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FACTORS INHIBITING THE WOUND HEALING PROCESS IN PATIENTS WITH DIABETIC FOOT ULCERS : A SCOPING REVIEW

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Abstract

Backgrounds; The number of people with diabetes mellitus (DM) continues to rise. One of the most common complications of this condition is diabetic foot ulcer (DFU). Delayed management of DFU can lead to more severe wounds. Various factors pose a high risk for the development of chronic wounds, amputation, or even death. **Objectives**; To identify the factors that inhibit the healing of diabetic foot ulcers. **Methods**; A scoping review of research and literature (2013-2022) was conducted using scoping review frameworks and following the five-stage framework described by Arksey and O'Malley. The review was reported in accordance with the PRISMA-ScR extension. Two databases were searched for research literature, followed by a manual search of reference lists of relevant topics. Inclusion criteria included articles focused on diabetic foot ulcers and articles on factors inhibiting wound healing. **Results;** The search identified a total of 537 articles from PubMed, which were filtered down to a total of 40 articles. The search from Scopus yielded a total of 28 articles, which were filtered down to a total of 51 articles. Further abstract and full-text screening, along with filtering for the last 10 years, resulted in a final selection of 14 articles. **Conclusions**; Factors inhibiting wound healing in diabetic foot ulcers include: Increased overall body protein metabolic demand, Negative nitrogen balance, Inadequate increased energy intake, High infection rates, High financial costs, Delayed wound care, Inappropriate antibiotic therapy, Peripheral vascular disease, Neuropathy, Advanced age, Malnutrition, Kidney disease, Improper footwear, Poor clinical management, Chronic inflammation, Poor blood sugar control, Elevated levels of destructive proteases, Long-standing diabetes, Abnormal foot structure, Smoking habits, History of ulcers or previous amputations.

Keywords: diabetes mellitus patients; diabetic foot ulcer; inhibiting factors; wound healing process.

BACKGROUND

Diabetes mellitus is a chronic disease that requires long-term medical attention to prevent the development of its complications. The progression of diabetic foot ulcers (DFU) increases the risk of patient mortality (Bekele & Chelkeba, 2020). Diabetic foot ulcer is a major source of preventable morbidity in adults with diabetes. The consequences of foot ulcers include decreased functional status, infection, hospitalization, lower extremity amputation, and death. DFU is a common and highly abnormal complication of diabetes. The pathway to ulceration, involving loss of sensation, ischemia, and minor trauma, is well known (Bekele & Chelkeba, 2020). Approximately 18.6 million people worldwide are affected by diabetic foot ulcers each year, including 1.6 million people in the United States. These ulcers precede 80% of lower extremity amputations in individuals diagnosed with diabetes and are associated with an increased risk of mortality (David G. Armstrong et al., 2023). Diabetes is one of the diseases that is difficult to cure once it appears and can lead to various complications if left untreated (Harding et al., 2019). One of its complications is diabetic foot ulcers.

Wound healing is a crucial physiological process for maintaining skin integrity post-trauma, whether from accidents or intentional injuries. Normal wound healing involves three sequential yet overlapping phases: the hemostasis/inflammatory phase, the proliferative phase, and the remodeling phase. Deviations in wound healing, such as excessive wound healing (hypertrophic scars and keloids) or chronic wounds (ulcers), disrupt normal physical function (Wang et al., 2018). In the care of diabetic foot ulcers, it is essential for all patients with diabetic foot ulcers to understand the factors that inhibit the healing of these wounds. By understanding these factors, patients can better aid the healing process of their diabetic foot ulcers. Based on the aforementioned background, the purpose of this study is to identify the factors that inhibit the healing of diabetic foot ulcers.

METHODS

Protocol and registration

We used a scoping review, guided by the PRISMA statement for scoping review reporting, to gather and summarize the existing literature on factors that inhibit the healing of diabetic foot ulcers.

The method used for conducting the review followed the five-stage framework described by Arksey and Malley. This was used to conduct the scoping study and reported in accordance with the PRISMA Extension for Scoping Reviews. Inclusion and exclusion criteria for the scoping review were determined at the outset.

Eligibility criteria

Inclusion Criteria:

1. Articles focusing on diabetic foot ulcers
2. Articles discussing factors inhibiting wound healing
3. Articles published in English

Exclusion Criteria:

1. Review articles
2. Articles published before 2014
3. Qualitative study designs

RESULTS AND DISCUSSION

Research studies

The search was conducted both electronically and manually. The search strategy consisted of three steps. First, an initial search was performed using the following electronic databases: Scopus and PubMed. The search was conducted using the keywords "diabetic mellitus type 2" as the problem, "health education" as the context, and "wound healing" as the content. The specific keywords used were "diabetic AND foot AND ulcer" for diabetic foot ulcers, "heal OR healing" for health education, and "advanced therapy OR advanced treatment" for wound healing. The search for articles involved filtering for the last 10 years, full text, English, clinical studies, and human subjects.

Study selection

The selection and inclusion of papers for this review involved a two-stage process: screening abstracts and titles, and then reading the full text to select articles that met the criteria for final inclusion.

Data extraction, analysis and synthesis

Once articles meet the criteria for final inclusion, they will be analyzed using the Elicit application. The results of the analysis in Elicit will be exported to Microsoft Excel to compile relevant data for further analysis. One template will be used to collect information on study characteristics, including: study title, author names, research country, research year, study design, research objectives, and sample size. A second template will gather characteristics of the factors inhibiting diabetic foot ulcer healing, as well as the study outcomes.

Results

The search identified a total of 537 articles from PubMed. After applying filters for the past 10 years, 398 articles remained; further filtering for full text reduced this to 392; filtering for English-language articles resulted in 386; filtering for human studies yielded 286; and filtering for clinical studies brought the total to 42 articles. However, two articles could not be located, resulting in a final total of 40 articles. In contrast, the search in Scopus initially yielded 28 articles, which, after filtering, was reduced to 13, resulting in a combined total of 53 articles from both databases. Next, duplicate screening using Mendeley identified two identical articles, reducing the total to 51. Abstract screening led to the exclusion of three articles, leaving 50 articles. Full-text screening, after consideration, resulted in the exclusion of 36 articles: 35 did not discuss factors inhibiting wound healing, and 1 article was published in 2009, which is outside the 10-year range. This left 14 articles included in the scoping review. The search flow is depicted in Figure 1.

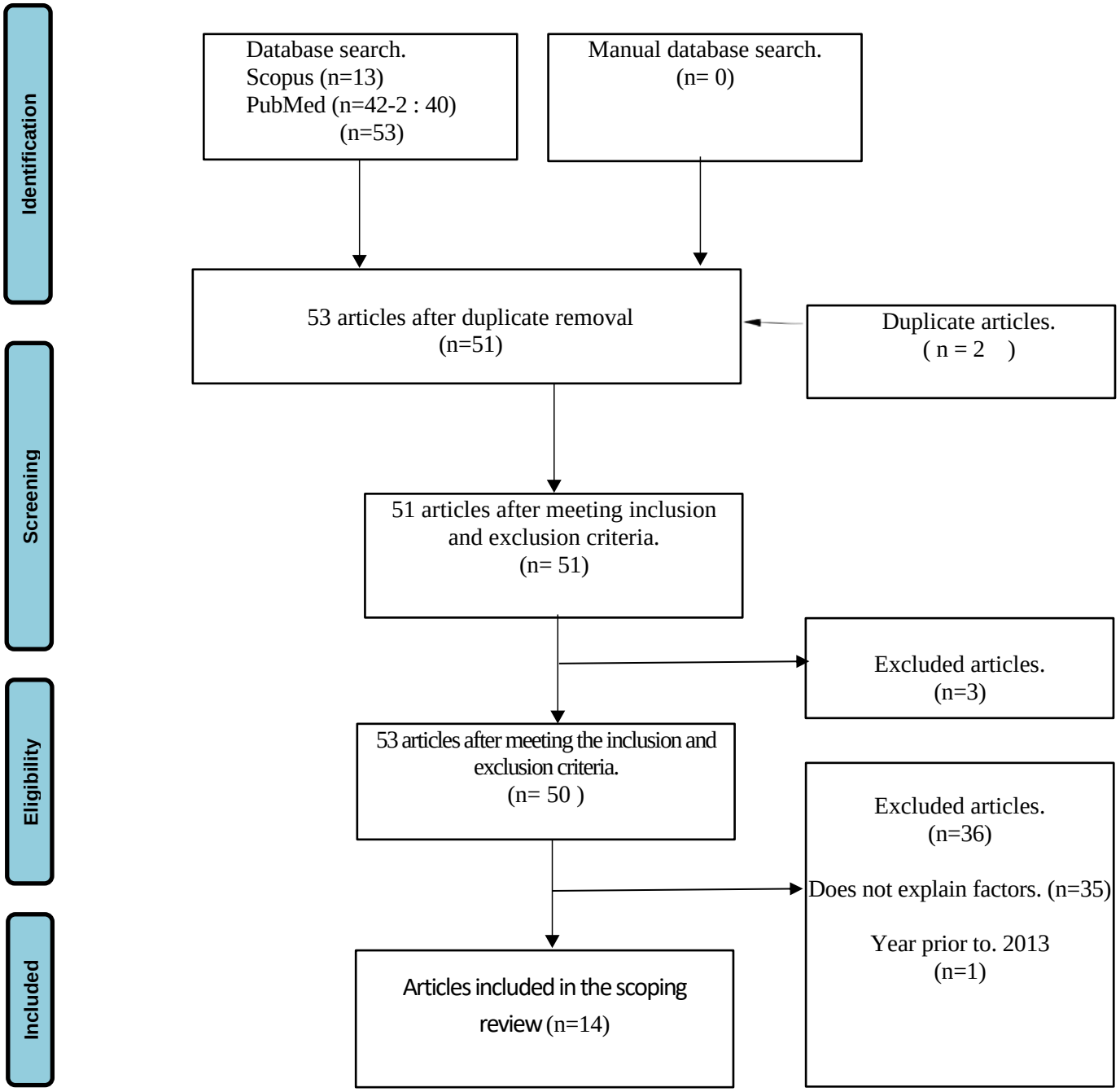

Figure 1 : Flowchart of the literature search process.

Table 1. Details of the reviewed papers.

Titel,Author,Country,year	Study Design and Purpose	Sample Description
Effects of Nutrition Intervention on Blood Glucose, Body Composition, and Phase Angle in Obese and Overweight Patients with Diabetic Foot Ulcers (Basiri, Spicer, & Ledermann, 2022)	The study design is a randomized controlled trial (RCT) with ethical approval and registration at ClinicalTrials.gov. The research aims to assess the impact of nutritional education and supplementation on long-term blood glucose control, body composition, and phase angle as indicators of cellular health and cell membrane integrity in patients with diabetic foot ulcers (DFU).	Number: 29 - Treatment group: Not specified - Control group: Not specified
Multiple Interventions for Diabetic Foot Ulcer Treatment Trial (MIDFUT): study protocol for a randomised controlled trial (Brown et al., 2020)	The study design is a multi-stage, multi-center, seamless Phase II/III randomized controlled trial with an open-label, parallel-group, and multi-group design, featuring blinded outcome assessment. It is a randomized and controlled trial with a parallel-group design, employing mixed-effects logistic regression and Cox proportional hazards regression models for Phase II and Phase III, respectively.	Number: 447 - Phase II: 245 - Phase III: 202
Diabetic foot ulcer amputation rate and associated factors in diabetes mellitus patients admitted to Nekemte referral hospital, western Ethiopia: a prospective observational study (Bekele & Chelkeba, 2020)	The study design is a prospective observational study. It was not conducted as a randomized, double-blind, controlled, or placebo-controlled study. It does not involve multiple sites, retrospective approaches, or specific hierarchical or crossover designs. It is neither a meta-analysis nor a systematic review.	Sample size: 115.
Outcomes Following Advanced Wound Care for Diabetic Foot Ulcers: A Canadian Study (Roth-Albin et al., 2017)	The study design is a retrospective cohort study conducted at a single Canadian advanced diabetic foot and wound care centre, approved by the Hamilton Health Sciences Research Ethics Board.	Total: 307 - Active treatment group: 154 - Control treatment group: 153
Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost (Zelen et al., 2016)	Prospective, randomized, controlled clinical trial with a parallel-group design, multi-center locations, blinding procedures, and intention-to-treat analysis.	Total: 100 Majority (92.0%) experienced obesity [body mass index (BMI) ≥30]. Eighty-three percent (83%)

A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers (Zelen et al., 2015)	Prospective, randomized, controlled, multi-center comparative effectiveness study.	Total: 60 - Apligraf: 20 - EpiFix: 20 - Standard Care: 20
Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers (Mathur et al., 2017)	The study design is a randomized controlled trial (RCT) conducted at a single tertiary teaching hospital over a period of 6 months.	Total: 30 - Group 1: 15 - Group 2: 15
A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers (Tettelbach, Cazzell, Sigal, et al., 2019)	Prospective, randomized controlled trial (RCT); multi-site; IRB-approved; conducted between August 2016 and March 2018.	Total: 155 - EpiCord: 101 - Alginate dressings: 54
Improving Dietary Intake of Essential Nutrients Can Ameliorate Inflammation in Patients with Diabetic Foot Ulcers (Basiri, Spicer, Levenson, et al., 2022)	Randomized controlled trial.	Total: 29 - Treatment group: 15 - Control group: 14
To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial (Campitiello et al., 2017)	Placebo-controlled randomized clinical trial.	Total: 60 - Integra Flow Matrix: Not specified - Wet dressings: Not specified
Er:YAG laser vs. sharp debridement in management of chronic wounds: Effects on pain and bacterial load (Hajhosseini et al., 2020)	Prospective, randomized, controlled, crossover clinical trial.	Total: 22 - Group 1 (Laser): 12 - Group 2 (Sharp): 10
A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics (Tettelbach, Cazzell, Reyzelman, et al., 2019)	Multicenter, randomized, controlled clinical trial.	Total: 110 - dHACM group: 54 - No-dHACM group: 56
Personalized Offloading Treatments for Healing Plantar Diabetic Foot Ulcers (Jarl et al., 2023)	-	-
Chinese medicine ulcer oil promotes the healing of diabetic foot ulcers (Jia et al., 2018)	Randomized controlled trial.	Total: 48 - Control group: 12 - Positive control (PC) group: 12 - UO group: 12 - ELS group: 12

Characteristics of the identified studies

The included studies are summarized in Table 1. There are four studies conducted in the USA (n=4), two studies in England and California (n=2), and one study each in China, Italy, London, Canada, Ethiopia, and Switzerland (n=1 each). Seven studies are randomized controlled trials (RCTs) (n=7), four are prospective observational studies (n=4), and there is one each of retrospective observational study, random placebo clinical trial, and randomized controlled clinical trial (n=1 each). The studies were conducted between 2015 and 2022. All studies involved patients with type 2 diabetes. The largest sample size was 445, while the smallest was 22.

Table 2. Characteristics of factors.

Titel,Author,Country,year	Inhibiting Factor	Result
Effects of Nutrition Intervention on Blood Glucose, Body Composition, and Phase Angle in Obese and Overweight Patients with Diabetic Foot Ulcers (Basiri, Spicer, & Ledermann, 2022)	Factors inhibiting wound healing in patients with DFU include increased metabolic demands, elevated whole-body protein metabolism, negative nitrogen balance, and inadequate energy intake, which leads to muscle wasting and poor wound healing. Adequate protein intake, along with non-protein energy sources, is crucial for improving wound healing.	Long-term blood glucose control, measured by HbA1c concentration.
Multiple Interventions for the Diabetic Foot Ulcer Treatment Trial (MIDFUT): Research Protocol for a Randomized Controlled Trial (Brown et al., 2020)	Factors inhibiting wound healing include high infection rates, financial costs, impacts on patient quality of life, delayed healing leading to adverse outcomes, and the need for cost-effective adjunctive therapies for non-healing wounds. (Confidence: 90) Interventions	Achieve at least a 50% reduction in the area of the index ulcer within 4 weeks post-randomization, with the time to heal the index ulcer compared to treatment as usual (TAU) alone.
Diabetic Foot Ulcer Amputation Rates and Related Factors in Diabetes Mellitus Patients Treated at Nekemte Referral Hospital, Western Ethiopia: A Prospective Observational Study (Bekele & Chelkeba, 2020)	Factors inhibiting wound healing in this study include inappropriate antibiotic therapy, advanced foot ulcers, and the prescription of antibiotics for non-infected foot ulcers. Proper management of diabetic foot infections can help prevent bacterial growth and accelerate wound healing. (Confidence: 90)	During the study period, 115 diabetic foot ulcer patients were treated at NRH; of these patients, 64 (55.65%) were male, with an average age of 44.4 ± 14.7. A total of 34 (29.57%) diabetic foot ulcer patients were overweight, and 16 (13.91%) were obese, while the mean ± standard deviation of body mass index (BMI) was 24.94 ± 3.69 kg/m², with a total of 56 (48.69%).
Outcomes Following Advanced Wound Care for Diabetic Foot Ulcers: A Canadian Study (Roth-Albin et al., 2017)	Factors inhibiting wound healing in DFU patients include chronic ulcers, ulcer size >1 cm², peripheral vascular disease, and multiple ulcers at initial presentation. Peripheral vascular disease (PVD) was found to be an independent predictor of delayed healing, amputation, and mortality.	The primary outcome measured in this study is the healing rate at 52 weeks after advanced wound care.

Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost (Zelen et al., 2016)	Peripheral vascular disease, neuropathy, poor blood glucose control, comorbid conditions, ischemia, infection, advanced age, malnutrition, diabetes, kidney disease, ill-fitting shoes, and poor clinical management.	- Proportion of wounds achieving complete closure during the 12-week study period - Average healing time within 12 weeks - Median number of grafts used per healed wound - Median cost of grafts per healed wound
A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers (Zelen et al., 2015)	Factors inhibiting wound healing include diabetes and associated morbidities, peripheral vascular disease, neuropathy, poor blood glucose control, persistent inflammation, cellular aging, growth factor deficiencies, biological burden, elevated levels of destructive proteases, and stem cell deficiencies.	- Percentage of wounds that achieved complete healing after 4 and 6 weeks of treatment with Apligraf, EpiFix, or standard care - Average healing time for each treatment group
Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers (Mathur et al., 2017)	Factors inhibiting wound healing in diabetic foot ulcers (DFUs) include risk factors such as male gender, a long history of diabetes mellitus (DM), peripheral neuropathy, abnormal foot structure, peripheral artery disease, smoking, previous ulcer or amputation history, and poor glycemic control. The underlying pathophysiological factors causing DFUs are neuropathy, ischemia, and infection, which are considered most critical. DFUs exhibit reduced angiogenic response and growth factor deficiencies, leading to delayed healing. Non-healing DFUs are resistant to conventional treatments.	The primary outcomes measured in this study are the absolute and relative reduction in wound size within 2 weeks compared to baseline parameters, as well as the percentage reduction in ulcer area between the LLLT group and the control group.
A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers (Tettelbach, Cazzell, Sigal, et al., 2019)	Factors inhibiting wound healing in chronic DFUs include disruptions in signaling cascades, persistently elevated levels of metalloproteinases, disturbances in bacterial-host interactions, hyperglycemia, neuropathy, peripheral artery disease, immune dysfunction, increased infection risk, and the need to accelerate closure of chronic DFUs to avoid costly complications. Additionally, the ability to obtain mesenchymal stem cells from fresh umbilical cord tissue and the biological properties of EpiCord highlight the potential for regenerative therapy based on umbilical cord tissue.	Percentage of complete ulcer closure in the study within 12 weeks, assessed using Silhouette camera.

Improving Dietary Intake of Essential Nutrients Can Ameliorate Inflammation in Patients with Diabetic Foot Ulcers (Basiri, Spicer, Levenson, et al., 2022)	Factors inhibiting wound healing in DFUs include chronic inflammation, high concentrations of reactive oxygen species (ROS), hyperglycemia, hypoxia, dysregulation of pro-inflammatory and anti-inflammatory molecules, low intake of essential nutrients, and accumulation of advanced glycation end-products (AGEs). (Confidence: 95)	Reduction in IL-6 at 12 weeks.
To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial (Campitiello et al., 2017)	The factors inhibiting wound healing in this paper include complex biological and molecular events required for optimal healing, unreliable wound healing development in diabetic ulcers, over 100 physiological factors known to contribute to impaired wound healing in individuals with diabetes, decreased or disrupted production of growth factors, angiogenic response, macrophage function, collagen accumulation, epidermal barrier function, granulation tissue amount, keratinocyte and fibroblast migration and proliferation, epidermal nerve density, bone healing, and the balance between extracellular matrix component accumulation and remodeling by MMPs. Additionally, intrinsic pathobiological abnormalities and extrinsic factors contribute to the complex wound microenvironment, along with reduced cytokine release including TNF-α, IL-1β, and VEGF by macrophages in diabetes.	Complete wound healing rate and healing time
Er:YAG laser vs. sharp debridement in management of chronic wounds: Effects on pain and bacterial load (Hajhosseini et al., 2020)	Factors inhibiting wound healing include bacteria, exudative fluid, aged cells, necrotic debris, and pain associated with sharp debridement. (Confidence: 95)	- Pain during debridement - Wound size before and after debridement - Bacterial count before and after debridement - Patient preferences
A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics (Tettelbach, Cazzell, Reyzelman, et al., 2019)	Factors inhibiting wound healing in diabetic patients include comorbid conditions such as peripheral vascular disease, neuropathy, and poor glucose control, as well as other underlying conditions. Recurrence of ulcers within 1 year after healing is common, with an estimated 40% of diabetic patients experiencing recurrence. Slow healing of lower extremity ulcers increases the risk of infection and potential amputation. Successful treatment of lower extremity ulcers in diabetic patients requires a team effort between the physician and a compliant, motivated	- Percentage of ulcers completely healed within 12 weeks - Incidence of total wound closure within 12 weeks - Healing time - Incidence of ulcer recurrence at the studied ulcer site during the follow-up phase

	patient. First-line standard management for diabetic foot ulcers may require months of treatment before healing, and advanced wound therapy may be necessary if the ulcer size does not decrease by at least 40% after 4 weeks of standard wound care.	
Personalized Offloading Treatments for Healing Plantar Diabetic Foot Ulcers (Jarl et al., 2023)	The factors inhibiting wound healing discussed in this paper include challenges and barriers related to inadequate use of non-removable knee-high devices, potential disruptions to daily activities, patient tolerance factors affecting device use, and misconceptions about the uniform need for offloading across all patients.	The effectiveness of non-removable knee-high offloading devices in reducing plantar tissue stress and accelerating the healing of diabetic plantar foot ulcers.
Chinese medicine ulcer oil promotes the healing of diabetic foot ulcers (Jia et al., 2018)	The factors impeding wound healing discussed in this paper include prolonged high blood glucose leading to the accumulation of AGEs and damage to endothelial cell function, PTP1B which negatively regulates the insulin signaling pathway, insufficient action of wound growth factors, and reduced VEGF expression in patients with endothelial vascular dysfunction.	The levels of PTP1B, VEGF, PDGF, and AGEs were measured using Western blot analysis on days 3, 7, and 14.

CONCLUSION

The factors discussed in various articles vary, including an increased metabolic protein requirement throughout the body, negative nitrogen balance, inadequate energy intake leading to muscle wasting and poor wound healing (Basiri, Spicer, & Ledermann, 2022). Additionally, high infection rates and significant financial costs can impede wound healing by delaying wound care (Brown et al., 2020). Inappropriate antibiotic therapy, chronic ulcers, peripheral vascular disease, neuropathy, comorbid conditions, ischemia, advanced age, malnutrition, kidney disease, ill-fitting footwear, and poor clinical management including persistent inflammation, poor blood glucose control, biological load, and elevated levels of destructive proteases are also mentioned in the aforementioned studies. Risk factors such as male gender, long-standing diabetes, abnormal foot structure, smoking habits, and a history of previous ulcers or amputations can further delay or hinder wound healing (Mathur et al., 2017).

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