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Is The Use Of Honey An Effective Dressing Option For The Treatment Of Diabetic Foot Ulcers?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not honey could be used as an effective topical treatment for diabetic foot ulcers in diabetic patients.

STUDY DESIGN: Review of three primary journal articles published in English between the years of 2008 and 2010.

DATA SOURCES: Two Randomized Controlled Trials comparing honey as a treatment for diabetic foot ulcers to either previous failed treatments or Povidone Iodine Solution, and a pilot prospective study, exploring the effectiveness of PEDYPHAR a royal jelly ointment. All articles were found using Pubmed, OVID and Cochrane Database.

OUTCOMES MEASURED: Healing time and percent of patients to reach wound closure or a state of healing ready for surgical closure was assessed in all of the studies. Healing was assessed by surgeons and was determined based on size of the ulcer and change in grade and stage using either the University of Texas Diabetic Wound Classification or the Wagner Classification, inflammation, presence of bacterial cultures and, presence of exudate.

RESULTS: The Shukrimi et al. study showed that honey used as a dressing for diabetic foot ulcers was as effective as the control group using Povidone Iodine in days for healing. Moghazy et al. demonstrated that honey used on different stages of diabetic foot ulcers was effective at providing healing in a relatively short duration. The pilot prospective study by Abdelatif et al. also portrayed efficient healing with the use of PEDYPHAR and healing time was completed in a timely manner. The only side affect noted in the three studies was in the pilot prospective study. Four patients encountered mild burning with application of the PEDYPHAR ointment, but still continued with its use.

CONCLUSIONS: All studies showed that honey was effective in allowing for healing improvements in treating diabetic foot ulcers. Further studies are needed to assess the stages in which honey is most efficient in healing and where surgery may be necessary before use of honey. In addition, comparing honey that is raw versus honey that has been heat-treated as is the kind for consumer consumption.

KEY WORDS: Honey and Diabetic Foot Ulcers

INTRODUCTION

Diabetes Mellitus is a chronic disease that is distinguished by high levels of glucose in the blood. Two types of the disease exist. Type 1 presents early in life and is an autoimmune condition where insulin producing beta islet cells of the pancreas are destroyed. Type 2 occurs due to a combination of insulin resistance of target cells and insufficient production of insulin.^{1,2} Insulin is the hormone accountable for the metabolism of sugar, carbohydrates and other foods, without it sugar remains in the blood and is not utilized by muscles and other tissues of the body. The increase in blood glucose levels for extended periods of time can result in damage to tissues, organs and nerves. Many complications of diabetes occur in the kidneys, eyes, heart, blood vessels and feet.¹

Diabetes is the leading cause of non-traumatic lower extremity amputations in the United States.³ This complication is commonly a result of untreated foot ulcers or infection of the lower leg and foot.³ Diabetic foot ulcers are a chronic complication of diabetes. They exist due to a combination of other problems that are caused by diabetes including peripheral neuropathy, peripheral arterial disease (PAD), and trauma to the foot.^{1,2,3}

Peripheral sensory neuropathy is one of the major reasons foot ulcers form. The neuropathy is caused by the deterioration of the nerves of the extremities which decreases sensation of pain and temperature in the foot.^{1,2} The decrease in sensation allows for major or recurring minor traumas to go unnoticed. Ulcers will develop in those areas that have increased pressure upon them including most commonly the heel and the underside or tips of the toes.¹ In addition to sensory loss, some motor deficits and muscle weakness result due to the nerve damage. This combination of motor and sensory loss causes a change in the mechanics of the

foot causing for pressures to be placed on areas not normally exposed to this type of stress. This increases the risk for ulcer formation.^{2,3}

The other major factor in foot ulcer development is peripheral arterial disease. This is caused by plaque buildup in the arteries which eventually decreases blood flow to the small vessels in the periphery of the feet.^{1,2,3} With a considerable decrease in blood flow, wounds are unable to heal due to the lack of oxygen, nutrients, and white blood cells all of which are carried in the blood.¹ With the combination of peripheral neuropathy, change in foot mechanics causing an increase in trauma, and lack of blood flow to the lower extremity, diabetes patients are very vulnerable to ulcers of the foot with an inability to heal these wounds in a usual time period.^{1,2,3}

Diabetes is a very common disease that affects approximately 25.8 million people.⁴ Of those patients 6.9% will have a foot ulcer in their lifetime.^{4,5} There are approximately 80,000 amputations done each year on diabetics and 80% of total amputations each year are due to ulcerations.^{4,5,6} In 2007, the CDC reported \$174 billion was used in treatments for diabetic patients.⁷ The average cost of healing one single ulcer is around \$8,000, if the ulcer is infected that cost increases to approximately \$17,000.⁶ Hospital inpatient visits for diabetics reach numbers of 691,000 and foot complications are the most common cause of these visits.^{6,7,8}

There is no cure for diabetes so the goal is to treat the disease early by first changing patient's lifestyles by encouraging incorporation of a healthy diet, decreased sugar intake, and increased physical activity. After lifestyle changes the next step is to use oral medications to decrease blood sugars like Metformin, Sulfonyureas and Incretins in addition to using injectable insulin.^{2,3} Also, comorbidities such as hyperlipidemia and hypertension are treated to avoid chronic complications.^{2,3} Ulcers are a common complication of diabetes, and their regular treatment includes debridement, irrigation, and application of some type of dressing including

hydrogels, foams, iodine, absorbant polymers or skin replacements. These dressings help to keep the wound moist for autolytic breakdown and healing as well as provide an antibacterial component. It is also important to protect against systemic infection so antibiotics are commonly given.^{1,2,3} If treatment is not effective the ultimate result is amputation.^{2,3} The treatment of diabetic foot ulcers has been expensive and the time of wound healing has historically been extensive.^{2,3,5} In this paper, honey is proposed as a topical dressing option that is both a cheaper and more accessible alternative with an equal efficacy as other dressing agents in its ability decrease bacterial load and promote ulcer healing.

Keywords: Diabetes Mellitus, foot ulcers, honey dressing, Diabetic foot ulcers

OBJECTIVE

The objective of this systematic review is to determine whether or not honey could be used as an effective wound dressing option in the treatment of diabetic foot ulcers.

METHODS

The criteria used for selection of studies included for the population any age and either gender patients that currently had a diabetic foot ulcer at any stage. Other inclusion criteria was used and varied between the individual studies. Abdelatif et al. 2008 included those patients that had limb threatening foot ulcers that were full thickness, greater than 2cm in diameter, with signs of cellulitis.⁸ Shukrimi et al. 2008 used inclusion criteria including only patients with non-insulin dependent diabetes and Wegner's grade-II Ulcers between the ages of 35-65, a transcutaneous oxygen tension of >30mmHg, and serum albumin >35g/dL.⁹

Exclusion criteria also varied between studies. Abdelatif et al. 2008 excluded patients that were younger than 18 or older than 70 years old. No patient could have been diagnosed with septicemia, septic shock, or multiple organ dysfunction syndrome.⁸ Moghazy et al. excluded

anyone pending amputation or immunocompromised patients⁵, and Shukrimi et al. 2008 excluded patients with multiple medical comorbidities, using steroid therapy, or a neutrophil count less than 2000/mm³.⁹

The intervention used in each of the studies was honey as a dressing for the wound care of diabetic foot ulcers. Of the three studies used in this review two are randomized controlled trials (RCT) and the third is a pilot prospective study. The study by Moghazy et al. 2010, one of the RCTs compared honey dressing to failed treatments that were previously done before this study began and the wound had no improvement for 3 months.⁵ Shukrimi et al. 2008, compared the honey dressing to a more common dressing solution, Povidine iodine.⁹ The final study by Abdelatif et al. 2008, the pilot prospective study investigated the effects of PEDYPHAR a new honey ointment in healing limb threatening diabetic ulcers.⁸ The outcomes measured in all of the studies included healing time and percent of patients that were considered healed by the end of the study. Healing was determined by size, grade, and stage of the ulcer using the University of Texas Diabetic Wound Classification and Wagner classification, as well as presence and type of exudates, and microbacterial load.

Key words in literature searches included honey and diabetic foot ulcers, honey and diabetes. All articles selected were published in English in peer-reviewed journals between the years 2008-2010. Literature searches were conducted using OVID, Pubmed and Cochrane database. The articles were selected based on clinical relevance to the topic question and if they included outcomes that were important to patients (POEMS). Inclusion criteria for articles included randomized, single blind, prospective studies with patient oriented outcomes published after 1996. Exclusion criteria included articles published before 1996, and articles with patients that had other diseases in addition to diabetes that may affect results. Statistics used included p-

value, relative risk ratio (RRR), absolute risk ratio (ARR), and number needed to treat (NNT).

The demographics of the studies used in this review are included in Table 1.

Table 1. Demographics of Included Studies

Study	Type	# of pts	Age	Inclusion criteria	Exclusion Criteria	W/D	Interventions
Abdelatif (2008) ⁸	Prospective pilot study	60	18-70	-limb-threatening diabetic foot ulcer (full thickness, >2cm in diameter, with signs of cellulitis)	-age <18 or >70 yo -septicemia, septic shock or multiple organ dysfunction syndrome	0	-groups 1&2 ulcers cleaned with saline and treated with 1-3 g PEDYPHAR ointment -group 3 had limited excision of gangrenous tissue and surgical debridement and then treated with 1-3 g PEDYPHAR ointment changed 2x wkly
Moghazy (2010) ⁵	RCT	30	Mean age= 52.3	-all patients with diabetic foot ulcers	- pending amputation, and immune-compromise patients	0	-wound was debrided, and washed with saline, and honey impregnated gauze was then applied to the wound and a fluffy dressing was applied with bandage to keep gauze in place. Dressings were changed when soaked
Shukrimi (2008) ⁹	Single blind RCT	30	31-65	-non insulin dependent DM patients with Type II Wagner Ulcer w/ transcutaneous oxygen tension of > 30mmHg, serum albumin > 35g/dL	-multiple medical co-morbidity, steroid therapy, neutrophil count less than 2000/mm ³	0	-wounds were cleaned with saline; a thin layer of honey was poured on wound and covered with sterile gauze or for control the wound was covered with povidone-soaked gauze; dressings were changed on daily basis.

OUTCOMES MEASURED

Abdelatif et al. measured the percent of patients to reach full healing and duration for them to reach that state. Wound healing was assessed by the odor, nature of wound exudates, erythema, edema, bacterial load and degree of cellulitis or bone infection at 3,9 and 24 weeks.⁸

Moghazy et al., recorded percent of patients healed and time for healing to occur by assessing changes ulcer size, inflammation, exudates, grade and stage of wound using the University of Texas Diabetic Wound Classification which classifies by the stage from A which is no infection

or ischemia to D where there is infection and ischemia, in addition to a Grade which is from 0 with an epithelized wound to a 3 where the wound penetrates a bone or joint.⁵ The outcomes measured in Shukrimi et al. were number of days for the ulcer to reach a proper state for wound closure assessed by qualitative measurements of granulation, epithelialization, and wound contracture.⁹

RESULTS

Shukrimi et al. compared clean, non-sterile pure honey as a wound dressing to Povidone Iodine (10%) solution as the control, in patients admitted for surgery with Wagner grade-II diabetic foot ulcers defined as a deep ulcer that penetrates down to the ligament or muscle without bone involvement or abscess formation⁸. This study reported continuous data that could not be converted to dichotomous. Mean days for healing was recorded and compiled from assessment of wounds by a surgeon blinded to the dressing material. With the use of the honey dressing mean days for healing was 14.4 days where number of days ranged from 7-26. The control group resulted in 15.4 days with a range from 9-36 days and the p-value for this data was less than 0.005 (Table 2). With a difference in mean days of approximately 1, the p-value makes this data statistically significant and the small difference in days was not due to chance alone but rather to the use of honey as a dressing which allowed for similar healing time between the honey group and control group. While the difference in healing time between the two groups is not drastically different this data is statistically significant and portrays the equality of the two products in healing diabetic foot ulcers.⁹

Table 2. Efficacy of Honey vs Povidone Iodine in Wagner grade II diabetic foot ulcers from.⁹

Treatment Type	Mean number of days to heal ulcer	Range of days to heal ulcer	Statistical Significance
Control (Povidone Iodine)	15.4 days	9-36 days	p<0.005
Honey (Experimental)	14.4 days	7-26 days	

Moghazy et al. reported values for the effectiveness of pure, raw untreated honey as a wound dressing for patients with any staged diabetic foot ulcer reporting to the surgery department. The control group comparison for this RCT was considered to be all prior treatments in the same 30 patients that had failed, determined by having no improvement in their ulcers for a 3 month period. This study had continuous data that was converted to dichotomous. Reported values included the control event rate (CER), which was 0; because all of the prior treatments had failed, the study considered all of the controls as a 0% success rate. The value reported for full success of the honey treatment was 43.3% (0.43) and this was the experimental event rate (EER). The relative risk reduction (RRR) was calculated as 0. The calculated absolute risk reduction (ARR) equaled 0.43 and the number needed to treat (NNT) was 3 patients (Table 3).⁵

The calculation of 0 for a RRR indicates there is a 100% difference in healing of wounds in comparing the control treatments and experimental honey treatment. In other words, the control treatments were completely unsuccessful. Therefore, the ARR is equal to the percent of the subjects that reached wound closure due to honey treatment. Finally, a NNT of 3, means that 3 patients with diabetic foot ulcers need to be treated with honey in order to have 1 additional patient benefit from the use of honey. This study reported that another 43.3% did have a decrease in their ulcer size with some healthy granulation tissue, but never reached a full healing by the completion of the study.⁵

The mean duration of time for the 43.3% of patients to reach wound closure was determined to be 2.3 ± 0.94 weeks (p-value= 0.0089) (Table 4). This value of days to reach wound closure is again statistically significant due to the low p-value. The days for wound healing to occur were not just by chance alone but rather due to the experimental honey use.⁵

Table 3. Efficacy of Honey vs previously failed treatments from Moghazy et al. 2010.⁵

Study	Control Event Rate	Experimental Event Rate	Relative Risk Ratio	Absolute Risk Ratio	Number Needed to	Statistical Significance
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	(CER)	(EER)	(RRR)	(ARR)	Treat (NNT)	(p-value)
Moghazy ⁵	0	0.433	0	0.433	2.3 (3)	p=0.0089

Table 4. Outcome of Honey Dressing on Wound closure patients from Moghazy et al. 2010⁵

	1 month		2 months		3 months		Total	
Result of Dressing:	# of Pts	Percent	# of Pts	Percent	# of Pts	Percent	# of Pts	Percent
Wound closure	4	13.3 %	4	13.3%	5	16.7%	13	43.3%
Mean Duration of Healing	2.3 weeks							
Standard Deviation	0.94		P-Value			0.0089		

The final pilot prospective study by Abdelatif et al., reported percent of patients that improved from their baseline diabetic foot ulcer with the use of PEDYPHAR a new ointment that combines natural honey and panthenol. Patients were placed into one of 3 groups based on severity of their foot ulcer. This determination was done using the Wagner classification of diabetic foot lesions (Group 1= full thickness: Wagner grades 1&2; Group 2= deep tissue infection or osteomyelitis suspected: Wagner grade 3; Group 3= gangrenous lesions: grade 4 and 5). Clinical responses were recorded at 3, 9, and 24 weeks. Of the 60 patients 50 belonged to Group 1 (26) or 2 (24) and 10 belonged to group 3. The patients in group 3 underwent surgical procedures prior to the treatment with PEDYPHAR, but all healed within 2 months of treatment.⁸

The remaining 50 patients had conservative treatment with only PEDYPHAR ointment. Of these patients, 96% reached wound closure without complication noted by the 9 week mark. All patients in group 1 attained full healing. However, 3 patients in group 2 (8%) failed the conservative PEDYPHAR treatment resorting to amputation, while the remaining 92% responded to the honey ointment with full healing (Table 5).⁸

Table 5. Efficacy of PEDYPHAR Honey Ointment on limb threatening Diabetic Foot Ulcers at weeks 3,9, and 24 in Groups 1 and 2 from Abdelatif et al. 2008.⁸

Group	Week 3	Week 9	Week 24
Group 1 (n=26)	Cured= 25 Improved= 1	Cured=26	Cured=26
Group 2 (n=24)	Cured=10 Improved= 13 Failure= 1	Cured= 23 Improved= 1 Failure= 1	Cured= 23 Improved= 1 Failure= 1

In reporting adverse effects of the honey in treatment of diabetic foot ulcers, only the Pilot prospective study reported such events. The PEDYPHAR ointment used in this study did contain panthenol rather than plain pure honey so this may have had some responsibility of the side effect on the patients. Of the 60 patients in this study by Abdelatif, et al. 2008, 4 patients reported a mild burning sensation with the use of the honey ointment, but this did not cause them to stop using the product.⁸ The 2 RCT studies did not mention any adverse effects of the pure honey treatment.^{5,9}

DISCUSSION

As the resistance of bacteria cultivating wound infections increases there is a greater need to find antibiotic ointments that are effective in decreasing bacterial load in addition to being cost efficient. In 2007, the FDA approved a drug called MEDIHONEY manufactured by Derma Sciences, which is a medical active Manuka honey from New Zealand, that is prepared on dressing material indicated for mildly exudative wounds including diabetic foot ulcers, leg ulcers (venous and arterial), pressure ulcers (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites and traumatic/surgical wounds.¹⁰ This product is not found in most pharmacies, and can be very expensive as most insurance plans do not cover its use.¹⁰

The studies focused on in this review researched the natural commercial honey product for consumption. This would be a cost effective alternative to other dressing treatments. Shukrimi et al. found significant data that supports the use of honey in Diabetic Foot Ulcers. This study only focused on Wagner grade-II lesions though, which leaves one to be unsure of the deeper lesions as Wagner grading scale goes up to a grade 5. This study fails to report the number of patients that reached a healing state ready for surgical closure verse failing the treatment and needing debridement, so although the days for healing in the honey group was

much less than for the control, more subjects may have completely failed the honey treatment and that was not reported.⁹

Moghazy et al. found a statistically significant value for patients fully healed and in a relatively short duration of time. It also had the low number of 3 for the NNT. This study had the main limitation of not reporting the previous failed treatments, and they did not provide one specific control within this study for comparison. Obvious from this study and others honey was found to be effective in decreasing exudates, bacterial load of skin wounds, and by keeping the wound moist it caused less pain with removal and allows for a better healing environment for the new granulation tissue formation for a lesser cost compared to commonly used dressings^{5,8,9,10,11}.

Abdelatif et al. also found data to support that honey is an effective treatment for diabetic foot ulcers. This study also helped to evaluate those patients with deeper ulcers at Wagner grade 4 and 5. The main limitation to this pilot study is that it is not an RCT so we did not have a control group for comparison and other treatments were done before using the honey.⁸

In addition to limitations mentioned above, all of these studies had small subject sizes and only one was single blinded. Blinding the evaluator of the wound is the most important for these studies. Patient blinding would not be needed because this is an objective assessment of their healing process. Limitations in searching for articles in this field were present because honey is a natural product that is not commonly used or thought of as a type of wound dressing. In addition, there are many different types of wound dressings manufactured by different pharmaceutical companies and trials are done commonly to test those products, but there was not a lot of research to be found for this natural product. There were only 2 RCTs found and those were the 2 used in this review.

CONCLUSION

The three studies used in this review all reported supportive data for effectiveness of honey in the treatment of diabetic foot ulcers. The data from Shukrimi et al, reported a statistically significant value for days to heal for honey dressing that was comparable to a more common solution that is used in treatment of foot ulcers. Moghazy et al. reported that with honey use, majority of the subjects reached improvements with their ulcers, and finally in the pilot prospective study subjects data that was reported portrayed high percentages of healing in a relatively short duration of time.

Future studies need to be done in this field of diabetic foot ulcers to determine at what level of a diabetic foot ulcer honey would be most efficient. In the studies included in this review this was not explicitly discovered. The Shukrimi et al. found significant data for Wagner grade-II lesions, but did not investigate ulcers worse than that grade. Moghazy et al used a different classification system making it hard to compare the work by Shukrimi et al. A study should be done with a certain number of subjects to fulfill both classification system requirements and compared. Also honey should be compared to other different types of dressings, because this review only contained an RCT comparing honey to Povidone Iodine.

In addition, honey needs to be standardized. Shukrimi et al. did not state if the honey they used was raw which would be non- heat treated. This could have some affect on results and wound healing if certain properties are changed by the heat, so a standard honey product also needs to be used. A study could be done to compare wound healing with raw honey vs. heat treated honey packaged for human consumption to see if there is any difference in its effectiveness.

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