Review Article

Journal of Clinical Review & Case Reports

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

Alaa Atamna* **and Avishay Elis**

[1]*Department of Internal Medicine C, Beilinson Hospital, Rabin Medical Center, Petah Tiqvaand Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv , Israel.*

***Corresponding author**
Alaa Atamna, MD. Department of Internal Medicine "C", Rabin Medical Center; Beilinson Hospital, Petah-Tiqva, 49100, Israel, E-mail: a.atamna86@gmail.com.

Submitted: 30 June 2017; **Accepted**: 07 Aug 2017; **Published**: 14 Aug 2017

Abstract

Diabetic foot ulcers are chronic, difficult to treat wounds that are associated with high morbidity andmortality. 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, itsuse had gradually faded. In the last years, MDT has re-emergedin 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-healingdiabetic foot ulcers.

Case presentation

A 67-year-old patientwas admitted because of long standing infected foot ulcer. His medical history includedpoorly controlleddiabetes 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 4cmX3cm ulcer at the planter aspect of the right foot, with worm and hyperemic area surrounding it. Signs of osteomyelitis werenot detected on foot X-RAY. Laboratory results revealed: white blood cells- 13000/mm^3, Hemoglobin 13.0 g/dl, platelets - 350000/mm^3, 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 repeatedsurgical debridement manipulations with concomitantempiric antibioticcourses,followed by10 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, includingvacuum assisted wound closure, hyperbaric oxygen therapy, growth factors, and MDT. MDT is an old-new treatment modality, whichwas 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-healingfoot 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 andduring 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 whowere swarmed with maggots had a pink granulation tissue without any sign of systemic infection. Further he used the technique to treatchronic 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 erathe technique was gradually neglected and its use fadedgradually [4-9].

The larvae life cycle

MDT uses sterile larvae of the common green bottle fly, (*Phaeniciasericata*) that are raised under controlled clinical conditions. *Phaeniciasericata* 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].

Maggotsremove 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, ammomiun bicarbonate and calcium carbonate which can alkalize wound bases and inhibit bacterial growth [18].

MDT was alsofound to have a synergistic effect on antibiotics. Arora *et al*. showed an enhanced antibacterial activity against staphylococcus aureus when ciprofloxacin was combined with maggots'execrations 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 secretionspromote fibroblast and keratinocyte migration, angiogenesis as well as enhancing vascular endothelial cell migration. In addition, they enhancemonocyte and macrophage growth factor production in theform of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), both of which stimulateendothelial 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 responsesof 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 beenreported, including mild febrile reactionsafter applying larvae to the wound. Other adverse events include ethicalissuesconcerning patient recruitment and staff acceptances, as well as larvae escape when inappropriate dressing is applied [25].

MDT clinical use

Clinical studies

Severalclinical 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 1: Summary of the reported literature on the clinical implication of MDT in the past decade.

Author	Study design	Sample size	Year	Country	Intervention and control	Outcomes
Sun *et al*. [25]	Meta-analysis	840	2014	China	MDT/ Hydrogel therapy	Time to healing, Healing rate
Markevich *et al*. [26]	RCT	140	2000	Israel	MDT/ Hydrogel therapy	Healing rate
Sherman *et al*. [27]	Retrospective	18	2003	USA	MDT Surgical and non-surgical therapy	Healing rate, Timetohealing; antibiotic usage
Wang *et al*. [28]	Retrospective	43	2010	China	MDT/ Conventional	Timetohealing
Gilead *et al*. [29]	Retrospective	435	2012	Israel	MDT	Time to healing, healing rate
Armstrong *et al*. [30]	Prospective	60	2005	USA	MDT	Healingrate;timetohealing; incidence ofinfection; amputation rate; antibiotic- freedays
Tantawi *et al*. [27]	Prospective	10	2007	Egypt	MDT	Healing rate

Marineauet al. [28]	Prospective	23	2011	Hawaii	MDT	Healing rate
Paul *et al*. [29]	Prospective	29	2009	Malaysia	MDT/ Surgical debridement	Healingrate; amputationrate; antibiotic usage
Wilasrusmee *et al*. [30]	Meta-analysis	111	2013	Thailand	MDT/ Conventional	Healing rate
Tian *et al*. [35]	Meta-analysis	356	2013	China	MDT/ Conventional	Healingrate, amputation rate, time to healing, number of antibiotic-free days
Zarchi and Jem *et al* [36]	Systematic review	637	2012	Denmark	MDT/ hydrogel or a mixture of conventional therapy (hydrocolloid, hydrogel and saline moistened gauze)	Time to debridement, Time to heal

To date, the only randomized controlled trial is the one conducted by Markevich *et al*. [26]. Itincluded 140 patients who were randomly assigned to receive eitherhydrogel therapyor 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 studythat 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 tissuewere observed. MDTwas 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 byMDT, All ulcers healed completely. The time duration in days that was taken to achieve bacterial negativity, granulationand healing of diabetic foot ulcerswere 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*. assessedat 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 groupwith 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]. Marineauet 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-analysisand 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 timein 195 patients pooled from four studies (Pooledstandardized 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. ondiabetic foot ulcer patients, whowere treated with MDT or conventional wound therapy, showed thatwound healingwas 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 ofwound 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 tothe control group in the percentage of achievingfull 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].

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 thanhydrogel or a mixture of conventional therapy modalities, including hydrocolloid, hydrogel and saline moistenedgauze [36].

Conclusion

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

References

1. Lipsky BA (1997) Osteomyelitis of the foot in diabetic patients. Clin Infect Dis 25: 1318-1326.
2. Boulton AJ (2004) The diabetic foot: from art to science. The 18th Camillo Golgi lecture 47: 1343-1353.
3. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, et al. (2004) Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 39: 885-910.
4. Manring MM, Calhoun JH (2011) Biographical sketch: William S. Baer (1872-1931). Clin Orthop Relat Res 469: 917-919.
5. Baer WS (2011) The classic: The treatment of chronic osteomyelitis with the maggot (larva of the blow fly). 1931. Clin Orthop Relat Res 469: 920-944.
6. Pechter EA, Sherman RA (1983) Maggot Therapy: The Surgical Metamorphosis. Plastic Recon. Surgery 72: 567-570.
7. Thomas S, Jones M, Shutler S, Jones S (1996) Using Larvae in Modern Wound Management. Journal of Wound Care 5: 60-69.
8. Thomas S, Jones M, Shutler S, Andrews A (1996) All You Need to Know About Maggots. Nursing Times 92: 63-76.
9. Fine A, Alexander H (1934) Maggot therapy, technique and clinical application. J Bone Joint Surg Am 16: 572 -582.
10. Wollina U, Karte K, Herold C, Looks A (2000) Biosurgery in wound healing-the renaissance of maggot therapy. J Eur Acad Dermatol Venereol 14: 285-289.
11. Strohal R, Dissemond J, Jordan O' Brien J, Piaggesi A, Rimdeika R, et al. (2013) An updated overview and clarification of the principle role of debridement. J Wound Care 22: S1-S52.
12. Chan DC, Fong DH, Leung JY, Patil NG, Leung GK (2007) Maggot debridement therapy in chronic wound care. Hong Kong Med J 13: 382-386.
13. Shi E, Shofler D (2014) Maggot debridement therapy: a systematic review. Br J Community Nurs Suppl Wound Care: S6-13.
14. Rafter L (2013) Using larval therapy in the community setting. Br J Community Nurs Suppl: S20, S22-25.
15. Tanyuksel M, Araz E, Dundar K, Uzun G, Gumus T, et al. (2005) Maggot debridement therapy in the treatment of chronic wounds in a military hospital setup in Turkey. Dermatology 210: 115-118.
16. Sherman RA (2009) Maggot therapy takes us back to the future of wound care: new and improved maggot therapy for the 21st century. J Diabetes Sci Technol 3: 336-344.
17. Margolin L, Gialanella P (2010) Assessment of the antimicrobial properties of maggots. Int Wound J 7: 202-204.
18. Prete PE (1997) Growth effects of Phaeniciasericata larval extracts on fibroblasts: mechanism for wound healing by maggot therapy. Life Sci 60: 505-510.
19. Arora S, Baptista C, Lim CS (2011) Maggot metabolites and their combinatory effects with antibiotic on Staphylococcus aureus. Ann Clin Microbiol Antimicrob 10: 6.
20. Horobin AJ, Shakesheff KM, Pritchard DI (2005) Maggots and wound healing: an investigation of the effects of secretions from Luciliasericata larvae upon the migration of human dermal fibroblasts over a fibronectin-coatedsurface. Wound Repair Regen 13: 422-433.
21. Bexfield A, Bond AE, Morgan C, Wagstaff J, Newton RP, et al. (2010) Amino acid derivatives from Luciliasericata excretions/secretions may contribute to the beneficial effects of maggot therapy via increased angiogenesis. Br J Dermatol 162: 554-562.
22. Van der Plas MJ, Baldry M, van Dissel JT, Jukema GN, Nibbering PH (2009) Maggot secretions suppress pro-inflammatory responses of human monocytes through elevation of cyclic AMP. Diabetologia 52: 1962-1970.
23. van der Plas MJ, van der Does AM, Baldry M, Dogterom-Ballering HC, van Gulpen C, et al. (2007) Maggot excretions/secretions inhibit multiple neutrophil pro-inflammatory responses. Microbes Infect 9: 507-514.
24. Cazander G, Pritchard DI, Nigam Y, Jung W, Nibbering PH (2013) Multiple actions of Luciliasericata larvae in hard-to-heal wounds: larval secretions contain molecules that accelerate wound healing, reduce chronic inflammation and inhibit bacterial infection. Bioessays 35: 1083-1092.
25. Sun X, Jiang K, Chen J, Wu L, Lu H, et al. (2014) A systematic review of maggot debridement therapy for chronically infected wounds and ulcers.Int J Infect Dis 25: 32-37.
26. Markevich YO, Mcleod-Roberts J (2000) maggot therapy for diabetic neuropathic foot wounds: a randomized study. Paper presented at 36th annual meeting of the European association for the study of diabetes, Jerusalem, Israel.
27. Sherman RA (2003) Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. Diabetes Care 26: 446-451.
28. Wang SY, Wang JN, Lv DC, Diao YP, Zhang Z (2010) Clinical research on the bio-debridement effect of maggot therapy for treatment of chronically infected lesions. Orthop Surg 2: 201-216.
29. Gilead L, Mumcuoglu KY, Ingber A (2012) The use of maggot debridement therapy in the treatment of chronic wounds in

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

30. Armstrong DG, Salas P, Short B, Martin BR, Kimbriel HR, et al. (2005) Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. J Am Podiatr Med Assoc 95: 254-257.
31. Tantawi TI, Gohar YM, Kotb MM, Beshara FM, El-Naggar MM (2007) Clinical and microbiological efficacy of MDT in the treatment of diabetic foot ulcers. J Wound Care 16: 379-383.
32. Marineau ML, Herrington MT, Swenor KM, Eron LJ (2011) Maggot debridement therapy in the treatment of complex diabetic wounds. Hawaii Med J 70: 121-124.
33. Paul AG, Ahmad NW, Lee HL, Ariff AM, Saranum M, et al. (2009) Maggot debridement therapy with Luciliacuprina: a comparison with conventional debridement in diabetic foot ulcers. Int Wound J 6: 39-46.
34. Wilasrusmee C, Marjareonrungrung M, Eamkong S, Attia J, Poprom N, et al. (2014) Maggot therapy for chronic ulcer: a retrospective cohort and a meta-analysis. Asian J Surg 37: 138-147.
35. Tian X, Liang XM, Song GM, Zhao Y, Yang XL (2013) Maggot debridement therapy for the treatment of diabetic foot ulcers: a meta-analysis. J Wound Care 22: 462-469.
36. Zarchi K, Jemec GB (2012) The efficacy of maggot debridement therapy-a review of comparative clinical trials. Int Wound J 9: 469-477.