rémigén+ ® as an alginate-based hydrogel matrix with ionic components to support regenerative processes in Chronic Diabetic Wounds.

Sergey Gordeev - Scientific Coordinator, Dr/PhD. rer. nat. Axel Schmid - Co-Developer, R&D Project Director, Dr. med. Wolfgang Keller - Medical Application Trials by Casuistic Cases Dialysis & Diabetic Feet and Christian M. Giger - Co-Developer R&D.

Abstract

Chronic diabetic wounds cause substantial disability and, in severe cases, death. The wound microenvironment is dynamic, and its pH and ionic composition critically influence healing. Abnormal pH, ion levels, and ion-channel function may contribute to impaired healing. This review summarizes how pH and ions - Ca^{2+}, Na^{+}, K^{+} and Mg^{2+} - affect wound healing and surveys rémigén+ as an alginate-based hydrogel matrix with ionic components. The rémigén+ composition implies a synergy between the hydrating, gel-forming function of alginate and the buffering/ionic regulation provided by the phosphate group and cations. This review draws on established scientific data on alginate matrices, ionic regulation, and pH regulation in skin and wounds, as well as related studies on the effects of Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} and phosphates on skin and wound healing. The aim of the review is to connect known biochemical and physiological principles with hypotheses about how rémigén+ influences skin tissue and what evidence in the literature supports these hypotheses.

Keywords: Chronic diabetic wounds; pH; ions; ionic environment; wound healing; review; rémigén+; calcium (Ca^{2+}); sodium (Na^{+}); potassium (K^{+}); magnesium (Mg^{2+}).

Introduction

Chronic diabetic wounds are a major complication of diabetes mellitus (DM), associated with poor prognosis, high recurrence rates, and a substantial risk of amputation, which imposes a heavy burden on patients and the health-care system [1][2]. Wound healing is a complex, multi-phase process that includes coagulation, inflammation, proliferation, and remodeling; these stages overlap and lack clear boundaries, making the overall course highly dynamic [3,4]. Limited oxygen supply and high oxygen consumption in the wound sustain a persistent inflammatory response and hinder healing [5,6]. Hyperglycemia further impairs healing by reducing vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α), promoting non-enzymatic glycation of key proteins, and disrupting cellular and extracellular matrix (ECM) functions, which inhibits angiogenesis and delays repair [7][8].

Recent advances in materials science, polymer chemistry, biomedicine, and chemistry have led to multifunctional biomaterials - hydrogels, bio-polymers and bio-glasses, foams, hydrocolloids, nanofibers, sponges, and semi-permeable membranes - that are designed to promote wound healing by supporting optimal microenvironments and enabling intelligent interactions with the healing process [9]. The wound microenvironment comprises internal components (cells, ECM, resident microbes and biofilms, immune cells) and external factors (pH, ion concentrations, oxygen, temperature, humidity, light, electrical and magnetic fields) that continuously influence repair [10]. After skin injury, dynamic and site-specific changes occur, and the evolving microenvironment can either facilitate or impede healing. Under chronic hyperglycemic conditions, the wound milieu is difficult to control, leading to persistent inflammation, biofilm formation, reduced perfusion, oxidative stress, and angiogenesis impairment, which together delay healing [10].

A central focus of current research is the interplay between pH and the ionic environment. The wound pH and the plasma/ionic content - including calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}) and magnesium (Mg^{2+}) - profoundly affect cellular processes, enzyme activity, signaling pathways, and ECM remodeling that drive healing. There are intricate, bidirectional relationships between pH and

these ions; imbalances in either dimension can disrupt cell function and delay repair. Consequently, improving diabetic wound healing may require restoring homeostasis of the ionic environment in skin tissues and modulating pH in tandem.

This review discusses: (I) how wound pH and these ions influence healing; (II) the mechanisms by which the ions of rémigén+ - Ca^{2+}, Na^{+}, K^{+} and Mg^{2+} - affect cellular activities, angiogenesis, inflammation, and ECM dynamics; and (III) the practical experience with rémigén+ as ion-responsive dressing that regulate or sense the ionic milieu to promote healing by tuning the wound environment and addressing the dysregulated ionic balance seen in chronic diabetic wounds.

Composition of rémigén+ and biological validity

Main Ingredients of rémigén+

Alginate matrix enriched with K^{+}, Ca^{2+}, Na^{+}, Mg^{2+} ions and phosphates. rémigén+ is a cosmetic serum developed by Swiss-SET GmbH (Switzerland). Its formulation includes the following ingredients: **Aqua (water)**: Solvent medium.; **Dipotassium phosphate (K_2HPO_4)**: Buffering agent, ensuring proper pH stability; **Dicalcium phosphate ($CaHPO_4$)**: Provides calcium ions for cellular signaling and structure; **Sodium phosphate (Na_2HPO_4)**: Additional buffering component; **Alginate ($(C_6H_8O_6)_n$)**: Natural polysaccharide extracted from brown seaweed, acting as a gel-forming agent and moisturizer; **Magnesium phosphate ($Mg_3(PO_4)_2$)**: Source of magnesium ions, essential for cell health and energy metabolism; This combination ensures effective hydration, nutrient supply, and protection for the skin, making rémigén+ suitable for daily care routines aimed at improving skin condition and appearance.

Main mechanism: Alginate creates a flexible hydrogel-like structure, retaining moisture and forming a hydrated protective layer on the skin's surface, offering an ideal environment for skin cells and their interactions with the surroundings. It supplies moisture and acts as a physical barrier, while phosphates and ions generate localized ionic buffering conditions and a pH micro-gradient. Calcium ions (Ca^{2+}) provide structural rigidity to the gel and serve as messengers, governing fibroblast and keratinocyte proliferation, migration, and extracellular matrix (ECM) remodeling. Magnesium ions (Mg^{2+}) act as cofactors for various enzymes and stabilize cellular membranes. Sodium (Na^{+}) and potassium (K^{+}) ions maintain membrane potential and ion transport across cell membranes.

Clinical effects: improved wound healing (including chronic/diabetic wounds), enhanced barrier function and skin comfort, influence on the skin microenvironment and microbiome through regulation of pH and ion balance. Those properties are essential for daily skincare and after dermatological procedures.

In general: rémigén+ acts as a local skin microclimate module - retaining moisture, regulating pH/ionic environment, and supporting regenerative processes.

The water phase (Aqua) delivers hydration and serves as a solvent for salts and the alginate matrix. Dipotassium phosphate (K_2HPO_4), sodium phosphate (Na_2HPO_4), and dicalcium phosphate ($CaHPO_4$) act as phosphate buffers, participating in ion exchange processes. Calcium ions (Ca^{2+}) play dual roles: structurally reinforcing the alginate gel and serving as messengers in Ca^{2+}-dependent signaling cascades. Magnesium phosphate ($Mg_3(PO_4)_2$) introduces magnesium ions (Mg^{2+}), which stabilize cell membranes and modulate enzymatic reactions. Alginate - the primary hydrogel polymer - provides hydration, surface protection, and potential regulation of local pH and ionic balance through ion exchange. Collectively, these components create a hydrogel-like matrix that:

- Retains moisture, creating an optimal environment for cellular regeneration.
- Partially buffers pH at the application site.

- Forms localized ion gradients (Ca^{2+}, Na^{+}, K^{+}) around the skin and wound surfaces.
- Modulates cellular signaling by influencing membrane potential and ion transport.

This composition implies a synergy between the hydrating, gel-forming function of alginate and the buffering/ionic regulation provided by the phosphate group and cations. This review draws on established scientific data on alginate matrices, ionic regulation, and pH regulation in skin and wounds, as well as related studies on the effects of Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} and phosphates on skin and wound healing.

The Role of Ions and Phosphates in the Skin (General Principles)

Effects of Ca^{2+} in Wound Healing

Ca^{2+} plays a key role in regulating cellular proliferation, differentiation, fibroblast migration, and activation of growth factors in wound healing. The Ca^{2+} gradient between the epidermis and dermis influences cellular activity and extracellular matrix functions. These principles are widely discussed in reviews on the role of Ca^{2+} in skin and wounds [20].

Calcium is involved in the earliest wound-signaling activity and plays an important role in regulating wound healing. [11] 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. [12] Together with other coagulation factors, it triggers the intrinsic coagulation cascade, accelerates the synthesis of thrombin, and promotes early fibrin formation. [13] 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. [14] 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. [15] 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. [16] [17]

Calcium (Ca^{2+}) is a key regulator of skin physiology, guiding keratinocyte differentiation, epidermal barrier formation, and Ca^{2+}-dependent signaling that influences proliferation, migration, and extracellular matrix remodeling. It also plays a critical role in wound healing by promoting epithelial cell migration and tissue regeneration, with Ca^{2+}-containing dressings helping to establish a moist, protective microenvironment. In diabetic foot ulcers, calcium-containing hydrogels or alginate-based dressings can aid hydration and regeneration as part of a multimodal treatment approach. Ca^{2+} can indirectly support epidermal renewal and the balance of barrier structures. Overall, Ca^{2+} is a fundamental regulator in skin with potential adjunctive value.

Effects of Mg^{2+} in Wound Healing

Mg^{2+} are the most abundant cations in cells, 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. 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. 3) Mg^{2+} promotes collagen synthesis, which is essential for the regeneration of mature wound tissue.

Mg^{2+} participates in metabolic and enzymatic processes, stabilizes membranes, and regulates the activity of a range of enzymes and signaling pathways. Mg^{2+} presence in the wound milieu correlates with regulation of cellular proliferation and tissue regeneration [18]. Mg^{2+}: a coenzyme of many enzymes; in the skin, it is associated with the regulation of fibroblast proliferation, the synthesis of ECM proteins, and the regulation of regenerative processes.

Effects of Na^+/K^+ in Wounds

Na^+ and K^+ form electrochemical gradients that maintain membrane potential, ion transport across cell membranes, and pH regulation. Their balance critically affects skin cell function and wound regeneration; disturbances of the ionic milieu are associated with skin pathologies and delayed healing [17]. K^+ and Na^+ maintain the osmolarity of the extracellular space and electrolyte balance; local ion fluctuations can affect cell signaling pathways and the migration of superficial cells.

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 [18] 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. [19] Additionally, K^+ can inhibit the differentiation of keratinocytes and increase the rate of Ca^{2+} inflow.

Effects of Phosphates in Wounds

Phosphates (K_2HPO_4, Na_2HPO_4/Na_3PO_4, $Mg_3(PO_4)_2$) ensure pH buffering and deliver cations essential for forming the alginate network and maintaining an optimal skin microbiome and metabolic environment. Numerous studies discuss the significance of phosphate buffering systems in relation to skin-pH and wound healing [20]. Within rémigén+, phosphates preserve matrix stability and facilitate ion transport.

In biomedical and cosmetic preparations, buffer systems are frequently employed to sustain pH stability and create a supportive environment for cells and tissues. By virtue of its buffering capabilities, rémigén+'s phosphate composition may enhance skin resilience and optimize healing conditions, particularly in cases where local pH and ionic balance are compromised, such as in chronic wounds or dermatological disorders involving a compromised skin barrier.

rémigén+ incorporates phosphate salts (K_2HPO_4, Na_2HPO_4/Na_3PO_4, $CaHPO_4$) and ions (Ca^{2+}, Mg^{2+}, Na^+, K^+). These components collectively create a localized buffering system, helping to maintain a balanced pH at the point of application.

There are two notable consequences of this buffering effect:

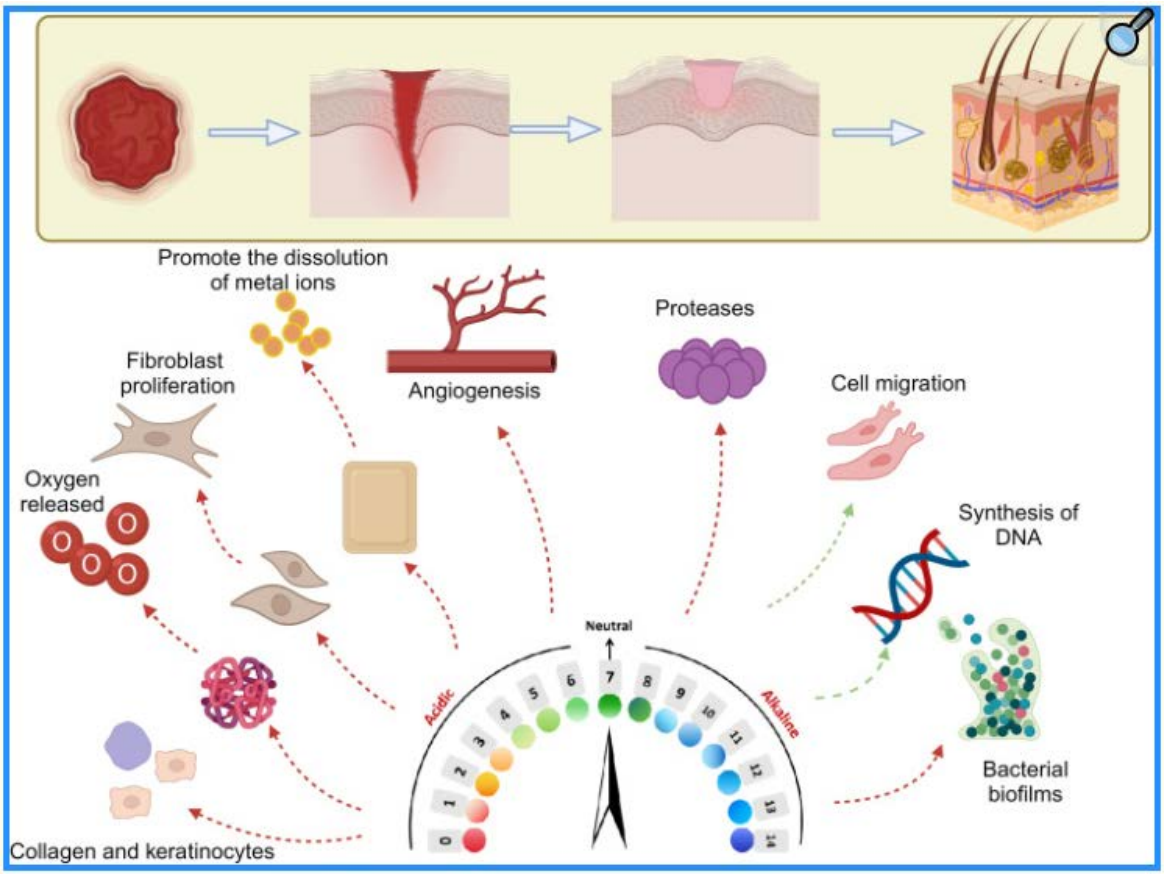
Stabilization of the Local Ionic Environment: By keeping the pH steady, rémigén+ favors enzyme activity, preserves the balance of microflora, and mitigates inflammation.

Partial Regulation of Surface pH: Regulating the skin's surface pH is crucial for managing protease activity and promoting efficient healing, particularly in chronic wounds.

It's important to note that the buffering action stabilizes rather than rigidly fixes the pH. When substantial amounts of acids or bases enter the mix, the buffer resists drastic pH alterations, working within its capacity to keep things consistent.

Proton gradient (pH) in tissue and its regulation

The pH of the skin and wound surfaces strongly influences biochemical processes: enzyme activity, skin microbiota, inflammatory responses, and wound healing rate. Normal skin surface pH is about 4.8-6.0; in wounds pH can fluctuate, and in chronic diabetic wounds it is often more alkaline (approximately 7.4-8.9, sometimes up to 9.25). Alkaline pH accelerates or slows certain stages of healing and affects protease activity and ECM interactions. Reviews emphasize that maintaining an optimal pH is a promising direction for wound-care materials, including alginate gels and hydrogels [Guo et al., 2024; CCID 2024; review of pH and wounds; other related sources]. [20]



The effects of pH on wound healing. Created in BioRender. Guo, J. (2024) https://BioRender.com/k20j084. [20]

Accordingly, phosphate salts and ions in rémigén+ composition influence the local pH at the application site, providing a more favorable environment for skin cells and regenerative processes, especially if the serum is used in conditions where wound-pH deviates from the optimal range.

An important point is the interplay between pH and the ionic milieu: pH changes can alter protein conformation and enzyme activity, and ionic gradients can modulate cellular signaling pathways; this interplay is discussed in current reviews of chronic diabetic wounds [21].

Water gradient and hydration

The alginate hydrogel matrix retains moisture and creates a water-rich environment, which is important for cellular proliferation and migration. A hydrated environment supports cell migration, collagen synthesis, and ECM remodeling, and reduces stress in wounds. Alginate hydrogels often show good moisturizing properties and adaptability to wound exudate levels; these properties are regularly discussed in reviews on alginates in skin cosmetics and dermatology [22].

Aquaporins and ion channels establish and regulate gradients of calcium, sodium, potassium, chloride, water, and protons in the epidermis. These elements have been found to play significant roles in skin biology and wound healing. These channels and ion gradients play an important role in acute wound healing.

Hemostasis, inflammation, proliferation, and maturation are the typical phases of wound healing. Each phase is processed by different cell types and molecular mediators. [23], [24], [25]. Specifically, the ionic environment has been shown to be critical in facilitating wound healing processes, such as cellular differentiation, migration, and proliferation. The pH gradient (i.e., proton gradient), also termed the “acid mantle,” establishes a low pH of 4-6 localized in the stratum corneum. (Fig. 1) [26]

Figure 1.

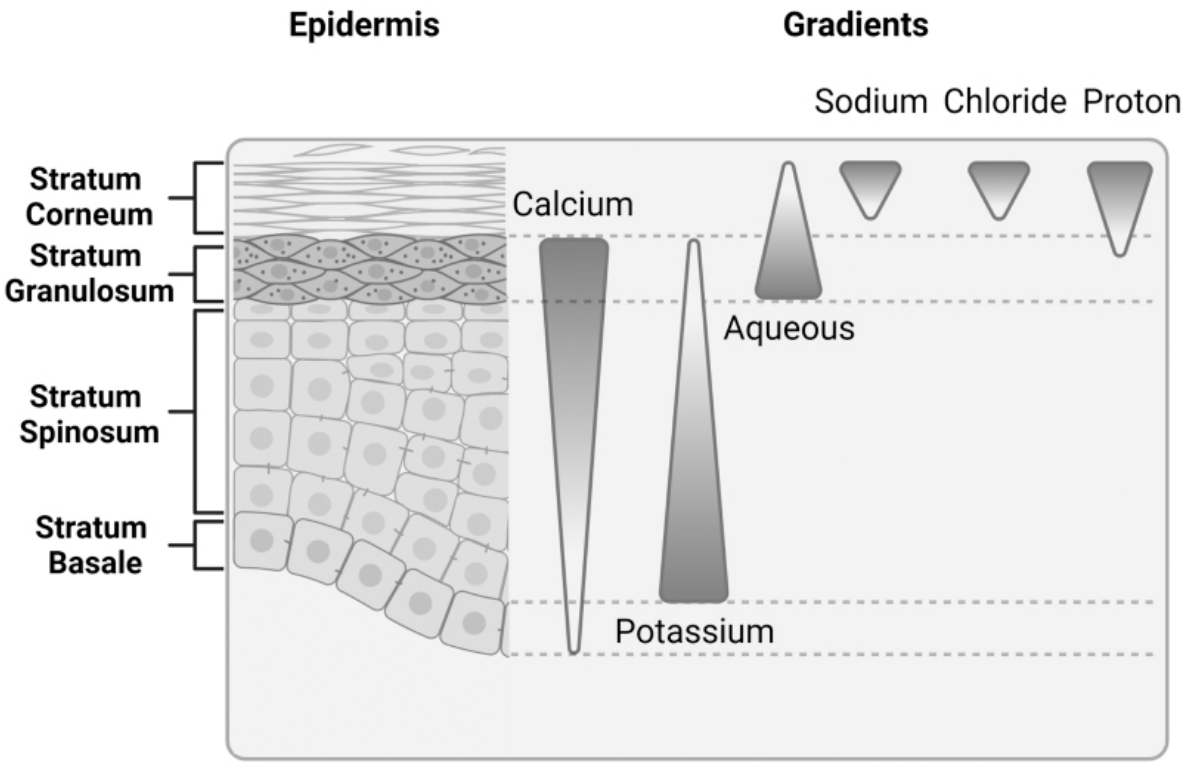


Figure 1. Gradients of ions and AQP3 in the epidermis. The gradients of ions and AQP3 are depicted as triangles with both dark shade and width to show high level, whereas lighter shade and decreased width show lower level. Those triangles are for illustrative purpose and do not have exact quantitative comparison across ions and the AQP3. AQP3, aquaporin 3. [26]

In the context of rémigén+, the aqueous phase provides transport of ions and phosphate components to the skin surface, which supports local regulation of water balance and metabolism in the skin.

Membrane potential and transdermal potential

The membrane potential of skin cells depends on the balance of Na^+, K^+, Ca^{2+}, and Mg^{2+}. These ions regulate ion transport, activate signaling pathways, and govern cell viability. In wounds and especially in diabetes, regulation of the ionic milieu can significantly affect cellular functions and healing speed. Modern reviews describe the roles of Ca^{2+}, Mg^{2+}, K^+, Na^+ in regulating membrane potential, transport, and signaling processes in skin and wounds [17] [26].

In the context of transdermal delivery, skin barriers and potentials (for example, the influence of water-ionic signaling on drug permeation) are highlighted in skin model and transdermal delivery studies; these data help understand how an alginate serum could influence local skin conditions [26] and obviously the permeation of actives present in rémigén+.

What is an alginate matrix and why is it important for skin?

Alginates are polysaccharides derived from brown algae that form hydrogel matrices when interacting with ions (often Ca^{2+}, Mg^{2+}). These hydrogels exhibit high water absorption, biocompatibility, form a barrier-like coating, and are capable of retaining moisture, creating a stable, hydrated environment on the skin. In cosmetic and dermatological contexts, alginates are used as humectants, film-forming, and pH-regulating materials [22] - this is the underlying mechanism that rémigén+ exploits as the basis for its matrix.

Alginate forms a biocompatible, modular gel-like matrix, retains moisture, provides a comfortable texture for masks and films, and can serve as a carrier of active ingredients for local action on the superficial layers of the skin. [22] Alginates in skincare are commonly used as moisturizers, film formers, and to regulate viscosity and texture. Their ability to regulate pH can be useful in a serum aimed at supporting skin microbiota and barrier function. [22].

Alginate is a versatile biopolymer extensively utilized in tissue engineering, particularly for wound healing applications. Due to its historical usage as a food additive, it's regarded as safe and biocompatible. It's valued for its biodegradability and controlled dissolution rates in biological fluids when crosslinked with exchangeable cations like calcium (Ca^{2+}). [22]

Calcium-Alginate (CA): When insoluble calcium-alginate comes into contact with wound exudates, calcium ions are gradually displaced by sodium ions from bodily fluids. This displacement generates a mildly viscous gel, which aids in achieving hemostasis by preventing bleeding and sealing minor injuries.

Sodium-Alginate (SA): Sodium-alginate fibers possess remarkable absorbency, drawing significant quantities of wound exudates. Upon saturation, these fibers transition into a gel-like state, forming a moist barrier atop the wound. This gel not only keeps the wound hydrated but also protects it from contamination, creating an optimal environment for healing.

By manipulating alginate's oxidation levels and reducing its molecular weight, researchers can fine-tune its mechanical properties and dissolution rates, enabling tailored adaptation for varied biomedical uses.

Thus, alginate-based composites combine versatility, biocompatibility, and tunable functional attributes, positioning them prominently in advanced wound-healing therapeutics.

Studies investigating alginate-based materials for transdermal delivery reveal intriguing insights into how these substances enhance permeation through the stratum corneum by altering lipid packaging and interacting with the skin's water and membrane phases. [22] Although originally focused on patches, creams, and powders, these findings shed light on the mechanisms by which alginate matrices engage with the skin. Such information is valuable for interpreting the effects of rémigén+ serum, given its alginate composition.

Research has explored alginate patches and powders in wound healing contexts, highlighting their capacity to manage water balance, ionic environments, and pH, depending on formulation and application techniques. These findings suggest analogous effects could occur when rémigén+ serum is applied directly to the skin without relying on traditional patch/powder formats. Reviews of alginate-based powders and patches emphasize principles of network formation and practical application methods, [27] [28] underscoring their relevance to rémigén+ serum.

Understanding how alginate systems in various formulations influence pH regulation and ion transport is important for assessing the potential role of rémigén+ in skin conditions. A review of alginate formulations notes the differences between powders, gels, and patches, as well as their effects on pH regulation and skin microflora [27] [28].

Safety and Biodegradation of rémigén+

Alginate-based matrices crosslinked with inorganic salts are typically well tolerated on human skin in cosmetic and dermal applications. Degradation occurs mainly through ion exchange and enzymatic processes, yielding benign constituents: Ca2+, Mg2+, Na+, K+, phosphate ions, and alginate oligosaccharides that re-enter normal metabolic pathways and are cleared by physiological processes. The rate of biodegradation depends on crosslink density, pH, moisture, and enzymatic activity; higher crosslinking slows degradation and helps maintain the hydrated microenvironment. Rare irritant or allergic reactions to alginates have been reported, but the overall safety profile is favorable under standard use conditions. For rémigén+ formulations, safety and biodegradation are expected to align with established alginate- and salt-containing products, with local effects limited to the skin surface and minimal systemic exposure.

The Role of rémigén+ alginate serum in healing and prevention of Chronic Diabetic Wounds

Hydration and barrier function

The alginate matrix creates a moist environment on the skin surface, maintaining the normalization of the hydrolipid balance and strengthening the barrier function of the epidermis by preserving the water content in the surface layers.

Alginate and Ca2+ form a hydrogel on the skin. Alginate forms "egg-box" structures when in contact with Ca2+ ions, forming a gel that retains moisture and creates a moist environment on the skin's surface. This promotes gentle hydration, reduces friction, and facilitates natural regenerative processes without aggressive drying.

Ionic support of cellular regulatory pathways

The transmission of calcium ions (Ca^{2+}) represents one of the earliest signaling responses triggered by ATP released from injured cells, thereby elevating cytosolic Ca^{2+} levels in neighboring cells. Under stable skin conditions, Ca^{2+} reaches peak concentrations in the outer granular layer, being minimal in the basal layer. Following skin trauma, detectable amounts of Ca^{2+} appear immediately in the wound site, supporting the blood clotting process. The elevation in Ca^{2+} persists for about five days post-wounding, coinciding with maximal inflammatory activity. Throughout the healing process, the wound's extracellular Ca^{2+} concentration fluctuates dynamically, remaining high during inflammation and proliferation phases before declining during remodelling. Upon wounding, the Ca^{2+} concentration in skin tissue rises sharply - up to 60 times higher than normal - and necessitates continuous clearance to prevent harmful build-up. [20] The transient receptor potential vanilloid (TRPV) family serves as a nonselective calcium-permeable cation channel widespread in mammalian

skin, controlling transmembrane Ca^{2+} balance and cellular depolarization. Different TRPV isoforms impact distinct cellular activities: TRPV1 and TRPV3 associate with cell demise, TRPV1 induces mitochondrial dysfunction and Ca^{2+} influx, while TRPV3 boosts keratinocyte multiplication through NF-kB signalling. Conversely, TRPV2 drives contraction of dermal fibroblasts and influences scarring. TRPV4 participates in organizing actin structures via Rho-related pathways. Nevertheless, Ca^{2+} dynamics differ markedly between acute and chronic diabetic wounds. [20]

Altered Ca^{2+} homeostasis and signaling characterize type 1 and type 2 diabetes. Common symptoms include raised baseline Ca^{2+} levels, weakened Ca^{2+} transport capacity, and blunted stimulus-triggered Ca^{2+} responses. In hyperglycemic environments, increased intracellular and extracellular Ca^{2+} in keratinocytes leads to membrane polarization disturbances, hampering the regular trafficking of lamellar bodies and impairing stratified lamellar membrane formation, consequently delaying skin barrier restoration. [20]

Impact of Calcium Ions (Ca^{2+}) on Wound Repair Process

Calcium ions play a pivotal role in early wound signaling and subsequent healing processes. Known as Factor IV, Ca^{2+} aids in forming blood clots initially upon injury, triggering the intrinsic coagulation cascade, synthesizing thrombin, and stimulating early fibrin formation. During inflammation, extracellular Ca^{2+} infiltrates neutrophils, raising intracellular calcium levels and regulating various leukocyte functions. Extracellular Ca^{2+} acts as a key mediator of epidermal homeostasis, initiating epithelial healing by altering intracellular calcium signaling and E-cadherin interactions, ultimately driving keratinocyte adhesion, differentiation, and survival. Lower extracellular Ca^{2+} concentrations support rapid keratinocyte proliferation, while higher levels prompt differentiation, critical for establishing the skin barrier. Excessively high Ca^{2+} concentrations impede keratinocyte migration and proliferation, potentially slowing down wound closure. Calcium also regulates angiogenesis, influencing endothelial cell migration, adhesion, and vascular development. Fibroblasts utilize intracellular Ca^{2+} for contraction, orchestrating actin remodeling and enhancing wound contraction. Supplemental extracellular Ca^{2+} bolsters cell metabolism, migration, collagen synthesis, and cytokine release. Additionally, Ca^{2+} sustains the integrity of the epidermal barrier enriched with proteins and lipids. Lastly, Ca^{2+} activates natural killer (NK) cells, vital components of the skin's innate immunity, amplifying immune defense against infections. [20]

Dressings incorporating calcium salts decompose upon contact with wounds, releasing Ca^{2+} ions. This mechanism fosters epithelialization, expedites wound healing, strengthens immune responses, suppresses microbial growth, and enhances fibroblast migration, collagen synthesis, and cytokine secretion. Various types of calcium-containing dressings demonstrate beneficial effects on wound repair, summarized in relevant tables. [20]

Role of Sodium (Na^{+})/Potassium (K^{+}) in Chronic Diabetic Wounds

Sodium ions contribute to osmoregulation and temperature maintenance through sweating. They distribute similarly across the skin layers, peaking at the base and diminishing towards the outer surface. Epithelial sodium channels (ENaCs) remain prominent in all epidermal layers except the stratum corneum, playing a central role in preserving sodium equilibrium. At later stages of wound healing, however, skin barrier deficiencies can disrupt Na^{+} homeostasis, leading to persistent inflammation. [20]

Potassium governs keratinocyte maturation and skin barrier functions. Unlike calcium, K^{+} abundance is greatest in the prickle-cell layer and drops toward the granular layer. An increase in extracellular calcium prompts K^{+} channel activation, driving hyperpolarization in immature keratinocytes. Two principal potassium channels - KCNH2 and KCNAJ8 - maintain K^{+} gradients. While KCNH2 conducts outward K^{+} flow, stabilizing membranes, KCNAJ8 facilitates inward K^{+}

currents, balancing depolarization. Notably, KCNH2 suppression and KCNAJ8 enhancement accelerate wound healing.[20]

Significance of Na^+/K^+ Balance

Through the Na^+/K^+ pump, trans-epithelial electrical fields guide wound healing. Each pump cycle consumes one ATP molecule to export three Na^+ ions and import two K^+ ions, generating the necessary electrochemical gradient. Potassium can suppress keratinocyte differentiation while augmenting calcium influx. [20]

Medications containing Na^+ and K^+ help eliminate surplus fluids in edematous tissues, promoting epithelialization and wound closure. Despite current knowledge, further exploration of their clinical benefits is warranted. [20]

Magnesium Ions (Mg^{2+})

Magnesium ions are among the most prevalent intracellular cations, integral to numerous biological processes. Key roles of magnesium in wound healing include:

Fibroblast Migration: Concentrations of Mg^{2+} affect fibroblast migration and adhesion. Solutions of $MgCl_2$ at 100 µmol/L and 1 mmol/L notably enhance fibroblast mobility. [20]

Angiogenesis: Mg^{2+} optimizes the migration of human umbilical vein endothelial cells, particularly at 100 µmol/L, and contributes to neovascularization. [20]

Collagen Synthesis: Essential for mature wound tissue regeneration, Mg^{2+} promotes collagen production. [20]

Materials and dressings incorporating Mg^{2+} showcase diverse benefits [20]: Alginate aerogel: Enhances macrophage activity and reduces inflammation, Aloe vera-alginate films: Facilitate wound healing. GelMA/Mg/Zn hydrogels: Demonstrate excellent biocompatibility, encourage re-epithelialization, and stimulate angiogenesis, Magnesium montmorillonite powders: Expedite vessel formation, collagen deposition, and tissue maturation. These findings highlight the therapeutic potential of magnesium-based approaches in wound management.

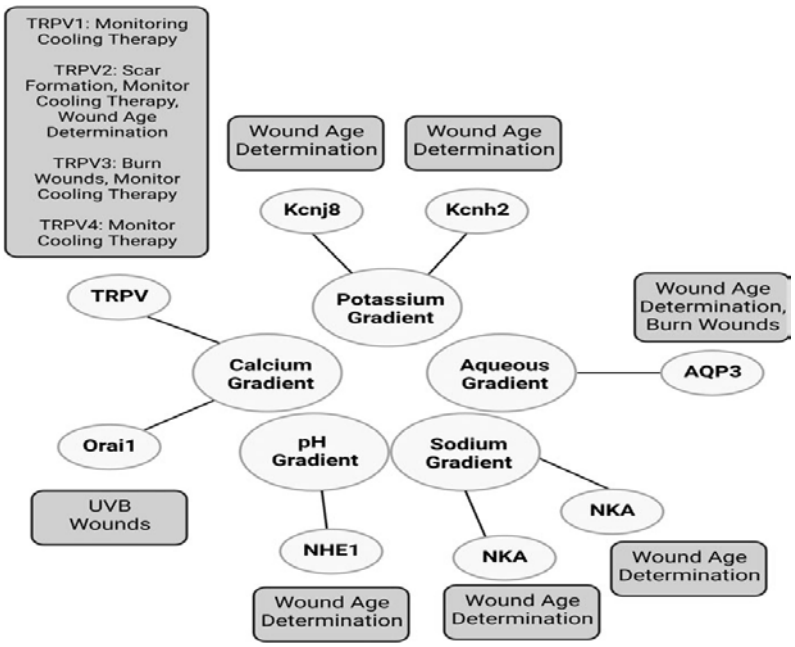


Figure 2. Selected Examples of Ion and Water Channels in epidermis and their implications in injuries and diseases. This figure depicts the associations between ion and aqueous gradients with their respective channels, pumps and exchangers. [20]

Interaction Between pH and Ionic Dynamics

Here we summarize preliminary observations regarding pH impacts on various ions:

Both intracellular pH (pHi) and extracellular pH (pHo) profoundly influence calcium ion (Ca^{2+}) levels, [20] causing dynamic variations in intracellular calcium. Here's what happens:

Extracellular Proton Effect: Extracellular protons (H^+) inhibit calcium currents, limiting Ca^{2+} influx.

Intracellular Proton Stimulation: On the contrary, intracellular protons stimulate calcium currents, promoting Ca^{2+} mobilization.

Orai Channels: Decreased extracellular pH (pHo) impairs Ca^{2+} influx through Orai channels, affecting calcium signaling.

Immune Response: Immune-related pH reductions trigger Ca^{2+} channel activation, intensifying cellular responses.

Additionally, varying concentrations of hydrogen peroxide (H_2O_2) alter the kinetic parameters of sodium (Na^+) and potassium (K^+) enzyme systems. [20] This modulation can either activate or inhibit respective enzymes, harnessing ATP-derived energy to generate transmembrane Na^+/K^+ gradients, establish membrane potentials, and enable neural and muscular excitability. [20]

Overall, these pH-dependent interactions reflect complex dynamics between pHi/pHo and intracellular/extracellular ions. Given their importance in wound healing, particularly within keratinocytes, further exploration of these relationships promises valuable insights into tissue repair mechanisms. [20]

Summary of Ionic Impacts on Wound Healing

Calcium (Ca^{2+}): Critical for early wound signaling, clotting, and cell adhesion/differentiation.

Potassium (K^+): Vital for keratinocyte differentiation and epidermal barrier function.

Sodium (Na^+): Supports osmotic balance and thermal regulation.

Magnesium (Mg^{2+}): Assists fibroblast migration and collagen production.

Understanding optimal pH and ionic compositions for chronic diabetic wounds holds immense promise. Capturing dynamic ionic fluctuations and developing intelligent dressings capable of modifying ionic profiles represent exciting areas for innovation. [20] Emerging technologies in wound pH regulation, multi-ionic composites, and safer ion administration strategies will continue advancing the field. [20]

Emergency Cases Highlight Regenerative Power of rémigén+: Revolutionizing Treatment of Diabetic Foot Ulcers

Let us consider the specific medical challenge posed by diabetic foot ulcers. This syndrome arises from peripheral circulatory issues and metabolic disturbances, presenting unique demands for wound-care and regenerative materials. Patients with diabetic foot ulcers experience prolonged healing delays due to neuropathy, hypertension, and impaired circulation. rémigén+ addresses these limitations by:

- Restoring hydrobalance and tissue mineralization.
- Supporting regenerative processes through ion-exchange mechanisms.
- Providing an optimal substrate for tissue reconstruction and regrowth.

The full details regarding the regeneration of diabetic feet using rémigén+ will be elaborated in a separate publication. However, this emergency case (Figure 3.) exemplifies the revolutionary potential of rémigén+ in avoiding amputation. Previously deemed irreversible, this trial (Case Ilona K., Germany, Diabetes type 1, date of birth 3 December 1962) demonstrates the exceptional regenerative possibilities offered by rémigén+. Strong correlations suggest that, under certain conditions, similar cases can avoid amputation entirely. Prevention emerges as the cornerstone, focusing on addressing underlying diseases like diabetes. Although further research is imperative, emerging evidence already reveals the transformative potential of novel treatment modalities.

Since its launch in 2016, rémigén+ has gained approval and acceptance among patients and healthcare professionals. Numerous documented cases, including this instance, substantiate its efficacy. Closely monitored by Dr. med. Wolfgang Keller, this case boasts over 1300 images and exhaustive hospital records, providing compelling visual and clinical evidence. Separately, Dr. Keller's studies on dialysis cases further affirm the product's positive impact, marking a paradigm shift in wound care. Intermediate results indicated mutual benefits for both patients and practitioners, laying the foundation for ongoing research.

Developed by Dr. rer. Axel Schmid, co-developed by Christian M. Giger and refined in 2018, rémigén+ embodies a milestone in regenerative medicine. Comprehensive experiments culminated in the final composition ("E 101 X040"), validated through rigorous testing. This proprietary blend yields unprecedented results. Documented in the official report titled "R&D Basic Document," these advances highlight rémigén+'s superiority in tackling complex wounds.

Diabetic foot ulcers stemming from peripheral circulatory issues and metabolic irregularities impose distinctive challenges for wound care. Patients endure extended healing periods owing to neuropathy, hypertension, and insufficient circulation. Addressing these hurdles, rémigén+ restores hydrobalance and tissue mineralization, supports regenerative processes via ion-exchange mechanisms, and provides an optimal substrate for tissue renewal. Case studies illuminate the profound benefits of integrating rémigén+ into multidisciplinary treatment paradigms. Beyond traditional therapies, rémigén+ stands as a contemporary solution for intractable wounds, advocating prevention and precision-targeted intervention.

The examination of case reports demonstrates the tangible benefits of integrating rémigén+ into multidisciplinary treatment protocols for diabetic foot ulcers. In conclusion, its potential extends beyond conventional remedies, representing a modern solution for challenging wounds requiring targeted therapeutic intervention as well as prevention of diabetic foot ulcers.

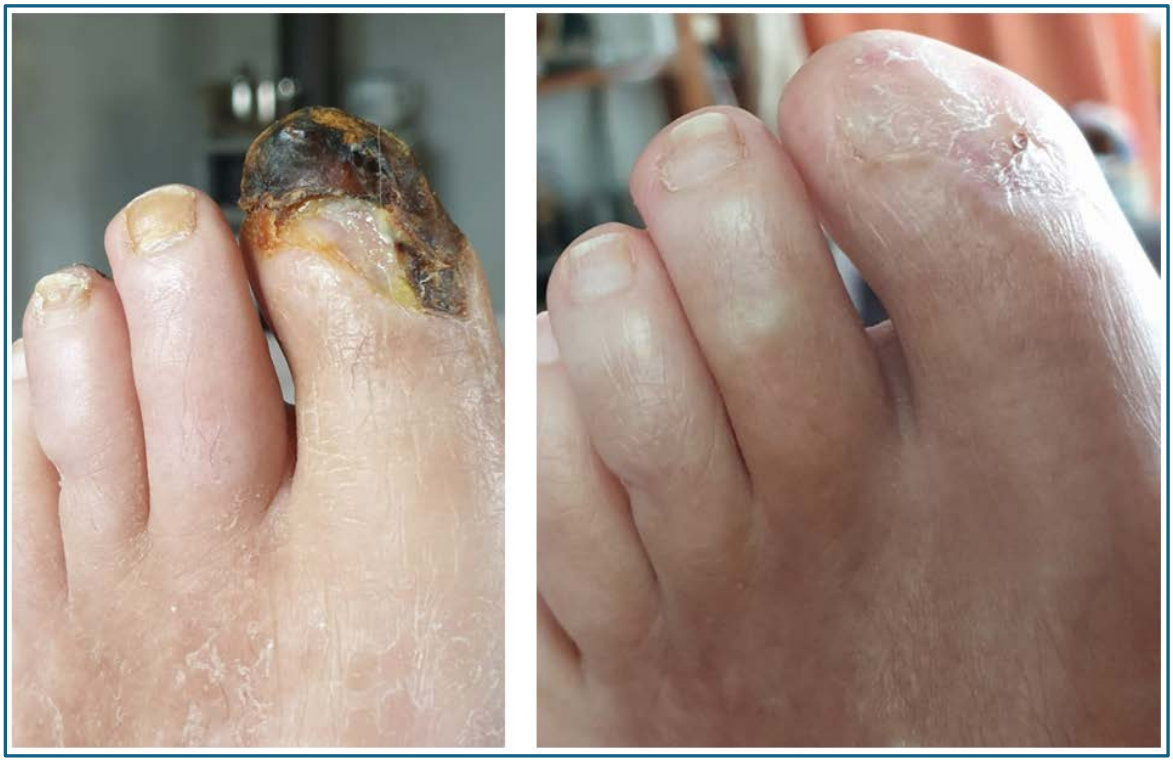


Figure 3. shows the regeneration of the necrosis in 4 months with rémigén+

Conclusion

rémigén+ presents a scientifically grounded approach to enhancing skin hydration, barrier function, and creating a favorable ionic environment. Phosphates combined with calcium and magnesium ions influence cellular metabolism and the microenvironment of the wound surface, supporting regenerative processes. Both pH and the ionic composition of wounds significantly impact the wound microenvironment, with abnormalities in pH, ion concentrations, and ion channels posing challenges in chronic diabetic wound healing.

Existing wound dressings leverage ionic efficacy, targeting pH adjustment and ionic balance. Empirical data indicate that wound pH critically influences healing efficiency, with deviations from physiological pH negatively impacting enzyme regulation, inflammation, and regeneration. Reviews highlight the potential of “smart” environments designed to modulate ionic balance and pH for improved wound healing. [20].

rémigén+, consisting of an alginate matrix with phosphate salts and ions (Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}), offers:

- Hydration and moisturization through the alginate hydrogel matrix.
- Partial regulation of local pH and ionic environment via phosphate buffers and cations.
- Influence on cell membrane potential and ionic fluxes, supporting regenerative processes.
- Maintenance of a favorable microenvironment for tissue regeneration and skin comfort.

These conclusions are consistent with current knowledge on the role of Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} in the skin, pH buffering, and regulation of cellular functions, as well as with data on the properties of alginates in cosmetics and their pH regulation. Consolidating research indicates that the pH of the wound microenvironment is a key factor in healing. Healthy skin typically has an acidic pH; wounds, and particularly chronic diabetic wounds, often exhibit a more alkaline

environment, which is associated with decreased enzyme regulation, increased inflammation, and slower regenerative processes.

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