Original Article

Efficacy of Maggot Debridement Therapy on Refractory Atypical Diabetic Foot Ulcers: An Open-Label Study

The International Journal of Lower Extremity Wounds
1–6

DOI: 10.1177/1534734620920403
journals.sagepub.com/home/ijl
SAGE

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Abstract

Atypical or refractory diabetic foot ulcers (DFUs) are still a major health problem. Maggot debridement therapy (MDT) by larva of *Lucilia sericata* is an ancient and a modern option for wound healing. It works by debridement, stimulation of wound healing, and disinfection. In this study, we aimed to evaluate the efficacy of MDT for healing atypical and refractory DFUs. Patients with atypical DFUs were selected and further evaluated for some predefined differential diagnoses like atypical fungal, parasitic, or bacterial infections, malignancy, trauma, and so on. Multiple MDT sessions were carried out. Ulcer size was measured before every MDT session. Complete wound healing, time to heal, and adverse effects were recorded as well. Forty-two DFU patients (26 men, 16 women) with 42 nonhealing atypical ulcers participated in this study. Complete wound healing was achieved in 35 patients (83.3%) by MDT. Complete debridement and then healing of the wounds happened in less than 1.79 $\pm$ 0.8 months. Four ulcers persisted, and 3 (7.1%) were eventually amputated. MDT may be considered as an effective treatment for atypical DFUs, which are unresponsive to conventional therapies.

Keywords

diabetic foot ulcer, Maggot, *Lucilia sericata*, larva, MD

Diabetic foot ulcer (DFU) is a serious complication of diabetes mellitus. The frequency of DFUs is around 6% worldwide.[1] DFUs are usually characterized as chronic wounds incapable of progressing through normal phases of healing.[2] DFUs can lead to lower limb amputation. There are different types of DFUs, including chronic pressure ulcers (neuropathic), ischemic ulcers, primary infectious ulcers, acute traumatic, and, finally, atypical wounds. A brief description of these ulcer types is presented in Table 1. One of the most complicated and crucial classes of wounds are atypical DFUs, defined as diabetic wounds that have unexpected location, presentation, behavior, or response during conventional therapy. These atypical ulcers, if not properly evaluated or managed, may lead to nonhealing DFUs. Nonhealing DFUs pose a great impact on health care systems. They put a great burden on the economy, society, patients, and their families.[1,3]

For a wound to heal, there are 4 important requirements: (1) stop ongoing trauma (eg, offloading), (2) control the infection, (3) provide sufficient vascular supply, and (4) provide adequate debridement.[4] Debridement, the removal of necrotic tissues from the wound, is a mandatory and vital step in DFU management. Although debridement seems to be a simple procedure, it is not always easy and the best methods to do it are still unclear.[5,6]

Maggot debridement therapy (MDT)—the application of live maggot on wounds[7]—is a known method of selective debridement in chronic ulcers that has been used widely before the introduction of antibiotics.[8] The emergence of antibiotic resistance in recent years has put MDT in the spotlight again.[9] The Food and Drug Administration has approved MDT for debridement of nonhealing necrotic skin and soft tissue wounds, including pressure ulcer, venous stasis ulcer, neuropathic foot ulcers, and nonhealing traumatic or postsurgical wounds. Maggots perform in at least 3 areas including debridement, stimulation of wound healing by producing granulation tissue, and disinfection.[10-12] Despite the impact of nonhealing DFUs, recent improvement in wound care methods has not been satisfying.[13] MDT has been used for a long time all over the world, but it is considered a new treatment in Iran. In the present study,

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Table 1. Khorshid Hospital Diabetic Foot Ulcer Classification System.

	Location	Pulse	Foot Appearance	Clinical Features
Chronic pressure (neuropathic)	Pressure site/callus	Present	Pink or yellow	Painless
Ischemic	Tip of fingers	Weak or absent	Purple	Painful/gangrene
Primary infectious	Below or between toes	Present	Pink or purple	Purulent/deep ulcers
Traumatic	Every location	Present	Normal	Usually geometric shaped
Atypical	Unexpected location	Present	Normal	Unexpected presentation or behavior

we evaluated the effects of MDT in healing atypical DFUs, where conventional therapy was ineffective or impractical.

Methods and Material

Study Design and Participants

This was a prospective open-label single-arm trial performed in Khorshid Hospital, Isfahan, Iran, during February 2014 to February 2016. The study was in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Isfahan University of Medical Science. Patients with diabetes who had foot problems were referred to DFU unit, Khorshid Hospital, Isfahan, Iran. These wounds were classified based on a classification system used in Khorshid Hospital (Table 1). This classification is based on ulcer's underlying mechanism, features, and behavior. In our DFU clinic, if the physical examination reveals foot ischemia, we check the arterial supply by Doppler ultrasonography, and if it reveals severe ischemia, we plan for angiography and then angioplasty or vascular surgery based on the findings. In traumatic ulcers, we try to discover the source and stop the ongoing trauma. In chronic pressure (neuropathic) ulcers, we try to correct deformities, design suitable shoe, and use total contact cast if appropriate. In the case of primary or secondary infected ulcers, depending on the severity and clinical signs of local or systemic infection/sepsis, empirical antibiotics are started and then changed by the results of culture of the wound secretions.

Patients with atypical DFUs were further evaluated for the presence of predefined differential diagnoses like atypical fungal, parasitic or bacterial infections, malignancy, trauma, and so on. Then, based on the findings, different treatment options were discussed with the patients and their care providers. If conventional debridement therapy was challenging or impractical for the ulcers, the possibility of MDT was also explained, and if eligible, informed written consent was obtained from the patients or their legal care providers. The inclusion criterion was having atypical DFUs with at least 25% necrotic or infected wound surface. The exclusion criteria were the following: having wounds near large vessels, being on dialysis, having known septic arthritis, having pseudomonas infection, and pregnancy.

If necessary, as mentioned, antibiotics were prescribed for patients with clinical signs of infection. In this study, all patients needed antibiotics and were prescribed appropriate antibiotics accordingly. The patients were informed about the possible side effects of MDT and were advised to contact the clinical team immediately if they experienced any warning signs. At baseline, data on age, sex, body mass index, diabetes mellitus duration, HbA1c, wound duration, antidiabetes regimes, and wound size were recorded.

Maggot Debridement Therapy

Sterile larvae of *Lucilia sericata* were used for MDT. The sterile larvae were purchased from Zist Eltiam Sepanta, Islamic Azad University, Isfahan (a company providing sterile larvae for clinical purposes; Isfahan, Iran). They were transferred to the hospital under sterile conditions in sterile plates. First, the wound and its surrounding area were washed and cleaned with sterile normal saline and sterile gauze. After cleaning the wound area, the MDT procedure was performed according to the following method: in order to keep the maggots within the wound bed, the wound borders were enclosed using zinc oxide ointment. Maggots floating in sterile normal saline were transferred to sterile gauze, which was immediately applied on the wound bed. There were approximately 10 to 15 maggots per cm^2 of the wound area. This sterile gauze was fixed on the wound by covering its surroundings, leaving a considerable part of the gauze free. Two more layers of sterile gauze were added on top of the first layer. This arrangement facilitated the absorption of wound exudates. The top layer was changed daily, while the first layer containing the maggots was kept in place for 48 to 72 hours. After this period, Maggots were removed by peeling the gauze slowly and washing them away with sterile normal saline. Subsequently, ulcers were washed and cleaned up again with sterile normal saline and sterile gauze. MDT was repeated 5 times. After the fifth session, if the wound was completely healed, we stopped MDT and followed the patient. If the wound did not heal completely, we evaluated the situation and discussed whether we

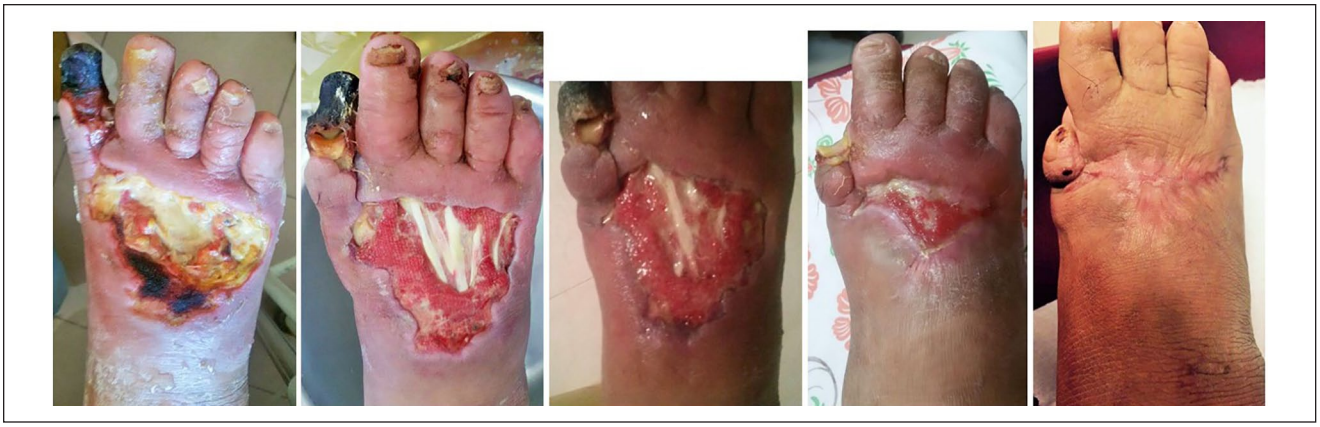

Figure 1. The process of wound healing after 4 sessions of maggot debridement therapy in case 14.

should continue MDT or turn to alternative treatments. All patients were followed-up until complete wound healing.

Outcomes

In the present study, the following outcomes were measured.

- *Complete wound healing*: the number of healed wounds were recorded. Complete wound healing was defined as full debridement and complete closure of the ulcers.
- *Time to heal*: defined as the time to achieve complete wound healing.
- *Wound size*: the length and width of wounds were measured before every MDT application. The area of the wounds was calculated using the approximate ellipse formula. In cases of bizarre-shaped ulcers, a camera was used to take photographs with markers (see Figure 1). As the depth of the ulcers was different, from superficial wounds restricted to skin thickness to deep ulcers involving tendons, muscles, and bones, it was not possible to analyze the ulcer depth statistically.
- Changes in necrotic and granulation tissue.
- *Adverse events*: we monitored the patients for MDT side effects including fever, chilling, and increasing pain.

Statistical Analysis

The complication rate and also the outcomes are presented as number (percentage). Quantitative data are presented as mean ± standard deviation (SD). Wilcoxon signed-rank test was used to compare nonparametric variables before and after treatment. P values $<.05$ were considered statistically significant. All the statistical analysis was carried out using SPSS 20 (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

The study was conducted in Khorshid Complex, a University Hospital in Isfahan, Iran, between 2014 and 2016. Forty-two patients with type 2 diabetes (26 males, 16 females) with 42 nonhealing atypical DFUs were included in the study. The mean ± SD age of the patients was 59 ± 8.2 years (range = 38-75 years). The mean ± SD of diabetes mellitus duration and ulcer duration was 14.5 ± 6.1 years and 7.8 ± 5.6 months, respectively. The baseline's mean ± SD ulcer size was 27.01 ± 27.97 cm^2. The patients were on antidiabetic regimes as follows: 19 on oral antidiabetic agents, 19 on insulin, and 4 on a combination of oral medication and insulin. All patients had antibiotics regimens. Twenty-seven of the patients were candidates for minor or major amputation. Detailed baseline characteristics of the participants are presented in Table 2. In addition, a summary of baseline characteristics of the patients is presented in Table 3.

MDT Application Results

Thirty-five patients (83.3%) achieved complete healing in less than 1.79 ± 0.8 (mean ± SD) months. Of them, 31 patients healed completely after ≤5 MDT sessions, and 4 patients underwent MDT for 10 to 15 times. Four of the ulcers persisted and did not heal completely. Three ulcers did not improve and eventually underwent amputation.

The ulcer surface area was measured after every MDT session. Compared with the wound initial size, the ulcer size decreased significantly after MDT ($P \leq .0001$). Necrotic tissue was debrided and granulation tissue formation increased during MDT.

We evaluated the participants for the incidence of adverse events. Five patients complained of pain during MDT, which was slightly more than the pain experienced during conventional treatments. Two patients reported chilling during their

Table 2. Patients' Characteristics in Details.

Number	Sex	Age (Years)	Initial Size (cm^2)	Final Size (cm^2)	MDT Duration (Months)	MDT Times	Fever, Pain, or Chilling	Ulcer Site	Characteristics
1	Female	56	7	2	2	5	Yes	Fingers 2 to 5	Unexpected presentation
2	Female	50	12	7	2	5	No	Finger 1	Ulcer with rapid osteomyelitis
3	Female	57	28	12	2	7	No	Amputation site	Refractory ulcer
4	Female	60	82	12	3	9	No	Plantar	Rapid and extensive destruction
5	Female	38	2	1	3	10	Yes	Fingers 2 to 5	Unexpected presentation
6	Female	60	47	38	2	6	No	Plantar	Rapid and extensive destruction
7	Female	46	16	5	2	5	No	Heel	Complicated ischemic/infectious
8	Female	54	5	2	2	5	Yes	Heel	Complicated ischemic/infectious
9	Female	55	20	8	2	5	Yes	Heel	Complicated ischemic/infectious
10	Female	48	2	0	2	5	No	Amputation site	Refractory ulcer
11	Female	65	12	5	2	5	No	Finger 1	Ulcer with rapid osteomyelitis
12	Female	52	7	1	1	4	No	Finger 1	Ulcer with rapid osteomyelitis
13	Female	50	66	9	1	4	No	Dorsum	Unexpected location
14	Female	47	20	0	1	4	No	Dorsum	Unexpected location
15	Female	51	12	2	1	3	No	Plantar	Rapid and extensive destruction
16	Female	59	19	6	1	4	No	Dorsum	Rapid and extensive destruction
17	Male	75	106	28	2	5	No	Plantar	Rapid and extensive destruction
18	Male	75	19	3	3	5	No	Fingers 2 to 5	Unexpected presentation
19	Male	61	28	3	1	3	No	Dorsum	Unexpected location
20	Male	66	40	6	2	6	No	Plantar	Rapid and extensive destruction
21	Male	60	71	3	3	7	No	Dorsum	Unexpected location
22	Male	64	63	16	3	8	No	Amputation site	Refractory ulcer
23	Male	75	5	1	2	4	No	Finger 1	Ulcer with rapid osteomyelitis
24	Male	65	63	24	4	15	Yes	Amputation site	Refractory ulcer
25	Male	66	12	5	2	5	No	Fingers 2 to 5	Unexpected presentation
26	Male	55	2	0	0	2	No	Finger 1	Ulcer with rapid osteomyelitis
27	Male	74	9	3	2	5	No	Malleolus	Refractory ulcer
28	Male	68	8	2	2	12	No	Finger 1	Ulcer with rapid osteomyelitis
29	Male	63	75	63	2	5	No	Dorsum	Unexpected location
30	Male	63	47	19	2	5	No	Plantar	Rapid and extensive destruction
31	Male	62	5	1	2	4	No	Fingers 2 to 5	Unexpected presentation
32	Male	65	7	1	2	4	No	Plantar	Rapid and extensive destruction
33	Male	51	3	1	1	3	No	Heel	Complicated ischemic/infectious
34	Male	62	12	3	2	8	No	Malleolus	Refractory ulcer
35	Male	63	7	0	1	3	No	Finger 1	Ulcer with rapid osteomyelitis
36	Male	63	77	11	2	5	No	Amputation site	Refractory ulcer
37	Male	63	44	8	2	5	No	Heel	Complicated ischemic/infectious
38	Male	59	8	0	1	4	No	Finger 1	Ulcer with rapid osteomyelitis
39	Male	58	7	4	1	3	No	Heel	Complicated ischemic/infectious
40	Male	61	3	0	1	3	No	Plantar	Rapid and extensive destruction
41	Male	62	59	16	2	6	No	Heel	Complicated ischemic/infectious
42	Male	71	1	0	0	2	No	Fingers 2 to5	Unexpected presentation

Abbreviation: MDT, Maggot debridement therapy.

first and second MDT sessions. We did not observe fever in our patients. Clinical outcomes are presented in Table 4.

Discussion

The outcome and duration of wound healing in atypical DFUs are broad; most of them lead to amputation or healing in a long time. In one study, the average time of a chronic atypical ulcer to heal has been 19 months (ranging from 2 to 120 months).[14] In this study, we evaluated the effectiveness of MDT application in atypical DFUs. A 6-week course of maggot therapy was associated with significant improvement in the healing process (83.3% of wounds healed completely). In another study on ischemic foot ulcers, Igari et al

Table 3. Baseline Characteristics of Patients.

	Female, N = 16	Male, N = 26	Total, N = 42
Age, years (mean ± SD)	53 ± 6.6	64 ± 5.9	59 ± 8.2
BMI, kg/m^2 (mean ± SD)	25.8 ± 2.3	26.3 ± 2.9	26.1 ± 2.7
HbA1c, mmol/L	6.92	7.77	7.36
DM duration, years (mean ± SD)	13.5 ± 6.2	15.1 ± 6.1	14.5 ± 6.1
Ulcer duration, months (mean ± SD)	7.8 ± 4.1	7.8 ± 6.5	7.8 ± 5.6
Ulcer size, cm^2 (mean ± SD)	22.31 ± 23.32	30.04 ± 30.59	27.1 ± 27.97

Abbreviations: SD, standard deviation; BMI, body mass index; DM, diabetes mellitus.

Table 4. Wound and Treatment Characteristics of Patients Treated With MDT.

Gender (N)	Initial Ulcer Size (cm^2)	Final Ulcer Size (cm^2)	MDT Duration in Months, Mean ± SD	Complications, n (%)		Outcome, n (%)		
				Chilling	Pain	Healed	Persist	Amputated
Female (N = 16)	22.31 (23.32)	6.88 (9.2)	1.81 ± 0.6	0 (0%)	4 (25%)	14 (87.5%)	1 (6.2%)	1 (6.2%)
Male (N = 26)	30.04 (30.59)	8.5 (13.62)	1.78 ± 0.09	2 (7.7%)	1 (3.8%)	21 (80.08%)	3 (11.5%)	2 (7.7%)
Total (N = 42)	27.1 (27.97)	7.88 (12.03)	1.79 ± 0.8	2 (4.8%)	5 (11.9%)	35 (83.3%)	4 (9.5%)	3 (7.1%)

Abbreviations: MDT, Maggot debridement therapy; SD, standard deviation.

reported that 63% of maggot-treated ulcers healed effectively. MDT saved lower limbs from amputation in another study.[15] However, maggot therapy was not effective in a limb with an ankle-brachial pressure index <0.6; thus, they suggested that for maggot therapy to work to its full potential, there must be adequate arterial blood supply.[16]

We observed a significant reduction in wound size after MDT. Bowling et al used MDT for methicillin-resistant *Staphylococcus aureus* (MRSA) colonized ulcers. Although they did not observe any significant reduction in size, 92% of MRSA colonization's was eliminated after 3 weeks of MDT.[17] It has been suggested that maggot secretions have bactericidal effects on both Gram-positive and Gram-negative bacteria including MRSA, *Pseudomonas aeruginosa* and *Escherichia coli*.[18]

In our study, granulation tissue was formed gradually and continuously during MDT. Marineau et al observed formation of robust granulation tissue in 17 out of 23 patients after MDT.[19] The maggots only consume the necrotic tissues and leave the viable tissues intact.[20] Furthermore, molecular studies have shown that the maggots secrete specific cytokines and growth factors which might play role in granulation tissue formation.[21]

All patients tolerated MDT well and there was no significant complication during the study. The above-mentioned studies have not reported any serious adverse events as well. Maggot therapy seems to be an inexpensive and safe method of wound debridement and boosts the wound healing process.

Besides above-mentioned findings, MDT efficiency is still a controversial subject. A recent meta-analysis on MDT for DFUs demonstrated that MDT is effective in achieving full healing, decreasing time to heal and amputation rate, and increasing number of antibiotic-free days. However, collated differences in the incidence of infection after MDT showed no significant difference between patients with and without MDT. The authors proposed that although the maggot therapy might be an effective and efficient treatment for diabetic patients with foot ulcers, the evidences are yet too weak to recommend MDT as a routine treatment.[22] Also, due to the absence of a standardized evaluation method, the assessment of the effects of MDT for the mentioned problems is difficult, thus MDT is not a well-established method yet.[10]

In conclusion, our findings suggest that MDT is an effective treatment for the atypical DFUs that are not adequately responsive to conventional therapies. MDT can be a safe, efficient, and inexpensive method in wound management, especially DFU healing process. The authors suggest further studies and RCTs with larger sample sizes and multi-arm designs to shed more light on MDT effectiveness.

Acknowledgments

We wish to thank all patients who participated in this study. We also like to thank Gholamreza Kabiri, MD, for his considerable help to activate MDT in our hospital; Mostafa Nikbakht, BS in Nursing, for his special hospitality to our patients; and Manijeh Siavash, nurse assistant for her kind help in management of the MDT clinic.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Deputy of Research, Isfahan University of Medical Sciences, Isfahan, Iran, supported the study.

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