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THE ROLE OF PROINFLAMMATORY CYTOKINE GM-CSF AS A THERAPY FOR DIABETIC ULCERS: A SYSTEMATIC REVIEW

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ABSTRACT
Diabetic ulcers represent a prevalent complication among patients with poorly controlled diabetes mellitus, often resulting from inadequate blood glucose regulation, neuropathy, peripheral artery disease, and suboptimal wound care. This systematic review aims to evaluate the therapeutic efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) for diabetic ulcers. The review utilized databases such as PubMed, ProQuest, and Google Scholar, with only six articles meeting the eligibility criteria for analysis. The findings suggest that GM-CSF exhibits therapeutic potential by enhancing neovascularization, promoting keratinocyte proliferation, facilitating granulation tissue formation, and reducing wound diameter. These results highlight the potential of GM-CSF as a therapeutic agent for diabetic ulcers. Nevertheless, the current body of research is limited, necessitating further studies with larger populations and diverse GM-CSF administration methods to substantiate these findings.

Keywords: diabetic ulcer; GM-CSF; therapeutic efficacy

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INTRODUCTION

Diabetes is a persistent metabolic disorder defined by heightened concentrations of blood glucose (also known as blood sugar). This disease can lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves over time.(Guo et al., 2023; Sapra & Bhandari, 2023) The precise cause of most types of diabetes remains unknown. In all forms of diabetes, sugar accumulates in the bloodstream due to insufficient insulin production by the pancreas. Both type 1 and type 2 diabetes can result from a mix of genetic and environmental factors.(Galicia-Garcia et al., 2020; Hossain et al., 2024) Diabetic ulcers are one of the most common complications in poorly controlled diabetes mellitus patients. Several causes of diabetic ulcers include poor blood sugar control, neuropathy, peripheral artery disease, and inadequate wound care.(Oliver & Mutluoglu, 2023).

Persistent high blood sugar levels can lead to damage in blood vessels and nerves across the body. This damage increases the risk of complications, such as poor wound healing and the development of ulcers, increasing the risk of complications such as slow wound healing, known as ulcers. Without prompt treatment, these ulcers can lead to tissue death, which can ultimately result in limb amputation or death.(Akkus & Sert, 2022; Burgess et al., 2021) Roughly 50% to 60% of ulcers develop infections, with approximately 20% of moderate to severe infections resulting in lower limb amputations. The five-year mortality rate for individuals suffering from diabetic ulcers is estimated to be around 30%. Moreover, the annual mortality rate for individuals with diabetic foot ulcers (DFUs) is 231 per 1000 people, compared to 182 per 1000 people among those with diabetes but without foot ulcers.(Armstrong et al., 2023).

The development of diabetic ulcers generally occurs in three stages. The first stage involves the formation of calluses due to neuropathy. Motor neuropathy can lead to physical deformities in the feet, while sensory neuropathy causes a loss of sensation, permitting continuous trauma to occur unnoticed. Additionally, skin dryness due to autonomic neuropathy also contributes to callus formation. Eventually, repeated trauma to the callus can cause subcutaneous bleeding, and the callus can erode and develop into an ulcer. Individuals with diabetes mellitus frequently suffer from severe atherosclerosis in the small blood vessels of the legs and feet, which leads to vascular disorders and contributes to diabetic foot infections. Because blood flow cannot reach the wound, the healing process is delayed, which can eventually lead to necrosis and gangrene.(Mieczkowski et al., 2022; Wang et al., 2022)

Frequent hyperglycemia, which refers to the elevation of blood glucose levels, results in increased concentrations of advanced glycation end products (AGEs) in the bloodstream.(Khalid et al., 2022) These AGEs significantly contribute to the production of high levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS). When the levels of ROS and RNS surpass the antioxidant capacity of tissues, it can lead to tissue damage.(Caturano et al., 2023) During the inflammatory phase of wound healing, ROS and RNS are essential as they facilitate the removal of necrotic tissue and pathogens. However, when present in excessive quantities, these reactive species can impede the transition from the inflammatory phase to the proliferative phase, thereby obstructing the formation of new healthy tissue.(Gonçalves et al., 2022; Polaka et al., 2022) Initial therapeutic approaches for diabetic foot ulcers include debridement, management of lower limb ischemia and foot infections, along with early referral for multidisciplinary care.(Armstrong et al., 2017).

The management of diabetic ulcers involves several key strategies, including surgical debridement, application of dressings to maintain a moist wound environment and manage exudate, off-loading to relieve pressure on the wound, vascular assessment, and control of infection and blood glucose levels.(Kim et al., 2023) These practices are typically overseen by multidisciplinary diabetic foot wound clinics. Despite this thorough approach, there remains potential for enhancing the outcomes of DFUs. Numerous adjuvant therapies have been investigated to accelerate DFU healing and lower amputation rates.(Doğruel et al., 2022; Everett & Mathioudakis, 2018) One potential management of diabetic ulcers is the use of GM-CSF, which has shown positive results in several studies.Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a glycoprotein with immunomodulatory properties.(Wessendarp et al., 2022) Diabetes mellitus can cause chronic inflammation that hinders the wound healing process. GM-CSF is a cytokine that enhances chemotaxis, the production of proinflammatory cytokines, and cell adhesion. Additionally, it plays a crucial role in modulating local inflammation and stimulating macrophage activation. However, unlike acute or healthy wounds, the activity of GM-CSF is suppressed in diabetic foot ulcers. In diabetes mellitus wounds, the proportion of monocytes is higher compared to activated macrophages, thus disrupting the inflammatory response. During the inflammatory phase, macrophages function to engulf apoptotic cells and infecting pathogens. The dynamic balance between M1 and M2 macrophages is crucial for an effective wound healing process.(Ead & Armstrong, 2023)GM-CSF can aid in wound healing by promoting keratinocyte proliferation, neovascularization, modulation of immune activity, and antimicrobial effects. Increased keratinocyte activity supports the re-epithelialization process. GM-CSF has also been shown to restore T lymphocytes and enhance the production of inflammatory cytokines such as IL-2, IL-6, TNF, TGF-β1, IFNγ, and MCP-1. Increased antimicrobial activity is associated with a higher number of PMNs. Three studies on individuals with diabetic wounds have shown that wounds treated with GM-CSF experience healing. Moreover, the administration of GM-CSF in these studies did not show significant side effects on the study samples.(Fang et al., 2007; Galkowska et al., 2006; Mann et al., 2001)The therapeutic potential of GM-CSF has been

extensively investigated in various studies, demonstrating its significant efficacy and safety in enhancing the healing process of diabetic ulcers. Therefore, this study seeks to review and analyze recent articles to assess and synthesize the clinical effectiveness of GM-CSF in treating diabetic ulcers compared to standard treatments or alternative therapies and to assess the potential mechanisms of action of GM-CSF in modulating immune responses and promoting tissue repair in patients with diabetic ulcers.

METHOD

Data Sources and Search Strategy

A systematic review was conducted to evaluate the clinical efficacy of GM-CSF in treating diabetic ulcers, adhering to the PRISMA 2020 guidelines. Data sources included studies available in three databases: PubMed, ProQuest, and Google Scholar. The search strategy utilized a combination of terms: 'GM-CSF' OR 'granulocyte macrophage colony stimulating factor' AND 'diabetic ulcer' OR 'diabetic wound'.

Inclusion and Exclusion Criteria

The inclusion criteria for studies in this systematic review were established according to the PICOS framework. The study population consists of patients with diabetic ulcers, where the intervention involves granulocyte macrophage colony stimulating factor (GM-CSF) compared to control or conventional therapy, with the outcome measured by ulcer healing.We excluded protocols, conference proceedings, presentations, posters, review articles, editorials, and news articles from the analysis. Additionally, studies without full-text access were omitted.

Data Extraction and Quality Assessment

Following the removal of duplicate records, we scrutinized abstracts and titles to pinpoint articles suitable for full-text review. The quality assessment of evidence for articles that met the inclusion criteria adhered to Cochrane's recommended guidelines, encompassing the evaluation of bias risk and eligibility level. The risk level in evidence was determined using the Cochrane risk- of-bias tool 2 (RoB 2), facilitated by the RevMan 5.4 tool.

RESULT

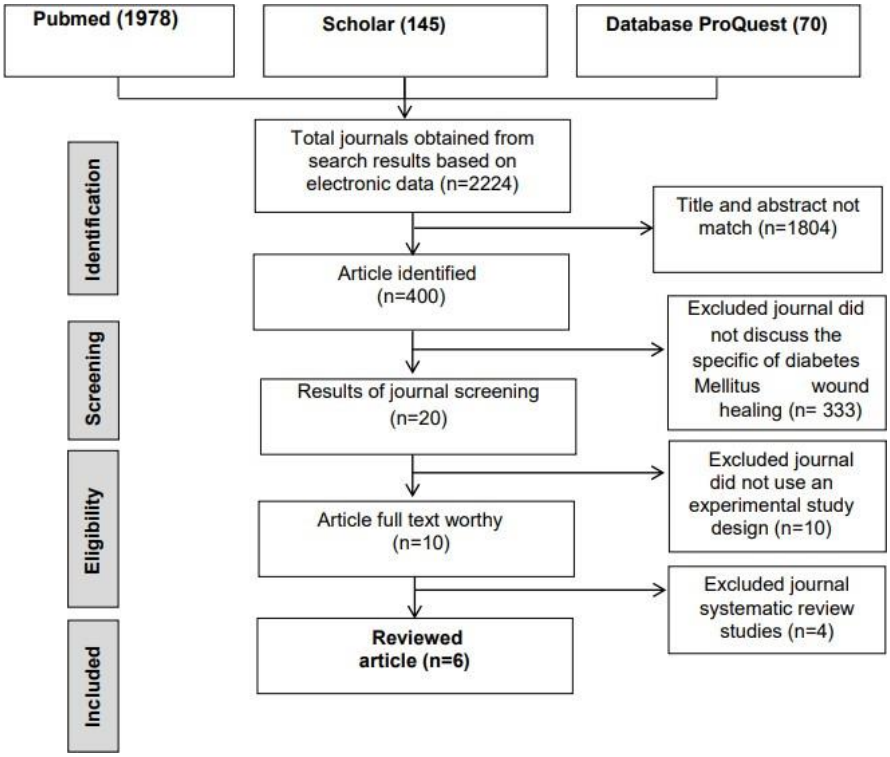

Figure 1. Study Selection with PRISMA algorithm

Study Selection

The article search strategy encompassed three electronic databases, utilizing relevant keywords, and resulted in 2,224 articles related to the topic. We excluded 1,804 articles based on titles and abstracts that did not fulfill the criteria and eliminated 414 articles that did not address the effects of GM-CSF on diabetic ulcer patients. Consequently, this systematic review analyzed only six articles. The process and results of the literature screening are presented in Figure 1.

Characteristics and Main Outcomes of the Studies

Nine selected RCTs encompassed 164 patients with ulcers, with 82 patients receiving GM-CSF treatment and the remaining 82 serving as the control group. Table 1 offers a concise summary of the characteristics and main findings of the included studies. Four studies explored the efficacy of GM-CSF versus conventional management for diabetic ulcers using wound healing diameter as a parameter. Two other studies assessed GM-CSF's effectiveness compared to conventional management by measuring keratinocyte proliferation. Additionally, two studies evaluated the effectiveness of GM-CSF against conventional management by counting the number of blood vessels at the end of the intervention. The interventions' durations varied from 4 to 14 weeks across all studies. Each study analyzed patient ulcer data, total ulcer healing rate, accelerated healing time, reduction in ulcer size, granulation tissue formation, recurrence prevention, and side effects of GM-CSF treatment. Due to the heterogeneity of the included studies regarding sample populations, outcomes, and study designs, conducting a meta-analysis was not feasible.

Total Ulcer Healing Rate

A total of six studies ((Agrawal et al., 2003; Liu et al., 2014; Mann et al., 2001; Naim et al., 1970; Yan et al., 2012; Yuan et al., 2015)) reported the overall ulcer healing rates after GM-CSF administration compared to conventional wound care. The ulcer healing rates in the GM-CSF group varied between 60% and 97.76%. In contrast, the control group that received conventional treatment displayed lower healing rates, with the minimum being 0%. Nevertheless, the control group exhibited a maximum healing rate of 60%. One study found that GM-CSF administration significantly increased blood vessel density in the ulcer following treatment. VEGF transcripts were located in keratinocytes at the ulcer margins both before and after GM-CSF treatment, while VEGF hybridization signals were distinctly present within the ulcer bed only after administration. In vitro analyses showed that VEGF transcription could be directly stimulated by GM-CSF in different monocytic cell lines.(Agrawal et al., 2003; Liu et al., 2014; Mann et al., 2001; Naim et al., 1970; Yan et al., 2012; Yuan et al., 2015)

Keratinocyte Proliferation

Two studies ((Mann et al., 2001; Yan et al., 2012)) reported a comparison of keratinocyte proliferation between GM-CSF and conventional therapy groups. The findings revealed that GM- CSF significantly boosted keratinocyte proliferation in comparison to conventional therapy. In the GM-CSF group, keratinocyte proliferation increased by more than four times compared to the control group.

New Blood Vessels

Studies ((Mann et al., 2001; Yan et al., 2012)) Both groups demonstrated an increase in blood vessels before and after treatment. However, the findings indicated that GM-CSF treatment resulted in a significantly greater increase in blood vessels compared to conventional therapy, with the rate of increase reaching up to ninefold in the GM-CSF group. The GM-CSF treatment resulted in a high number of new blood vessels, with 46 vessels per high-power field compared to 5 vessels per high-power field in the control group.

Granulation Tissue Formation

One study observed a quicker and more extensive rate of granulation tissue formation in the GM-CSF group compared to the control group. The wound area in the GM-CSF group showed a marked decrease, and although the control group's wound area was nearly filled with granulation tissue, the condition in the GM-CSF group was notably better.(Liu et al., 2014)

Side Effects of the Treatment

All articles ((Agrawal et al., 2003; Liu et al., 2014; Mann et al., 2001; Naim et al., 1970; Yan et al., 2012; Yuan et al., 2015)) indicated the GM-CSF group exhibited no side effects throughout the studies, with the longest follow-up period extending up to four years post-intervention. One study noted side effects in two participants in the control group, manifesting as infections unresponsive to antibiotic treatment, which ultimately necessitated below-knee amputation.

Quality of Evidence and Risk of Bias

This review utilized the Cochrane risk-of-bias tool 2 (RoB 2) for designing randomized controlled trials, with assistance from the RevMan 5.4.1 software. Among the nine studies reviewed, eight exhibited a high risk of bias related to outcome assessment blinding. Most of theincluded studies followed a single-blind design, with only one study implementing double- blinding for both participants and researchers (Figure 2).

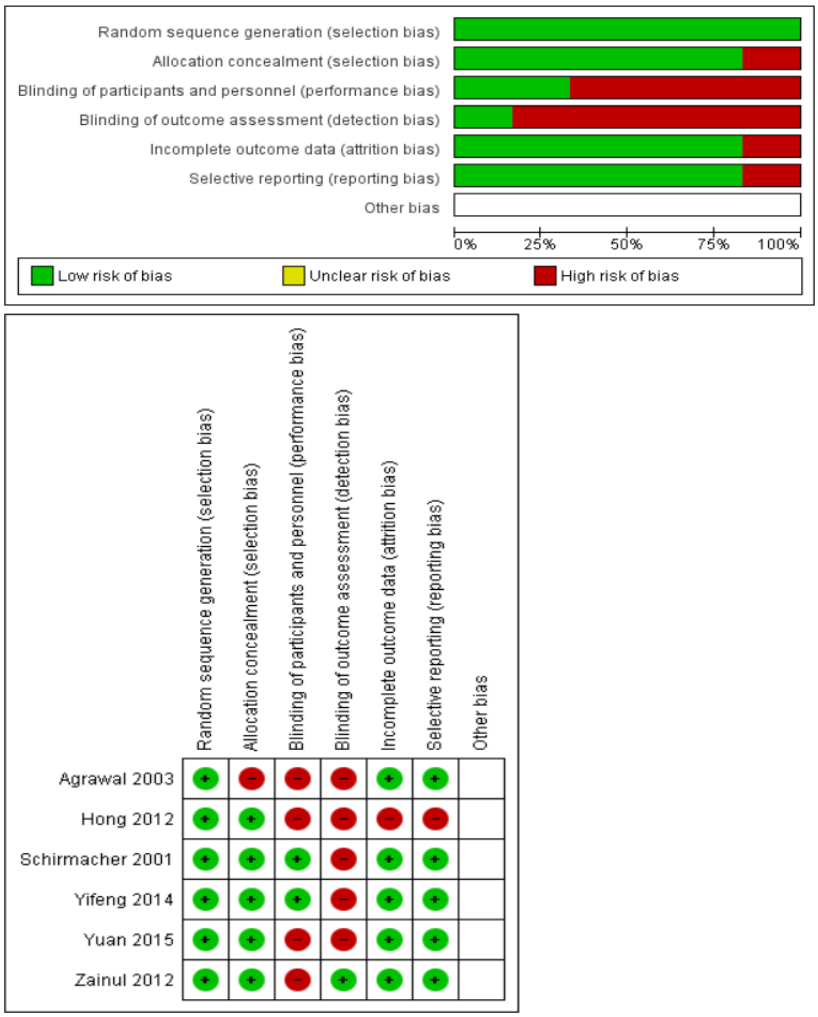

Figure 2 Study bias risk assesment.

Table 1.

Study results from the included study

Author (Year)	Study Design	Total sample/ intervention	Intervention	Control	Duration Intervention	R
Schirmacher, 2001(Mann et al., 2001)	Experimental, in vivo	9/5	GM-CSF transgenic	Negative control (solvent)	16 days	Blood vessels: Intervention : 97.7 Control : 59.69 ± Keratinocytes: Intervention : 51 ± Control : 34 ± 8
Yifeng, 2014(Liu et al., 2014)	Experimental, in vivo	8/4	rhGM-CSF topical gel	Negative control (solvent)	14 weeks	Wound healing r Intervention : (41 Control : (31 ± 9)
Agrawal, 2003(Agrawal et al., 2003)	Experimental, clinical trials	32/16	rhGM-CSF injection	Normal saline	12 weeks	Wound area redu Intervention : from to 1.38 cm² at wee Control : from 30. week 12
Yan, 2012(Yan et al., 2012)	Experimental, clinical trials	65/32	rhGM-CSF hydrogel	Hydrogel without rhGM-CSF	14 days	Wound healing r Intervention : 97.5 Control : 85.9 ± 6.8
Yuan, 2015(Yuan et al., 2015)	Experimental, clinical trials	42/21	rhGM-CSF	Mupirocin	4 weeks	Wound diameter Intervention : 97.5 Control : 85.9 ± 6.
Zainul, 2012(Naim et al., 1970)	Experimental, in vivo	8/4	rhGM-CSF injection	Dexamethasone	7 days	Keratinocytes: Intervention : 186 Control : 39 cells p Neovascularizatio Intervention : 46 n HPF Control : 5 new bl

DISCUSSION

Diabetic foot ulcer (DFU)'s pathological mechanisms are explained through a triad, which consists of neuropathy, secondary infection stemming from foot trauma, and vascular insufficiency. (Raja et al., 2023) The lack of protective sensation in the feet makes diabetic patients susceptible to trauma and ulceration. This sensory impairment is caused by hyperglycemia- induced upregulation of sorbitol dehydrogenase and aldose reductase, resulting in increased production of sorbitol and fructose. The accumulation of these glucose metabolites results in osmotic stress, subsequently impairing nerve cell conduction and myoinositol synthesis.(Kaur et al., 2023; Ramirez-Acuña et al., 2019) Moreover, diabetes can lead to autonomic neuronal dysfunction, which impairs sweat production, making the feet prone to dryness, fissuring, and skin cracking. Additionally, motor neuron dysfunction can result in muscle atrophy and structural abnormalities in the feet, causing elevated pressure at specific zones of the plantar foot and thereby increasing the risk of ulcer formation (Raja et al., 2023)

The normal wound healing process can be delineated into four primary stages. Initially, during the "hemostasis" phase, there is vasoconstriction, platelet aggregation, and the mobilization of circulating coagulation factors to the wound site. Following this, the "inflammation" phase is marked by the recruitment of inflammatory cells and the release of inflammatory mediators. Macrophages release matrix metalloproteinase (MMP)-9, while neutrophils produce neutrophil extracellular traps (NETs).(Raziyeva et al., 2021) As the inflammation diminishes, the "proliferation" phase ensues, characterized by the proliferation

and migration of skin cells such as keratinocytes to the wound bed, with the secretion of epidermal growth factor (EGF) aiding in this process. During the final remodeling phase, new tissue is formed and structured through the extracellular matrix and neovascularization. This process involves fibroblasts secreting fibroblast growth factor (FGF) and vascular endothelial cells secreting vascular endothelial growth factor (VEGF).(Farooq et al., 2021) These sequential stages ensure the effective healing of wounds, restoring the structural and functional integrity of the skin.(Deng et al., 2023).

Numerous theories have been posited to elucidate why certain wounds, including DFU, transition to a chronic, non-healing state. Despite the etiological diversity among chronic wounds, they frequently exhibit shared pathophysiologic characteristics. These characteristics involve the interactions of multiple cell types, components of the extracellular matrix, and regulatory immunologic factors. Chronic wounds are notably marked by a significant reduction in cellular division, which subsequently hampers cellular growth and proliferation.(Zhao et al., 2016) Diabetic foot ulcers frequently stagnate during the inflammatory phase, largely due to the accumulation of advanced glycation end products (AGEs). The presence of AGEs exacerbates oxidative stress and inflammation, contributes to skin rigidity, and diminishes the adhesion of innate immune cells. Furthermore, the suppression of the immune-cell-signaling p38/MAPK pathway impedes the removal of damaged cells and hinders the migration of primary skin cells (keratinocytes).(Lazarus et al., 2022).

A deficiency in GM-CSF results in diminished neutrophil and macrophage chemotaxis and infiltration, lowered expression of signal transducer and activator of transcription 3 (STAT3), inadequate macrophage differentiation, and a decrease in efferocytotic function.(Sawaya et al., 2020) Additionally, PPAR-γ expression is impaired, and the transition from pro-inflammatory M1 macrophages to pro-healing M2 macrophages is hindered. These insufficiencies in macrophage function obstruct granulation tissue formation, angiogenesis dependent on vascular endothelial growth factor (VEGF), and the differentiation of contractile myofibroblasts. Collectively, these factors contribute to delayed wound healing.(Briganti et al., 2024; Lazarus et al., 2022)This systematic review sought to evaluate and synthesize the clinical efficacy and safety of GM-CSF in treating diabetic ulcers, as compared to standard care or alternative therapies. The findings suggest that GM-CSF effectively enhances the overall ulcer healing rate, shortens theulcer healing time, reduces ulcer size, promotes granulation tissue formation, and boosts keratinocyte proliferation. However, the results varied due to differences in sample sizes, GM- CSF formulations, concentrations, and intervention durations across the studies.

A recent case series supports the findings of the systematic review regarding the potential benefits of rhGM-CSF as an adjunctive therapy for diabetic foot ulcers. In the study, neuropathy was assessed using objective measures such as motor nerve conduction velocity and sensory threshold tests. Wound area was measured quantitatively with ImageJ software, and treatment response was defined as a reduction in ulcer size to less than 5% of the initial area. Standard wound care was consistently applied, and rhGM-CSF was administered locally through infiltration. Although data from the accompanying randomized controlled trial are unpublished, preliminary results showed a statistically significant pro-healing effect. These findings reinforce the potential of rhGM-CSF to enhance wound healing and reduce complications in patients with diabetic foot ulcers. (Zhang et al., 2024)Another study conducted on diabetic mice also demonstrated that delayed wound healing in diabetes mellitus (DM) could be aided by GM-CSF administration. The research reported a reduction in GM-CSF production during the early phase of diabetic wounds, followed by decreased leukocyte infiltration. Additionally, the study noted a delay in wound closure in diabetic mice not

receiving GM-CSF, with a one-week delay in wound closure observed in DM mice without GM-CSF compared to non-DM mice without GM-CSF. GM-CSF administration significantly accelerated the delayed wound healing found in diabetic mice without GM-CSF. This study also showed significant increases in IL-6 and monocyte chemoattractant protein (MCP)-1 following exogenous GM-CSF injection. Both play roles in wound healing, with interleukin-6 inducing keratinocyte proliferation and MCP-1 recruiting neutrophils and mononuclear cells. GM- CSF administration also reduced collagen deposition, restored microvascular formation, and normalized macrophage and neutrophil infiltration levels to non-DM levels.(Zhang et al., 2024) A case report provided evidence of ulcer healing with GM-CSF application. Granulocyte- macrophage stimulating factor was administered via intradermal injection of 400 mcg twice weekly for two months. The patient experienced no clinical side effects or abnormal blood count results. The diabetic ulcer improved after one year of treatment.(Lazarus et al., 2022).

Granulocyte-colony stimulating factor (G-CSF) is known to enhance the release of neutrophil endothelial progenitor cells from the bone marrow and improve neutrophil function, which is often compromised in individuals with diabetes, making it a potentially valuable adjunctive therapy in diabetic foot infections. A systematic review aimed to evaluate the effectiveness of adjunctive G- CSF, compared to placebo or no growth factor, in improving infection outcomes, cure rates, and wound healing in diabetic patients with foot infections. The review included five randomized controlled trials with a total of 167 participants, in which various G-CSF regimens were tested. While the addition of G-CSF did not significantly improve infection resolution or wound healing, it was associated with a significantly lower risk of lower extremity surgical interventions, including amputations, and a reduced duration of hospital stay. These findings suggest that, although current evidence is limited, G-CSF may offer clinical benefits by decreasing the likelihood of surgery and shortening hospitalization time, supporting its consideration in the management of diabetic foot infections, particularly in cases where limb preservation is critical. (Cruciani et al., 2013).

Findings from an experimental study using a diabetic mouse model support the results of the systematic review by demonstrating the potential role of exogenous GM-CSF in improving wound healing in diabetes. The study revealed a 50% reduction in endogenous GM-CSF levels in diabetic wounds compared to non-diabetic ones, highlighting an impaired healing environment.diabetic mice, suggesting the benefits of GM-CSF are specific to impaired diabetic wound healing. These results underline the therapeutic relevance of GM-CSF in enhancing wound repair in diabetes and support its consideration as an adjunctive treatment in clinical settings. (Fang et al., 2007) Subcutaneous GM-CSF injections were also found to aid in the healing of chronic refractory wounds. Nine out of 29 wounds healed completely in 6 weeks, 11 reduced by 50%, and 7% showed minimal response after GM-CSF injection. More than 20 wounds healed within 3 weeks. GM-CSF enhances wound healing by increasing granulocyte and macrophage activity, antimicrobial activity, phagocytosis, and oxidative metabolism. Its impact on leukocyte infiltration, monocyte accumulation, fibroblast, myofibroblast, and keratinocyte proliferation, and angiogenesis induction also contribute to wound healing. GM-CSF facilitates wound healing by inducing TNF synthesis and release, which interacts with other cytokines.(Mann et al., 2001; Shiomi & Usui, 2015).

This aligns with previous findings showing the beneficial role of GM-CSF in diabetic wound healing, as further demonstrated by a recent study utilizing injectable hydrogels for the sequential delivery of GM-CSF and VEGF. In this model, GM-CSF effectively initiated the inflammatory phase, while VEGF promoted angiogenesis, leading to increased vascularization, reduced wound depth, and improved granulation tissue formation by day 10. The study highlights the importance of addressing impaired inflammatory and angiogenic

responses in diabetic wounds and supports the use of GM-CSF as a critical early-phase mediator to enhance healing outcomes. These results further strengthen the evidence supporting GM-CSF as a promising adjunctive therapy in the management of diabetic foot ulcers. (Kinali et al., 2024) Diabetic neuropathic ulcer patients showed complete healing by week 4 after rhGM-CSF administration. The study reported that diabetic ulcers responded better than vascular ulcers to rhGM-CSF application. Another study found that diabetic ulcer patients receiving GM-CSF injections healed faster than the placebo group. The perilesional GM-CSF injection effect was evident by the first week and significantly responded by the twelfth week. Approximately 87.5% of participants in the GM-CSF group experienced complete healing, compared to only 25% in the placebo group. Both studies reported no significant side effects after GM-CSF administration.(Agrawal et al., 2003)

CONCLUSION

All analyzed articles addressed the total ulcer healing rate following GM-CSF administration compared to conventional therapy, showing that GM-CSF significantly enhanced the total ulcer healing, with rates reaching up to 100%, outperforming conventional therapy. The studies demonstrated that GM-CSF effectively doubled the total ulcer healing rate compared to the control group. Additionally, the articles indicated that GM-CSF accelerated the ulcer healing process, with the fastest healing time being 21 days, compared to conventional therapy. GM-CSF significantly hastened ulcer healing relative to the control. None of the analyzed articles reported any adverse effects during the observation period after GM-CSF administration.(Agrawal et al., 2003; Liu et al., 2014; Mann et al., 2001; Naim et al., 1970; Yan et al., 2012; Yuan et al., 2015) This systematic review has certain limitations. The variability among the included studies, regarding different variables, makes it challenging and currently unfeasible to conduct a comprehensive meta-analysis for all variables. Sample sizes in each study were also relatively small. Additionally, 89% of the studies exhibited a high risk of bias due to less rigorous outcome assessments. Future research should employ double-blind RCT designs with larger sample sizes to enhance research quality. Despite these limitations, this systematic review has significantly contributed to demonstrating the clinical effects of GM-CSF for treating DFU.

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