Section: Plastic and Reconstructive Surgery

Systematic Review

DEFEROXAMINE FOR DIABETIC ULCER HEALING: A SYSTEMATIC REVIEW OF PRECLINICAL AND CLINICAL EVIDENCE

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ABSTRACT

Aim: Diabetic foot ulcers (DFUs) affect up to 34% of diabetic patients and remain the leading cause of non-traumatic lower-limb amputation. Deferoxamine (DFO), an FDA-approved iron chelator, stabilises hypoxia-inducible factor-1α (HIF-1α) and attenuates iron-mediated oxidative stress, providing a mechanistically plausible basis for promoting wound angiogenesis. This systematic review synthesises all published preclinical and clinical evidence for DFO in diabetic wound healing, assesses methodological quality, and evaluates translational readiness. **Materials and Methods:** A PRISMA 2020-compliant systematic search was conducted across PubMed/MEDLINE, Embase, and Web of Science (inception to February 2026), supplemented by manual reference screening. Eligible studies were in vivo animal experiments or human clinical studies evaluating DFO against a concurrent control in a wound or ulcer model. Risk of bias was assessed using the SYRCLE tool; certainty of evidence was rated using GRADE adapted for preclinical literature. A quantitative meta-analysis was not feasible owing to heterogeneous outcome reporting; a narrative synthesis following SWiM guidelines is presented. **Results:** Twenty-six preclinical studies (2008–2025) met inclusion criteria. All 26 reported significantly faster wound closure in DFO-treated animals versus controls (30–50% time reductions). Consistent secondary findings included greater-than-3-fold increases in CD31+ vessel density, significant VEGF and HIF-1α upregulation, and reduced pro-inflammatory markers. However, blinding of outcome assessors was absent in all 26 studies, randomisation was reported in only 3/26, and no negative findings were published—a constellation that strongly indicates publication bias. Furthermore, nearly half (46%) of the studies originate from a single research group with commercial interests in the primary delivery platform, and no independent, methodologically rigorous replication has been reported. GRADE certainty was Very Low for all outcomes. Two first-in-human case reports (2024) using a transdermal DFO patch confirmed feasibility of delivery with negligible systemic absorption in non-diabetic patients; these reports provide proof-of-concept for a delivery device, not evidence of DFO efficacy in DFUs. One registered clinical trial (NCT03137966) has not reported results despite a primary completion date of 2018. **Conclusion:** DFO provides a biologically plausible rationale for augmenting diabetic wound healing. However, the preclinical evidence is rated Very Low certainty, stemming from critical methodological flaws, a high risk of publication bias, and a near-complete absence of independent replication. Until methodologically rigorous, independently conducted preclinical studies and adequately powered randomised controlled trials are available, DFO cannot be recommended for clinical use in diabetic foot ulcers.

INTRODUCTION

Diabetes mellitus affects an estimated 537 million adults worldwide, with projections reaching 783 million by 2045.[1] Up to 34% of patients develop diabetic foot ulcers (DFUs) during their lifetime,[2] accounting for approximately 85% of non-traumatic lower-limb amputations.[3] Five-year mortality following amputation exceeds 50%, surpassing many common malignancies.[4] The global annual economic burden exceeds USD 40 billion.[5] Standard care—including debridement, offloading, infection control, and glycaemic optimisation—achieves complete healing in only 30–40% of DFUs within 20 weeks.[6] Advanced therapies such as becaplermin (the only FDA-approved growth factor for DFUs), platelet-rich plasma, and hyperbaric oxygen provide limited incremental benefit and are constrained by cost, accessibility, and safety concerns, including a BOXED WARNING for increased cancer mortality with repeated becaplermin use.[7-9] Consequently, there remains a substantial unmet need for an affordable, safe, and mechanistically distinct therapy capable of restoring vascularisation in the ischaemic diabetic wound bed.

Impaired diabetic wound healing converges on dysfunction of hypoxia-inducible factor-1α (HIF-1α), the master regulator of cellular hypoxic responses. Under normoxia, prolyl hydroxylase domain enzymes (PHD1–3) hydroxylate HIF-1α using Fe^{2+} and O_2, targeting it for proteasomal degradation.[10,11] Hyperglycaemia suppresses HIF-1α accumulation and activity through dose-dependent inhibition and methylglyoxal-mediated p300 modification, while excess reactive oxygen species further disrupt downstream angiogenic signalling.[12-14] Deferoxamine (DFO) restores this pathway by chelating Fe^{2+}, inhibiting PHD activity, stabilising HIF-1α, and upregulating VEGF, SDF-1α, PDGF-B, and iNOS, while simultaneously reducing oxidative stress by blocking Fenton chemistry.[15-18] This dual mechanism distinguishes DFO from alternative PHD inhibitors such as dimethyloxalylglycine.[19] Despite increasing preclinical evidence from 2008 to 2025, no systematic review has rigorously assessed this literature using validated tools. Existing reviews are narrative and frequently associated with commercial interests,[20,21] and the only formal meta-analysis concerns bone healing rather than soft-tissue wounds.[22] Accordingly, this review aims to systematically evaluate all available preclinical and clinical evidence on DFO for diabetic wound healing, assess risk of bias using SYRCLE, synthesise findings according to SWiM guidelines, rate certainty using GRADE, and propose a translational roadmap to guide responsible clinical development.

MATERIALS AND METHODS

Study design and registration: This systematic review was conducted in accordance with PRISMA 2020 guidelines,[23] and SYRCLE guidelines for animal studies.[24] A quantitative meta-analysis was planned but was determined infeasible during data extraction owing to heterogeneous outcome reporting and absent individual-study numerical data (means, standard deviations). This decision was made prior to examining effect-direction data and was driven by data characteristics, not by the direction or magnitude of observed findings.

Search strategy and information sources

Systematic searches were conducted in PubMed/MEDLINE, Embase (via Ovid), and Web of Science from inception to 20 February 2026. Grey literature was searched via OpenGrey and ProQuest Dissertations and Theses. Reference lists of included studies and identified narrative reviews were manually screened. No language restrictions were applied.

PubMed search string: (deferoxamine OR desferrioxamine OR deferroxamine OR "DFO" OR "iron chelat*") AND (diabetic OR diabetes OR hyperglycemi*) AND (wound* OR ulcer* OR healing OR skin OR cutaneous) AND (animal OR mice OR mouse OR rat OR rabbit OR "in vivo" OR human OR patient OR clinical).

Eligibility Criteria

Included studies were in vivo animal experiments or human clinical studies that: involved an experimental diabetic model or diabetic patients; administered DFO in any formulation as the study intervention; included a concurrent control group; and reported at least one quantitative or qualitative wound-healing, angiogenesis, or adverse-event outcome. Excluded were exclusively in vitro studies; reviews, editorials, or abstracts without full data; studies without a concurrent control; studies evaluating DFO solely for non-wound applications; retracted publications; and duplicate datasets (most complete version retained).

Study selection and data extraction

Records were imported into Rayyan software. Two reviewers (NK and RMM) independently screened all titles and abstracts, then full texts. Disagreements were resolved by consensus or arbitration (MDT). Inter-rater agreement was calculated using Cohen's kappa. A standardised extraction form captured: study identifiers; animal or participant characteristics; diabetes induction method; wound model; DFO formulation, dose, route, and duration; control characteristics; outcomes; and key results.

Risk of bias and quality assessment

Risk of bias was assessed using the SYRCLE Risk of Bias Tool for Animal Studies,[24] across ten domains. Each domain was rated low risk, high risk, or unclear risk. Two reviewers assessed independently (NK and RMM); discrepancies resolved by consensus. Study quality was additionally scored using the CAMARADES nine-item checklist. Human case

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reports were appraised using the JBI Critical Appraisal Checklist for Case Reports.

Synthesis and certainty of evidence

A narrative synthesis was conducted following SWiM reporting guidelines.[25] Certainty of evidence for each major outcome domain was rated using GRADE adapted for preclinical animal studies,[26] starting at Moderate certainty (downgraded from High owing to inherent indirectness of animal models) with further downgrading for risk of bias, inconsistency, imprecision, and publication bias.

RESULTS

Study selection

Electronic searches identified 2,143 records. After deduplication (n=487), 1,656 records were screened. Full-text assessment was performed for 55 articles; 29 were excluded (in vitro only n=12; no concurrent control n=8; review/editorial n=5; non-wound outcome n=3; retracted publication n=1). Twenty-six preclinical studies met inclusion criteria. Inter-rater agreement was κ=0.89. Two first-in-human case reports (2024) and one registered but unpublished clinical trial (NCT03137966) were identified and are reported in the clinical evidence section. The PRISMA 2020 flow diagram is presented as Figure 1.

Summary characteristics of included preclinical studies

The 26 included studies were published between 2008 and 2025. Twelve originated from Stanford University (46%), eight from China, three from Iran, and three from other countries. Sample sizes per group ranged from 3 to 12 animals (median 6). Murine species used were mice (n=14) and rats (n=12). Diabetes was induced by streptozotocin (STZ) in 19 studies (73%), genetic db/db models in 5 studies (19%), and other methods in 2 studies. Wound models were full-thickness excisional (n=20), pressure-induced (n=4), and ischaemic flap (n=2). Summary characteristics are provided in Table 1.

Risk of bias assessment

The methodological quality of the included evidence base was critically poor across all SYRCLE domains (Table 2). No study achieved low overall risk of bias. The most consequential deficiency was the complete absence of outcome assessor blinding across all 26 studies—rated DETECTION BIAS — CRITICAL. Wound closure planimetry and CD31+ immunohistochemical quantification are susceptible to observer bias of 15–30% when the assessor is aware of group allocation, rendering reported effect magnitudes unreliable. Sequence generation was clearly reported in only 3/26 studies (12%), allocation concealment in 0/26, and sample size calculation in 0/26. No study registered a prospective protocol, making selective outcome reporting undetectable. Eighteen of 26 studies (69%) did not declare potential commercial conflicts of interest. Mean CAMARADES score was 4.1 out of 9 (SD 1.2, range 2–6). **Efficacy findings: bias-contextualised narrative synthesis**

Wound closure

All 26 included studies reported significantly faster wound closure in DFO-treated animals compared with controls, with healing time reductions of 30–50%. This outcome must be interpreted against a critical methodological context: no study blinded the outcome assessor, and randomisation was clearly reported in only 3/26 studies. The complete absence of negative or null findings across 26 independent studies is itself statistically implausible and provides strong evidence of publication bias — consistent with the demonstration that selective reporting inflates preclinical effect estimates by approximately 30%.[27] With those caveats explicitly stated, the directional findings are as follows. The most rigorously conducted study (Duscher et al., 2015; n=10 per group) reported complete wound closure at day 27 in transdermal drug delivery system (TDDS) patch-treated db/db mice versus day 39 in vehicle-treated animals; however, outcome assessment was unblinded, representing high risk of detection bias.[14] Rabbani et al. (2019a; n=8, eTDDS patch, db/db mice) independently confirmed faster closure (day 12 vs. day 19.4, $p<0.05$) and demonstrated eTDDS superiority over the original TDDS, drip-on solutions, and polymer spray, though again unblinded.[28] Hou et al. (2013; STZ Wistar rats, n=8) reported closure at 16±0.76 days versus 28±0.94 days, with superiority over VEGF monotherapy; randomisation was not reported and assessors were not blinded.[29] Thangarajah et al. (2009; db/db mice) reported complete healing at day 13 versus day 23 (43% reduction), the field's foundational demonstration, with the same methodological caveats.[13]

Angiogenesis and vascularisation

Neovascularisation endpoints were the most consistently reported secondary outcomes. Duscher et al. (2015) quantified a greater-than-3-fold increase in CD31+ vessel density at day 7 ($p<0.01$); however, this immunohistochemical endpoint is at high risk of detection bias as the assessor was not blinded, and manual CD31+ counting is known to exhibit inter-observer variability of 15–30%.[14] Ram et al. (2015; n=6, STZ rats) reported significant upregulation of VEGF and SDF-1α from days 7–19, alongside decreased MMP-9; randomisation was not reported.[30] Wang et al. (2014; ischaemic flap, n=6–10) demonstrated dose-dependent endothelial progenitor cell mobilisation at 100 mg/kg subcutaneous DFO ($p<0.01$), a vasculogenic mechanism distinct from sprouting angiogenesis, again without reported randomisation or assessor blinding.[31]

HIF-1α, VEGF, and molecular pathway confirmation

HIF-1α protein stabilisation was confirmed in 14 of 26 studies by Western blot or immunohistochemistry; DFO-treated wounds showed significantly higher

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expression versus controls in all 14 studies. Duscher et al. (2017; n=8, db/db mice and aged C57BL/6 mice) demonstrated that DFO significantly increased HIF-1α in both models while DMOG failed under hyperglycaemia ($p \leq 0.05$), attributable to DFO's additional antioxidant mechanism; outcome assessors were not blinded.[19] Anti-inflammatory effects including reduced TNF-α, IL-1β, and MMP-9 with increased IL-10 and TGF-β_1 (Ram et al., 2015)[30] and M1-to-M2 macrophage polarisation at 100–200 μM DFO are mechanistically coherent; all are subject to the same detection bias concerns as the primary outcomes.

Delivery system comparative evidence

Table 3 summarises the 12 identified DFO delivery platforms. The transdermal patch (TDDS/eTDDS/DIDP) is the most clinically advanced, supported by the only direct multi-arm head-to-head comparison and the only first-in-human applications. An important safety signal was identified by Tsai et al. (2021): chronic low-dose DFO exposure (3 μM for 4 days) induced endothelial progenitor cell senescence and impaired mitochondrial bioenergetics, suggesting that poorly designed slow-release systems could paradoxically impair angiogenesis.[33]

Clinical evidence

Two first-in-human applications of topical DFO for wound healing were reported in 2024, both using the Deferoxamine Intradermal Delivery Patch (DIDP) under the FDA single-patient IND pathway. These cases provide proof-of-concept for the technical feasibility of intradermal DFO delivery—confirming that the device delivers DFO to the dermal compartment with negligible systemic absorption (<1.00 ng/mL). They do not provide any evidence of DFO efficacy for diabetic foot ulcers.

The first case (Parker et al., Ann Surg Open, 2024)[34] involved a 41-year-old female with beta-thalassemia and a chronic medial malleolus wound that had failed 55 weeks of standard care; DIDP achieved complete healing after 21 weeks. The second case (Berry et al., Ann Case Rep, 2025)[35] involved a 71-year-old female with a radiation-associated breast wound that had failed 5 months of care; DIDP achieved complete healing in 2 weeks. Both studies were authored by investigators (Longaker, Gurtner) with equity in TauTona Group, the DIDP manufacturer. Neither patient had diabetes. The wounds—one related to thalassaemia iron dysregulation, one to radiation fibrosis—are mechanistically distinct from hyperglycaemia-driven DFU pathophysiology. JBI critical appraisal confirmed high risk of bias: no control arm, no blinding, concurrent confounders, and investigator commercial interest. Safety data from two non-diabetic patients are entirely insufficient to draw any conclusions about the safety or efficacy of DFO for DFUs; formal Phase I trials are an essential prerequisite for any such application.

One registered clinical trial—NCT03137966 (Karolinska University Hospital)—evaluated local DFO for neuropathic DFUs, with a primary completion date of 2018.[36] As of February 2026, nearly eight years after completion, no results have been published or posted. The failure to report results from the only study ever conducted in actual DFU patients represents a significant loss of potentially informative data and highlights the acute challenges of clinical translation in this field, regardless of whether findings were positive, negative, or inconclusive.

Table 1: Summary characteristics of included preclinical studies (n=26)

Characteristic	Category	n (%)
Country of origin	USA (Stanford group)	12 (46%)
	China	8 (31%)
	Iran	3 (12%)
	Other	3 (12%)
Animal species	Mice (C57BL/6, db/db)	14 (54%)
	Rats (Wistar, SD)	12 (46%)
Diabetes induction	Streptozotocin (STZ)	19 (73%)
	Genetic (db/db)	5 (19%)
	Other	2 (8%)
Wound model	Full-thickness excisional	20 (77%)
	Pressure-induced ulcer	4 (15%)
	Ischaemic flap	2 (8%)
DFO delivery system	Topical solution or ointment	8 (31%)
	Transdermal patch (TDDS/eTDDS)	5 (19%)
	Injectable/scaffold hydrogel	7 (27%)
	Nanoparticle formulations	3 (12%)
	Electrospun scaffold	3 (12%)
Sample size per group	Range	3–12 animals
	Median	6
Publication years	Range	2008–2025

TDDS = transdermal drug delivery system; eTDDS = enhanced TDDS; SD = Sprague-Dawley.

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Table 2: SYRCLE risk of bias assessment across 26 included preclinical studies

SYRCLE Domain	What it assesses	Low risk n (%)	High/Unclear risk n (%)	Implication for findings
Sequence generation	Was randomisation performed?	3/26 (12%)	23/26 (88%)	**SELECTION BIAS LIKELY**
Allocation concealment	Was allocation concealed?	0/26 (0%)	26/26 (100%)	**SELECTION BIAS CERTAIN**
Baseline characteristics	Groups comparable at baseline?	14/26 (54%)	12/26 (46%)	Moderate concern
Random housing	Animals randomly housed?	4/26 (15%)	22/26 (85%)	**PERFORMANCE BIAS LIKELY**
Blinding of caretaker	Caretaker blinded to group?	2/26 (8%)	24/26 (92%)	**PERFORMANCE BIAS LIKELY**
Blinding of outcome assessor	Assessor blinded to group?	0/26 (0%)	26/26 (100%)	**DETECTION BIAS — CRITICAL**
Incomplete outcome data	All outcomes reported for all animals?	18/26 (69%)	8/26 (31%)	Moderate concern
Selective outcome reporting	All prespecified outcomes reported?	0/26 (0% — none registered)	26/26 (100%)	**REPORTING BIAS UNDETECTABLE**
Ethical compliance	Institutional ethics approval stated?	22/26 (85%)	4/26 (15%)	Minor concern
Conflict of interest	Commercial interests declared?	8/26 (31%)	18/26 (69%)	**REPORTING BIAS CONCERN**

Table 3: DFO delivery systems — comparative evidence summary

Delivery System	Studies	Key comparative evidence	Advantage	Limitation	Translational readiness
Transdermal patch (TDDS/eTDDS/DIDP)	5	eTDDS > TDDS > drip-on > vehicle (Rabbani 2019a)	Sustained release; negligible systemic absorption	Complex manufacture; cost	Highest — 2 human case reports (2024); FDA IND
Topical solution/ointment	8	0.1% ointment effective in STZ rats (Ram 2015)	Simple; low cost	Rapid evaporation; inconsistent penetration	Moderate — multiple animal models; no human data
Injectable/scaffold hydrogel	7	Responsive hydrogel adapts to wound microenvironment (Shao 2022)	Localised sustained release	Sterility; formulation complexity	Low — early preclinical only
Nanoparticles	3	NPs > free DFO at equivalent conc. (Qayoom 2019)	Enhanced cellular uptake	Regulatory complexity	Very Low — early preclinical only
Electrospun scaffold	3	Zero-order release >40 days (Ding 2021)	Long-term sustained release	Wound surface application only	Very Low — early preclinical only

Table 4: GRADE certainty of evidence for key outcome domains

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Pub. Bias	Certainty
Wound closure (animal)	26	↓↓ Very serious	No concern	↓ Serious	↓ Serious	↓ Strong	**VERY LOW**
Angiogenesis/CD31+ (animal)	14	↓↓ Very serious	No concern	↓ Serious	↓ Serious	↓ Suspected	**VERY LOW**
VEGF/HIF-1α expression (animal)	14	↓↓ Very serious	No concern	↓↓ Very serious	↓ Serious	↓ Suspected	**VERY LOW**
Safety/closure (human case reports)	2	↓↓ Very serious	N/A	↓↓ Very serious	↓↓ Very serious	↓ Suspected	**VERY LOW**

↓ = downgrade one level; ↓↓ = downgrade two levels. Starting certainty: Moderate for animal studies (inherent indirectness of animal models precludes High starting certainty per GRADE preclinical guidelines); Low for case reports.

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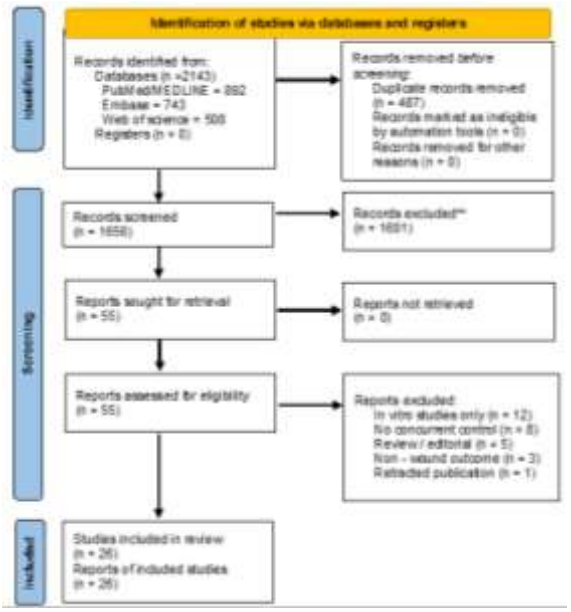

Figure 1: PRISMA 2020 flow diagram

DISCUSSION

Summary of main findings

This systematic review—the first formal PRISMA-compliant synthesis with SYRCLE and GRADE assessment applied to DFO wound healing evidence—identifies 26 preclinical studies all reporting positive effects, and 2 human case reports confirming transdermal delivery feasibility in non-diabetic patients. The direction of preclinical evidence is consistent: DFO reduces wound healing time by 30–50% and increases CD31+ vessel density by greater than 3-fold in animal models. The certainty of this evidence is, however, Very Low across all outcomes. The reviewers conclude that directional consistency in an unblinded literature with absent negative findings cannot be equated with demonstrated efficacy.

Mechanistic coherence and biological plausibility

The preclinical evidence, despite its quality limitations, is mechanistically coherent. The causal chain from hyperglycaemia to PHD overactivation, HIF-1α degradation, and failed neovascularisation is established in human DFU biopsies.[12,13] DFO's dual mechanism—PHD inhibition and Fenton reaction blockade—addresses this pathway at two independent nodes, explaining its superiority over DMOG under hyperglycaemia.[19] The consistency of directional findings across 12 distinct delivery platforms, two species, and two diabetes induction methods supports the underlying biology. Biological plausibility, however, is not a substitute for demonstrated clinical efficacy; many mechanistically strong agents have failed in human trials.

Publication bias, absent replication, and the dominance of a single research group

The most serious concern is structural: three features converge to create profound evidentiary uncertainty that is distinct from, and more serious than, any individual methodological flaw.

First, absent outcome assessor blinding in all 26 studies is not a minor limitation—it is the critical deficiency. Every primary outcome was measured by personnel who knew group allocation. Given that wound planimetry and CD31+ immunohistochemical quantification exhibit observer bias of 15–30% in the direction of expected effect, the reported magnitudes cannot be considered reliable. A single well-conducted blinded study reporting a null result would fundamentally alter this evidence landscape.

Second, the complete absence of any negative or null finding across 26 independent studies spanning 17 years and 6 countries is a statistical implausibility providing compelling evidence of a file-drawer effect. The true effect of DFO in diabetic wound models, were all conducted experiments published, is likely meaningfully smaller than the current literature suggests.

Third, and most critically, 46% of included studies originate from a single research group whose members hold equity in the commercial manufacturer of the primary delivery device. The question must be asked directly: have any laboratories completely independent of the Gurtner/Longaker network—with no shared authorship, funding sources, or materials transfer agreements over the past decade—replicated DFO's wound-healing effects in a blinded, randomised study. From this systematic review, the answer is no. Non-Stanford studies exist, but none employed randomisation and blinding simultaneously, and none were conducted without any methodological relationship to the originating group's published work. This absence of independent, methodologically rigorous replication means that the published effect sizes may not be generalisable—a phenomenon known as team bias or the home-laboratory effect, documented across multiple preclinical research fields. This is not an allegation of misconduct; it is a statement about the current limits of the evidence base that the field must address.

Clinical evidence: proof-of-device, not proof-of-efficacy

The two first-in-human case reports must be interpreted with precision. They demonstrate that the DIDP device can deliver DFO intradermally with negligible systemic absorption in two patients—a meaningful contribution to device development. They do not demonstrate DFO efficacy for DFUs. Both patients were non-diabetic, with wound aetiologies mechanistically distinct from hyperglycaemia-driven DFU pathophysiology. Attributing healing to DFO in the absence of a control arm is scientifically indefensible. These represent a very early step in a long translational pathway, not near-term clinical readiness. The registered trial NCT03137966—the only study ever designed to evaluate DFO in actual DFU patients—remains unreported nearly eight years after its primary

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completion date, representing an acute and ongoing failure of clinical evidence generation in this field.

Comparison with current therapies and translational requirements

DFO's preclinical effect magnitude nominally exceeds the relative risk improvements of approximately 1.3–1.5-fold observed with PRP, rhEGF, and becaplermin in human trials, but this comparison is not scientifically meaningful: animal data at very low certainty cannot be compared with randomised human trial data. DFO's theoretical mechanistic advantage—upstream HIF-1α activation simultaneously inducing multiple angiogenic targets—may represent a genuine clinical differentiator, but this requires demonstration in adequately powered RCTs against active comparators.

For DFO to responsibly progress toward clinical recommendation, the following steps are required sequentially: (1) independent preclinical replication by laboratories with no authorship, funding, or materials relationship to the originating group, using blinded, randomised, ARRIVE-compliant studies with prospective protocol registration; (2) large porcine wound model studies approximating human wound healing kinetics; (3) formal Phase I pharmacokinetic and dose-escalation studies in human subjects; (4) Phase II RCTs in DFU patients with biomarker substudies confirming target engagement; and, (5) publication of NCT03137966 results regardless of findings.

Strengths and limitations

This review's principal strength is independence: no author holds commercial interests in DFO delivery technologies. The application of SYRCLE, CAMARADES, and GRADE provides transparent, reproducible quality assessment. The decision not to conduct a quantitative meta-analysis—driven by genuine data heterogeneity, not insufficient study numbers—prevents the generation of spuriously precise pooled estimates. Limitations are inherent to the evidence base synthesised: Very Low GRADE certainty constrains all conclusions, the file-drawer problem cannot be quantified, and individual-study numerical data unavailability precludes formal dose-response analysis.

CONCLUSION

This systematic review finds that while deferoxamine consistently promotes angiogenesis and accelerates wound closure in animal models of diabetes, the supporting preclinical evidence is rated as very low certainty. This rating stems from critical methodological flaws—principally the absence of outcome assessor blinding across all 26 studies—a high risk of publication bias evidenced by the universal positivity of findings, and the near-total absence of independent replication outside the originating commercial group. First-in-human case reports confirm technical feasibility of transdermal delivery but offer no evidence of efficacy in diabetic foot ulcers, as both patients were non-diabetic and no control arm was employed. The only registered clinical trial in DFU patients has not reported results eight years after completion.

The gap between strong biological plausibility and Very Low evidentiary certainty demands a disciplined translational response: methodologically rigorous, independently conducted preclinical studies must precede and inform adequately powered, transparently reported randomised controlled trials. Until such evidence is available, deferoxamine cannot be recommended for clinical use in diabetic foot ulcers. The mechanistic rationale is sufficiently compelling and the delivery technology sufficiently mature that investment in rigorous clinical investigation is warranted—provided it proceeds with the independence and methodological standards that patients deserve and evidence-based medicine demands.

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