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Implications of pH and Ionic Environment in Chronic Diabetic Wounds: An Overlooked Perspective

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Abstract: The high incidence of disability and fatality rates associated with chronic diabetic wounds are difficult problems in the medical field. The steady-state and regular changes of the microenvironment in and around the wound provide good conditions for wound healing and achieve a dynamic and complex process of wound healing.The pH value and ionic environment composed of a variety of ions in wound are important factors affecting the wound microenvironment, and there are direct or indirect connections between them. Abnormalities in pH, ion concentrations, and channels in skin tissue may be one of the reasons for the high incidence and difficulty in chronic diabetic wounds healing. Currently, different wound-dressing applications have been developed based on the efficacy of ions. Here, the effect of pH in wounds, concentrations of calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}) and the metal ions silver (Ag^{+}), copper (Cu^{2+}), iron (Fe^{2+}/Fe^{3+}), zinc (Zn^{2+}), and magnesium (Mg^{2+}) in skin tissue, their roles in wound healing, and the application of related dressings are reviewed. This manuscript provides new ideas and approaches for future clinical and basic research examining the treatment of chronic diabetic wounds by adjusting ion concentrations and channels.

Keywords: Chronic diabetic wounds, pH, Ions, Ionic environment, Wound healing, Review

Introduction

Chronic diabetic wounds are a major complication associated with diabetes mellitus (DM), and they are associated with a poor prognosis and high recurrence rates, often leading to amputation,[1] representing a huge burden for both affected individuals and the entire healthcare system.[2] Wound healing is a complex process which includes coagulation, inflammation, proliferation, and remodeling stages. These four stages overlap without obvious boundaries during the healing process.[3,4] The limited oxygen supply and elevated oxygen consumption of the wound, resulting in persistent inflammatory response, are the main reasons for the difficult wound healing.[5,6] In addition, high-glucose can also reduce the activity of vascular endothelial growth factor (VEGF) and hypoxia-inducing factor-1α (HIF-1α),[7] increase the non-enzymatic glycosylation of many important proteins, resulting in abnormal cell and Extracellular matrix (ECM) functions, which inhibiting angiogenesis and delaying wound healing.[8] In recent years, advances in materials engineering, polymer science, biomedicine, and chemistry have led to the development and enhancement of multifunctional biomaterials, such as hydrogels, foams, hydrocolloid, nanofibers, sponges, and semi-permeable membranes, which are designed to promote wound healing.[9]

The wound microenvironment is a critical factor in wound healing, which includes internal microenvironments comprising various cells and the extracellular matrix, bacterial load, microorganisms, pH, ions, oxygen, temperature, humidity, light, electricity, and magnetism for the external microenvironment.[10] Specific and complex

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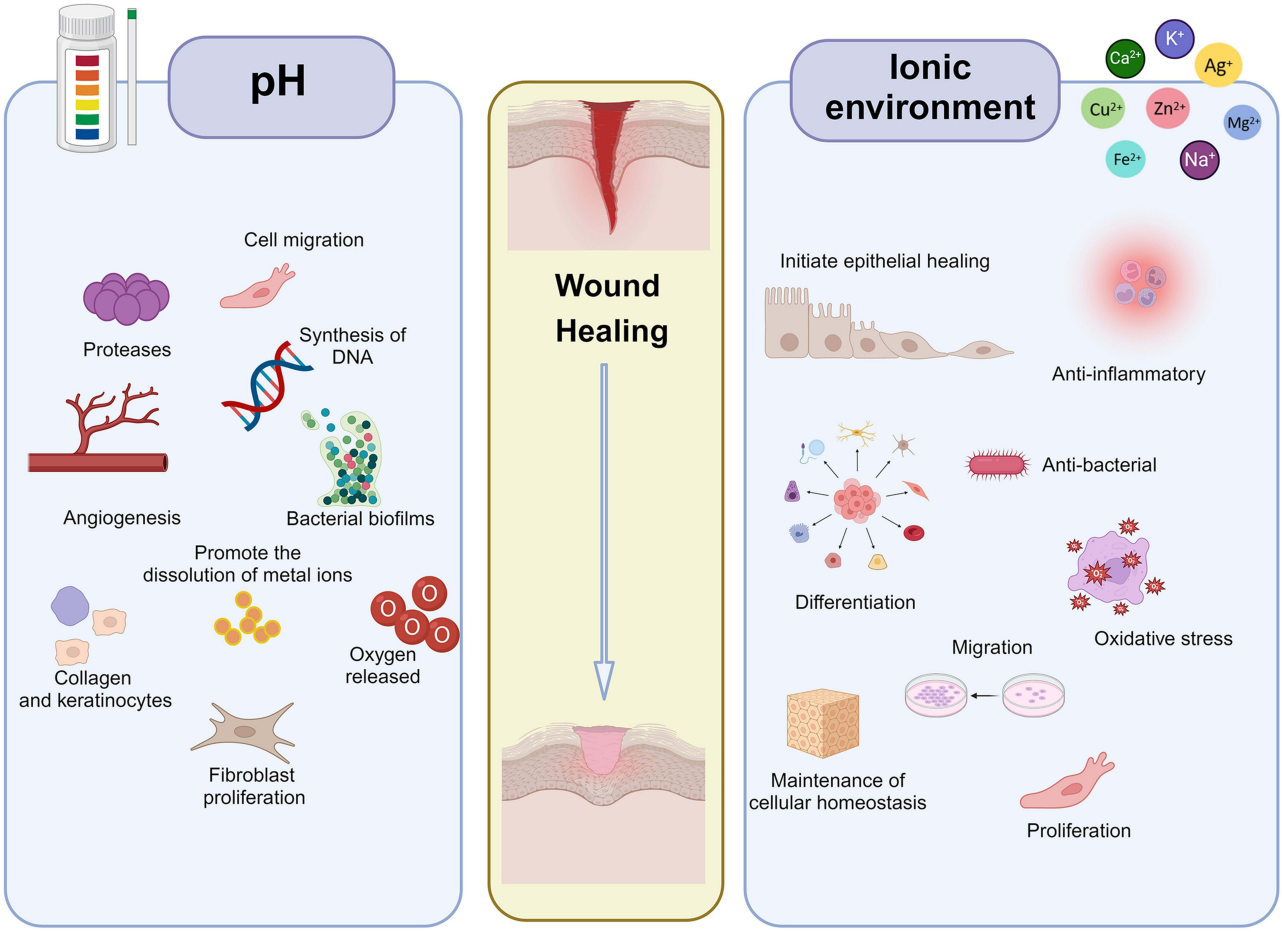
Graphical Abstract



microenvironmental changes occur in and around the wound after skin damaged, and the steady-state and regular changes in the microenvironment provide good conditions for wound healing to achieve a dynamic and complex process. The dynamic microenvironment directly or indirectly regulates the function and location of cell activities and maintains skin homeostasis. Owing to the continuous presence of a high-glucose environment, the wound microenvironment cannot be effectively controlled. Persistent inflammation and biofilm formation, which completely disrupt the microenvironment balance, and the limited blood supply leads to tissue oxidative stress disorders and angiogenesis obstruction, delaying the process of wound healing.[10] The pH of wounds has gained more attention as an important factor influencing wound healing. The ionic environment is included in the wound microenvironment and not only exists in the wounds but also continuously affects wound healing as an external factor. The plasma content of and ionic channels for calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}), and other external metal ions, such as copper (Cu^{2+}), iron (Fe^{2+}/Fe^{3+}), silver (Ag^{+}), zinc (Zn^{2+}), and magnesium (Mg^{2+}), in the skin tissue affect wound healing. In addition, there is a complex and remarkable relationship between pH and ions.

Therefore, it is necessary to study the abnormal ionic environment of diabetic wounds to restore homeostasis of the ionic environment in skin tissues and achieve wound healing. In this study, the effects of pH in wounds, the presence of Ca^{2+}, Na^{+}, and K^{+}, as well as the external metal ions Cu^{2+}, Fe^{2+}/Fe^{3+}, Ag^{+}, Zn^{2+}, and Mg^{2+} in skin tissue, their role in wound healing and the application of related dressings are reviewed. Intelligent dressings with various ionic compounds interacting with pH have sufficient promise in the treatment of wounds. The purpose of this study is provide new ideas

and innovative framework for future clinical and basic research focused on the treatment of chronic diabetic wounds by adjusting ionic environment.

Ionic Environment of the Wounds

Kruse proposed the wound microenvironment could be divided into the "external microenvironment" and the "internal microenvironment" for the first time in 2015. The external microenvironment is defined as the outside of the wound immediately adjacent to the wound. And the internal microenvironment is defined as the space below but adjacent to the surface of the wound bed, which is composed of various cells and extracellular matrix. The external and internal microenvironment are constantly exchanged and influenced by each other.[11] Ions are very important for the immune environment, and the mechanism underlying innate immune stimulation and T cell activation is mediated by essential metal ions.[12] Metal ions transport is critical for mitochondrial functions and cellular metabolism, including oxidative phosphorylation, ATP production, mitochondrial integrity, mitochondrial volume, enzyme activity, signal transduction, proliferation and apoptosis.[13] They can also affect cell death or apoptosis, for example, iron ions are involved in cell radiation apoptosis.[14]

Ions affect the internal and external microenvironment of wounds, and dynamic changes in the multi-dimensional, temporal and spatial ionic environment affect wound healing at different stages. The plasma contents of Ca^{2+}, Na^{+}, K^{+}, Cu^{2+}, Fe^{2+}/Fe^{3+}, Ag^{+}, Zn^{2+}, Mg^{2+}, and other ions in skin tissue constitute the ionic environment, which affects wound healing. Furthermore, hyperglycemic environment, hypoxia and inflammation can result in an abnormal ionic environment in skin tissue, affecting and delaying the process of wound healing. The Components of ionic environment in the wound shown in Figure 1.

Figure 1 Components of ionic environment in the wound.

The pH and Chronic Diabetic Wounds

The Changes of pH in Wounds

The pH is an inverse logarithmic measure of the thermodynamic activity of hydrogen ions (H^+) in solution. The value of the H^+ concentration index is commonly known as the pH value, with a larger value indicating a lower ion concentration. Since the 1970s, the pH of wounds has gained increasing attention as an important factor influencing wound healing. Owing to the secretion of organic acids by skin keratinocytes, the pH of the normal skin surface is between 4.8 and 6.0, and the pH gradient of the cuticle increases to 6.8 with the arrival of the lower stratum corneum. Currently, there are no reports of significant differences based on sex or race. However, the pH of the skin changes with age. The pH of newborn skin is neutral or alkaline after birth, whereas during infancy and old age, the pH is slightly elevated compared to that of normal adults.[15,16]

When the acute wounds occur and the integrity of the skin is compromised, alkaline tissue fluid and plasma in the broken capillaries overflow, the pH in wound increase significantly.[17] The pH of the microenvironment of an acute wound is approximately neutral, with an average value of 7.44.[18] However, the pH of the wound constantly changes during the process of wound healing. When wound healing enters the coagulation or inflammatory stage, the previous blood supply to the wound is interrupted, glycolysis and lactic acid production increases, local tissue carbon dioxide stasis occurs, and the pH decreases.[19] As the inflammatory response of the wound weakens, necrotic tissue is cleared, the blood supply is reestablished, glycolysis is replaced by an aerobic reaction, and the pH increases. At the later stage, with wound epithelialization and reduction, the pH becomes neutral before regeneration of the stratum corneum.[20] Subsequently, the increased oxygen demand of the wound tissue leads to glycolysis and lactic acid production in the wound tissue, as well as increased epithelial secretion at the edge of the wound, and the wound pH again decreases.[21] Moreover, in terms of the location, the pH of the wound center is higher than that of the entire wound surface.[22] However, the change of pH will be abnormal in chronic wounds.

The Changes of pH in Chronic Diabetic Wounds

Compared to acute wounds, chronic diabetic wounds have a relatively alkaline environment, with higher pH values ranging from 7.42 to 8.90.[18] The pH of chronic diabetic wounds can be as high as 9.25.[23] One reason is that exposure of the blood and interstitial fluid to the external environment or the urea enzyme-mediated release of ammonia from urea can lead to a more alkaline pH in the wound. When the chronic diabetic wounds reach the epithelial reformation stage, the pH again becomes acidic. The pH of chronic diabetic wounds increases, ultimately leading to excessive protease levels, decreased tissue inhibitor of metalloproteinase (TIMP), increased reactive oxygen species (ROS) and infection.[24,25] This can lead to biochemical imbalances and consequent extracellular matrix (ECM) abnormalities, where fibroblast activity is reduced, and ECM components essential for wound healing process are destroyed.[19] Furthermore, long-term inflammation in chronic diabetic wounds, defective epithelial reformation and damaged matrix remodeling are also observed.[26,27]

Effects of the pH on Wounds

The pH of the wound microenvironment indirectly or directly affects all biochemical reactions during wound healing. Specifically, the pH affects infection, antibacterial activity, oxygen release, angiogenesis, protease activity and bacterial toxicity in the wounds. 1) The H^+ concentration in the wound directly affects the activity of proteases in the tissue, and a decrease in pH from 8 to 4 can reduce protease activity by 80%.[28] 2) The oxygen content in the tissue affects the wound healing, and healing is possible when the oxygen tension is greater than 40mmHg. In an acidic pH environment, the level of oxygen released by oxygenated hemoglobin is increased, and when the pH is decreased by 0.60, oxygen dissociation from oxyhemoglobin increases by 50%. Further, if the pH is decreased by 0.90, the oxygen dissociation from oxyhemoglobin will increase by 5-fold.[29] 3) Regarding the influence on bacterial biofilms, biofilms exist in 60–100% of chronic wounds, and the pH required for the growth of human pathogenic bacteria is greater than 6.0.[30] A low pH inhibits growth, and therefore, bacterial infections and biofilms are easily formed in an alkaline wound microenvironment.[31] Moreover, the wounds become alkaline after bacterial colonization, and a long-term alkaline

environment is one cause of wound healing difficulties. 4) Regarding the influence on angiogenesis and cell proliferation, during wound proliferation, the acidic wound microenvironment stimulates angiogenesis and the production of collagen (increased transforming growth factor [TGF]).[32,33] When the pH is greater than 7.50, cell migration and DNA synthesis are suppressed in an approximately linear manner with an increasing pH.[34] In an acidic environment, fibroblasts (increased by platelet derived growth factor [PDGF] release) and keratinocytes proliferate actively, and myofibroblast contractility is enhanced.[35] 5) Regarding the influence on the antibacterial activity of dressings, the bioavailability of active free metal ions in the wound is affected by many factors, including the solubility of metal ions, which increases as the pH decreases.[36] The activity of gentamicin, an aminoglycoside antibiotic, exhibits a 90-fold increase in efficacy at pH 7.80 compared to that at pH 5.50.[30] Moreover, a decrease in the pH can enhance the activity of silver ion dressings and increase their antibacterial effect.[36,37] As most chronic wounds contain bacterial biofilms and require clinical intervention with antibiotics, the pH of the wound microenvironment should be considered when selecting the most appropriate antibacterial agents to enhance the effects of drugs. 6) Regarding the influence on bacterial toxicity, reducing the pH and creating a more acidic environment also reduces the toxicity of bacterial end products, such as ammonia, which is released from urea via the action of urease. Ammonia is toxic to the wound tissue and creates an alkaline environment that is not conducive to wound healing.[38]

Applications of pH in Wound Treatment

Currently, the pH of wounds can be measured clinically using a pH meter with a flat glass electrode or pH litmus paper, which results in no obvious pain for patients and allows for convenient measurements with a low cost. However, there are certain drawbacks, such as differences in the interpretation of litmus paper colors by clinicians, which can lead to inaccurate results. In addition, the problem of how electrodes touching patient wounds can be kept sterile and not cross-infected has been reported.

Many acids have been used to treat wounds in recent years, most of which are antibacterial agents. One commonly used acid is hypochlorous acid, which is a naturally occurring bactericidal agent produced by the innate immune process within the body that can remove debris and microorganisms from diabetic foot wounds. The use of hypochlorous acid can reduce bacterial load, relieve wound odor and pain, reduce systemic antibiotic use and promote wound healing.[39] Another commonly used acid is citric acid. In a histopathological study of chronic wounds infection, its use increased local tissue oxygenation to promote epithelium formation, facilitated the wound healing process by promoting fibroblast growth and neovascularization, increased wound microcirculation, promoted healthy granulation tissue formation, and accelerated wound healing.[40] Additionally, a retrospective review of studies examining acetic acid, boric acid, citric acid, ascorbic acid, alginic acid, hyaluronic acid and other acids, in the context of wound acidification, determined that acid-based drugs can control infections and promote epithelial tissue growth and wound healing with obvious effects.[41] In summary, based on alkaline changes in the pH of chronic diabetic wounds, wound acidification could become a future treatment modality for chronic diabetic wounds.

The pH measurement is simple, convenient and easy to implement clinically. The pH-based interventions for chronic diabetic wounds can be used as a clinical treatment approach, but there are still some associated problems. Strategies to effectively and continuously maintain the acidification of the alkaline microenvironment of chronic diabetic wounds need to be determined, and the dressing change time for acid drugs or wound dressings requires further study. Owing to the dynamic change in the pH of chronic diabetic wounds, multiple factors should be considered when adjusting the pH, including the epithelial regeneration rate, granulation growth conditions, and drug efficacy changes. Additionally, chronic diabetic wound acidification treatments might require further consideration. The effects of pH on wound healing shown in Figure 2.

Ionic Environment of Chronic Diabetic Wounds

Ca^{2+} and Chronic Diabetic Wounds

The Changes of Ca^{2+} in Wounds

The transmission of Ca^{2+} is thought to be one of the earliest wound signaling events initiated by the ATP released by damaged cells, which increases the cytoplasmic Ca^{2+} from surrounding cells.[42] During the skin homeostasis, the Ca^{2+}

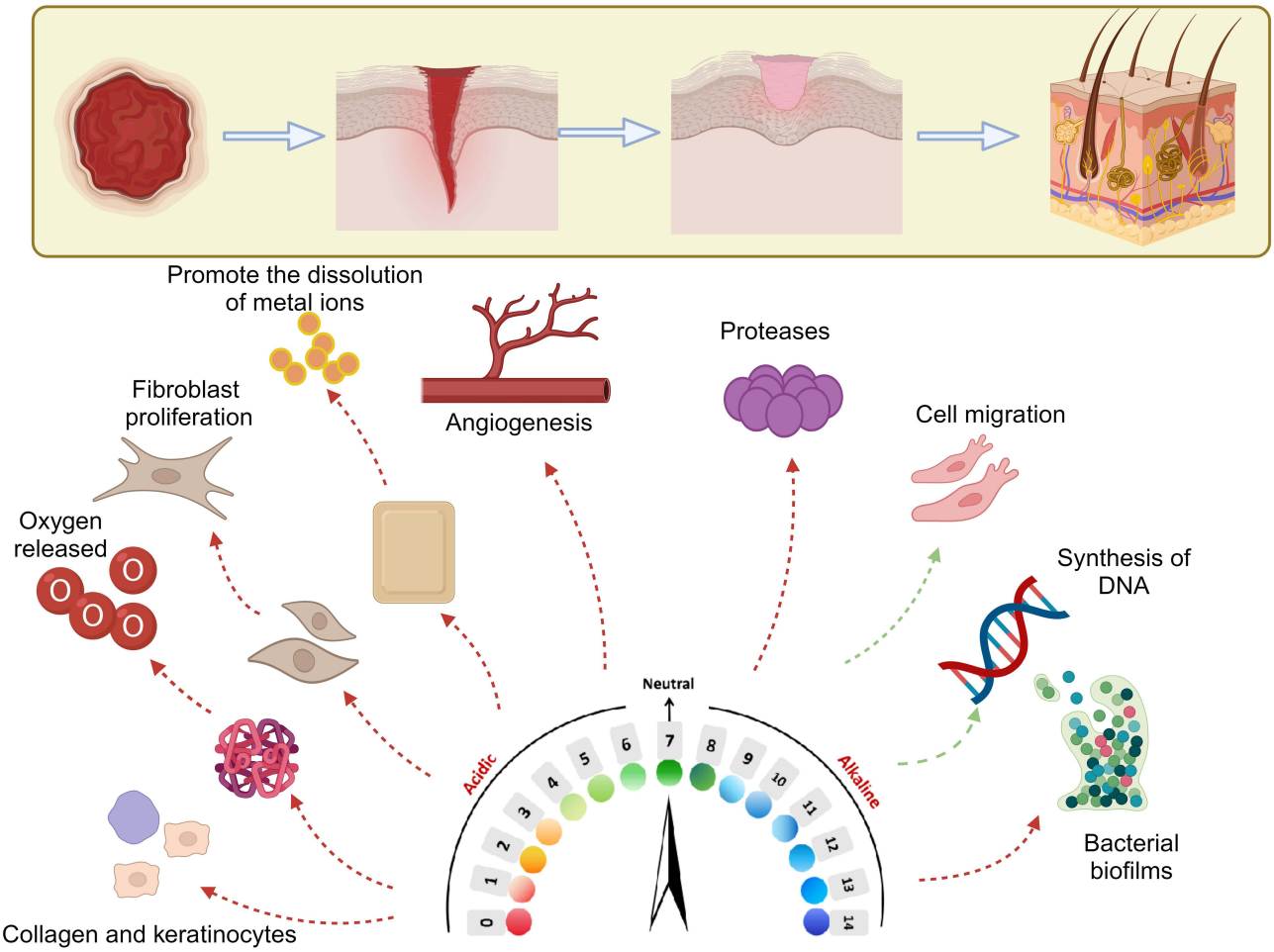


Figure 2 The effects of pH on wound healing. Created in BioRender. Guo, J. (2024) https://BioRender.com/k20j084.

concentration peaks in the outer granular layer and is lowest in the basal layer.[43] Immediately after skin damage, Ca^{2+} can be detected in the wound bed, facilitating the clotting process.[44] The Ca^{2+} increase lasts for 5 days after wound formation and overlaps with the maximum inflammatory activity.[45] The concentration of Ca^{2+} in the wound changes dynamically with the progression of the healing process. The extracellular concentration of Ca^{2+} has been demonstrated to persist during the inflammatory and proliferative stages after the onset of injury and then decrease during the remodeling stage.[45] After wound is formed, the Ca^{2+} concentration in the skin tissue increases, and the highest concentration can reach more than 60-fold that in normal skin.[46] Moreover, the cells in the wound must continuously remove excess Ca^{2+} while maintaining a low Ca^{2+} concentration to maintain the normal living environment of the cells required for wound healing. Transient receptor potential vanilloid (TRPV) is a calcium-permeable non-selective cation channel widely expressed throughout mammalian skin tissues, and modulates the transmembrane levels of Ca^{2+} and depolarization of the cells.[47,48] TRPV1, TRPV2, TRPV3 and TRPV4 channels are expressed in basal and supra-basal keratinocytes. TRPV1 and TRPV3 channels are associated with cell death, whereas TRPV1 channels induce mitochondrial damage and Ca^{2+} inflow.[47] Further, TRPV3 promotes keratinocyte proliferation via calcium/calmodulin-dependent protein kinase II–induced nuclear factor kappa-B.[49] TRPV2 channels stimulate growth factor-β1 and smooth muscle actin-mediated contractions, ultimately leading to the contraction of dermal fibroblasts, affecting scar formation.[48] Meanwhile, TRPV4 channels are involved in the organization of actin junctions via Rho-mediated processes.[50] However, the changes of Ca^{2+} in chronic diabetic wounds are different from those in acute wounds.

Ca^{2+} in Chronic Diabetic Wounds

Abnormal cellular Ca^{2+} homeostasis and signaling is a common feature of T1DM and T2DM. These abnormalities are typically manifested by increased resting Ca^{2+} levels, decreased Ca^{2+} transporter activity, and reduced stimulation-induced Ca^{2+}signaling.[51] The increase in intracellular and extracellular Ca^{2+} concentrations in keratinocytes under high-glucose conditions can cause membrane depolarization and disrupt the inward movement of the cell membrane and lamellar body exocytosis, thus affecting the formation of a stratified lamellar membrane between cells and delaying skin barrier repair.[52]

Effects of Ca^{2+} in Wound Healing

Calcium is involved in the earliest wound-signaling activity and plays an important role in regulating wound healing.[53] Regarding blood clotting, Ca^{2+}, also known as factor IV, promotes the formation of blood clots during the initial clotting phase after wound formation and blood coagulation.[54] Together with other coagulation factors, it triggers the intrinsic coagulation cascade, accelerates the synthesis of thrombin, and promotes early fibrin formation.[55] For the regulation of neutrophil functions, during the inflammatory phase of wounds, at high levels, extracellular Ca^{2+} enters neutrophils to increase intracellular calcium, which then regulates neutrophilic functions.[56] Regarding the initiation and promotion of the epithelial healing process, extracellular Ca^{2+} is a key regulator of epidermal homeostasis that initiates epithelial healing by inducing intracellular calcium and E-cadherin mediated signaling, ultimately providing calcium signals to promote keratinocyte adhesion, differentiation and survival.[44] Ca^{2+} can regulate the differentiation of keratinocytes, induce keratinocyte differentiation and proliferation in the stratum corneum, which is important for the formation of the skin barrier.[52,57] Keratinocyte proliferation is inversely proportional to the extracellular Ca^{2+} concentration, with faster cell proliferation at low Ca^{2+} concentrations and cell differentiation at high Ca^{2+} concentrations.[58] High Ca^{2+} concentrations in the wound inhibit the proliferation and migration of keratinocytes and are believed to delay wound healing.[59] To promote collagen synthesis and angiogenesis, Ca^{2+} is a key signaling molecule that regulates multiple signaling pathways involved in angiogenesis.[60] Ca^{2+} influx into endothelial cells plays a crucial role in their migration, adhesion, proliferation and angiogenesis.[61] Higher Ca^{2+} concentrations in the wound can also increase collagen synthesis and blood vessel formation.[62] Regarding promoting the functions of fibroblasts, fibroblasts primarily use intracellular Ca^{2+} for contraction, and this helps to reduce the size of wounds by mediating actin remodeling and cadherin recruitment at intracellular junctions.[63,64] Extracellular Ca^{2+} supplementation increases cell metabolic activity, migration, Matrix metalloproteinase (MMP) production, collagen synthesis, cytokine release and decreases cell contractility. Ca^{2+} also maintains the functions of the epidermal barrier, which is rich in proteins and lipids.[43] Regarding activation of the skin's innate immune system, Ca^{2+} is one of the primary activators of natural killer (NK) cells, which are major players in the innate immune system of the skin. Individuals with diabetes are prone to defects in NK cell activity, ultimately leading to an increased risk of infection.[65–67] NK cells are activated in the wound, exert cytotoxic effects, produce the immune-regulatory cytokines IFN-γ and TNF-α,[68] activate macrophages and other immune cells. The activated macrophages participate in wound debridement and are the key regulatory factors involved in wound healing.[69,70]

Applications of Ca^{2+} for Wound Treatment

The principle of Ca^{2+} applications for wound treatment is that the dressing can decompose Ca^{2+} after contact with the wound, accelerate wound epithelialization and healing by promoting the immune response, increasing bacteriostasis and increasing the migration of skin fibroblasts, collagen synthesis and cytokine release.[64,71–78] The names and main effects of dressings related to Ca^{2+} are shown in Table 1.

Na^+/K^+ and Chronic Diabetic Wounds

Na^+/K^+ in Wounds

Na^+ plays a role in osmotic buffering and thermoregulation via sweat in the body.[78,79] In the skin, Na^+ exhibits the same gradient distribution from the center of the cuticle to the top surface of the outermost layer.[80] Its spatial distribution along the outer layer of the epidermis suggests that sweat glands play a role in wound healing. Sweat could be a key source and carrier of Na^+ to the outer epidermis, and the amount of Na^+ in the stratum corneum of the skin increases during

Table 1 Ca^{2+} Treatment for Wounds

Dressing or materials	Main effects
Calcium alginate dressing	After dressing contact with wound, Ca^{2+} can activate NK cells, promote skin immune response and reduce the inflammatory response, up-regulate the proportion of type I/III collagen in diabetic wounds and promote wound healing.[71–73]
Chitosan calcium alginate dressing	Inhibit inflammation and promote angiogenesis.[74]
Chitosan/gelatin/nanocrystalline cellulose/calcium peroxide films	Facilitate bacteriostasis against Escherichia coli.[75]
Calcium fluoride containing composite hydrogel dressings	Promote wound re-epithelialization and skin cell migration, increase inflammatory cell recruitment in vivo. Enhance migration of fibroblasts and endothelial cells, inhibited bacterial growth in vitro.[64]
Extracellular calcium and calcium releasing nanoparticles	Extracellular calcium can increase the migration of skin fibroblasts, collagen synthesis and cytokine release, reduce the contractility of cells.[76]
Polymeric composite dressings containing calcium-releasing nanoparticles	Promote angiogenesis, collagen synthesis, wound re-epithelialization and fibroblast migration, promote diabetic wound healing.[77]
Calcium phosphate nanoparticles	Promote wound healing.[80]

sweating.[81] Epithelial sodium channels are strongly expressed in all epidermal layers, except for the stratum corneum. Their expression increases in highly differentiated keratinocytes and play a major role in maintaining sodium homeostasis.[82] During the mature stage of wound healing, after epithelialization, skin barrier dysfunction often leads to Na^+ dysregulation due to wound dehydration, ultimately resulting in chronic inflammation.[83]

In the skin, K^+ is involved in wound healing by regulating the terminal differentiation of keratinocytes and cuticle barrier functions.[84] In contrast to Ca^{2+}, K^+ levels peak in the spinous layer and decrease to their lowest levels in the granular layer.[85] K^+ channels are activated in response to an increased extracellular Ca^{2+} concentration.[86] Thus, an increase in the extracellular Ca^{2+} levels after skin barrier breakdown leads to an increase in K^+. In turn, these K^+ modifications induce the hyperpolarization of less differentiated keratinocytes. The two main epidermal potassium channels involved in maintaining potassium gradients are Kcnh2 and Kcnj8. Kcnh2 is a voltage-activated potassium channel that hyperpolarizes the plasma membrane by conducting K^+ out of the cell, thereby maintaining keratinocytes.[87] Kcnj8 channels are inwardly rectified K^+ channels that maintain membrane potential depolarization.[88] Interestingly, Kcnj8 activation and Kcnh2 inhibition promote wound healing and facilitate the net inflow of potassium into cells.

Effects of Na^+/K^+ in Wounds

Regarding the Na/K pump-mediated formation of transepithelial potential (TEP), the wound electric field is considered the most important guiding signal for wound healing,[89] and the regulation of TEP can promote the wound healing by controlling the intensity of the wound electric field. In the skin epithelium, Na/K pumps are expressed asymmetrically to establish the TEP, which is sensitive to Na channel inhibitors. During each pumping cycle, the pump molecule releases three Na^+ ions and takes up two K^+ ions via consumption of the energy generated by the hydrolysis of one ATP molecule.[90] Additionally, K^+ can inhibit the differentiation of keratinocytes and increase the rate of Ca^{2+} inflow.

Applications of Na^+/K^+ for Wound Treatment

The principle of applying Na^+ and K^+ in wounds treatment is that the drugs themselves contain Na^+ and K^+, which can remove excess water in the edema-associated cells and tissue cells, and promote wound epithelialization and healing. The clinical application of Na^+ and K^+ deserves further research and development. The names and main effects of dressings related to Na^+ and K^+ are shown in Table 2.

Table 2 Na^+/K^+ Treatment for Wounds

Dressing or materials	Main effects
Sodium humate	The production of sodium salt in an alkaline environment can shorten the treatment time and promote the healing of diabetic wounds.[91]
Liquid potassium saccharum	Potassium chloride, sodium chloride and hypertonic sugar can remove the excess water in and between the edema cells, and this is conducive to the proliferation of histiocytic cells.[92]

Other Ions and Chronic Diabetic Wounds

Ag^+

The content of silver in the human body is very low (approximately 2 μg/L), and it can enter the body through inhalation, oral ingestion, skin contact and other routes. Ag is an inert metal that produces Ag^+ when ionized via contact with an aqueous environment, and it is an effective antibacterial agent.[93] Data from in vitro microbiological studies indicate that Ag^+ at 1 ppm can exert a bactericidal effect.[94] Its antimicrobial mechanisms include the following. The key to the antibacterial mechanism of Ag^+ is its ability to induce the production of reactive oxygen species. After passing through the peptidoglycan cell wall and entering the bacterial cells, Ag^+ destroys the DNA and bacterial proteins involved in key metabolic processes, ultimately resulting in the suppression of bacterial replication and death. Ag^+ destroys the negatively charged structure of the bacterial surface, thus destroying or weakening the cell membrane structure and resulting in cell membrane property changes and cell death.[95,96] Ag^+ binds to membrane proteins and respiratory chains, thereby affecting bacterial ATP production, consumption, and death. Additionally, Ag^+ promotes the proliferation of keratinocytes and fibroblasts.[97] Moreover, Ag^+ and chloride ions can combine to form AgCl, which is not conducive to healing, and thus, the maximum concentration of Ag^+ in the wound is approximately 1 μg/mL.[98] Moreover, Ag^+ can exhibit a broad spectrum, high antibacterial activity, inhibit the activity of bacteria, fungi and viruses. It can also inhibit inflammation and infection, downregulate MMP and cytokine expression, improve active oxygen components and diabetic effects.[99]

The application of silver-based compounds for wound treatment began in the 1970s. The antibacterial properties of Ag^+ play a major role in the effects of Ag-containing dressings. As such, silver-containing dressings are suitable for the treatment of chronic diabetic wounds and are the first choice when there is no clear indication of the bacterial type associated with diabetic foot infection. The names and main effects of dressings related to Ag^+ are shown in Table 3.

Cu^{2+}

Cu can catalyze the intracellular oxidation process and inhibit viruses and bacteria, and it exerts good antibacterial and antiviral effects for wound treatment.[108] The average mass concentration of Cu^{2+} in normal human serum was reported as 0.94

Table 3 Ag^+ Treatment for Chronic Diabetic Wounds

Dressing or materials	Main effects
Nanocrystalline silver	Bactericidal, anti-inflammatory, down-regulates MMPs and cytokine levels.[100–102]
Carboxymethyl cellulose silver	Antibacterial, promotes fibrin production and provide a moist wound environment.[97]
Silver ion alginate dressing	Absorbs exudates, maintains wound moisture, improves the regeneration ability of epidermal cells, accelerates the movement of epidermal cells, halts bleeding and stabilizes the biofilm, promotes wound healing.[103,104]
Sulfampyrimidine silver	Reduces wound microorganisms.[105]
Silver nanoparticles	Broad-spectrum and high antimicrobial activity against including, Bacteria: Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus; Fungi: Candida albicans and Aspergillus Niger; Viruses: hepatitis B and human immunodeficiency virus. Promotes wound healing and anti-diabetic effects.[106,107]

±0.11 mg/L, and no significant change in the Cu^{2+} concentration was observed within seven days after wound formation. The concentration was found to gradually increase with the healing process and reached 1.24±0.25 mg/L after 21 days, and returned to normal levels after 42 days.[109] Cu^{2+} can affect the activity of various enzymes, promote nucleic acid metabolism and protein synthesis, induce the synthesis of collagen fibers and collagen, all of which suggest its great value for wound treatment. Moreover, Cu^{2+} exhibits an antibacterial effect similar to that of Ag^{+}, does not induce bacterial resistance. In clinical, enhanced Cu^{2+} activity can stimulate the formation of capillaries in wounds, and wound dressings containing Cu^{2+} can promote wound healing.[110] The copper peptide formed by the combination of Cu^{2+} and glycine-histidine-lysine (GHK) is a copper complex isolated from the serum that promotes the synthesis of elastin and collagen, enhances blood vessel growth, improves antioxidant capacity, and stimulates the production of glucose-polyamines in the skin to assist skin proliferation and self-repair.[111] In conclusion, Cu^{2+} has two main functions in the process of wound healing. 1) It exerts a protective effect on the skin and prevents oxidative damage to the skin, and 2) it triggers the recombination process of the skin and initiates the removal of damaged skin and the regeneration of normal skin.[112]

Fe^{2+}/Fe^{3+}

The physiological role of Fe in the skin is complex, it's levels are not constant and increase during the process of aging.[113] Fe accumulates in the epidermis, and its concentration increases from the outer layer to the inner layer, with the highest concentration reaching 7.33 ± 0.98 μmol/g in the basal layer of the epidermis.[114] Fe ions homeostasis depends on the expression and activity of transcription factors, Fe regulatory and storage proteins. In chronic wounds, the Fe content is higher than that in acute wounds.[115] The reason why chronic wounds are difficult to heal might be related to the anemia induced by chronic disease and the dysregulation of local cutaneous iron hemostasis. Fe exerts several effects on the wound surface. 1) Fe can affect the tissue oxygen content. Fe deficiency will lead to iron deficiency anemia, ultimately resulting in tissue hypoxia. Tissue hypoxia caused by iron deficiency anemia can inhibit fibroblast division, collagen production and new blood vessel growth, thus directly affecting wound healing.[116] 2) Fe can influence collagen synthesis. Fe deficiency results in harmful effects on collagen synthesis. Collagen attaches to growing cells, and the blockage of collagen synthesis negatively affects wound healing.[117] 3) Fe can also influence oxidative stress levels. When free Fe in the local environment is excessive, it can disrupt REDOX homeostasis by inducing oxidative stress, which plays a key role in wound healing. Fe mainly exists stably in the form Fe^{2+} (electron donor) and Fe^{3+} (electron acceptor),[118] and it can affect all stages of wound healing. 4) Fe overload affects the activation of macrophages. ROS induced by the fenton reaction and pro-inflammatory cytokines secreted by persistent M1 macrophages cause a state of high oxidative stress and inflammation in the wounds.[119] 5) Fe overload leads to fibroblast senescence. Oxidative stress caused by iron overload is the main cause of fibroblast senescence and is related to the disruption of lysosomal functions, an increase in iron storage proteins, and a reduction in iron death sensitivity. Moreover, the persistence of senescent fibroblasts hinders the normal progression of chronic skin wound healing.[120] Fe-chelating agents or pharmacological drugs containing Fe could thus provide future research directions for the treatment of chronic wounds. The names and main effects of dressings related to Cu^{2+} and Fe^{2+}/Fe^{3+} are shown in Table 4.

Zn^{2+}

The zinc (Zn) content is approximately 1.4–2.4 g in normal adults, and this can maintain the health of skin tissue and improve immune functions.[126] When the skin tissue is damaged and a wound surface appears, the Zn content changes. In burn wounds, the Zn^{2+} content in skin tissue decreases on days 1–3 and increases on day 7.[127] Large amounts of Zn^{2+} are consumed during wound healing and inflammation. Moreover, oral or local topical Zn supplementation can be used to increase the Zn^{2+} content and promote wound healing. Oral Zn supplementation is also beneficial for improving blood Zn levels, the application of Zn-containing medical dressings to wounds can help to increase the Zn^{2+} content in the skin.[128] Furthermore, Zn can promote an increase in capillaries, granulation tissue and fibroblasts[129] and can effectively promote the healing of various wounds, such as burns, surgical wounds, lower limb ulcers, bedsores and skin inflammation.[130–133] Additionally, Zn is an important coenzyme involved in tissue repair and is a component of many proteins.[134,135] It also plays an important role in coagulation,[135] cellular immune regulation,[134] epithelial regeneration and extracellular matrix deposition.[136] Zn^{2+} can participate in the regulation of cell proliferation and differentiation or the preservation of

Table 4 Treatment Utilizing Cu^{2+} and Fe^{2+}/Fe^{3+}

Ions	Dressing or materials	Main effects
Cu^{2+}	Cellulose fibers containing algae ultrafine powder	Upon contact with wound exudate, Cu^{2+} is released by ion exchange.[121]
	Microbacterium nanfibrogenin and alginate	Reactive to pH and possess antibacterial activities.[122]
	Conventional dressing	Reduces the risk of infection and antibiotic resistance.[123]
Fe^{3+}	Iron chelator (Deferoxamine)	Most commonly used to treat iron over-load. Applied topically to the skin in experiments.[124]
Fe^{2+}/Fe^{3+}	Sodium alginate deferriamine hydrogel dressings	Promote angiogenesis and diabetic wound healing.[125]

bacterial cell membrane structures,[137] stimulate epidermal cell proliferation, promote collagen deposition by fibroblasts, inhibit inflammatory factors, promote cell proliferation and migration, promote granulation tissue formation and angiogenesis and accelerate the epithelialization process of the wound surface by regulating the inflammatory response in the skin.

Numerous clinical studies have demonstrated that the use of Zn-containing medical dressings on wounds can shorten healing time.[127] In the context of wound treatment, Zn is primarily present in dressings in the form of zinc oxide (ZnO) or zinc sulfate ($ZnSO_4$); here, ZnO particles are insoluble in water and dissolved in an aqueous solution containing proteins. Thus, Zn^{2+} can be released continuously and slowly into the wound, but $ZnSO_4$ does not exhibit a slow-release effect.[138]

Mg^{2+}

Mg^{2+} are the most abundant cations in cells,[139] and is closely related to soft tissues. 1) The concentration of Mg^{2+} affects the migration and adhesion of human skin fibroblasts in a dose-dependent manner, 100 μmol/L and 1 mmol/L $MgCl_2$ solutions can significantly promote the migration of fibroblasts.[140] 2) Mg^{2+} can regulate the migration of human umbilical vein endothelial cells at a peak concentration of 100μmol/L, and it also promotes angiogenesis.[141–145] 3) Mg^{2+} promotes collagen synthesis, which is essential for the regeneration of mature wound tissue.[139] The names and main effects of dressings related to Zn^{2+} and Mg^{2+} are shown in Table 5.

Table 5 Treatments Utilizing Zn^{2+} and Mg^{2+}

Dressing or materials	Main effects
Alginate aerogel	Increase the availability and anti-inflammatory activity of macrophages.[146]
Aloe vera-alginate film	Promotes wound healing.[147]
Calcium alginate hydrogel and bacterial cellulose	Good bacteriostatic performance.[148]
Zinc chloride	It may enlarge the wound surface.[149]
Silver and zinc cream	Antibacterial zinc supplement, enhances enzyme activity, and promotes wound healing.[128,150]
GelMA/Mg/Zn hydrogel	Good biocompatibility, promotes wound re-epithelialization, angiogenesis.[151]
Magnesium montmorillonite powder	Accelerates the formation of vessels, collagen deposition and maturation.[139]
Intelligent microneedle patch with MgH_2	Promote angiogenesis and reduce microvascular disease.[152]

The Connection of pH and Ionic Environment

Currently, there is little relevance with respect to the effect of wound pH on the ionic environment. This section is a preliminary summary of the effects of pH on various ions that might not be present solely within the trauma, with the objective of providing ideas for exploring the effects of the ionic environment of subsequent traumas. Cardiomyocyte intracellular pH (pH_i) and extracellular pH (pH_O) affect Ca^{2+}, leading to dynamic changes in intracellular calcium ions. Extracellular H+ ions inhibit Ca^{2+} currents, and intracellular H^+ ions stimulate Ca^{2+} currents.[153] The inhibition of Ca^{2+} inward flow occurs through Orai channels at a reduced pH_O. Moreover, a decreased pH associated with the immune response promotes Ca^{2+} channel activation.[154] Different concentrations of H_2O_2 have diverse effects on the kinetic parameters of the Na^+ and K^+ enzyme systems, which can lead to activation or inhibition of the corresponding enzymes, converting the energy of ATP into a transmembrane Na/K gradient, generating membrane potentials, and supporting excitability in neurons and myocytes.[155] Further, H^+/metal ion co-transportation, the extrusion of essential metal ions from phagocytic lysosomes, can activate antimicrobial functions in macrophages.[156] In summary, there are complex effects of pH_i and pH_o on various ions inside and outside the cell. Keratinocytes are the key cells affecting wound healing, and the relationship between changes in intracellular and extracellular pH, the effects on various ions, and the roles in wound healing are worthy of further research. The effect of Ca^{2+}, K^+, Na^+, Ag^+,Cu^{2+}, Fe^{2+}/Fe^{3+}, Zn^{2+} and Mg^{2+} on wound healing shown in Figure 3.

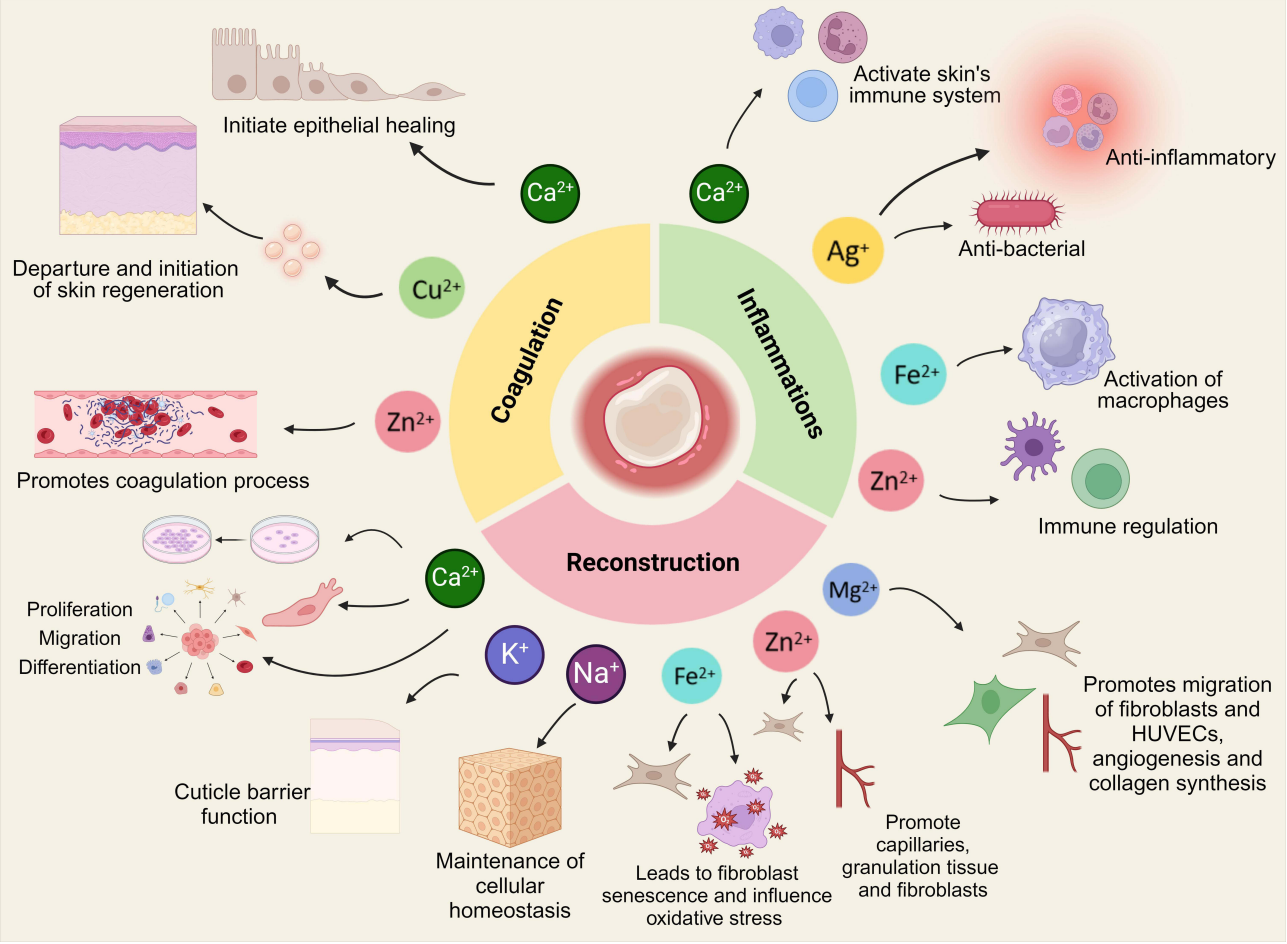


Figure 3 The effects of Ca^{2+},K^+, Na^+, Cu^{2+}, Fe^{2+}/Fe^{3+}, Ag^+, Zn^{2+} and Mg^{2+} on wound healing. Created in BioRender. Guo, J. (2024) https://BioRender.com/h85r722.

Conclusion

The pH and ionic environment hold great potential in the treatment of wounds. It is critical to explore the pH changes and ionic environment that best favor chronic diabetic wound healing. As ions in wounds are dynamically changing, methods to capture the nodes of dynamic changes in the ionic environment may be the key to clinical treatment, and the development of smart dressings may be an important means of altering the ionic environment. It is worth noting that although metal ions have many advantages, certain ions may be toxic when the concentration is too much, and the amount of exogenous metal ions absorbed through the wound or skin needs to be further investigated.This manuscript provides new ideas and points for future clinical and basic research. How to regulate the local pH of wounds, the dynamic regulation of ion concentration and channels, the development of multiple ionic composite dressings, and the safety of metal ion absorption in wounds are the focus of future research, which are relevant in wounds treating.

Core Tip

Wound microenvironment is an important factor affecting wound healing, among which complex changes of ionic environment affect wound healing. In this paper, the effect of pH in wounds, concentrations of Ca^{2+}, Na^{+}, and K^{+} and external metal ions Ag^{+}, Cu^{2+}, Fe^{2+}/Fe^{3+}, Zn^{2+}, and Mg^{2+} in normal and diabetic skin tissues, wound healing effects and the application of relevant dressings were reviewed. This paper provides a new idea and method for future clinical and basic research to explore the treatment of chronic diabetic wounds by adjusting ion concentration and channels.

Abbreviations

Ag, Silver; ATP, Adenosine triphosphate; Ca, Calcium; Cu, Copper; DNA, Deoxyribonucleic acid; ECM, Extracellular matrixFe, Iron; GHK, Glycine-histidine-lysine; HIF-1α, Hypoxia-inducing factor-1α; K, Potassium; Mg, Magnesium; MMP, Matrix metalloproteinase; Na, Sodium; NK cell, Natural killer cell; PDGF, Platelet derived growth factor; pH, Hydrogen ion concentration; pH_i Intracellular pH; pH_O, Extracellular pH; ROS, Reactive oxygen species; TEP, Transepithelial potential; TGF, Tubuloglomerular feedback; TIMP, Tissue inhibitor of metalloproteinase; TRPV, Transient receptor potential vanilloid; VEGF, Vascular endothelial growth factor; Zn, Zinc; $ZnSO_4$, Zinc sulfate; ZnO, Zinc oxide.

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Disclosure

The authors report no conflicts of interest in this work.

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