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SYMPOSIUM

Use of Sugar on the Healing of Diabetic Ulcers: A Review

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Abstract

With the advent of several innovative wound care management tools, the choice of products and treatment modalities available to clinicians continues to expand. High costs associated with wound care, especially diabetic foot wounds, make it important for clinician scientists to research alternative therapies and optimally incorporate them into wound care protocols appropriately. This article reviews using sugar as a treatment option in diabetic foot care and provides a guide to its appropriate use in healing foot ulcers. In addition to a clinical case study, the physiological significance and advantages of sugar are discussed.

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Epidemiology of Diabetic Foot Ulcers

Diabetes is a worldwide epidemic; there were more than 230 million individuals with diabetes in 2006. According to consensus, this number is expected to reach 350 million by 2030. Worldwide, diabetes results in one major limb amputation every 30 seconds, over 2500 limbs lost per day.[1] These amputations are generally preceded by diabetic foot ulcers (DFUs), which are a common lower extremity complication of diabetes. Diabetic foot ulcers are largely preventable complications, with a 25% lifetime risk in patients with diabetes.[2] While most of these ulcers can be treated successfully on an outpatient basis, some will persist and become infected. Ulcerations are pivotal events in limb loss for two important reasons: (1) they allow an avenue for infection[3] and (2) can cause progressive tissue necrosis and poor wound healing in the presence of critical ischemia. In adults with diabetes, infections involving the foot rarely develop in the absence of a wound; ulcers being the most common type of wound in this population.[3] Ultimately, nearly one-fifth of patients with lower extremity diabetic ulcers will require amputation of the affected limb, resulting in staggering costs for both the patient and the health care system. Foot ulcers therefore play a central role in the causal pathway to lower extremity amputation.[4] Clearly, effective treatment of foot ulcerations is of central importance in any plan for amputation prevention. Therapeutic techniques that assist wound healing can potentially reduce the need for expensive surgical procedures and impact health care costs substantially.

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Cost of Diabetic Foot Ulcer Care

As previously mentioned, diabetic wounds affect millions of people in the United States and impose an enormous medical, psychosocial, and financial impact. The total national cost of diabetes in the United States is approximately $174 billion dollars per year. The largest portion of this cost is attributed to inpatient hospital stays and nonhealing wounds, which constitute a significant portion of the increasing cost of diabetes and account for approximately 20% of diabetes patient hospitalizations.[5] Furthermore, Medicare expenditures for patients with diabetic wounds average three times higher than those for Medicare patients in general.[6] The prolonged, sometimes interrupted, healing process of diabetic wounds affects the patient's quality of life because of impaired mobility and loss of productivity. This healing process of diabetic wounds is a significant challenge to health care professionals.

Diabetic Foot Ulcer Challenges

Diabetic ulcerations are caused by a combination of factors such as arterial ischemia and neuropathy.[7] These factors serve as an impediment toward timely healing of ulcers. Diabetic ulcers in the lower extremity are not only difficult to heal, but closure is often temporary. The difficulty in healing is multifactorial, including intrinsic flaws in blood supply, angiogenesis, and matrix turnover, as well as extrinsic variables such as infection and repeated trauma. Moreover, chronically debilitating, immobilizing, and age-related changes compound the problem of ulcer healing because of changes in global structural physiology such as nutritional status, skin turgor, joint mobility, fat pad density over bony prominences, and muscle strength.[7] Regardless of the cause, a lack of immediate attention to these wounds can often serve as a precursor to serious health problems because of associated infections that may lead to amputations, or the wounds may induce life-threatening situations.[8] Many different therapies have been developed over the years to address diabetic wounds, but the severity and frequency of these lesions continue to plague patients physically and financially. One method to heal diabetic ulcers that has received attention is the use of sugar to heal these wounds.

Sugar as a Wound-Healing Modality

Methods to heal wounds have been studied for the past four or five millennia. Surgery's earliest known document on the care of wounds is *The Edwin Smith Surgical Papyrus*, dated around 1700 BC, which describes the treatment of a number of difficult wounds encountered on the battlefields of Egypt.[9] Since then, our knowledge of the physiology of wound healing has been elucidated, but timely and efficient wound healing has remained somewhat elusive, especially in areas where technology and modern wound care supplies are limited. However, natural resources have been used extensively for wound care with acceptable results. The use of sugar for wound healing is one of the earliest known methods. In premodern times, the idea that sugar can facilitate the healing of wounds has been documented.[10,11] Mesopotamians were known to wash wounds with water or milk and subsequently dress them with honey or resin. Mesopotamians also documented the severity of wounds and which conditions were optimal for facilitating the rate at which the wounds would heal. Other substances, in conjunction with sugar, such as plant derivatives, wine, and vinegar were explored and implemented to determine their efficacy in wound healing.[10] In 1679, Scultetus made use of finely powdered sugar to clean wounds.[12] Zoinin, in 1714, promoted the value of sugar for promoting wound and ulcer healing.[13]

In modern times, the use of sugar as a general treatment for the healing of wounds has received much attention in Latin America, Europe, and Asia.[14–24] Currently, Brazil is the world's leading producer of sugar, with 566 million tons cultivated in the 2008–2009 market year. Brazil is projected to increase production to 605 million tons for the 2009–2010 market year.[25] This vast production makes sugar readily available and cheap. These attributes make the use of sugar an attractive candidate for the healing of wounds, especially in economically challenged areas. Moreover, certain types of wounds such as chronic wounds may benefit from a more cost-effective method of wound healing. The use of sugar to heal diabetic ulcers is such an example.

Although Latin America, Europe, and Asia have held an interest in using sugar for wound healing, its use has not been widely practiced in the United States.[26,27] The use of sugar in a wound appears counterintuitive since there is evidence that systemic hyperglycemia impairs host defenses and may inhibit healing.[28,29] There is counterevidence, however, that systemic hyperglycemia and local hyperglycemia do not promote impaired wound healing by themselves.[30–32] Direct instillation of sugar in the wound apparently exerts a local osmotic effect that promotes granulation tissue formation, reduces edema in wounds, lowers wound pH thereby enhancing the bacteriostatic effect, promotes dilation of small blood vessels, promotes bacterial lysis, and inhibits bacterial growth by lowering the water activity available that is required for the growth of most bacterial organisms.[15,16,27,33–35] This technique has been employed in the treatment of burns, postoperative wounds, mediastinitis, diabetic ulcers, and a variety of other wounds.[32,36,37] Since sucrose is not metabolized outside the intestinal tract, local application of sugar would not be expected to lead to systemic absorption; however, this treatment, when used in large open wounds, has been associated with one case of acute renal failure and severe hyponatremia.[38] Debure and colleagues[38] reported a case of a 64-year-old male who was being treated with granulated sugar for an infected pneumonectomy cavity. The patient developed severe hyponatremia (129 mmol/liter) and acute renal failure with an osmolar gap and elevated sucrose levels in the urine and blood. Once the sugar was removed from the infected cavity, the patient resumed urine flow, and a diagnosis of sucrose-induced osmotic nephrosis was concluded. The authors do note that topical use of sugar has not been associated with toxic events and that the patient had mild renal insufficiency prior to sugar therapy. With this caveat, the use of sugar for treatment of wounds is safe, easy to teach, cost-effective, and worthy as an alternative modality for the treatment of refractory wounds.

Physiological Rationale for Sugar on Wound Healing

In 1980, Herszage and associates[39] described the treatment of infected wounds and superficial lesions with simple granulated sugar in 120 patients, with a cure rate of 99.2%. Of the 120 patients, the ages ranged from 3 months to 94 years old, with 70 men and 50 women. Six diabetes cases were among the sample group, and the healing time for these diabetes cases varied from 9 days to 17 weeks, with a mean of 5 weeks. The study was not limited to any specific wound type. However, Herszage and associates[39] were able to make several conclusions with regard to sugar therapy: (1) treatment with sugar destroys bacteria nonspecifically, (2) sugar's action is controlled by "water activity," (3) sugar treatment draws macrophages toward the wound, (4) the action of sugar treatment promotes cleansing of the wound, and (5) sugar acts as a remover of edema and a local reducer of inflammation in wounds (**Figure 1**). At the time, no studies demonstrated the physiologic effect of sugar with regard to wound healing, although clinical success was observed. The conclusions noted by Herszage and associates[39] prompted a more scientific study to characterize sugar's activity on microbial organisms. Chirife and coworkers[15,16] postulated that an aqueous solution in an organism's environment can be concentrated by the addition of a solute, such as sucrose, and thus impair microbial growth by altering the water activity (a_w) of the aqueous solution of an organism's environment. The concept for this postulation stems from the fact that every microorganism has a limiting a_w below which it will not grow. The experiments conducted by Chirife and coworkers[15,16] used *Staphylococcus aureus* because, of all the bacteria, *S. aureus* is the organism that can tolerate the lowest a_w (0.86)[40,41] in order to proliferate. Using the equation $a_w = x_1 \bullet \exp(-k \bullet x_2^2)$, where x_1 and x_2 are molar fractions of water and sucrose, respectively, to calculate the a_w of sucrose solutions, Chirife and coworkers[15,16] were able to adjust the media with sugar to progressively

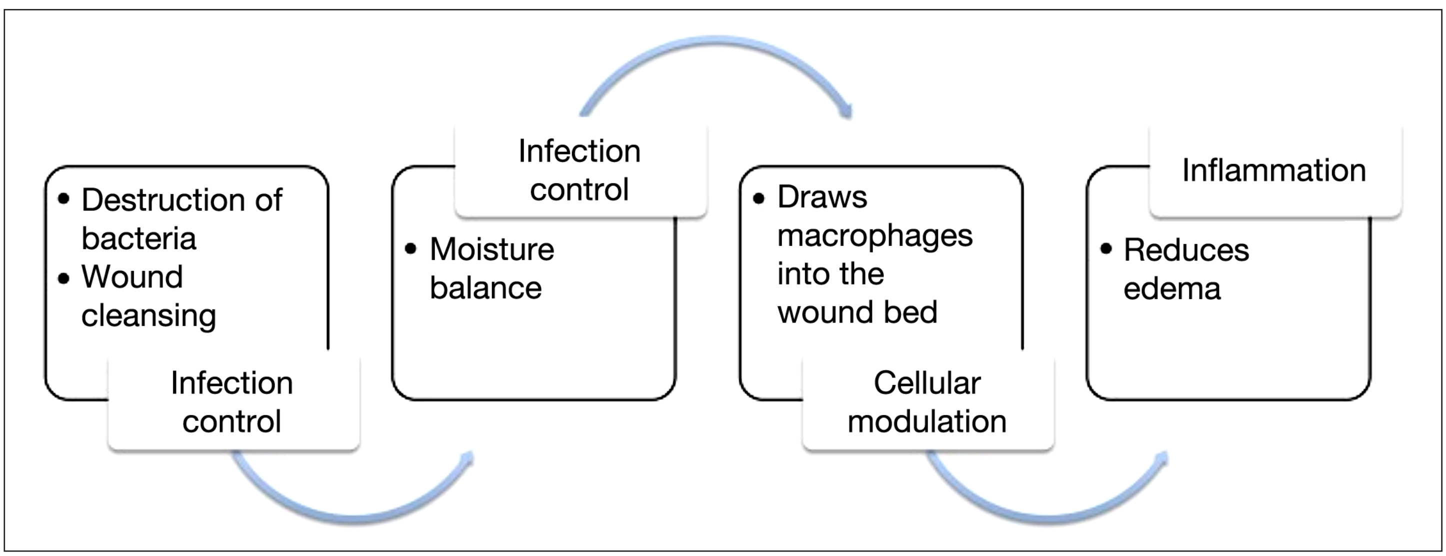

Figure 1. Physiological rationale for the use of sugar on wound healing.

lower a_w levels until a reduction to an a_w level of 0.858 (195 g sugar/100 g water) achieved complete growth inhibition with decreasing cell numbers of *S. aureus* throughout the incubation period. These results suggest that one must maintain a concentration of approximately 195 g sugar/100 g water to correspond to an a_w level ~0.86 in order to inhibit *S. aureus* proliferation.[15,16] Therefore, a concentration of 195 g sugar/100 g water would theoretically inhibit the proliferation of all bacteria. By following this rationale, the antibacterial effect of sugar would also limit the bacterial production of ammonia, amines, and sulfur, all of which cause malodor.[42,43] In an already infected wound, sugar dressings play a beneficial role, in addition to lowering the a_w, by reducing the pH to around 5 while causing less toxicity compared to most antiseptics.[32] Furthermore, sugar, via hygroscopic action, can facilitate the reduction of edema in the surrounding tissues of a wound.[39]

The acceleration of reepithelialization and reduction of bacterial pathogens have been documented using a Methicillin-resistant *S. aureus*-infected animal wound model.[22] Shi and colleagues[22] evaluated skin ulcers of db/db mice and used a sugar paste composed of povidone-iodine for wound healing. Histopathological confirmation of the wounds showed a statistically significant increase in reepithelialization rate and decrease in colony-forming units in the wound bed. Other variables measured were granulation tissue formation and capillary number. There was no difference in the amount of granulation tissue formed, and there were fewer capillaries noted in the sugar paste arm, but the result was statistically insignificant. In another study, the previously mentioned authors demonstrated that sugar paste and povidone-iodine up-regulated intracellular and extracellular urokinase-type plasminogen activator levels, transforming growth factor-α production in keratinocytes, and the expression of extracellular matrix receptor integrins α1, α2, α3, α4, α5, and β1 in both keratinocytes and fibroblasts, whereas sugar paste and sugar alone accelerated collagen synthesis in fibroblasts.[44]

For DFU to heal, a moist wound environment provides optimal conditions for healing.[45] Sugar and sugar pastes can achieve this environment and contribute the mechanical debridement of the wound bed.[11,46] This moist environment is achieved by sugar forming hydrogen bonds with wound exudate, causing the water activity of the sugar at the wound surface to rise.[47] This in turn produces a moist environment for angiogenesis to occur.[48]

Case Studies of Sugar Used to Treat Diabetic Ulcers

Few comparative studies have been performed on the efficacy of sugar to treat diabetic ulcers, both in countries where resources are scarce and in countries where drugs and technology are more readily available. A brief review of the existing reports is discussed here.

In 1958, Rostenberg and coworkers[18] reported the use of sugar paste composed of powdered cane sugar, wool fat, and compound benzoin tincture to treat 19 patients with a variety of ulcers, including stasis ulcers, trophic and/or decubitus ulcers, sclerodermatous ulcers, radiation ulcers, and mixed peripheral vascular disease ulcers. The sugar paste was applied twice daily. Nine patients had their ulcers healed at the end of one year. Of these 9 patients, 4 had trophic and/or decubitus ulcers and 5 had stasis ulcers. While the authors do not mention whether the patients had diabetes or discuss the mechanism of action of the sugar paste, the study reports successful healing of certain ulcer pathology.

The mechanism of action of sugar's effect on wounds was first reported by Herszage and associates.[39] As mentioned previously, Herszage and associates[39] described the treatment of infected wounds and superficial lesions with simple granulated sugar in 120 patients, with a cure rate of 99.2%. Commercial granulated sugar was applied to the wounds every 24 h in ordinary cases and every 8 h in serious cases during the first 48 to 72 h, after which the interval resumed to every 24 h. Of the 120 patients, 6 cases had diabetes and had a healing rate that varied from 9 days to 17 weeks, with a mean of 5 weeks. The authors reported the decrease in the odor of infected wounds and the decrease of purulent secretions. Moreover, the use of sugar as a wound-healing agent was justified by satisfying the necessary specifications of antiseptic: broad-spectrum antibiosis, rapid effect, low toxicity, persistence of activity, and efficacy.[49]

One of the largest series of wounds treated with sugar was performed by Knutson and colleagues.[27] Granulated sugar directly instilled into the wound and covered with gauze soaked in povidone-iodine was used to treat 605 patients (out of 759 total patients) with traumatic wounds, burns, and ulcers over a 5-year period. The authors noted that, regardless of the type of wound, burn, or ulcer and despite contamination of many of the wounds at the time of initial survey, all wounds, burns, and ulcers rapidly became clean with sugar and povidone-iodine treatment. The contaminated tissue rapidly became free of purulent material and surrounding erythema. The wounds quickly became free of odor as well. The wounds also healed with minimal or no scarring. The overall healing rate progressed more rapidly than with other modalities of wound care as reflected by the reduction of required visits to the physical therapist at the authors' respective institutions. The authors reported that 79.7% were treated with the sugar and povidone-iodine combination, with healing times reduced by 25% represented by required physical therapy visits compared to physical therapy visits for wounds in 1976. Of the 605 cases, 13 were diabetic ulcers. The authors noted that the healing time for diabetic wounds, and those wounds complicated by vascular insufficiency tended to be somewhat longer, although successful, compared to patients with normal vasculature.

Silvetti[36] described a method to treat chronic wounds and ulcers using a sequence involving irrigation with a balanced salt solution followed by irrigation with an amino acid solution and finally covering the wound with powdered sugar. A total of 58 patients were treated with this method. The wounds involved were large open traumatic wounds, burns, decubitus ulcers, stasis ulcers, and diabetic ulcers. There were no adverse reactions to the treatment sequence. Three cases showed no improvement due to terminal condition, malnourishment due to alcoholism, and noncompliance to treatment regimen. The number of diabetes cases was not specified; however, similar observations were seen as previous studies regarding rapid control of infection and purulence, easily removed necrotic tissue, and rapid growth of granulation tissue.

Viau and associates[19,20,50] reported several cases of ulcer treatment with granulated sugar. In their first case study, 21 patients with ulcers varying from sacroiliac, heel, back, scalp, and trochanter were evaluated over a 9-month period.[19,20] Eighteen ulcers had satisfactory results, with 9 ulcers completely healed and 9 ulcers with decrease of wound dimension and decrease of bacterial contamination. In their next case study, Viau and associates[50] treated 38 wounds, pressure sores, and leg ulcers with granulated sugar over a 9-month period. The authors reported an 89.5% satisfactory healing result. Five of the 38 cases were ulcers (2 stasis ulcers and 3 mixed arterial ulcers), and 4 of those 5 cases healed with satisfactory result. The only case that did not heal was a mixed arterial ulcer. The mixed ulcer cases were not specified to include diabetic ulcers. The authors report consistent observations with previous studies regarding the sugar's antibacterial effects within these wounds, although further studies are needed to clarify the reasons why sugar therapy failed within a mixed-pathology ulcer.

The first study to specifically address the use of sugar for the healing of DFU was a report of two cases by Anania and coworkers.[51] The authors used a mixture of 70–80% granulated sugar by weight with appropriate amounts of povidone-iodine ointment and povidone-iodine solution to make a sugar paste with a consistency similar to peanut butter. This method was similar to the one described by Knutson *et al.*[27] The sugar paste was administered four times per day and was covered by gauze. The first case was a diabetes patient who had a draining ulceration between the fourth and fifth metatarsals on the plantar surface and an abscess between the fourth and fifth metatarsal heads on the dorsal surface extending into the digits. The culture results yielded *Corynebacterium* species and *Bacteroides melaninogenicus*. The previously described treatment regimen developed granulation tissue and covered the exposed tendons and bone within 4 weeks. The second case was a diabetes patient with multiple right foot infected ulcers, two in the longitudinal arch and one at the hallux. The culture results yielded polyflora consisting of *Proteus mirabilis*, *Corynebacterium*, *Streptococcus* group D, *Morganella morganii*, *Escherichia coli*, *Klebsiella*, α-hemolytic *Streptococcus*, *Citrobacter*, and *Pseudomonas aeruginosa*. Within 4 weeks of treatment with sugar paste, the wound appeared clean with granulation tissue and no signs of infection. The observations were similar to previous reports regarding antimicrobial activity, edema reduction, debridement of necrotic tissue, promotion of granulation tissue, and promotion of epithelial tissue.

The second study to specifically address the use of sugar for the healing of DFU was performed by Kilic[33] who published a case report of one patient with a diabetic ulcer on the left foot that was treated with granulated sugar. The author performed twice daily dressings with bandages to hold the granulated sugar in place and found similar observations as previous authors, such as decreased odor, inhibition of bacterial growth, and debridement of necrotic tissue. One notable observation was that, once granulation tissue was well established, the granulated sugar caused bleeding of the wound bed. In this instance, the author reconstructed the tissue with a skin graft once adequate granulation tissue formed, but he concluded that granulated sugar treatment leads to faster healing of diabetic ulcers, shorter hospital stays, and less cost for dressing supplies. Kilic's conclusions require a larger trial to determine sugar's efficacy for decreasing inpatient hospital stays and cost of dressing supplies. Currently, no studies exist to support Kilic's claim.

Another case report that specifically evaluated the use of sugar in the treatment of leg ulcers was performed by Lisle.[52] In this case report, however, the patient had developed multiple resistances to topical applications, was allergic to systemic antibiotics, and had four multipathogen-infected venous stasis ulcers that had been recurrent for 17 years. Sugar paste made from caster sugar, icing sugar, hydrogen peroxide, and polyethylene glycol was used to treat the four ulcers on her lower extremities. The observations made were reduction in odor, reduction of exudate, reduction of pain, increased granulation tissue, and suppression of Methicillin-resistant *S. aureus*, β-hemolytic streptococci, and mixed enteric flora in the wound. All four of the patient's wounds were completely healed at the end of treatment.

Discussion

The rationale for the use of sugar has been presented by multiple reports documenting sugar's antimicrobial effect and the ability to reduce wound exudate, odor, and edema. However, the evidence is lacking in the cellular and molecular interactions between sugar and the wound environment. More research is needed to evaluate if sugar is able to attenuate the impaired wound healing of diabetes patients. A prospective trial of sugar for the treatment of diabetic ulcers would also help to answer the question of whether sugar is effective for healing diabetic ulcers as well as decreasing hospital stays and costs.

As clinicians, scientists, and researchers, we face a daunting uphill task in the management of DFU despite advances in treatments. The evidence for many treatments is lacking, and high costs as well as clinical experience remain essential permissive factors for the success of the interventions. The ability to perform a comprehensive foot examination and to monitor changes are becoming increasingly important for diabetes patients.[53] However, research in wound healing and therapeutic modalities can complement clinical management in accurate evaluation, risk stratification, and healing both acute as well as chronic wounds. Organized prevention efforts coupled with timely and aggressive interventions when needed can improve patient outcomes and reduce amputation rates.[54]

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