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Role of an acidic environment in the treatment of diabetic foot infections: A review

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Abstract

Management of diabetic foot ulcers is the biggest challenge to the clinician, as conventional antibiotic therapies and local wound care have their own limitations. They are not effective for control of infections and promotion of healing because of cytotoxic effects. In view of cytotoxicity of routinely used topical antiseptic agents, this article focuses on the search of an ideal topical antiseptic agent that is safe and effective in controlling infectious agents and also in promoting the healing process. This review focuses on the use of various acids such as citric, acetic, hyaluronic, and hypochlorous acids as topical agents in diabetic foot infections. This article also focuses on the different roles of acids in the treatment of diabetic foot infections.

Key Words: Diabetic foot ulcer; Infection; Management; Topical agents; Acids; Role of acids

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Core Tip: Diabetic foot ulcer is the most serious complication of diabetes mellitus. The biggest challenge is to find an ideal topical antiseptic agent that is safe and effective in controlling infectious agents and promoting the healing process. This article focuses on the use of acids as topical agents to control diabetic foot infections, with special emphasis on the different roles of citric, acetic, hyaluronic, and hypochlorous acids in the effective management of diabetic foot ulcers.

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INTRODUCTION

Diabetes mellitus is a global public health problem. The global diabetes prevalence in 2019 was estimated to be 9.3% and is expected to rise to 10.2% by 2030 and 10.9% by 2045[1]. Development of foot ulcers is one of the most serious complications of diabetes mellitus. The annual risk of foot ulceration in diabetic patients is 2% whereas the lifetime risk is 12%-25%, which increases further in the presence of peripheral neuropathy[2-6]. Intrinsic factors such as loss of sensation because of peripheral neuropathy, vascular insufficiency because of microvascular disease, and impaired immune response along with mechanical factors such as increased plantar pressure associated with foot deformity and calluses, local trauma, and infection are the important risk factors[3,7,8].

Infection is the most common sequela of diabetic foot ulceration, and once established, it becomes progressively severe and more difficult to treat. An infected foot ulcer is the most common cause of diabetes-related hospital admission, and if not treated well in time, it is the most common cause leading to lower extremity amputation[8]. It has been reported that nearly 28% of patients with diabetes require lower limb amputations and majority of amputations (50%) are needed because of uncontrolled infections. Thus, diabetic foot infection is the leading cause of nontraumatic lower extremity amputation[10,11]. Eradication of the infectious agent to control infection and sepsis, especially in a chronic diabetic foot ulcer, is paramount to the success of healing. Hence, finding a safe and effective antiseptic agent to control/eradicate infection as well as hasten the healing process should be the prime objective in the management of diabetic foot infections.

MICROBIOLOGY OF DIABETIC FOOT INFECTIONS

Foot infections in diabetics are most commonly caused by bacteria. Both aerobes and anaerobes have been shown to cause infection[12-17]. Fungi are also known to be associated with foot infections in diabetics[18,19]. Polymicrobial etiology has been reported to be more common than monomicrobial infection. Bacteriological analysis shows a predominance of both Gram-positive and Gram-negative bacteria. Among the Gram-positive aerobic bacteria, *Staphylococcus aureus* (*S. aureus*) is the most common bacterium. Coagulase-negative *Staphylococci* and *Streptococci* are the other bacterial pathogens isolated from foot infections. Among the Gram-negative aerobes, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp., *Acinetobacter* spp., etc. are common isolates. Among anaerobic bacteria, *Peptostreptococci*, *Clostridia* and *Peptococci* are the common Gram-positive isolates and *Bacteroides* spp., *Prevotella* spp., *Fusobacterium* spp., etc. are common Gram-negative anaerobic isolates. Among fungi, *Candida* spp., *C. albicans* in particular, has been reported to be the most common[12-19].

MANAGEMENT OF DIABETIC FOOT INFECTIONS

A critical part of the management of diabetic foot ulcers is to treat the infection to reduce microbial load quantitatively to a level that can be resolved by the host immune system. As most of the etiological agents associated with diabetic foot infections are known to form biofilms and are resistant to multiple antimicrobial agents, they are difficult to eliminate from the infection site. It has been observed that biofilm formation is associated with increased virulence and delayed wound healing [20]. Biofilms release a variety of toxic components during the taxis of neutrophils and discourage the process of phagocytosis. In chronic wounds, formation of biofilms discourages wound healing by increasing the inflammatory response [21].

The ideal management of diabetic foot infections should positively and potentially reduce the incidence of infection-related morbidities, duration of hospital stay, the cost of treatment, and most importantly, reduce limb amputations [22]. Compared with other wounds, diabetic foot ulcers are more prone to infection, and infection is one of the most important factors that delay wound healing. Hence, good wound care for control of infection is critical for successful wound healing [23], but successful treatment of diabetic foot infections is the biggest challenge for the following reasons: (1) Parenterally or orally administered antimicrobial agents have been shown not to reach adequate levels in chronic granulation tissue and have no effect on growing bacterial populations in granulating wounds [24]. Biofilm formation by infecting agents in diabetic foot ulcers makes wound healing and infections difficult to resolve by hampering local access of antimicrobial agents and because diabetes hampers the immune system [25]. Biofilm formation not only helps to prevent phagocytosis but also helps to increase the resistance of infecting agents to antimicrobial agents [26,27]. In a previous study, we found that in spite of *in vitro* susceptibility of infecting agent isolated from patients to antimicrobial agents, administration of the antimicrobial agent to patients did not result in successful outcomes. The result indicates that systemic antimicrobial therapy may not have practical and potential value in such cases, making local wound care the backbone of treatment [28]. And (2) Many topical antiseptic agents are used for wound care in diabetics. Some are good in controlling infections but their cytotoxic effect on the cells involved in the wound healing process and other cells like dermal and epidermal cells limit their use. Available experimental data show that majority of the agents retard healing by interfering with the normal process and can be harmful rather than useful. Studies show that these agents should be avoided, especially in the treatment of diabetic foot ulcers [29-32].

Hydrogen peroxide is the most commonly used antiseptic for washing diabetic foot ulcers, but is toxic to newly formed epithelium [33], because it kills fibroblasts, which have an important role in healing and epithelialization. In addition, it may also destroy normal cells surrounding the wound [34]. Povidone-iodine (betadine) is another commonly used antiseptic agent, but because it is also cytotoxic to fibroblasts and other cells involved in wound healing, it fails to promote good wound healing. Most studies show that it impairs wound healing and reduces wound strength [30,35-37]. Sodium hypochlorite (Dakin's solution) has also been reported to be toxic to fibroblasts and keratinocytes and has been found to delay the process of epithelialization and neovascularization. It has also been reported to retard collagen synthesis and inhibit migration of neutrophils in a wound bed [38-42]. Silver nitrate has also been reported to slow down the process of epithelialization and may delay wound healing [30,38]. Many other antiseptic agents such as iodine, alcohol, chlorhexidine, mafenide acetate, silver compounds, and benzalkonium chloride, *etc.* have been reported to retard wound healing [31,38,43-45]. In view of these observations, the treatment of diabetic foot ulcers has always been a big challenge to the clinician as conventional therapies (antibiotic therapy and local wound care) have limitations. Infection is the most common and most important reason for nonhealing/poor healing of diabetic foot ulcers. Infecting organisms are most difficult to eliminate from the infection site. Infections of diabetic foot ulcers need special attention, and if not controlled well in time, may become limb threatening and sometimes life threatening by progressing to osteomyelitis or gangrene, which can lead to septicemia, amputation and death. The biggest challenge is the search of an ideal topical antiseptic agent that is safe and effective in controlling/eradicating infectious agents from the infection site and as well as promoting/hastening the healing process.

Use of acids as topical agents in diabetic foot infections

Various acids, such as citric, acetic, hyaluronic, and hypochlorous (HOCl) acids are topical agents used in the treatment of diabetic foot infections. Citric acid (2%-3%) has been used to treat a variety of infected wounds and ulcers such as necrotizing fasciitis,

lepromatous ulcers, burns infections, surgical site infections, post-operative wounds in HIV/AIDS patients, traumatic wounds, diabetic foot ulcers, and many others[46-55]. In our initial study, citric acid was successfully used to treat diabetic foot ulcers infected with multiple antibiotic-resistant strains of *P. aeruginosa*[52]. Later on, citric acid was found to be effective against *S. aureus* also. Considering its activity against *S. aureus*, a case report published in 2000 described the successful treatment of a diabetic foot infected with multiple antibiotic-resistant *P. aeruginosa* and *S. aureus* and not responding to conventional antibiotic therapy and local wound care by application of a 2% citric acid solution[53]. A subsequent study reported the activity of citric acid against multiple antibiotic-resistant *E. coli* (MAREC). The in vitro sensitivity of *E. coli* to citric acid was reported in 2008, with successful use of 3% citric acid gel to treat diabetic foot ulcers infected with MAREC, with complete elimination of MAREC from infected sites and successful healing following 29-42 applications of citric acid[54]. A study published in 2010, found that citric acid was effective against almost all aerobic bacterial pathogens commonly associated with diabetic foot ulcers, i.e. *S. aureus*, *P. aeruginosa*, *E. coli*, *Klebsiella* spp., *S. albus*, *Citrobacter* spp., Streptococci and *Proteus vulgaris*. That study reported that citric acid was found effective in control of diabetic foot infections and successful management of Wagner grades I and II ulcers, and even Wagner grade III ulcers without deep osteomyelitis. The success rate was more than 94% in Wagner grade I and II ulcers, and 86.21% in Wagner grade III ulcers[13]. A recent case study described the treatment of a 70-year-old man with a diabetic leg ulcer that developed at the operative site 2 years after coronary artery bypass graft surgery. The ulcer was infected with methicillin-resistant *S. aureus* (MRSA) and had not responded to conventional treatment for months. It was successfully treated by application of 3% citric acid once daily for 30 d[55]. These studies of infected diabetic foot ulcers did not report any adverse effects, which shows that citric acid was found to be a safe and most effective topical antimicrobial agent for the treatment of diabetic foot ulcers. Citric acid has been found effective in chronic plantar ulcers in diabetic individuals with uncontrolled blood sugar levels and infected with multiple antibiotic-resistant bacteria not responding to conventional therapies for months (See Figure 1).

Acetic acid has been used for the treatment of skin and soft tissue infections and burn wound infections caused by *P. aeruginosa*[56-58]. It is rarely used in the treatment of diabetic foot infections and infections caused by other microbial agents. Agrawal *et al*[59] reported that acetic acid controlled the overgrowth of many common isolates in addition to *P. aeruginosa*, including *Streptococcus*, *S. aureus*, *Proteus mirabilis*, *Citrobacter* spp., *C. albicans*, *Aspergillus niger*, *A. fumigatus* and *Cryptococcus neoformans*. In a previous study, 52-year-old man with diabetic foot ulcer infected with *P. aeruginosa* was successfully treated with 3% acetic acid. Application of acetic acid once daily for 12 d successfully eliminated *P. aeruginosa* and resulted in successful healing of the ulcer[60]. Agrawal *et al*[59] reported remarkable improvement in raw areas in 7-14 d. They noted similar results even in cases with exposed tendons and crush injuries in diabetic patients, and even in infections caused by antibiotic-resistant strains. Fejfarová *et al*[61] also reported favorable outcomes of reduced ulcer dimensions using 1% acetic acid in diabetic foot ulcers, but the difference was not statistically significant.

Hyaluronic acid has been used in the management of diabetic foot ulcers in previous studies[62-65]. Lee *et al*[62] reported higher mean percentages of wound area reduction, wound depth reduction, and increase of healthy granulation tissue in the experimental group than in the control group indicating the potential of hyaluronic acid dressings to accelerate diabetic wound healing. A meta-analysis by Chen *et al*[63] found that hyaluronic acid was beneficial in treating diabetic foot ulcers by increasing the rate of wound healing, evidence that further supports the use of hyaluronic acid in the treatment of diabetic foot ulcers. In a study conducted by Lee *et al*[64], hyaluronic acid treatment achieved a significantly higher complete healing rate(84.6%) than was observed in the control group(41.6%). Healing was faster in the hyaluronic acid group and had a shorter mean duration of achieving a 50% ulcer size reduction without any adverse events, indicating that hyaluronic acid was safe and effective in treating diabetic foot ulcers. A study by Hwang *et al*[65] also concluded that hyaluronic acid dressing without additional substances was a safe and effective treatment for diabetic foot ulcers.

HOCl is another option for acid treatment of infected diabetic foot ulcers. HOCl has been reported to be effective against *Candida* spp., *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp. and MRSA. It was found comparatively more effective than hydrogen peroxide and povidone-iodine as a potent antimicrobial agent as well as being a better wound healing agent in diabetic foot ulcers, as evidenced by the formation of healthy granulation tissue and a significant reduction in number of organisms on quantitative culture. HOCl has also been reported to soften the wound



Figure 1 Diabetic foot ulcer. A: Before application of citric acid ointment; B: After 6 applications of citric acid ointment; C: After 16 applications of citric acid ointment; D: After 43 applications of citric acid ointment; E: Before application of citric acid ointment; F: After 25 applications of citric acid ointment.

surface eschar, clean and remove necrotic tissue and biofilms from diabetic foot infections. When compared with hydrogen peroxide and povidone-iodine, HOCl was found to cause a significant reduction in the quantity of exudate, had broad spectrum antimicrobial activity against a variety of microbes, and caused significant reductions in bacterial count and bacterial burden. HOCl appears to be a potent topical antiseptic to treat diabetic foot ulcers. It effectively controls the bioburden without impeding the process of wound healing[66-70].

THE ROLE OF ACIDS IN THE TREATMENT OF DIABETIC FOOT INFECTIONS

The various acids used to treat diabetic foot infections are known to have different roles in controlling infections caused by a variety of microbes and in promoting healing by participating in different stages in the healing of diabetic foot ulcers. Apart

from the specific roles of different acids, the acidic environment created by all acids helps in the following ways. (1) Antimicrobial property: Application of acids to the wound surface creates an acidic environment. A pH of < 6.0 at the wound surface makes it an environment unsuitable for the growth and multiplication of most pathogenic bacteria, which require an optimum pH of 7. Acids thus have antimicrobial property that helps in rapid cleaning of infected surfaces[71]. (2) Inhibition of enzyme activity: The acidic environment inhibits the activity of proteolytic enzymes such as elastase and plasmin produced by various bacteria and by wound itself. The proteases are highly active in alkaline conditions. The acidic environment slows/inhibits their activity and formation of their end products, which are toxic to the healing process[71, 72]. (3) Increase in oxygenation: The acidic environment improves tissue oxygenation, which increases resistance to infection, promotes wound healing, and boosts the immune response as well. Improvement of oxygenation increases the production of oxygen radicals that kill bacteria[71,73,74]. (4) Decrease in the toxicity of bacterial end products: The acidic environment helps to reduce the toxicity of bacterial end products, *e.g.*, ammonia, which are toxic to the process of wound healing[71,75]. And (5) Promotion of angiogenesis: The acidic environment promotes angiogenesis, which increases the microcirculation of nutrients and oxygen and boosts fibroblast growth, thereby enhancing epithelialization that leads to faster wound healing[71,76].

SPECIFIC ROLES OF ACIDS

Citric acid

Citric acid is known to have key roles in the process of wound healing. As shown in Table 1, it helps in the management of a variety of infected wounds, including diabetic foot ulcers, in a number of ways.

Antibacterial activity: Citric acid is inhibitory to all bacterial pathogens commonly associated with diabetic foot ulcers. However, it has not been found effective against fungal pathogens. MICs (minimum inhibitory concentrations) in the range of 500-2500 µg/mL against different bacterial isolates from diabetic foot ulcers and nondiabetic traumatic wounds have been reported. *P. aeruginosa* (MIC 500-1000 µg/mL) has been found to be the most susceptible and *Klebsiella* spp. (MIC 2000-2500 µg/mL) least susceptible to citric acid[13,51].

Decrease in the wound surface pH: Decrease in pH has an important role in wound healing. It is a biochemical indicator of wound healing processes and can be used to monitor the progression of wound healing. Wounds treated with citric acid show a pH ranging from 4 to 6, which is not suitable for the growth and multiplication of most bacterial pathogens that cause infection, and thus helps in effective elimination of bacteria from the infection site, leading to rapid cleaning up of infected surfaces. In addition, lowering the pH of wound surfaces also helps to reduce bacterial toxicity (*e.g.*, endotoxins and metalloproteinases), altering protease activity, *etc.* Microbiological evaluation after application of citric acid shows significant reductions in bacterial counts, or no growth, suggesting that citric acid effectively controls the infection[13,76-79].

Fibroblastic growth, neovascularization, and epithelialization: Histopathological studies show that application of citric acid boosts fibroblastic growth and promotes neovascularization, which increases the microcirculation of nutrients and improves oxygenation. This enhances epithelialization and increases the migration of epithelial cells from the surrounding skin. Epithelialization in turn acts as stimulus for the deposition of ground substance and formation of healthy granulation tissue, thereby leading to faster wound healing[13,51,76]. A significant increase in granulation tissue compared with control treatment has been reported after application of citric acid[77].

Notable clinical changes: Application of citric acid results in significant reduction in wound size, early reduction in the amount of discharge and sloughing, and reduces hospital stay[76,77,79]. Significant reductions in common signs of inflammation such as edema, wound discharge, and erythema were noted in a study by Tandon *et al*[77].

Role of acetic acid

In most of the studies, acetic acid has been reported to be inhibitory to *P. aeruginosa* only[56-58]. However, Agrawal *et al*[59] found that it has antibacterial activity against bacterial pathogens commonly associated with wound infections, and antifungal

Table 1 Important roles of various acids in treating diabetic foot ulcers

Order of efficacy	Name of acid	Roles
1	Citric acid	Antibacterial activity[13,51]; Decrease in pH-preventing growth and multiplication[13,76,79]; Fibroblastic growth, neovascularization and epithelialization[13,51,76,77]; Notable clinical changes[76,77,79]
2	Acetic acid	Mainly antipseudomonal activity[55-57]; Anti biofilm activity[81-83]
3	Hyaluronic acid	Reduces inflammatory response[22,84,85]; Increases angiogenesis and promotes granulation[22,84,85]; Proliferation of keratin cells[22,84,85]; Contributes to scarring[22,84,85]; Scavenger of free radicals and tissue degrading enzymes[85,86]; Controls tissue hydration[87]
4	Hypochlorous acid	Antimicrobial activity[70]; Wound debridement[70]; Anti-biofilm activity[70]; Promotes granulation[66]

activity as well. An in vitro study by Lineaweaver *et al*[80] showed that 0.25% acetic acid was toxic to fibroblasts, slowed wound epithelialization, and limited neutrophil function. It is well tolerated in vivo and gives superior results in the treatment of wounds infected with *P. aeruginosa*[57]. Bjarnsholt *et al*[81] reported that acetic acid lowered the pH and was effective in removing biofilms. It kills planktonic bacteria as well as helps eradicate bacteria growing in biofilms. Halstead *et al*[82] found that acetic acid was active against drug-resistant and biofilm-producing bacteria. In a study by Bjarnsholt *et al*[81], acetic acid was found effective against planktonic cells as well as biofilms of *P. aeruginosa* and *S. aureus*, and was found to have potential clinical use as a topical agent to eradicate biofilms in chronic infections caused by *P. aeruginosa*.

Role of hyaluronic acid

Hyaluronic acid is known to have a key role in every phase of wound healing. During the inflammatory phase, it binds to fibrinogen to initiate the clotting pathway, allows inflammatory cell migration, creates edema to allow cell infiltration and inhibits migration of neutrophils to reduce inflammatory response. During the granulation phase, it promotes cell mitosis and increases cell migration and angiogenesis. During re-epithelialization, it is associated with the proliferation of keratin cells and facilitates their migration. During the remodeling phase, it contributes to normal and pathological scarring[22,83,84]. Hyaluronic acid also serves as a scavenger of free radicals and tissue degrading enzymes that cause prolonged inflammation in chronic wounds[84,85]. It has been also reported to have important role in controlling tissue hydration[86].

Role of HOCl

HOCl has antibacterial as well as antifungal activity. It kills pathogens without causing cytotoxicity to keratinocytes or fibroblasts. The killing of pathogens promotes the natural healing process. It has been reported to be an effective wound cleaning and debriding agent by softening the wound surface eschar and removing necrotic tissue and biofilms from infected diabetic foot ulcers[70]. It significantly reduces the number of microbes in wounds and promotes rapid formation of healthy granulation tissue [66].

CONCLUSION

The results of various studies show that conventional antibiotic treatment and local wound care with routinely used topical antiseptic agents have limitations. In view of cytotoxic effects on the cells involved in the process of wound healing, various acids are better options to treat diabetic foot infections. Citric acid, hyaluronic acid, and HOCl in a decreasing order of efficacy, and to a lesser extent acetic acid can be used as better alternatives to control infection and promote the healing of diabetic foot ulcers.

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