Maggot debridement therapy for the treatment of diabetic foot ulcers: a meta-analysis

• **Objective:** To assess the potential efficacy of maggot debridement therapy (MDT) compared with standard care for diabetic foot ulcers (DFUs).

• **Method:** A meta-analysis was performed on the evidence for MDT for DFUs. Databases, including PubMed, Web of Science, the Cochrane Library, EMbase, EBSCOhost, Springer Link, ScienceDirect and Ovid-Medline, were electronically searched for randomised controlled trials, case-control studies and controlled clinical trials, up to 31 December 2012, and relevant references of the included articles were also manually searched. The literature was screened, the data were extracted and the methodological quality of the included studies was assessed. Meta-analyses were performed on the included data, for the outcomes healing rate, time to healing, incidence of infection, amputation rate and antibiotic-free days or antibiotics usage.

• **Results:** Overall, four studies comparing MDT with standard therapy on a total of 356 participants were included. The results of meta-analyses suggested that the MDT group was significantly superior to the control group in the percentage of DFUs to achieve 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); however, collated differences in incidence of infection after intervention revealed no evidence of a difference between the MDT and control groups (RR=0.82, 95%CI=0.65; 1.04, p=0.10).

• **Conclusion:** Although MDT may be a scientific and effective therapy in treatment of DFUs, the evidence is too weak to routinely recommend it for treatment. Large studies and sample sizes are needed to assess the efficacy and safety of MDT in the treatment of DFUs.

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maggot debridement therapy, diabetic foot ulcer, infection, meta-analysis

People with diabetes have a 12–25% lifetime risk of developing a foot ulceration,[1,2] while about 6% of people with diabetes have had foot ulceration in the UK.[3] Diabetic foot ulcers (DFUs) have been associated with higher mortality[4] and reduced quality of life.[5,6,7]

The annual cost of treatment and care for diabetic foot ulcers (DFUs) in the UK was estimated as £17 million in 1994,[8] while the cost attributable to caring for a DFU during the 2–3 years after diagnosis is about $28 000 in the USA.[9] In 2012, a report from the London School of Economics estimated that, in total, £14 billion was spent on treating diabetes and its complications every year, with the cost of complications of diabetes around 3–4 times higher than the cost of prescribing diabetes medication.[10]

The removal of devitalised tissue is an essential component of DFU care,[11] as the 'necrotic burden', supported by devitalised tissue, impedes the healing process. Although the natural process of wound debridement, known as autolytic debridement, is considered the safest method of debridement,[12] it can be slow and is not always the most beneficial treatment for progressing a wound towards healing.[13] If the process of debridement is accelerated, healing may be achieved more quickly.[14] A large number of specialists assert that health professionals have the power to alter outcomes by choosing a more appropriate intervention, and that this should be based on their assessment of patient need[15] and the TIME (tissue, infection/inflammation, moisture balance and edge of wound) concept.[16]

Maggot debridement therapy (MDT), also known as maggot therapy, larvae therapy, larval therapy, biodebridement and biosurgery, has a long history of use in the treatment of chronic and infected wounds.[17–20] MDT is a form of mechanical debridement, whereby live maggots, raised in sterile conditions, usually *Lucilia sericata* (common green bottle fly), are placed on necrotic/sloughy wounds.[21] The treatment became popular in the USA, in the 1920s and 1930s, when Baer[17] and others successfully treated several cases of osteomyelitis.[22–26]

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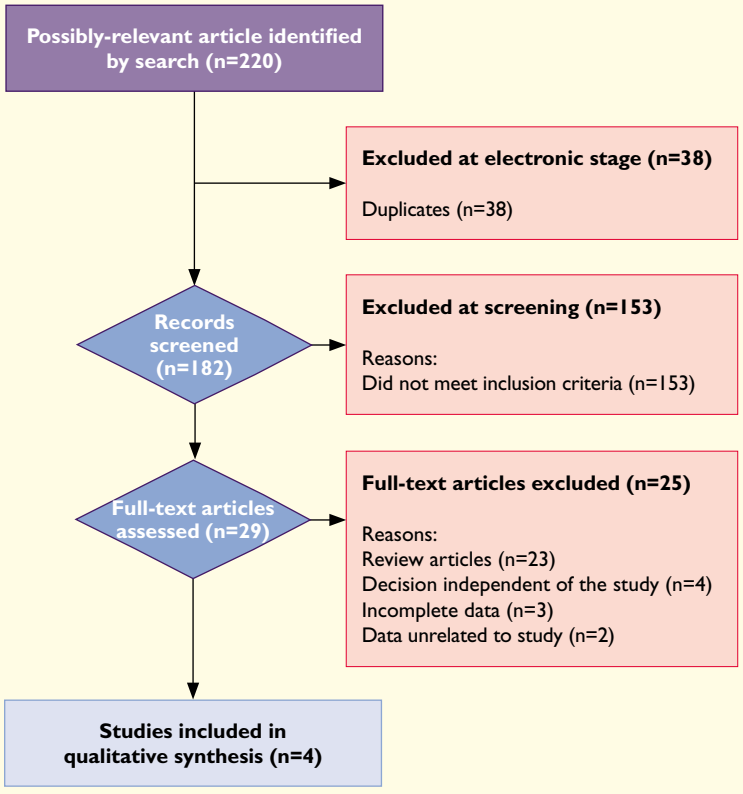
In recent years, the MDT is re-emerging, due to the rise in chronic wounds and the emergence of antibiotic resistant strains of bacteria, such as meticillin-resistant *Staphylococcus aureus* (MRSA).[27,28] Some divergence has emerged in the medical society regarding the curative effect of MDT and other interventions.[29] Therefore, the objective of this article was to assess the potential efficacy of MDT in patients with DFUs.

Using the PICO acronym (population, intervention comparison and outcome), the population of interest was patients with DFUs, in any health-care setting; the intervention was MDT compared with standard therapy, and the outcomes of interest were healing rate, time to healing, incidence of infection and the rate of amputation.

Method

Seven electronic databases were searched for articles published up to 31 December 2012, including PubMed, the Cochrane Library, EMbase, EBSCOhost Online Research Databases, Springer Link, ScienceDirect, Web of Science and Ovid Medline. The following search terms were used: ['maggot debridement therapy' OR 'maggot therapy' OR 'MDT' OR 'larva* therapy' OR 'biodebridement' OR 'biosurgery'] AND ['diabetic foot' OR 'diabetic feet' OR 'foot, diabetic' OR 'feet, diabetic'] AND ['random*']. The reference lists of selected articles were also hand searched to identify any relevant articles.

Fig 1. Article retrieval and screening



Selection criteria

Randomised controlled trials (RCTs), controlled clinical trials and case-controlled studies in which MDT was used for the treatment of DFUs were considered for inclusion in the meta-analysis. Classification of DFUs in people with diabetes consists of neuropathic, ischaemic and neuroischaemic, depending on the relative contributions of the diabetic complications of peripheral neuropathy and arterial disease underlying the ulcer.[30] For this meta-analysis, there were no requirements regarding definition of DFUs or classification of the wound (such as the six-grade Wagner-Meggitt classification). Non-ambulatory patients were also eligible. The following measured outcomes were included:

- Healing rate
- Time to healing
- Incidence of infection
- Amputation rate
- Antibiotic-free days or antibiotics usage.

Trials involving simultaneous MDT and standard treatment, and mixed-aetiology foot ulceration were excluded. Only English-language articles were eligible for inclusion.

Data extraction and quality assessment

Searches were conducted and data extracted by two independent searchers (XT and XML). Each trial identified in the search was evaluated for design, patient eligibility criteria and outcome measures. Any disagreement between searchers concerning the eligibility of a trial was resolved by consulting a third searcher (GMS or YZ). Duplicate studies and records were excluded based on screening of titles and abstracts. All remaining articles were screened in full text.

Quality assessment of the trials included in the study was conducted by each searcher according to the Cochrane Handbook for Systematic Reviews of Interventions.[31]

Outcome measures

The outcome measures of interest were: the healing rate of DFUs, defined as either full re-epithelialisation or according to the University of Texas Medical Branch (UTMB) grading system; time to healing; incidence of infection, diagnosed based on bacterial colonisation of DFU swab results; and rate of amputation. Use of antibiotics between the two groups was also analysed.

Statistical analysis

The ratio of healed ulcers, amputated limbs, infected ulcers and time to heal were calculated for patients treated with MDT versus controls. Homogeneity

Table 1. Characteristics of the trials identified and included in the quantitative synthesis

Author	Country	Age (years)	No. of patients	Interventions		Methods	Outcomes
				MDT	Controls		
Markevich et al.[32] (2000)	Israel	53.6 ± 15.4	140 (70/70)	Larval therapy	Hydrogel	RCT	Complete healing
Sherman[33] (2003)	America	N/S	28* (14/14)	MDT	Conventional therapy	Retrospective case-control	Complete healing; Time to healing
Paul et al.[34] (2009)	Malaysia	30.0 ± 69.2 32.0 ± 82.5	54 (25/29)	MDT with *L. cuprina* and subcutaneous insulin	Surgical debridement and subcutaneous insulin	Prospective case-control	Complete healing; Antibiotic usage; Amputation
Armstrong et al.[35] (2005)	England	71.7 ± 6.8 72.7 ± 6.8	60 (30/30)	MDT	Standard wound care	Case-control	Complete healing; Time to healing; Incidence of infection; Antibiotic usage; Amputation

* Six wounds were treated with MDT, six with standard therapy and eight with standard therapy then MDT, so the sample is 14 in each group

Fig 2. Comparison of healing rates

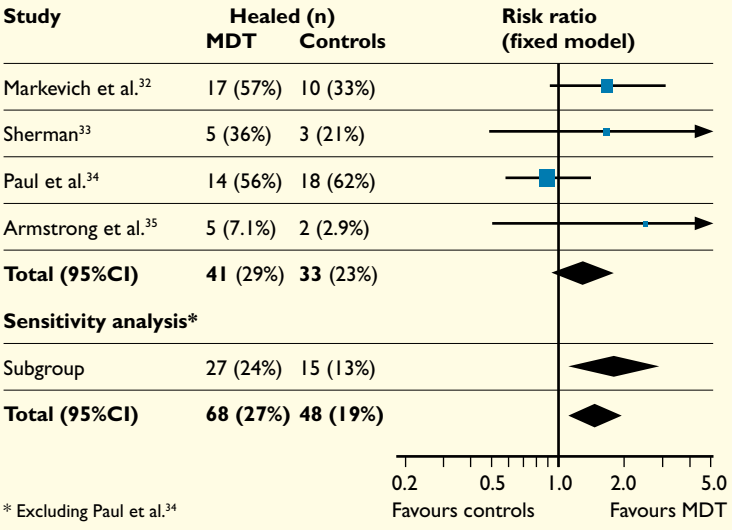
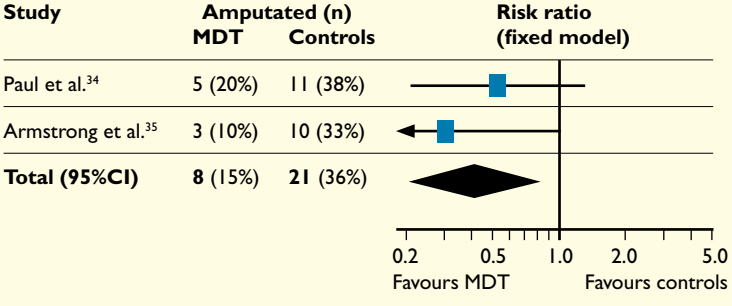


Fig 3. Comparison of amputation rates



in the included studies was evaluated using the I^2 statistic. If I^2 was ≥50%, the trials were considered to be heterogeneous and a random effects model was selected. If I^2 was <50%, the studies were considered to be homogeneous and a fixed effects model was used.

Summary statistics of the differences in the ratio or mean were calculated for the individual studies using two-sided Student's t-tests. A p-value<0.05 was considered to indicate statistical significance. Sensitivity analysis was conducted based on leave-one-out cross validation, using a single observation from the original sample as the validation data, and the remaining observations as the training data. All analyses were performed using the Comprehensive Meta-Analysis statistical software (v5.2.0; BioStat).

Results

A total of 220 trials were assessed in the initial literature search, with four studies,[32–35] involving a total of 356 participants, meeting the inclusion criteria and included in the final analysis. The flow diagram of literature retrieval and trial selection is given in Fig 1.

Trial characteristics

A total of 356 participants were included in the four studies, consisting of 180 participants in the MDT group and 176 participants in the standard-treatment group. The main characteristics and outcomes from each individual trial are recorded in Table 1. One study was reported in abstract form only;[32] however, detailed efficacy data was available via a secondary publication.[29] In the Sherman study,[33] 18 patients with 20 DFUs were treated. Six patients were treated

with MDT, six with standard treatment and eight with standard treatment first, followed by MDT; therefore, for the purposes of this analysis, the sample size was 14 (6+8) in both groups.

Healing rate

All of the trials reported the healing rate for treatment of DFU from the MDT group and control group, respectively. Two trials[34,35] (n=54 and n=60, respectively) reported complete healing of both the MDT and control groups. All four trials were included in the meta-analysis examining the effect of MDT on foot ulceration in patients with diabetes mellitus. There was homogeneity in the complete healing after intervention among the four studies (χ^2=4.23, I2=29%); therefore, a fixed-effects model of analysis was used. Pooled differences in complete healing after intervention revealed no evidence of a difference between the MDT and control groups (relative risk [RR]=1.33, 95% confidence interval [CI]=0.94; 1.88, p=0.11; Fig 2).

However, one of the four trials[34] defined the concept of complete healing differently from the other trials (defined as UTMB grading system), which may have resulted in an error when collating the outcomes. A sensitivity analysis, based on leave-one-out cross validation, was conducted, which demonstrated a difference between the results of Paul et al.[34] and the remaining studies.[32,33,35] The collated outcomes of the remaining studies supported the hypothesis, revealing a statistically significant difference between MDT and control groups in terms of healing (RR=1.80, 95%CI=1.07; 3.02, p=0.03; Fig 2).

Amputation rate

Two trials[34,35] reported the amputation rate in the MDT and control groups; both trials were included in the meta-analysis, examining the effect of MDT on amputation in patients with DFUs. The amputation rates after intervention among the two studies were homogeneous (χ^2=0.55, I^2=0%); therefore, a fixed-effects model of analysis was used. Collated differences in amputation rate after intervention revealed a significant difference between the MDT and control groups (RR=0.41, 95%CI=0.20; 0.85, p=0.02; Fig 3).

Incidence of infection

Two studies[34,35] reported the incidence of infection in the MDT and control groups; both trials were included in the meta-analysis. The recorded incidence of infection after invention in the two studies was homogeneous (χ^2=0.67, I^2=0%); therefore, a fixed-effects model of analysis was used. Pooled differences in incidence of infection after intervention revealed no evidence of a difference between the MDT and control groups (RR=0.82, 95%CI=0.65; 1.04, p=0.10; Fig 4).

Fig 4. Comparison of incidence of infection

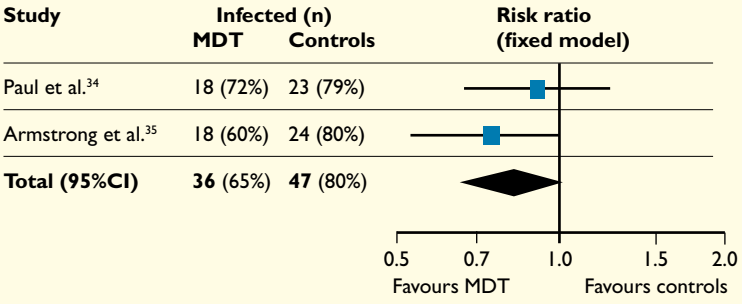
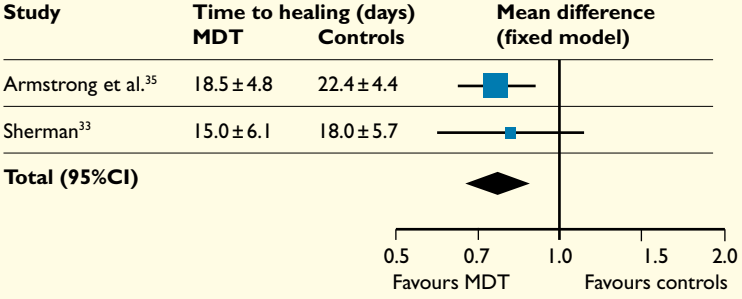


Fig 5. Comparison of time to healing



Time to healing

Two trials[33,35] reported total time to healing for the MDT and control groups; both studies were included in the meta-analysis. Time to healing was homogeneous between the two studies (χ^2=0.13, I^2=0%); therefore, a fixed-effects model of analysis was used. Collated differences in time to healing after intervention revealed a significant difference between the MDT and control groups (RR=–3.70, 95%CI=–5.76; –1.64, p=0.0004, Fig 5).

Antibiotic usage

Two of the studies[34,35] reported use of antibiotics in the MDT and control groups. As the method of recording this information differed between the studies, the results could not be collated. To analyse this aspect, descriptive analysis was used. In one of the studies, 96% (n=24) of participants were prescribed antibiotics to prevent infection;[34] this proportion was significantly lower than in the control group (97%, n=28; p<0.05). The other trial[35] reported the number of antibiotic-free days; this outcome revealed that the mean number of antibiotic-free days in the MDT group was significantly greater than in the control group (126.8±30.3 days vs 81.9±42.1 days; p=0.001).

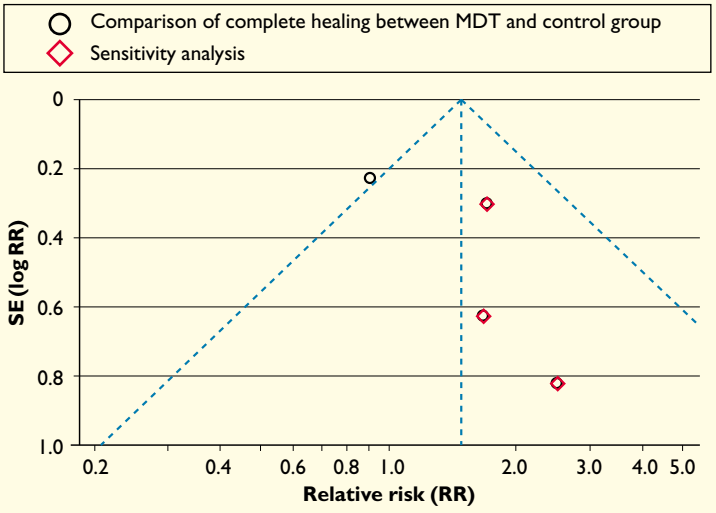
Quality assessment

A total of four trials were included in this study. Only one of the trials was an RCT;[32] however, there

Fig 6. Risk of bias summary: authors' judgments about each risk of bias item for each included study

	Paul et al., 2009	Armstrong et al., 2005	Markevich et al., 2000	Sherman, 2003
Random sequence generation (selection bias)	?	?	?	?
Allocation concealment (selection bias)	—	?	—	—
Blinding of participants and personnel (performance bias)	—	?	—	—
Blinding of outcome assessment (detection bias)	—	?	—	—
Incomplete outcome data (attrition bias)	?	?	?	+
Selective reporting (reporting bias)	?	?	?	+
Other bias	?	?	?	?

Fig 7. Funnel plot of publication bias



was
not adequate sequence generation or allocation concealment, and it did not address incomplete outcome data or other potential bias. The remaining three trials were case-controlled studies. Additionally, the baseline was unclear in one of the trials.[32] The quality assessment outcome is summarised in Fig 6.

Publication bias

A funnel plot was performed on all included studies to determine publication bias from the literature. The analysis outcome showed asymmetry (Fig 7), which suggests publication bias possibly exists in the included trials.

Discussion

MDT is approved by the Food and Drug Administration (FDA) and registered in the USA under the FDA section 510(k).[16] It was used widely in medical treatment before antibiotics were discovered.[36] MDT consists of the application of sterile fly maggots, usually *Lucilia sericata*, to a wound, construction of an enclosure around the treatment, and removal and replacement of maggots every 48–72 hours.[37,38] Different mechanisms of wound healing by MDT have been suggested, including:[39]

- Liquefaction of necrotic tissue by secretion of proteolytic enzymes
- Digestion of necrotic tissue as food by larvae; mechanical washing out of bacteria by the serous exudate caused by the irritating effect of maggots in the wound
- Destruction of bacteria in the alimentary tract of the maggots, and in the wound, by their excretions, which contain antibacterial substances
- Change in the wound of an acidic pH to a beneficial alkaline pH as a result of the ammonia and calcium carbonate excreted by the maggots
- Secretion by the maggots of substances with healing properties, such as allantoin and urea
- Formation of granulation tissue resulting from mechanical stimulation of viable tissue caused by the continuous crawling of the larvae and the excretion of growth-stimulating factors.

To our knowledge, this is the first meta-analysis to evaluate the effectiveness of MDT for treating DFU. Definition of complete healing was inconsistent among the four trials, and sensitivity analysis revealed that the data from the Paul et al. study[34] influenced the analysis for the collated outcomes. This lack of consistency was reflected in the finding that there was no evidence of a difference between healing rates for MDT compared with standard treatment (p=0.11). The consistent finding from the remaining three trials was that MDT resulted in a significantly greater proportion of patients to achieve complete healing compared with the control group (p=0.03).

The findings of this meta-analysis suggest that MDT may be more effective than standard treatment interventions, decreasing the time to healing and the rate of amputation for DFUs; however, there was no evidence that MDT reduces the incidence of infection compared with standard care.

Limitations

There are a number of limitations to this meta-analysis, that need to be acknowledged. Firstly, and perhaps most notably, only a small number of trials

met the inclusion criteria, thus reducing the power of the analyses. Only English-language literature was considered for publication, so it is possible that other relevant trials may have been identified, if the search had been extended to literature in other languages.

In one study,[34] *Lucilia cuprina* was used rather than *Lucilia sericata*, but the curative effect is considered to be closely related.[16] Furthermore, the Markevich study was only available as an abstract, but detailed efficacy data was obtained via a secondary publication.[29] The small sample and the differences in classification of participants and study methods among the trials included may have affected the outcomes of the meta-analyses. For example, some of the studies involved diabetic neuropathic foot ulcers,[32,35] and the study by Markevich et al. had a duration of only 10 days. The differences in wound aetiology and tge methodological heterogeneity could have led to some bias in the meta-analysis.

Conclusion

There is insufficient high-quality evidence available in the current literature regarding the effectiveness of MDT for the treatment of DFUs. Hence, the findings from this meta-analysis are by no means definitive. Nevertheless, the findings suggest that MDT may be more effective in increasing healing rate and antibiotic-free days, and decreasing rate of amputation and time to healing compared with control interventions. There is a need for high-quality RCTs to clarify the effectiveness of MDT for the treatment of DFUs. ■

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