Using honey to heal diabetic foot ulcers

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Abstract

Diabetic ulcers seem to be arrested in the inflammatory/proliferative stage of the healing process, allowing infection and inflammation to preclude healing. Antibiotic-resistant bacteria have become a major cause of infections, including diabetic foot infections. It is proposed here that the modern developments of an ancient and traditional treatment for wounds, dressing them with honey, provide the solution to the problem of getting diabetic ulcers to move on from the arrested state of healing. Honeys selected to have a high level of antibacterial activity have been shown to be very effective against antibiotic-resistant strains of bacteria in laboratory and clinical studies. The potent anti-inflammatory action of honey is also likely to play an important part in overcoming the impediment to healing that inflammation causes in diabetic ulcers, as is the antioxidant activity of honey. The action of honey in promotion of tissue regeneration through stimulation of angiogenesis and the growth of fibroblasts and epithelial cells, and its insulin-mimetic effect, would also be of benefit in stimulating the healing of diabetic ulcers. The availability of honey-impregnated dressings which conveniently hold honey in place on ulcers has provided a means of rapidly debriding ulcers and removing the bacterial burden so that good healing rates can be achieved with neuropathic ulcers. With ischemic ulcers, where healing cannot occur because of lack of tissue viability, these honey dressings keep the ulcers clean and prevent infection occurring.

Introduction

In the recently published paper “What is the future of diabetic wound care?”[1] the authors give an excellent review of the reasons why diabetic wounds do not heal, and provide data on the magnitude of the problem this causes. They point out that many of the nearly 2 million cases of chronic diabetic foot ulcers in the USA ultimately result in amputation, with a 2-year survival rate after these amputations of only 50%–60%. They then go on to discuss at length the need for new smart matrix therapies, and how the development of these will require a multidisciplinary

translational research approach. Considering that the research on tissue-engineered skin substitutes was started approximately 20 years ago yet this form of therapy has barely started to get into regular clinical practice, there is obviously an immediate need for an effective therapy for chronic diabetic ulcers. It is proposed here that the modern developments of an ancient and traditional treatment for wounds, dressing them with honey, have allowed this immediate need to be met.

Historical usage of honey

The ancient Egyptians, Assyrians, Chinese, Greeks and Romans all used honey, in combination with herbs and on its own, to treat wounds.[2] Aristotle (c.350 BC) wrote of honey being a salve for wounds and sore eyes,[3] and Dioscorides (c.50 AD) wrote of honey being “good for sunburn and spots on the face” and “for all rotten and hollow ulcers”.[4] The usage of honey has continued into present-day folk-medicine; for example, it is a traditional therapy for infected leg ulcers in Ghana.[5] In recent times It has been "rediscovered" by the medical profession,[2] possibly because the "antibiotic era" is coming to an end as increasing numbers of bacterial strains develop resistance to antibiotics.[6]

Modern clinical evidence for the effectiveness of honey

The clinical evidence in support of the effectiveness of honey in wound care has been comprehensively reviewed.[7] This review summarises the findings of 17 randomised controlled trials involving a total of 1965 participants, and 5 clinical trials of other forms involving 97 participants treated with honey. All of these found that honey was more effective than the conventional wound care practices used as controls, other than one trial on burns where, only in respect of control of infection, was early surgical tangential incision found to be more effective than dressing the wounds with honey. The review also summarises the findings 16 trials on a total of 533 wounds on experimental animals, where again honey was found to be more

effective than the controls in assisting wound healing. There is also summarised a large amount of evidence in the form of case studies that have been reported. Ten publications have reported on multiple cases, totalling 276 cases. There are also 35 reports of single cases.[7] This evidence is far greater than that for modern wound dressings. It is possibly the myriad of advertisements for modern wound dressings, and little for honey, that gives clinicians the impression that there is much evidence is behind the modern dressings and none behind honey, when in fact only poor-quality trials exist to support the modern wound dressings that are in use.[8] Perhaps the most heavily advertised wound dressings are the nanocrystalline silver dressings, but if the PubMed database is searched for evidence to support their use it can be seen that there is in fact very little good clinical evidence that has been published other than two recent trials. A conclusion reached in a recent systematic review of publications on the use of advanced dressings in the treatment of pressure ulcers has found that their generalised use in the treatment of pressure ulcers is not supported by good research evidence.[9] There is now a general movement towards evidence-based medicine. In this, decisions should be made on the basis of the available evidence. If randomised controlled trials of the highest quality have not been conducted, then it is necessary to consider evidence of a lower quality. Advertising, other than that which presents good clinical evidence, should not be allowed to influence decisions.

Usage of honey on diabetic ulcers

Although there is a vast amount of literature reporting the effectiveness of honey in healing wounds, there has been little published specifically on the treatment of diabetic foot ulcers with honey. Diabetic ulcers are chronic wounds, and there is a large amount of evidence for the effectiveness of honey on chronic wounds. Seven clinical trials, with a total of 255 participants, have been conducted using honey on chronic wounds, with positive results for honey being reported from all of these.[7] There have also been more than one hundred case reports of honey being more effective than conventional treatment for chronic wounds.[7] Diabetic ulcers were

included in one report in the list of recalcitrant wounds and ulcers of varied aetiology that "showed remarkable improvement" when treated with honey. These were all wounds showing no signs of healing, or were increasing in size, after 1–24 months of conventional treatment.[10] In another report, on using honey to treat septic wounds, chronic ulcers, burns, and pyogenic abscesses, 6 patients were diabetic, 5 having a septic foot and 1 with an abscess in the thigh.[11] Healing time was 7, 10, 14 and 30 days for four the foot wounds, 15 days for the abscess, and no improvement after 56 days for a foot wound on one patient who was ill. Another report, on a single case, was on treatment of diabetic foot ulcers, 8 x 5 cm and 3 x 3 cm, on a 79 year old patient.[12] The ulcers remained unhealed after 14 months treatment with an orthotic device, antibiotics, topical therapies by a wound care expert and four lots of surgery. MRSA, VRE and Pseudomonas were present in wound tissue. After commencing treatment with honey, the ulcers were granulating within 2 weeks, and healed within 6 and 12 months. Two years later the ulcers had not recurred. Although honey gave healing of these ulcers where nothing else had worked, the healing was still fairly slow. This possibly because "supermarket honey" was used, which is honey that is usually processed in a way that destroys all of the antibacterial activity and possibly removes other beneficial components. In the other two reports unprocessed honey was used, which would have had its therapeutic properties undamaged.

Antibacterial activity of honey

There have been many publications on laboratory studies showing that honey has very broad spectrum antibacterial activity.[13] But most of these do not take into account that honeys can vary as much as 100-fold in the potency of their antibacterial activity.[14] Only in the more recent publications was the testing of the sensitivity of various species of bacteria to honey done using honeys selected to have antibacterial potency near the median level found in surveys of large numbers of samples. Laboratory studies with Manuka (*Leptospermum scoparium*) honey with antibacterial potency near the median level for active Manuka honey have shown the MIC

(minimum inhibitory concentration, *i.e.* the concentration down to which honey could be diluted by wound exudate and still prevent bacterial growth) to be 2–3% for *Staphylococcus aureus*,[15] 3.3–4% for coagulase-negative staphylococci,[16] 5.5–9% for Pseudomonads,[17, 18] 2.7–3% for MRSA,[19] and 3.8–5% for VRE.[19] The antibacterial potency of the honeys used in the various honey wound-care products now on sale manufactured from *Leptospermum* honey (Manuka honey and Jellybush honey) is higher than that of the honey used these studies, but there are other wound-care products manufactured from honeys not selected to have high levels of antibacterial activity.[20]

Another consideration is the type of antibacterial activity in honey. Most honeys owe their antibacterial activity (beyond that just due to the osmotic effect of the high sugar content) to the production of hydrogen peroxide by an enzyme that the bees secrete into the nectar harvested to make honey.[13] But some Manuka and Jellybush honeys have also a high activity due to a phytochemical antibacterial component which comes from the nectar of some varieties of *Leptospermum*. Although in laboratory testing the MIC values recorded are near the same for mid-range honeys of either type, this would not be the case on a wound. There is in wound fluid, and more so the cells in wound tissues, the enzyme *catalase* which rapidly breaks down hydrogen peroxide, so honeys other than the *Leptospermum* ones would have their antibacterial activity greatly decreased. Also to be noted is that all types of honey vary from batch to batch in their antibacterial potency. Much of the Manuka and Jellybush honey on sale as a food item has little or none of the phytochemical antibacterial component, but the *Leptospermum* honey on sale as medical products has standardised high levels of it.

Why honey works well on diabetic ulcers

A wound will not heal if it is infected. Toxins produced by bacteria can stop the growth of cells which repair the wound. Bacterial proteases can digest away the matrix necessary for tissue

156 replacement, and digest cell growth factors. Also, components of the outer coat of the bacteria
157 can stimulate a strong inflammatory response and the resultant inflammation then prevents
158 healing and if severe can activate proteases to cause ulceration. Foot infections are a serious
159 complication of diabetes and a leading cause of diabetes-related hospitalizations. Amputation
160 may be needed when infections fail to respond to therapy. The development by bacteria of
161 resistance to antibiotics has become a major global problem. Methicillin-resistant
162 *Staphylococcus aureus* (MRSA) has become a major cause of infections, including diabetic foot
163 infections. Initially it was associated only with hospital-acquired infections, but now is also a
164 problem in the community. The effectiveness of honey in clinical usage in clearing infection with
165 MRSA[12, 21-24] and VRE[12] has been reported. As well the antibacterial action, there have been
166 many reports of honey having a rapid debriding effect, which painlessly lifts off slough and
167 necrotic tissue (which are reservoirs of bacteria on the wound), making surgical debridement
168 unnecessary.[25]
169
170 Diabetic ulcers, instead of going through the normal four overlapping stages of healing,
171 hemostasis, inflammation, proliferation and remodelling, seem instead to be arrested in the
172 inflammatory/proliferative process.[1] This allows for infection and inflammation, which preclude
173 healing. The potent anti-inflammatory action of honey is likely to play an important part in
174 overcoming this impediment to healing in diabetic ulcers. The anti-inflammatory action of honey
175 was noted by Dioscorides two millennia ago, who wrote of honey being good for sun-burn,[4] and
176 since then a large amount of clinical and histological evidence for it has accumulated, which has
177 been reviewed.[26] The anti-inflammatory action of honey would decrease the excessive activity
178 of collagenase and elastase, a feature of inflammatory conditions and which causes the
179 premature degradation of collagen and growth factors in chronic wounds.[1] A characteristic of
180 the extracellular matrix in wounds in diabetes is the presence of advanced glycation and
181 lipoxidation end products which stimulate oxidative stress and inflammation in wounds.[1] The

excellent antioxidant properties of honey would be beneficial in counteracting these effects. It is of note in this respect that another advantage of using active Manuka honey instead of other types of honey is that it does not generate hydroxide free radicals like honey with antibacterial activity due to hydrogen peroxide does, and rapidly quenches any formed by the Fenton reaction.[27]

The good results achieved on diabetic ulcers with honey may also be due to honey directly moving the wounds on from the arrested state of healing. It has been observed that honey promotes tissue regeneration through stimulation of angiogenesis and the growth of fibroblasts and epithelial cells.[25]

The slow healing rates seen in diabetic wounds could also be due to lack of insulin or lack of responsiveness to insulin. As well as regulating the uptake of glucose into cells, insulin functions as a growth hormone, and it has been shown that intravenous infusion or topical application of insulin improves the rate of wound healing.[28-30] Honey has an insulin-mimetic effect: when administered by inhalation as an aerosol, honey significantly reduced random blood glucose (measured 30 min after inhalation), significantly reduced the fasting blood glucose level (3 hours after inhalation), and the intensity of hyperglycemia was significantly lowered in the glucose tolerance test after honey inhalation.[31]

Modern developments in the usage of honey

In the “rediscovery” of the use of honey for wound care there has been a lack of awareness of some ancient wisdom. Four millennia ago the Ancient Egyptians mixed cotton fibres and fat into honey to create a dressing that would hold the honey on a wound.[32] It is necessary to create a retentive dressing of some sort, because at body temperature honey becomes very runny and

flows off a wound. It takes very little dilution of honey with wound exudate to make the honey very watery. The water content of honey is bound up on the sugar molecules in honey, so it does not easily wet absorbent dressing materials. This means that if honey is applied to a wound, whether directly or placed on an absorbent dressing, when the dressing is held on the wound the honey tends to be squeezed out laterally. To get the honey to be retained well on the wound it needs to be soaked into the absorbent dressing before it is applied. Various sorts of such honey-impregnated dressings are now available as sterile medical products.[20]

In our initial work on clinical use of honey dressings we used a Gamgee type of dressing impregnated with honey. We found that with heavily exuding wounds it was necessary to change the dressing up to three times a day, as the exudate flushed the honey from the side of the dressing facing the wound to the outside of the dressing pad or even right through it and into the secondary dressing. This left no honey in contact with the wound bed, with the consequence that healing was slow, adhesion of the dressings occurred, and maceration of skin around the wound occurred. This situation was greatly improved when we changed to using a honey-impregnated alginate fibre dressing pad instead, as the alginate fibres transform to a gel when wound exudate is absorbed into them. (This also has the advantage of the hemostatic properties of alginate.) Thus the honey is held in a soft gel in contact with the wound bed rather than being flushed into the secondary dressing, so less frequent changes of dressings are needed. By keeping sufficient honey in contact with the wound bed, by changing the dressings frequently enough to cope with the level of exudate, the level of exudate will decrease because of the anti-inflammatory activity of honey. Less frequent dressing changes will be needed then. However, if dressings are not changed frequently enough and the honey is washed away, then the anti-inflammatory activity will also be washed away and the wound will remain highly exudative. Another form of dressing has been developed in which the honey is combined with sodium alginate to gel it, giving a rubbery material which swells as it absorbs exudate.[33] This

has a massive capacity to absorb exudate without the honey being flushed from the wound bed. Commercialisation of this dressing is proceeding, and it is expected to be available for clinical evaluation soon.

By updating the ancient wisdom of using a honey selected as the best for medical use (we use active Manuka honey with a high level of the non-peroxide antibacterial activity that is unique to *Leptospermum* honey, processed with minimal heating to avoid damaging its therapeutic properties) and creating a dressing material to hold the honey in place on the wound (we use alginate dressings pads impregnated with this honey) we have been able to get very good results with diabetic ulcers. We use honey dressings on neuropathic foot ulcers where despite pressure off-loading healing is inhibited by the presence of Pseudomonas and Staphylococcus aureus. We use these dressings to debride the ulcers and reduce the bacterial burden. Good healing rates are then achieved. With ischaemic foot ulcers, where healing cannot occur because of lack of tissue viability, we use honey dressings to prevent infection of these ulcers whilst waiting for re-vascularisation to be carried out. We find that if there is enough blood flow then diabetic ulcers which are due to a combination of ischemia and neuropathy will heal with off-loading of pressure. We find that honey is particularly useful for diabetic ulcers that are otherwise difficult to debride particularly where bacterial loading may be a confounding factor in the creation of slough.

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