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REVIEW

Hypochlorous Acid for Wound Healing in Diabetic Rats: Effect on MMP-9 and Histology

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Background: People who suffered type 2 diabetes have impaired healing of wounds due to the large number of circulating inflammatory cells resulting from high blood sugar levels. The wound healing process involves various complex processes including the degradation of extracellular matrix, a process characterized by an increase in matrix metalloproteinase-9 (MMP-9). Conventional management of diabetic wounds usually involves systemic blood sugar control and topical antimicrobial treatment, including hydrogen peroxide and povidone-iodine, which are known to be cytotoxic to the cells involved in the wound healing cascade. Finding a safe, non-toxic, and effecting wound cleansing still poses a challenge, and hypochlorous acid (HOCl) could act as a potential candidate.

Purpose: Unveiling an HOCl ion as an agent for diabetic wound management and MMP-9 as a marker for delayed diabetic wound healing.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram is used to find and select related, eligible literatures for the review. The authors used several databases such as Pro Quest, Scopus, Springer link and Science Direct. In addition, and to expand the data, the database on Google Scholar was also opened. Then, the compiled data are analyzed to form results and discussions to the research question.

Results: Five eligible articles passed the inclusion criteria and reviewed for data synthesis. From 5 pieces of literature, it was found that the use of HOCl ions can be a good choice of topical agent in the management of diabetic wounds and decrease the activity of MMP-9, which act as a marker for delayed healing of diabetic wounds.

Conclusion: Topical agent, in this case HOCl ion, shows good results and can be used as an option in the management of diabetic wounds and MMP-9 can be used as a predictive marker in the management of diabetic wounds.

Keywords: diabetic wound, HOCl ion, hypochlorite acid, MMP-9, wound healing

Introduction

According to the estimate by the International Diabetes Federation (IDF), the prevalence for diabetes in the world is 415 million and is expected to increase to 642 million in 2040. IDF estimated an increase in the number of Indonesian adults with diabetes from 10 million in 2015 to 16.2 million people in 2040. The World Health Organization (WHO) estimates an increase in the number of people with diabetes mellitus in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030.[1,2]

Diabetes mellitus (DM) is a metabolic disease characterized by increased blood sugar levels. The main subtypes of DM are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), which are generally caused by defects in insulin secretion (T1DM) and/or inadequate insulin action (T2DM). In people with diabetes, wound healing is disturbed by tissue necrosis and excessive inflammation, and this causes the wound bed which is rich in matrix metalloproteinase (MMP) to slow vascularization and produce a hypoxic surrounding environment. At the cellular level, diabetic wounds are characterized by an accumulation of senescent cells and a slow response to tissue repair.[3]

Literatures obtained from Cochrane regarding topical agent widely used in the management of diabetic ulcers are silver dressing, since silver dressing could provide comfort to patients, fewer complications in wounds, widely available, and its

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ability to be applied across various types of wounds. The disadvantage of silver dressing is that it is relatively expensive. Another widely used topical agent is povidone-iodine, an antiseptic agent used in wound cleaning. These antiseptics are proven to be successful in eradicating microbes, yet their cytotoxicity effects still raise concern.

Hypochlorous acid (HOCl) has the potential for its antimicrobial activity due to its ring chlorination and oxidation of amino acids, oxidation of sulfhydryl enzymes, loss of intracellular contents, decreased oxygen and nutrients uptake, inhibition of DNA, protein, and ATP synthesis, and oxidation of respiratory components.[4] HOCl exhibits several immunomodulatory, anti-inflammatory, and wound healing properties. It has a strong antimicrobial activity; therefore, microorganisms cannot reproduce or survive within its presence.[5–8] Other clinically relevant biological properties of HOCl include decreasing the activity of neutrophil-generated leukotrienes (LTB4), histamine, interleukin (IL)-2, IL-6, and in high concentrations could downregulate the activity of MMPs including MMP-7, MMP-9, and collagenases. HOCl could diminish the degranulation of mast-cell and cytokine release induced by immunoglobulin E and induce advantageous effects of keratinocytes and fibroblast migration.[9–11]

Previous research has been conducted to explore the use of HOCl ions in various health and sanitation contexts. Recent studies have been conducted to explore the potential of using HOCl ions in diabetic mice for wound healing. One study involved administering a HOCl ion solution to diabetic mice, and the results showed that the use of HOCl ions could speed up the wound healing process in diabetic mice.[1,12]

The wound healing process involves various processes including the degradation of extracellular matrix. MMP is a family of zinc endopeptidases which play a role in degrading all components of the extracellular matrix. They are key players in every phase of wound healing because they degrade proteins, destroy the extracellular matrix, facilitate migration to the center of the wound, remodel granulation tissue and regulate the activity of several growth factors. Several studies have shown that MMP is a predictive marker for impaired diabetic wound healing. In the process of wound healing, a systematic review by Garcia et al showed that there was an increase of MMP levels in acute wounds, despite not as high as in chronic wounds. High concentrations of MMP-9 in diabetic wounds indicate a poor wound healing. In current literatures, there have been several reviews reviewing the use of HOCl ions in diabetic wounds, yet none included the involvement of MMP-9 marker for the treatment of diabetic wounds with HOCl ions. Thus, the authors choose to review the use of HOCl ions in diabetic wounds by using MMP-9 as an indicator of healing.

Methods

In this study, the steps needed to retrieve relevant study are described in Figure 1. where the initial step taken was to open the website and enter keywords to enter and access the destination page. Next, the data page appears. Article searches were carried out using keywords in English in the Pro Quest, Scopus, Springer link and Science Direct databases. In addition, and to obtain data, the database on Google Scholar was also opened. The inclusion criteria for obtaining the desired literature are 1) articles are in English, 2) national and international research articles regarding the use of hypochlorous acid ions in rat models with diabetic wounds, 3) search journals limited to the last 5 years 4) unlimited articles on one research design. The keywords used are "HOCl in Diabetic Foot Ulcer" OR "Effects of HOCl in Diabetic Foot Ulcer on Animal Model" OR "MMP-9 as marker in Diabetic Foot Ulcer Healing" Exclusion criteria are non-full-text articles, no journal content related to treatment using HOCl ions on Diabetic Feet. Data extraction and analysis of each downloaded article is carried out by the author. The results were analyzed according to themes. Next, the data were organized according to theme analysis and in a narrative review. Eligible research will be summarized, identifying the name of the author, country, research objectives and main findings. The lack of existing research on the influence of HOCl on the levels of MMP-9 in diabetic wound healing poses an opportunity for authors to explore a niche area in research. This gap highlights the need for further investigation and this review acts as a pioneer to explore the specific connection.

Results

In the search obtained from Pro Quest we found 18 articles, a search using Scopus used advanced methods and found 38 articles, via Springer link we found 22 articles, Science Direct produced 30 articles, and other sources 2 articles. After adding them up, there were 110 articles. Then, filtering based on duplications resulted in 68 with duplications, leaving 30

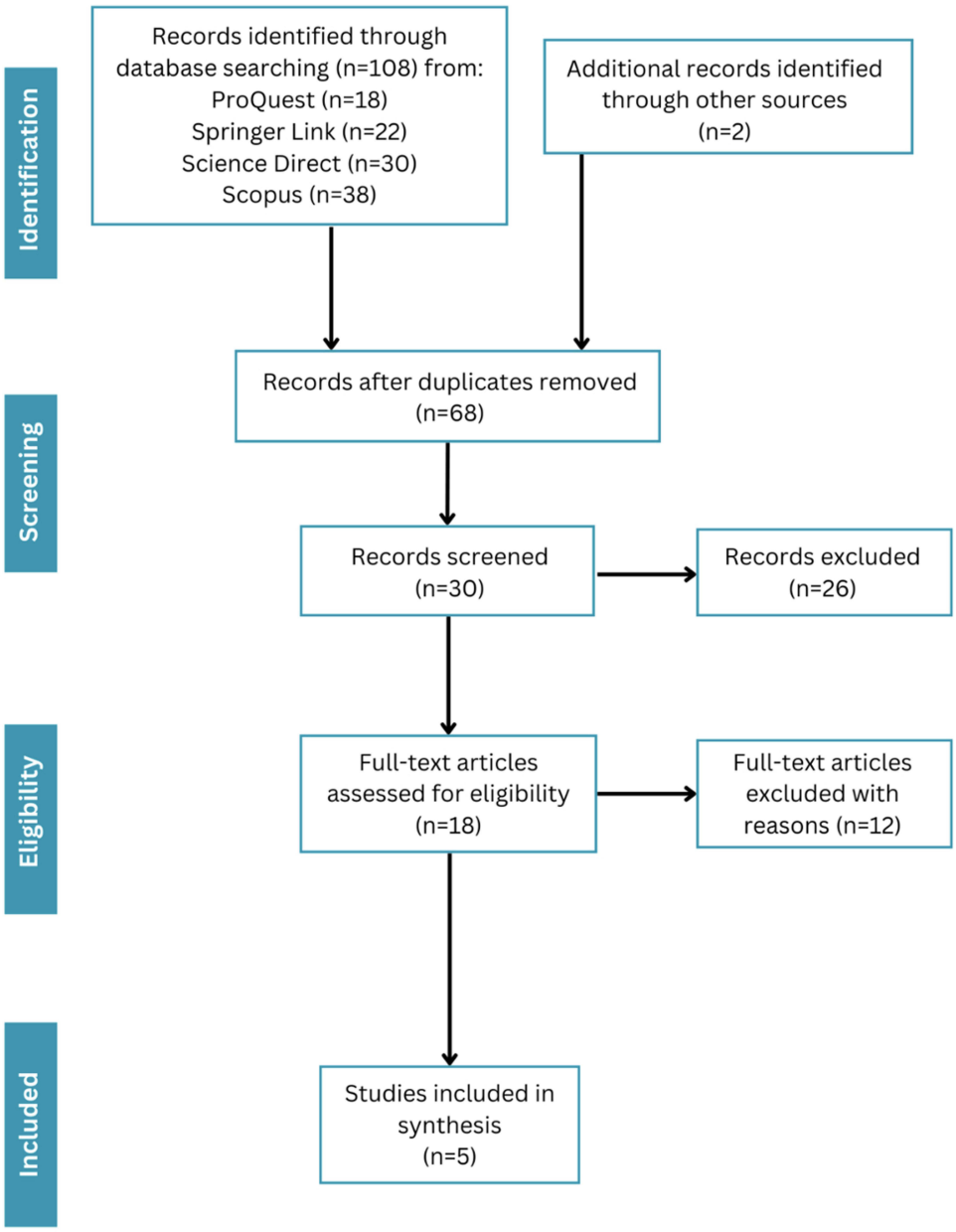

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to find relevant studies. Adapted from Page M J, McKenzie JE, Bossuyt OM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372 :n71. Creative Commons.

articles. Then, filtering was carried out based on title/topic, resulting in 26 articles. Filtering based on Open Access/Full Text resulted in 18 articles. A total of 12 articles were excluded because they were not in English, then 5 articles were eligible for synthesis/review, as described below on Table 1.

Discussion

The HOCl (hypochlorite) ion is known as hypochlorous acid which was initially used for water purification and disinfection. Effective antimicrobial properties against various microorganisms, including bacteria, viruses, and fungi, are known to exist in HOCl. The mechanism of HOCl in wound healing involves various processes that contribute to purification, infection control, and tissue regeneration. This is supported by the research from Nizer et al, in which they examined the response of Gram-negative bacteria to HOCl and found that it induces wound healing compared to group without the use of HOCl. Further research conducted by Kuwabara et al found that in their study of wound healing in

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Table 1 Current Studies on the Relationship Between MMP-9 and Diabetic Wound Ulcers

No	Author, Year	Title	Study Type, Model	Strengths & Limitations	Methodology	Results
1	Jindatanmanusan et al, 2018[13]	Wound Fluid Matrix Metalloproteinase-9 as a Potential Predictive Marker for the Poor Healing Outcome in Diabetic Foot Ulcers	Clinical trial, twenty-two patients with type 2 diabetes	**Strengths**: non-invasive, addresses and identifies potential biomarker for diabetic ulcers **Limitations**: the number of patients is relatively small leading to low statistical power of results, different investigating laboratories as sample collection sites	Analyzing MMP-9 levels on patient wound samples using the enzyme-linked immunosorbent assay (ELISA)	The group of patients with poor wound healing quality had higher MMP-9 levels compared to the group with good wound healing
2	Zhou et al, 2019[14]	TET2-interacting long noncoding RNA promotes active DNA demethylation of the MMP-9 promoter in diabetic wound healing	In vitro, human diabetic skin tissue	**Strengths**: uncovers a novel, important signature in diabetic skin ulcers, the TET2-interacting long noncoding RNA (TETILA) **Limitations**: only provide information on the effect of MMP-9 activation on wound healing but not to hypochlorous ion (HOCl)	TET2 is a DNA methylation protein which induces MMP-9 promoter demethylation leading to its activation. This study induces TET2 dependent DNA demethylation by using RNA immunoprecipitation-LncRNA microarray, RNA pull-down, and luciferase reportase assays	TETILA promotes MMP-9 promoter demethylation, which constitutively activate MMP-9 and impairs the balance of ECM synthesis and degradation. Activation of MMP-9 disrupts the process of diabetic wound healing
3	Nguyen et al, 2018[15]	Validation of Matrix Metalloproteinase-9 (MMP-9) as a Novel Target for Treatment of Diabetic Foot Ulcers in Humans and Discovery of a Potent and Selective Small-Molecule MMP-9 Inhibitor That Accelerates Healing	In vitro diabetic human wound samples, in vivo diabetic mice model	**Strengths**: the use of diabetic human sample to accurately resemble its pathology to the mice model, shows insights on how MMP-9 contribute to wound healing process **Limitations**: targeting MMP-9 alone might not address all aspects of the wound healing impairment	Immunohistochemistry, quantitative PCR, biochemical and wound healing assays	Upregulation of MMP-9 levels was shown to be a factor that exacerbates pathology in diabetic wounds

Abbreviations: MMP-9, metalloproteinase-9; ELISA, enzyme-linked immunosorbent assay; LncRNA, long non-coding ribonucleic acid; PCR, polymerase chain reaction; ECM, extracellular matrix.

diabetic mice treated with HOCl, there was a significant increase in healing of infected wounds and a decrease in the number of bacteria when compared to the control group. Histological examination showed significant granulation tissue and capillary formation developed.[5,6,12,16]

The use of HOCl ions has also been proven to reduce inflammation in wounds. The anti-inflammatory mechanism of HOCl ions involves suppressing the expression of inflammatory mediators and inhibiting the activation of inflammatory cells. By reducing inflammation, HOCl ions help create an optimal environment for wound healing by promoting tissue regeneration and faster recovery. This is supported by research by Chopra et al which found that as many as 75% of diabetic ulcer patients had thick purulent exudate and then after 10 days of using HOCl there was no longer any exudate. Although the results of this study are promising, further research is still needed to understand the mechanism of action in more detail and explore the potential use of HOCl ions in humans in the context of wound healing in diabetes.[6,7]

Matrix metalloproteases (MMP) are a family of zinc endopeptidases which have the capacity to degrade all extracellular matrix (ECM) components which play an important role in the wound healing process in various conditions including DM. Research by Jindatanmanusan et al showed that the presence of MMP-9 in one group of diabetic wound patients was a predictor of the quality of wound healing. The group with higher MMP-9 levels had poorer quality of healing compared to the group with normal MMP-9 levels. High levels of MMP-9 indicate ongoing inflammatory phase, since this enzyme is expressed by the two important inflammatory cells, neutrophils and macrophages. Other research by Zhou et al also shows the same result, namely that MMP-9 activity can interfere with diabetic wound healing. More specific research was conducted by Nguyen et al, who examined the validation of MMP-9 as a novel target for treating diabetic foot ulcers in humans and found that increased regulation of MMP-9 level was proven to be a factor that worsens the pathology of diabetic wounds. Thus, MMP-9 could act as a predictive marker for diabetic wound healing.[13–15]

HOCl Basic Concept

HOCl (hypochlorite) ions are the ionic form of hypochlorous acid, which is an important compound in water purification and disinfection. HOCl is a strong oxidizing agent and has antimicrobial properties that are effective against a variety of microorganisms, including bacteria, viruses, and fungi. HOCl is formed through the reaction between chlorine (Cl_2) and water (H_2O) in the presence of hydrogen ions (H^+). This reaction produces hypochlorite ions (OCl^-) and hydronium ions (H_3O^+). Hypochlorite ion (OCl^-) is a biologically active compound and is responsible for the disinfectant and antimicrobial properties of HOCl.

HOCl ions work by disrupting the structure and function of microorganisms. It can penetrate the cell membranes of microorganisms and damage cellular components such as proteins, nucleic acids, and enzymes. As an oxidizer, HOCl can also oxidize cellular components and disrupt the biochemical activities of microorganisms. The use of HOCl in water disinfection and purification is essential in the health-care industry, drinking water sanitation, and swimming pool maintenance. The advantage of HOCl as a disinfectant agent is its ability to kill various microorganisms effectively without leaving dangerous residues.[6,16]

HOCl Ion Mechanism on Wound Healing

The HOCl (hypochlorite) mechanism in wound healing involves various processes that contribute to purification, infection control, and tissue regeneration. The following are some of the main mechanisms of HOCl in wound healing. HOCl has strong antimicrobial properties. When applied to wounds, HOCl can kill bacteria, viruses and fungi that can infect wounds. This helps reduce the load of pathogenic microorganisms and prevents subsequent infections. HOCl can influence the inflammatory response in wounds. In the early stages of healing, HOCl helps activate immune cells, such as neutrophils, to fight infection. However, too much HOCl can cause damage to healthy tissue due to its oxidative properties. Therefore, regulating the HOCl balance in wounds is very important.

Promotion of tissue healing, HOCl can stimulate the production of growth factors and extracellular matrix that are important for tissue recovery. These include increased collagen production, angiogenesis (formation of new blood vessels), and proliferation of regenerative cells. HOCl can also help clean wounds of necrotic tissue or debris, facilitating a better healing process. Regulation of the acidity of the wound environment: HOCl can influence the acidity of the environment around the wound. Proper pH is important for optimal enzymatic activity and cell proliferation. HOCl helps

maintain appropriate pH to support an effective healing process. The use of HOCl in wound care has been shown to be effective in promoting wound healing, controlling infection, and reducing healing time. However, it is important to use HOCl carefully and according to the instructions of an experienced doctor or nurse.[5,6]

HOCl Ion's Anti-Inflammation and Antimicrobe Activity

The body will try to produce endogenous HOCl in the presence of pathogens that have the potential to cause infection and inflammation. The HOCl is originating from active leukocytes through the enzyme heme myeloperoxidase (MPO), which produces hypochlorous acid from hydrogen peroxide $O_2 \rightarrow H_2O_2 + Cl \rightarrow HOCl$. HOCl is the ionic form of hypochlorous acid, which is a weak acid. The mechanism of HOCl in wounds is inhibition of DNA synthesis, protein inhibition through oxidation of thiol-containing proteins and inhibition of bacterial growth by reducing DNA replication and bacterial wall synthesis.[17] The anti-inflammation and antimicrobial activity of HOCl within the cells is further explained in Figure 2.

Emerging clinical evidence supports the use of HOCl in the management of inflammatory skin conditions. In Tanaka et al's research, the nuclear factor NF-kB, which regulates inflammation in cells and aging, is involved in the pathogenesis of various inflammatory skin diseases. HOCl ions suppress the expression of inflammatory mediators and inhibit the activation of inflammatory cells. Previous research by Leung et al found that hypochlorous acid-dependent cysteine oxidation prevents the regulation of inflammation by NF-kB in mouse model.[18]

Similar findings are found on human keratinocytes, in which HOCl prevents the NF-kB-dependent gene expression which targets the NF-kB signaling. Jandova et al showed in their study the mechanism which might potentially modulating the skin inflammation condition. The study shows topical HOCl could prevent the inflammation gene expression. It also explains the effect of HOCl exposure to acutely inflamed skin using SKH-1 reporter expressing activation protein 1 (AP-1)-driven luciferase transgenic mice. It showed a decrease of AP-1 driven inflammatory gene which plays a role in the skin inflammation and the downregulation of inflammatory cytokine IL-19.[19] Research by Fukuyama et al also demonstrated a decrease in inflammatory cytokine IL-12 expression on skin tissues.[20]

Latest Research on the Use of HOCl Ions in Diabetic Mice for Wound Healing

Recent research has been conducted to explore the potential of using HOCl ions in diabetic mice for wound healing. One study involved administering a HOCl ion solution to diabetic mice, and the results showed that the use of HOCl ions could speed up the wound healing process in diabetic mice. This study observed that mice receiving HOCl ion treatment

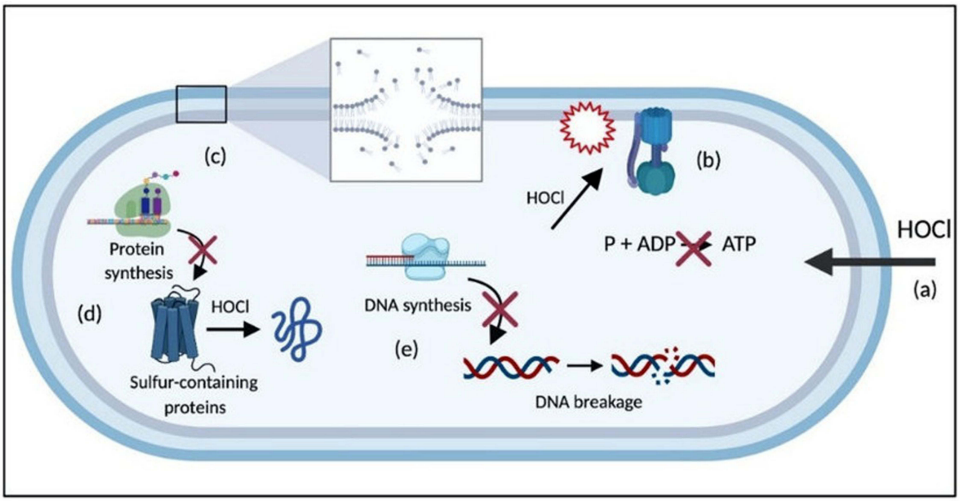

Figure 2 Mechanism of how HOCl targets in a bacterial cell. (a) HOCl penetrates bacterial cell, (b) transporters and proteins, disrupts ATP production, (c) loss of membrane stability, (d) protein synthesis, (e) DNA breakage and impairment of DNA synthesis. Reprinted from da Cruz Nizer WS, Inkovskiy V, Overhage J. Surviving reactive chlorine stress: responses of gram-negative bacteria to hypochlorous acid. Microorganisms. 2020;8(8):1–27. Creative Commons.[12]
Abbreviations: P, phosphate; HOCl, hypochlorous acid; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

experienced increased granulation tissue formation, angiogenesis, and cell proliferation, which are important in effective wound healing. Additionally, other research shows that HOCl ions also have powerful antimicrobial effects, helping to reduce the risk of infection in wounds and promoting a cleaner environment for healing.[1,12]

In one study, diabetic mice were given topical treatment using HOCl ion solution on their skin wounds. The results showed a significant improvement in the wound healing process, including accelerated granulation tissue formation, increased vascularization, and increased epithelial cell proliferation. This indicates that HOCl ions have a positive effect in accelerating the wound healing process in diabetic conditions. Further research also revealed that the use of HOCl ions can reduce inflammation in wounds, increase the production of growth factors, and modulate the expression of genes related to wound healing.[16,21]

Other studies have also highlighted the powerful antimicrobial activity of HOCl ions. Pathogenic bacteria commonly associated with wound infections, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, are highly susceptible to the action of HOCl ions. HOCl ions effectively kill these bacteria and inhibit the growth of other microorganisms. This could potentially reduce the risk of wound infections that often occur in individuals with diabetes, who tend to have compromised immune systems.[21]

Apart from that, the use of HOCl ions has also been proven to reduce inflammation in wounds. The anti-inflammatory mechanism of HOCl ions involves suppressing the expression of inflammatory mediators and inhibiting the activation of inflammatory cells. By reducing inflammation, HOCl ions help create an optimal environment for wound healing by promoting tissue regeneration and faster recovery. This is supported by research by Chopra et al, which found that as many as 75% of diabetic ulcer patients had thick purulent exudate and then after 10 days of using HOCl there was no longer any exudate. Although the results of this study are promising, further research is needed to understand the mechanism of action in more detail and explore the potential use of HOCl ions in humans in the context of wound healing in diabetes.[5,12,21,22]

Clinical Research on MMP-9 Regulating Diabetic Wound

MMPs are a group of zinc-dependent enzymes, which are involved in wound healing by degrading almost all ECM protein components. According to substrate and domain structure, MMPs can be classified as collagenases (such as MMP-1, MMP-8 and MMP-13), matrilysins (such as MMP-7), stromelysins (such as MMP-3, MMP-10 and MMP-11), gelatinases (MMP-9). Usually, MMPs are inactive and exist as latent precursors of "zymogens" in vivo and become active forms when stimulated with external stimuli such as cytokines and growth factors. An important mechanism for modulating MMPs is through endogenous inhibitors such as tissue inhibitors of metalloproteinases (TIMPs).[23–25]

High levels of MMP-9 in serum, wound fluid and skin tissue of diabetic individuals are a signal indicating a poor healing process and are associated with failed dermal grafting of diabetic wounds. Research by Jindatanmanusan et al reported that the MMP-9 content in wound fluid from patients with poor healing was dynamic and clearly higher when compared to patients with good healing, where MMP-9 levels remained low during wound management. Patients with good wound healing. At week 0 MMP-9 levels were shown to be a predictor of good or poor healing during the 12-week follow-up. In addition, compared with patients with diabetic wounds that did not heal, the levels of pro-MMP-9 and active-MMP-9 in wound fluid from patients with diabetic wounds that healed were significantly reduced, while the levels of TIMP-1 and TGF-1 increased significantly.[13,26,27]

MMP-9 levels in the serum of patients with good wound healing were lower compared to patients with poor wound healing at the first visit and decreased by 5-fold after 4 weeks of treatment, while serum MMP-9 levels in patients with poor wound healing showed just minor change.27 Research by Dinh et al, reported that high levels of TNF-a, monocyte chemoattractant protein-1 (MCP-1), MMP-9, fibroblast growth factor (FGF)-2 could be detected in serum from patients with non-healing wounds. Results from skin biopsies also showed that diabetic individuals had infiltration of immune cells, increased expression of MMP-9 modulated signaling related to insulin, leptin, and growth factors but the modulation was poor. MMP-9 is increased in diabetic wound patients with bacterial infection involvement when compared to non-diabetic patients with wounds. MMP-9 can be a biomarker for diabetic wound therapy. Another study showed that MMP-9 levels in diabetic wounds result from the neutrophil mass releasing cytokines such as

MMP-8, MMP-9 and ROS. Excessive ROS production will activate NF-kB signaling, which triggers MMP-9 regulation and slows wound healing.[15,28,29]

Future Directions

Diabetic wounds are one of the serious complications of diabetes and their incidence is increasing rapidly, thus proper management of each factor is believed to reduce the incidence of diabetic wounds. Topical agents such as HOCl ion reveal a good results and can be used as an option in the management of diabetic wounds, while MMP-9 can be used as a predictive marker in the management of diabetic wounds. Current research on the effect between the HOCl and MMP-9 is very limited. Future research direction should be focused on the effect of concentrated HOCl ions to the activity of MMP-9 while also on other molecules and pathways that might be significantly involved and are predictive markers in the wound healing process. The other molecules are, but not limited to, histamine, IL-2, IL-6, other types of MMPs, and collagenases. These to ensure that HOCl would not only act as an antibacterial agent for diabetic wound healing management but also would comprehensively accelerate the diabetic wound healing process in a proper way.

Conclusions

The hypochlorous (HOCl) ion has molecular characteristics that could speed up the healing of wounds. It has been discovered that a high level of MMP-9 indicates a poorer wound healing process. At high concentrations, HOCl has the capacity to induce fibroblast and keratinocyte migration while downregulating the activity of MMPs, such as MMP-7, MMP-9, and collagenases. As a result, MMP-9 may serve as a predictor of the rate at which diabetic wounds will heal, and HOCl could accelerate healing by decreasing the activity of MMP-9.

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Disclosure

The authors report no conflicts of interest in this work.

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