Maggot Bio-Debridement Therapy for Diabetic Foot ulcers–Literature Review

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Abstract
Diabetic foot ulcers are chronic, difficult to treat wounds that are associated with high morbidity and mortality. Several therapies have been proposed as adjuncts to the traditional wound care, among them is the maggot debridement therapy (MDT).

MDT had been used for decades for treating non-healing wounds. However, with the beginning of the antibiotic era, its use had gradually faded. In the last years, MDT has re-emerged in clinical use, mainly because of the rise of anti-microbial resistance.

Herein we summarize the last decade accumulated data on the clinical implication of the treatment by maggot debridement for non-healing diabetic foot ulcers.

Case presentation
A 67-year-old patient was admitted because of long standing infected foot ulcer. His medical history included poorly controlled diabetes mellitus, hypertension and hyperlipidemia, for which he was treated by Metformin, Glargine insulin, Enalapril and Atorvastatin. On admission: body temperature was 36.4 °C, blood pressure 130/70 mmHg, heart, lungs and abdominal examination was unremarkable, peripheral pulses were intact, there was a 4 cm × 3 cm ulcer at the planter aspect of the right foot, with worm and hyperemic area surrounding it. Signs of osteomyelitis were not detected on foot X-RAY. Laboratory results revealed: white blood cells - 13000/mm³, Hemoglobin 13.0 g/dl, platelets - 350000/mm³, CRP 5.0 mg/dl, and glucose - 175 mg/dl, kidney, liver function tests and electrolytes were normal, hemoglobin A1C - 8.4%. An ankle brachial index and continuous wave doppler analysis were reported normal two month prior to admission. During the last year, he had repeated surgical debridement manipulations with concomitant empirical antibiotic courses, followed by 10 sessions of hyperbaric oxygen therapy, all without any improvement. An adjuvant therapy by maggot debridement therapy (MDT) was suggested. Three cycles of MDT were applied; each cycle lasted for 3 days. A great improvement was noticed in wound healing after 10 days of MDT.

Introduction
Diabetic foot ulcers are chronic, difficult to treat wounds that are associated with high morbidity and mortality. They are considered the most common admission diagnosis for diabetic patients in the developed world [1]. Multiple factors are involved in the etiology of diabetic foot ulcers, including peripheral neuropathy, external trauma and peripheral vascular diseases [2].

Several therapies have been proposed as adjuncts to the classic triad of diabetic foot ulcer management-medical therapy (glycemic control and antibiotic treatment), revascularization, and surgical debridement, including vacuum assisted wound closure, hyperbaric oxygen therapy, growth factors, and MDT. MDT is an old-new treatment modality, which was approved by the FDA in 2004, as a medical device indicated for treating chronic non-healing wounds [3].

Herein we summarize the accumulated data in the last decade’s literature on the clinical implication of MDT for diabetic non-healing foot wounds.

Historical perspective
MDT is an old technique in wound care, one of the first written reports on larval therapy and its beneficial effects in the wounds of soldier’s date back to 1557 which is credited to Ambroise Paré, a chief surgeon to France’s Charles IX and Henri III and during the Civil War (1861-1865) when, Confederate surgeons Joseph Jones and J.F. Zacharias began using maggots to treat wounds. MDT was strongly implicated in clinical use after the World War I, when Dr. William S. Baer (1872-1931) - an American military surgeon noticed that the wounds which were swarmed with maggots had a pink granulation tissue without any sign of systemic infection. Further he used the technique to treat chronic osteomyelitis with great response. In addition, Baer and his colleagues Fine and Alexander had developed a method for growing maggots in a sterile environment. With the introduction of the antibiotic era the technique was gradually neglected and its use faded gradually [4-9].

The larvae life cycle
MDT uses sterile larvae of the common green bottle fly, (Phaenicia sericata) that are raised under controlled clinical conditions. Phaenicia sericata belongs to the Diptera order of insects that are able to...
infest living hosts. Eggs are hatched in 12-24 hours giving out 1-2mm long larvae who feed on necrotic tissue in the moist environment of wounds. The larvae grow rapidly and mature in approximately 5 days measuring around 10mm in length, when they pupate to become adult flies [10].

**Mechanisms of MDT**
The mechanism of action and effect of MDT is multifactorial.

**Debridement**
Debridement is an essential intervention in the management of acute and chronic non-healing wounds by inducing the functional process of tissue repair [11]. MDT debrides wounds through two main mechanisms: mechanical - maggots use a mouth hooks for movement and attachment, creating a probing action that facilitate wound debridement [12]; secretion of proteolytic digestive enzymes which liquefy necrotic tissue, degrade eschar, enhance formation of plasmin and induce fibrinolysis, thatencourage the breakdown of the fibrin slough that accumulate in chronic wounds [13].

Maggots remove devitalized tissue effectively with minimal tissue trauma and remarkable reduction in odor emanating from the wound [14-15]. A full maggot debridement requires an average of 2-3 maggot cycles lasting 3-5 days each [16].

**Disinfection**
Chronic bacterial colonization or infection of wound is one of the major factors interfering proper wound healing. Margolin et al. reported a completely is of Methicillin resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococcus* and *Candida albicans* cultures, observed 24 hours after application of live maggots in all culture plates. The lysis persisted for more than 5 days after the maggot application [17]. Furthermore, maggots’ secretions contain ammonia, ammonium bicarbonate and calcium carbonate which can alkalize wound bases and inhibit bacterial growth [18].

MDT was also found to have a synergistic effect on antibiotics. Arora et al. showed an enhanced antibacterial activity against *staphylococcus aureus* when ciprofloxacin was combined with maggots’ excretions and secretions compared to the effect of maggots’ excretions, secretions and ciprofloxacin as single agents [19].

**Wound healing enhancement**
Several experimental studies showed that maggot excretions and secretions promote fibroblast and keratinocyte migration, angiogenesis as well as enhancing vascular endothelial cell migration. In addition, they enhance monocyte and macrophage growth factor production in the form of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), both of which stimulate endothelial cell migration and proliferation. Horobin et al. showed that maggot excretions and secretions promote fibroblast migration upon a fibronectin-coated surface [20]. Bexfield et al. detected three prominent amino acid like compounds (histidine, valinol and 3-guanidinopropionic acid) in maggot excretions and secretions that had a selective proliferative effect on endothelial cells [21].

**Anti-inflammatory**
Maggot secretions were found to inhibit pro-inflammatory responses of human neutrophils and monocytes without affecting the antimicrobial activities of the phagocytes. They also reduced complement activity up to 99.9% in all pathways through the breakdown of complement proteins [22-24].

**Side effects**
Minor side effects had been reported, including mild febrile reactions after applying larvae to the wound. Other adverse events include ethical issues concerning patient recruitment and staff acceptances, as well as larvae escape when inappropriate dressing is applied [25].

**MDT clinical use**
**Clinical studies**
Several clinical studies had been published during the past two decades to investigate the role of MDT in the management of non-healing diabetic wounds. They are detailed in Table 1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Sample size</th>
<th>Year</th>
<th>Country</th>
<th>Intervention and control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun et al. [25]</td>
<td>Meta-analysis</td>
<td>840</td>
<td>2014</td>
<td>China</td>
<td>MDT/Hydrogel therapy</td>
<td>Time to healing, Healing rate</td>
</tr>
<tr>
<td>Markevich et al. [26]</td>
<td>RCT</td>
<td>140</td>
<td>2000</td>
<td>Israel</td>
<td>MDT/Hydrogel therapy</td>
<td>Healing rate</td>
</tr>
<tr>
<td>Sherman et al. [27]</td>
<td>Retrospective</td>
<td>18</td>
<td>2003</td>
<td>USA</td>
<td>Surgical and non-surgical therapy</td>
<td>Healing rate, Time to healing, antibiotic usage</td>
</tr>
<tr>
<td>Wang et al. [28]</td>
<td>Retrospective</td>
<td>43</td>
<td>2010</td>
<td>China</td>
<td>MDT/Conventional</td>
<td>Time to healing</td>
</tr>
<tr>
<td>Gilead et al. [29]</td>
<td>Retrospective</td>
<td>435</td>
<td>2012</td>
<td>Israel</td>
<td>MDT</td>
<td>Time to healing, Healing rate</td>
</tr>
<tr>
<td>Armstrong et al. [30]</td>
<td>Prospective</td>
<td>60</td>
<td>2005</td>
<td>USA</td>
<td>MDT</td>
<td>Healing rate; Time to healing; incidence of infection; amputation rate; antibiotic- freedays</td>
</tr>
<tr>
<td>Tantawi et al. [27]</td>
<td>Prospective</td>
<td>10</td>
<td>2007</td>
<td>Egypt</td>
<td>MDT</td>
<td>Healing rate</td>
</tr>
</tbody>
</table>
To date, the only randomized controlled trial is the one conducted by Markevich et al. [26]. It included 140 patients who were randomly assigned to receive either hydrogel therapy or MDT. The rate of wounds that were successfully debrided and achieved complete healing during the 10 days follow up period was twice in the MDT treated group as compared to the ones treated with hydrogel therapy.

**Retrospective studies**

Sherman et al. showed in a retrospective study that non-healing diabetic wounds that were treated by MDT were completely debrided by 4 weeks compared to those that were treated conventionally, in which coverage of only 33% of the wound surfaces with necrotic tissue were observed. MDT was also associated with hastened growth of granulation tissue and greater wound healing rates [27].

In a retrospective study conducted on 25 diabetic patients with foot ulcers and 18 patients with pressure ulcers who were treated by MDT, All ulcers healed completely. The time duration in days that was taken to achieve bacterial negativity, granulation and healing of diabetic foot ulcers were all significantly shorter in the maggot therapy group than in the control group (12±2.5 vs. 16.1±38, p=0.004; 3.1±1.2 vs. 6.3±1.2, p=0.000; and 26.4±12.6 vs. 39.6±13.4, p=0.042, respectively [28].

Gilead et al. retrieved retrospective data of 435 patients with 723 wounds, 48% were diabetic. Almost all of the patients (82.1%) achieved complete wound debridement in a mean MDT duration of 4.65 days (median=3) [29].

**Prospective studies**

Armstrong et al. assessed a case-control study the potential efficacy of MDT in 60 non-ambulatory patients with diabetic foot wounds. Of the patients who healed, time to healing was significantly shorter in the maggot therapy than in the control group with conventional treatment.

(18.5± 4.8 vs 22.4 ± 4.4 weeks). MDT was associated with significantly more antibiotic-free days during follow-up in patients who (126.8± 30.3 vs.81.9 ± 42.1 days). MDT also reduced short-term morbidity by reducing the rate of amputation (10% vs. 33%) [30].

Another study followed prospectively after the time to complete debridement in 10 patients with 13 diabetic ulcers. Complete debridement was achieved with MDT in a mean of 1.9 weeks [31]. Marinea et al. conducted a prospective study on 23 patients with complex diabetic wounds who were treated with MDT, 17 of them exhibited complete debridement with the formation of robust granulation tissue within their wounds [32].

Another prospective case control study showed that MDT is as effective as surgical debridement [33].

**Meta-analysis and systematic reviews**

Three meta-analyses and one systematic review, that were published during the last 5 years, showed a significant clinical advantage of MDT over standard therapy in the treatment of non-healing diabetic wounds.

A recent meta-analysis by Sun et al. showed that MDT had significantly shortened the healing time in 195 patients pooled from four studies (Pooled standardized mean difference = -0.95, CI95% [-1.24, -0.65]) and improved the healing rate in 840 patients pooled from 8 studies (RR=1.8, CI95% [1.24-2.6], p=0.005) in chronically infected wounds [25]. Another retrospective cohort study by Wilasrusmee et al. on diabetic foot ulcer patients, who were treated with MDT or conventional wound therapy, showed that wound healing was significantly higher in the MDT group than in the conventional treatment one after adjusting for significant variables like: duration and size of ulcers, ankle brachial index, and glycated hemoglobin (RR=7.87, p= < 0.001). Pooling the results with four previous cohort studies to create meta-analyses revealed that the chance of wound healing was 20% significantly higher with MDT than the conventional one (RR=1.77, 95% CI [1.01, 3.11]) [34].

Meta-analysis by Tian et al. had compared MDT with standard therapy on 356 participants. The results suggested that the MDT group was significantly superior to the control group in the percentage of achieving full healing (RR=1.8, 95% CI=1.07; 3.02; p=0.03), amputation rate (RR=0.41, 95% CI=0.20; 0.85; p=0.02), time to healing (RR= -3.70, 95% CI= -5.76; -1.64; p=0.0004) and number of antibiotic-free days (126.8 ± 30.3 days vs 81.9 ± 42.1 days; p=0.001) [35].

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Study</th>
<th>Type of study</th>
<th>Year</th>
<th>Country</th>
<th>Treatment</th>
<th>Control</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
<th>Outcome 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinea et al. [28]</td>
<td>Prospective</td>
<td>23</td>
<td>2011</td>
<td>Hawaii</td>
<td>MDT</td>
<td>Conventional</td>
<td>Healing rate; amputation rate; antibiotic usage</td>
<td></td>
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<tr>
<td>Paul et al. [29]</td>
<td>Prospective</td>
<td>29</td>
<td>2009</td>
<td>Malaysia</td>
<td>MDT</td>
<td>Surgical debridement</td>
<td>Healing rate; amputation rate; antibiotic usage</td>
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<tr>
<td>Wilasrusmee et al. [30]</td>
<td>Meta-analysis</td>
<td>111</td>
<td>2013</td>
<td>Thailand</td>
<td>MDT</td>
<td>Conventional</td>
<td>Healing rate</td>
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<tr>
<td>Tian et al. [35]</td>
<td>Meta-analysis</td>
<td>356</td>
<td>2013</td>
<td>China</td>
<td>MDT</td>
<td>Conventional</td>
<td>Heating rate, amputation rate, time to healing, number of antibiotic-free days</td>
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<td></td>
</tr>
<tr>
<td>Zarchi and Jem et al [36]</td>
<td>Systematic review</td>
<td>637</td>
<td>2012</td>
<td>Denmark</td>
<td>MDT</td>
<td>Hydrogel or a mixture of conventional therapy (hydrocolloid, hydrogel and saline moistened gauze)</td>
<td>Time to debridement, Time to heal</td>
<td></td>
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</tr>
</tbody>
</table>

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A systematic review by Zarchi and Jemec included three randomized clinical trials and five non-randomized studies with maggot debridement activity as an outcome variable. They showed that MDT is significantly more effective than hydrogel or a mixture of conventional therapy modalities, including hydrocolloid, hydrogel and saline moistened gauze [36].

Conclusion
MDT is considered an efficient modality in the treatment of non-healing diabetic wounds for centuries. However, its use has faded gradually since the introduction of antibiotics. Never the less, with the rise of anti-microbial resistance in the last decades, MDT re-emerged in clinical practice.

Despite the lack of high quality evidence on MDTs’ efficacy and safety, the clinical studies reporting on the benefits of MDT are promising. With better MDT application process due to the advancement in technology and the more acknowledgment of the pluripotent properties of MDT, its use might rise and become an easy, efficient, and safe option for treating diabetic non-healing ulcers.

Compliance with Ethical Standards
Funding: none.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Ethical approval: The study was approved by the hospital’s Ethics Committee.

Informed consent: not applicable.

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hospitalised and ambulatory patients. J Wound Care 21: 78, 80, 82-85.


