Review paper

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The potential use of *Lucilla sericata* larvae in the local treatment of wounds in diabetic foot syndrome – a literature review

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Abstract

Introduction: The increasing prevalence of diabetes poses a heightened risk of vascular complications in the lower limbs. The costs associated with wound management are substantial, accounting for approximately 1-3% of total healthcare expenditures in developed countries. Implementing and maintaining preventative, interdisciplinary, and comprehensive care have become prioritized objectives for scientific societies.

Aim of the study: This study conducts a literature review and analysis concerning the application of *Lucilia sericata* larvae in the local treatment of wounds in diabetic foot syndrome.

Material and methods: Literature analysis spanning from 2012 to 2023 was conducted, utilizing PubMed and Termedia databases with key words such as diabetic foot ulcer, *Lucilia sericata*, and maggot debridement therapy. Exclusion criteria comprised studies that treated wounds locally using methods other than larval therapy.

Conclusions: Larval therapy in patients with diabetic foot syndrome accelerates wound debridement by stimulating reparative processes within the wound. The use of *Lucilia sericata* larvae may contribute to the reduction of antibiotic therapy duration, decreased hospitalization rates, and lowered amputation risks.

Key words: maggot debridement therapy, diabetic foot ulcer.

Introduction

The increasing average lifespan in developed societies, low physical activity, and the obesity epidemic are the primary predisposing factors for the development of diabetes and atherosclerosis. Impaired tissue perfusion and oxygenation lead to the formation of chronic wounds and tissue destruction, resulting in self-care limitations, frequent hospitalizations, the risk of amputation, and higher mortality rates [1, 2]. The occurrence of skin and subcutaneous tissue destruction in the lower limbs in the course of vascular diseases (diabetic foot ulcer – DFU, peripheral arteriosclerosis disease – PAD, chronic venous insufficiency – CVI) is a global problem affecting an ever-growing population of chronic patients. The increasing number of individuals with diabetes, estimated at around 500 million worldwide, means that one-third of them will experience a hard-to-heal wound during their lifetime. Therapeutic strategies and challenges in maintaining continuous care for these patients constitute major areas of focus for national and global scientific societies. The low awareness of prevention and prehabilitation in this patient group contributes to an increased risk of infection, prolonged treatment duration, and, ultimately, limb loss [3]. According to research conducted by Wukich *et al.*, patients with diabetes are significantly more concerned about amputation than death; limb loss is associated with disability and loss of bodily integrity [4]. Based on the International Working Group on the Diabetic Foot (IWGDF) definition, Diabetic Foot Ulcer (DFU) is the disruption of skin continuity, accompanied by infection and tissue destruction in patients with diabetes, along with concomitant neuropathy and/or PAD. The majority of amputations are preceded by tissue damage in the foot. It is estimated that limb loss may affect up to half of this group, increasing the risk of death within 5 years [5]. Armstrong *et al.* estimated that the lifetime probability of developing a hard-to-heal wound is 19-34%. The risk of ulcer recurrence is high, with 40% of patients experiencing it within a year, and amputations are performed in up to 25% of patients with hard-to-heal wounds in DFU [6-8]. It is estimated that 10-25% of the diabetic population has diabetic foot ulcers. Over 50 million people will have DFUs by 2030 [9-11]. The 5-year mortality rate for major amputations averages 56.6%. These results were compared to the mortality reported for all cancers, which was 31%. Ischemia likely accounts for only 10% of DFUs, while 90% are due to neuropathy, occurring either independently or in combination with ischemia, foot deformities, and gait instability, increasing the risk of tissue damage within the foot. Complications in the course of DFU are considered a major cause of disability worldwide, significantly prolonging hospitalization periods and, consequently, increasing healthcare expenses [12, 13]. Experts emphasize the need for comprehensive, interdisciplinary care to improve the quality of life for patients. Broadly defined primary prevention, the development of a network of highly specialized facilities for treating diabetes complications using endovascular techniques and vascular surgery, and wound management utilizing recommended methods and techniques, are all long-term future plans being pursued [14]. Implementing such strategies aims to minimize complications in the course of DFU, a leading cause of disability worldwide, significantly extending treatment periods and increasing healthcare costs [12, 13, 15]. This initiative, known as the "Kazimierz Declaration", was launched during the conference of the Polish Wound Management Association (Polskie Towarzystwo Leczenia Ran – PTLR) in June 2023, and it received widespread support from numerous practitioners and experts specializing in the field of hard-to-heal wounds.

The costs of wound treatment are high, accounting for approximately 1-3% of total healthcare expenditures in developed countries [16-18]. The frequency of hard-to-heal wounds varies and depends on several factors influencing the state of the observed group (sample), especially age, self-care capabilities, and clinical condition. Data from the United States indicate that over 2% of the population, nearly 5.7 million people with chronic wounds, represents a financial burden of approximately $20 million [19]. This issue is encountered in most healthcare systems, with a higher frequency in developing countries, where the number of amputations is significantly higher due to the distribution of diabetic patients and pre-diabetic conditions.

The dynamic development of medicine through the provision of drugs, products, and modern therapies aims to improve the quality of life for patients by minimizing potential complications. The presence of hard-to-heal wounds in diabetic patients contributes to reduced productivity, increased work absenteeism, predisposing to social isolation, and widespread suffering. Efforts should be made to minimize the duration of wound treatment and mitigate factors that disrupt this process [20]. The Polish society ranks among the European leaders in terms of the incidence and morbidity of vascular diseases. The treatment of DFU requires a multidisciplinary approach and combined therapy due to the high degree of clinical problem diversity, both at the time of ulcer occurrence and in terms of prevention [21, 22].

The aim of this study is to review the literature on the use of *Lucilia sericata* larvae for debridement and stimulation of reparative processes in diabetic foot syndrome.

Material and methods

A critical literature analysis was conducted spanning the years 2012-2023, utilizing PubMed and Termedia databases, based on the following keywords: *diabetic foot ulcer*, *Lucilia sericata*, and *maggot debridement therapy*. Selected volumes were limited to English and Polish languages. Works discussing the utilization of MDT in the treatment of diabetic foot ulcers of various etiologies were considered. Manuscript evaluation focused on issues pertaining to debridement, larval defensin activity, reduction in antibiotic therapy, amputation prevention, wound healing processes, and healing time. Exclusion criteria encompassed studies involving localized wound treatment using alternative forms of therapy, including acute and surgical therapies, in vitro or animal studies, case studies, reports, or articles involving fewer than 10 participants (Fig. 1).

As a result of keyword preselection, 11,380 volumes were identified for the term "diabetic foot ulcer", from which 36 publications were selected for the development of the research concept (randomized studies: 2; meta-analyses 2; literature reviews: 8; original papers: 22). The process of selecting works is presented in Figure 1. The acquired data were organized and presented in subsections: local wound management in the debridement phase, larval therapy of diabetic foot syndrome, antimicrobial activity of *Lucilia sericata* larvae, and stimulation of reparative processes in larval wound therapy.

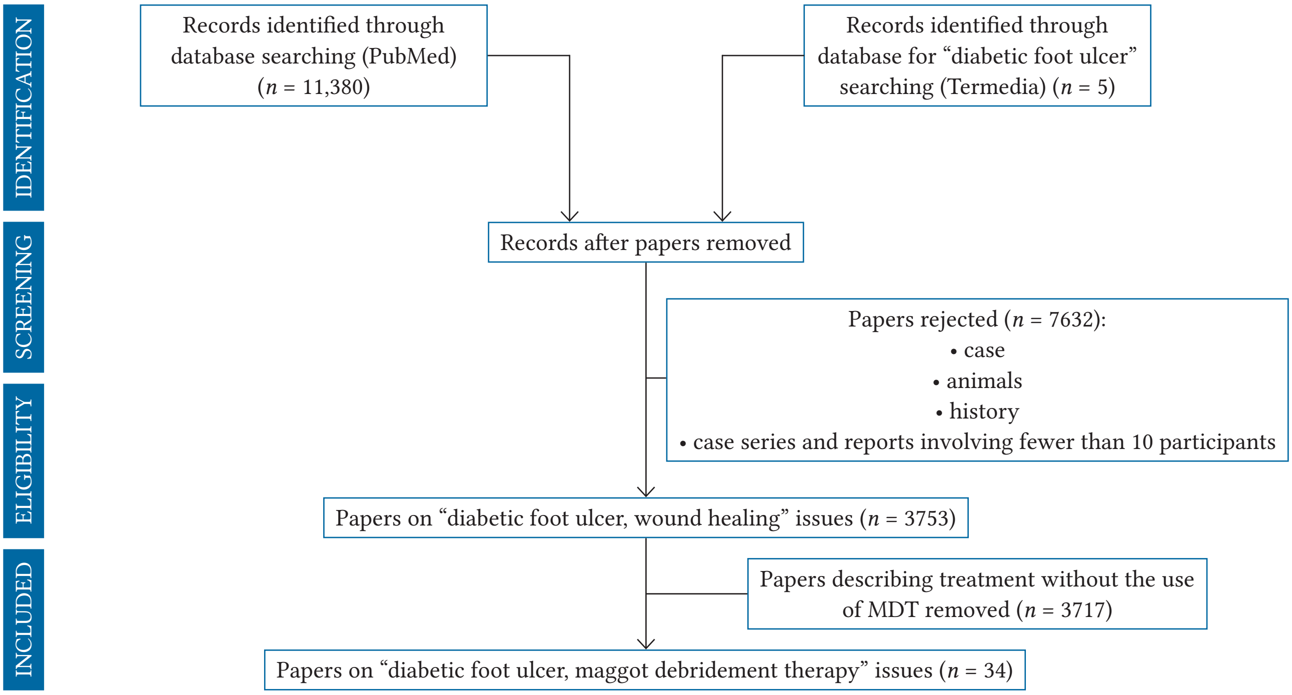

Figure 1. Protocol for the inclusion of works in the literature review

Local wound management in the debridement phase

Diabetes mellitus (DM) is a chronic endocrinological disease characterized by hyperglycemia resulting from disrupted insulin production within the body. The care and treatment of individuals with diabetes should be carried out by an interdisciplinary team based on established clinical guidelines [5, 14]. Education, lifestyle modification, and promotion of health-related activities constitute fundamental educational measures preceding the multispecialty treatment, which may encompass revascularization procedures, surgical interventions, orthopedics, skin grafting, and soft tissue reconstruction. Managing comorbid conditions and controlling diabetes represent the second pillar of comprehensive patient care [23]. Fernando *et al.* suggest that a multidisciplinary team approach can reduce amputation rates and lead to an improved quality of life for patients with diabetic foot ulcers (DFU) [24]. Hard-to-heal wounds in the context of diabetic foot syndrome are characterized by complex pathology, stemming from impaired angiogenesis, persistent inflammation, bacterial colonization evolving into biofilm formation, and concomitant neuropathy and/or microangiopathy (Fig. 2) [25]. Persistent hyperglycemia contributes to disruptions in processes responsible for protein synthesis, keratinocyte and fibroblast migration and proliferation, while also potentially causing endothelial cell dysfunction [26]. Impaired wound healing process is associated with abnormalities in coagulation, angiogenesis, nerve cell regeneration, and extracellular matrix (ECM) production. In this pathological state, several molecular components, including receptors, proteolytic enzymes, and neuropeptides, undergo alterations, resulting in delayed wound healing [27].

The preparation of the wound bed through the elimination of necrotic tissue should be based on expert consensus from TIMERS [28] and Wound Hygiene [29, 30]. The first recommended action, following the assessment of the patient's condition and the diagnosis of the wound's etiology, is the selection of a method for debriding devitalized, dead tissue, which in many cases is the source of infection and systemic infection. Each debridement method has its advantages and disadvantages, and the possibilities of their application are determined by practice guidelines, the individual decision of the person managing local treatment protocols based on wound examination, and the availability of equipment and technical resources [31]. There are no strict rules indicating the frequency of wound debridement; however, systematic performance of this procedure using the chosen technique removes bacterial biofilm and prevents its reformation, thereby facilitating the repair processes and shortening the inflammatory process [32]. The use of tissue tension-reducing agents enhances the effectiveness of the procedure [33, 34]. The choice of the optimal cleaning method depends on various factors, including the etiopathogenesis of the wound,

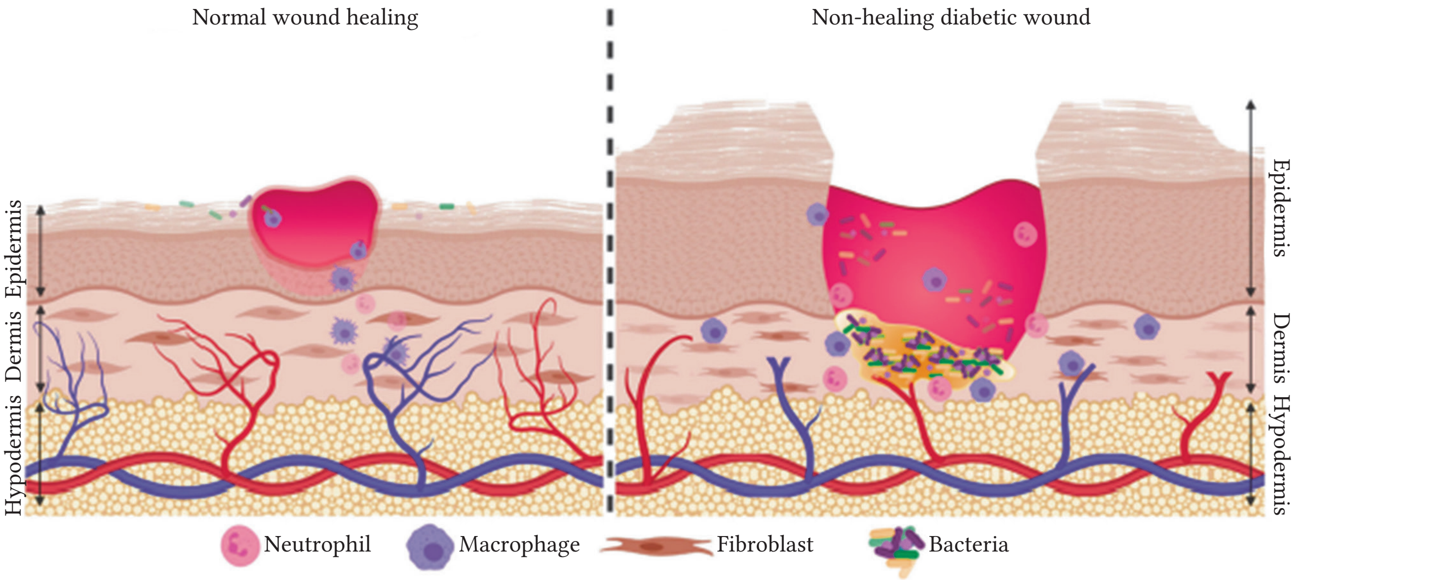

Figure 2. The pathophysiology of wound healing in diabetes [25]

coexisting diseases, the patient's clinical history, pain threshold, clinician's skills, as well as the preferences and economic capabilities of the patient (MDT and NPWT are not reimbursed in Poland and may appear costly) (Fig. 3).

The gold standard is the acute or delayed debridement of devitalized and dead tissues. However, extensive removal of necrosis, exposing live tissue, is a highly specialized procedure that should not be performed routinely. It is recommended in cases of fulminant infection associated with fasciitis or tendon inflammation, in the presence of bone infection or sepsis risk. This method requires hospitalization, an operating room, specialized medical staff, and anesthesia [34]. The benefits of rapid wound debridement include shortened healing time, reduced infection risk, and often the avoidance of debilitating amputations, especially in cases of infection and abscess formation in DFU [35].

A method that allows for selectivity and "protection" of healthy tissues is the maggot debridement therapy (MDT), approved by the Food and Drug Administration (FDA) in 2004. It is recognized that the pioneer of maggot therapy, as it is applied today, is R.A. Sherman who in 1990 opened a sterile laboratory at the Veteran Administration Hospital Medical Centre, in Long Beach, California. His team carried out a prospective study involving patients with pressure wounds following spinal cord injury, where it was shown that in comparison to conservative methods, wound debridement was more effective and required less time, while safety measures and sterile larva culture were maintained [36]. Larval wound therapy is limited to *Lucilia sericata* larvae as a medical product. It allows for highly selective wound debridement of dead tissue and stimulates repair processes through physical contact with the wound surface and the release of growth factors [37]. The method is relatively simple and can be effectively and safely conducted by medical personnel in various settings, including home care, outpatient clinics, and hospitals. However, despite the simplicity of the method, authors emphasize its demanding nature in terms of therapy supervision, especially when using free-range larvae in deep and penetrating wounds [38–40]. The use of biodebridement worldwide in the era of "antibiotic resistance" is gaining increasing recognition among experts dealing with the management of hard-to-heal wounds. In the last decade, the medical larvae of *Lucilia sericata* have been hailed as "healing maggots" due to their diverse biochemical properties that stimulate wound healing processes [41]. In Poland, in 2023, the expert team of the PTLR developed the first national recommendations for the use of medical larvae. The method was formally named Larval Wound Therapy – LWT (*terapia larwalna rany* – TLR) [42]. Literature analysis indicates that MDT/LWT should be recommended as adjunctive therapy in combination with conventional treatment methods such as acute debridement, antibiotic therapy, active dressings, and negative pressure wound therapy (NPWT) [2, 14, 38, 43, 44].

Wound larval therapy in diabetic foot syndrome

Local application permits the use of larvae from the *Lucilia sericata* (*Phaenicia sericata*) species, originating from the blowfly family, bred under controlled, sterile

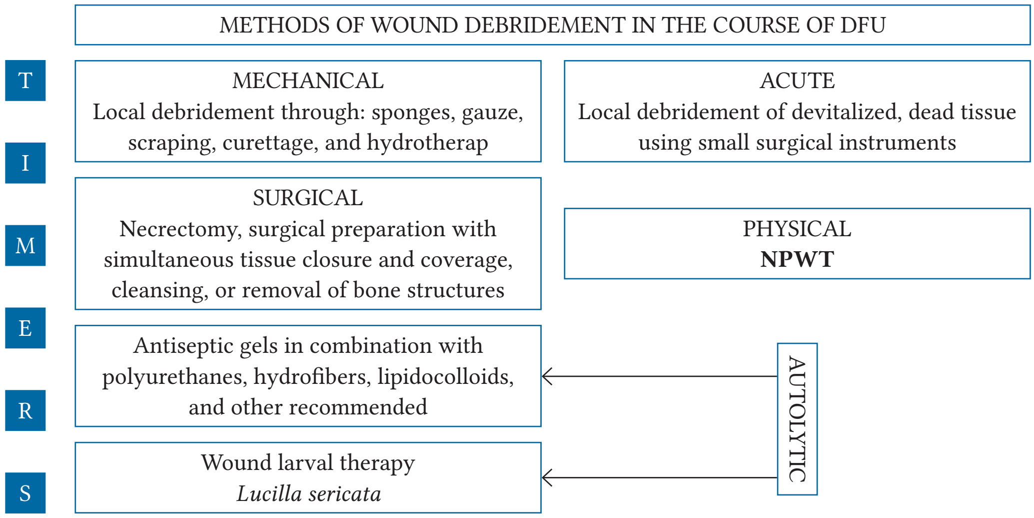

Figure 3. Local wound debridement options in the course of DFU

conditions. Larvae can be used either in a loose form or in a biobag; in local wound care during DFU, free larvae are more commonly used due to the risk of penetration into necrotic destruction along tendons and bones [38]. Larval therapy is based on three mechanisms: mechanical and autolytic debridement of necrotic tissue, secretion of anti-inflammatory, anti-biofilm, bactericidal, and wound-healing-promoting substances [35, 37, 38]. The larvae, residing within the wound, exhibit high selectivity, liquefying necrotic tissue through digestive enzymes, resulting in characteristic brown exudate, followed by extracorporeal absorption of softened dead tissue without damaging granulation tissue [45, 46]. The primary criteria for qualifying for MDT/LWT are infected, necrotic wounds where typical wound debridement procedures are not feasible, are contraindicated for various clinical reasons, or may yield low cleansing effects. A contraindication for therapy is a wound showing granulation characteristics without necrotic tissue, qualifying for standard treatment [42]. In the case of abscess formation, it is advisable to evacuate the discharge, drain the wound, and then consider the feasibility of MDT, especially in highly vascularized areas and/or in patients with coagulation disorders or taking anticoagulant medications, with strict adherence to safety protocols under the supervision of an experienced clinician [42, 47]. MDT should not be used in patients allergic to products used in larval breeding (brewer's yeast, soy proteins) or during larval disinfection [46].

Before qualifying a patient for therapy, their readiness should be assessed not only in terms of the physical preparation of the wound bed but also from a psychological perspective. Specialized centers use a questionnaire-based assessment to evaluate the patient's acceptance of larval therapy [47]. Education and informed consent according to the application protocol should be mandatory. Personal observations strongly suggest that individuals with diabetes are a preferred group for wound cleansing using this method; sensory disturbances of the hypalgesia type make the presence of larvae in the wound practically imperceptible. Similar observations were confirmed by Shi *et al.* in a systematic review comparing pain in diabetic and non-diabetic patients, finding that diabetic patients experienced consistently low levels of pain during MDT, whereas pain intensified in the non-diabetic group [48]. In other groups of patients with vascular etiology wounds, the initial sensations reported by patients are skin-related sensations such as itching, crawling sensation, pain, and feelings of disgust linked to the appearance of larvae, which are associated with ugliness, putrefaction, especially in patients over 70 years of age and women [49]. Patients with PAD should be prepared for therapy, which should be implemented after restoring circulation in the affected limb. Campbell and Campbell reported that natural stress reactions in patients decreased after initiating therapy [50]. Zarchi and Jemec compared a group receiving MDT with a group where wounds were cleansed using hydrogel and found a higher level of pain in the larval group; however, the discomfort did not decrease the quality of life, and the number of reported problems during therapy was low [51]. A cohort study conducted by Campbell and Campbell in a group of 68 patients (67% diagnosed with diabetes and PAD) confirmed the high effectiveness of MDT. In the studied group of patients, 90% of wounds were cleansed within 1 week [50]. Syam *et al.* concluded that biodebridement is effective in diabetic foot syndrome, indicating rapid debridement of necrotic tissue, a lower bacterial load, and accelerated repair processes [52]. Literature analysis suggests that the activity of larval mechanisms, such as cleansing, bactericidal activity, and stimulation of repair processes, is short-term, lasting no more than a few weeks. The effectiveness of cleansing is measurable, as the effect can be assessed directly after larvae evacuation from the wound. Within 24 hours, *Lucilia* larvae can eliminate 20-25 mg of necrotic tissue [38]. However, the phenomenon of wound healing itself can only be assessed after complete wound closure, which occurs at different individual times. Sherman suggested that the most favorable effects could be achieved by using MDT as a maintenance form, i.e., wound revitalization repeated at a set time sequence [48]. Campbell and Campbell point out the high effectiveness of MDT as a last-resort therapy, estimating that approximately 60% of patients experienced successful treatment, resulting in amputation avoidance [50]. The same hypothesis was examined by Tian *et al.*, who, after comparing the results of reviewed studies, concluded a significant reduction in the number of amputations after implementing MDT [53]. Sun *et al.*, when assessing the MDT-treated group and the conventionally treated group, made the bold claim that patients not receiving MDT were even twice as likely to undergo amputation compared to patients subjected to biodebridement [54].

The antimicrobial activity of *Lucilia sericata* larvae

In a hyperglycemic environment, the formation of biofilm is promoted, which is one of the causes of delayed or completely inhibited wound healing processes in hard-to-heal wounds [25-27]. Biofilm, as a multidimensional structure composed of bacteria, viruses, fungi, enclosed within a specific polymeric matrix, is highly resistant to antibiotic treatment and unresponsive to the host's immune response. This structure disrupts tissue repair processes and generates a localized inflammatory state, without clinical signs of infection [34]. The pathway to systemic infection with symptomatic manifestations depends on bacterial species, their interactions, and the host's immune response. Malone *et al.*, in a conducted meta-analysis, confirmed the presence of biofilm in 78.2% of chronic wounds [32].

The constant production and modification of bacterial resistance to antibiotics pose a significant challenge to the healthcare sector. Treating patients with resistant bacterial strains requires an innovative approach that reduces the risk of infection and mortality due to complications [56]. Scientific reports indicate that in the coming years, an increasing number of bacteria will acquire new resistance mechanisms. Contemporary medicine is characterized by a lack of new antibiotics and limited prospects for their development. Additionally, frequent and unjustified antibiotic therapy directly contributes to the development of persister cells, a subpopulation of cells capable of rebuilding the biofilm population [32, 34, 57].

Excretions and secretions (ES) reduce the proinflammatory response by demonstrating antibacterial activity (lucifensin I and II, lucilin, proline). Larval excretions, such as ammonia, calcium carbonate, and ammonium carbonate (resulting in a specific odor during therapy), increase the pH of the wound bed, thereby limiting bacterial proliferation in an alkaline environment [2, 48]. Diabetic foot is most commonly colonized by bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus ligdunensis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *E. faecalis*, and *Finegoldia magna* [58]. The use of medical larvae in local wound treatment reduces the burden, especially of *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria [2, 37, 38, 45, 46]. Analyzing the available literature, randomized studies by Malekian *et al.* are noteworthy. In their study involving 50 patients with DFU, they confirmed the antimicrobial effect of larvae; the number of *S. aureus* infection cases in the MDT-treated group was significantly reduced after 48 hours compared to the control group ($p = 0.047$). The number of cases of *P. aeruginosa* infection was significantly reduced after 96 hours ($p = 0.002$) [59]. Similar conclusions were drawn by Yan *et al.*, who also indicated an antimicrobial effect against *Candida albicans* fungi [60].

Larvae are typically applied according to a developed algorithm (5-10 larvae per cm^2). Szczepanowski *et al.*, when assessing the colonization of vascular ulcers and diabetic foot ulcers, pointed out that the larval density per unit wound surface enhances their antibacterial activity and reduces the likelihood of the presence of *Corynebacterium*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* MSSA, *Streptococcus coagulase*-negative, but increases the likelihood of contamination with *Proteus mirabilis* in the wound bed [61]. Contamination with *Proteus mirabilis* may be due to the fact that this bacterium constitutes the natural gut microflora of *L. sericata*, providing them with natural defense against pathogenic microorganisms from the outside [46, 62]. Tian *et al.*, in a meta-analysis comparing MDT with standard therapy, suggested that the MDT group significantly outperformed the control group in terms of the percentage of wounds completely healed (p = 0.03), amputation frequency (p = 0.02), time to healing (p = 0.0004), and the number of days without antibiotic therapy (p = 0.001). However, the frequency of post-MDT infections showed no difference compared to the control group (p = 0.10) [53].

The authors indicate that in patients treated with MDT, it was possible to significantly reduce the number of days of antibiotic therapy by reducing the bacterial load compared to the group of patients treated with other selected methods [48, 54, 63].

Stimulation of repair processes in the larval wound therapy

In the last decade, there has been a growing interest in larval biotherapy due to various biochemical properties that stimulate wound healing processes. Isolating chemical substances from ES offers expanding possibilities for research into the utilization of protein defensins in the treatment of wounds with different etiologies. Sherman was the first to demonstrate the effectiveness of medical larvae in wound healing during the course of DFU [64]. Larval excretions and secretions (ES), and their vibrating movements induced by physical contact with the wound bed stimulate the migration of human keratinocytes and fibroblasts, thus promoting wound healing processes [64, 65]. Wang *et al.* confirmed the impact of larval defensins on stimulating endothelial cell activity, thereby promoting wound angiogenesis in patients with diabetic foot syndrome [66]. Larval therapy is considered an important complementary treatment strategy for PAD patients, especially after revascularization treatment [67].

In Nishijima *et al.*'s studies, better wound bed preparation and graft viability were achieved in the MDT group [67]. A meta-analysis by Tian *et al.* comparing conventionally treated and MDT-treated groups pointed to a significant difference in healing rates, indicating the positive effects of larvae [53]. Polat *et al.*, evaluating the healing rate in a sample of 36 chronic ulcers, also noted the positive effects of larvae, with 80.6% of wounds healing within 1-2 months after MDT implementation [68]. In their systematic review, Sun *et al.* assessed wound healing indicators in the course of diabetic foot syndrome in comparison to venous ulcers or pressure ulcers, indicating an equivalent positive effect of MDT compared to conventional therapy but noting that the healing time was shorter in the MDT group. Shi and Sholer indicated that MDT implementation resulted in faster granulation and shorter healing times, especially for pressure ulcers and diabetic foot ulcers [48]. Wilasrusmee *et al.*, comparing healing rates in DFU patients conventionally treated versus the MDT group, identified a sevenfold higher healing rate in the MDT group, significantly contributing to shorter treatment duration and reduced costs [69]. In an exploratory study analyzing the transcriptome related to keratinocytes, endothelial cells, and monocytes, Dauros Singorenko *et al.* demonstrated that larval ES products modulate the immune response, indirectly influencing processes such as cell migration and angiogenesis through cytokine release [70].

Larval wound therapy is a highly effective method, but like any other, it may have negative consequences. Literature analysis indicates potential problems that may arise during MDT, including itching, pain, and discomfort at the thought of larvae crawling in the wound [38, 46]. Bleeding, fever, signs of infection, or allergic reactions are potential symptoms that can lead to serious systemic disorders [48]. The patient's natural reaction to a previously unfamiliar therapy is fear and concern about the larvae escaping from the wound bed. Thoroughly preparing the patient and their family, familiarizing them with the procedure, explaining the potential effects of therapy, both positive and negative, establishing a strong patient-provider relationship, and ensuring care by trained medical personnel all positively influence the patient's perception of this treatment method. In Poland, MDT is not reimbursed by the National Health Fund (*Narodowy Fundusz Zdrowia* – NFZ); however, considering the rapid cleansing and antimicrobial effects, ultimately accelerating the healing process, it is cost-effective in the long term.

Conclusions

Ulcers in the course of diabetic foot have become one of the leading causes of mortality and morbidity in diabetic patients, as well as a common reason for hospitalization, placing a significant burden on healthcare systems. Prevention and treatment require a multidisciplinary approach. Larval therapy accelerates wound debridement and stimulates wound healing processes. The use of *Lucilia sericata* larvae may contribute to reducing antibiotic therapy duration, lowering the number of hospitalizations, and mitigating the risk of amputations.

Disclosure

The authors declare no conflict of interest.

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