is between 7 and 7.5. Therefore, treatment aims to create a pH that supports skin and fibrous cell proliferation and healing.

4. Conclusions

There are simple components in wound treatment that determine its success. First, the metabolic situation for undisturbed wound healing must be established. Lactate fuels cells by imitating hypoxia under normoxic conditions and encourages metabolic processes such as vasculogenesis and angiogenesis, improving the vascularization and local oxygen tension. Lactate is the key to normalizing the oxygen tension, the acceleration of wound healing, and initiating metabolic processes in fresh wounds and “dead” ulcers, as demonstrated in chronic wounds by Nischwitz et al. [49]. A normally vascularized wound after lactate treatment is less prone to infections, which has been demonstrated for pigskin.

The control and regulation of the wound pH with adequate dressings or topical measures can improve wound healing, prevent the chronification of wounds of all etiologies, and restart the healing process.

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