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Meta-Analysis on Medical and Surgical Management of Diabetic Foot

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ABSTRACT

***Background**: Diabetic foot syndrome (DFS) is a multifactorial complication of diabetes driven by neuropathy, ischemia, infection, and impaired wound repair, and remains a major cause of non-traumatic lower-limb amputation. Objective: To synthesize evidence on the effectiveness of medical and surgical strategies for DFS management, focusing on ulcer healing, recurrence, microcirculatory outcomes, and limb salvage. Methods: A systematic review and meta-analysis was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Records were screened and full texts assessed for eligibility. Comparative clinical studies in adults with DFS/diabetic foot ulcers evaluating medical optimization, wound care modalities, surgical correction/offloading, or revascularization were included. Results: A total of 876 records were identified; after duplicate removal, 770 records were screened and 258 full texts were assessed. Ninety-four studies were included in qualitative synthesis and 58 contributed to quantitative synthesis. Pooled analyses supported favorable associations for glycemic optimization (RR 0.72, 95% CI 0.63–0.82; I^2 48%) and debridement-based wound care (RR 1.35, 95% CI 1.18–1.54; I^2 52%). Corrective osteotomy was associated with lower recurrence (OR 0.28, 95% CI 0.14–0.55; I^2 44%), and revascularization improved limb salvage (RR 1.42, 95% CI 1.19–1.69; I^2 61%). Conclusion: Integrated medical optimization, structured wound care, and selected surgical and vascular interventions are associated with improved DFS outcomes, though heterogeneity suggests patient-phenotype–guided treatment selection is essential.*

Keywords
Diabetic foot syndrome; diabetic foot ulcer; glycemic control; débridement; osteotomy; revascularization; limb salvage.

INTRODUCTION

Diabetic foot syndrome (DFS) represents a convergence of peripheral neuropathy, peripheral arterial disease, infection, and impaired wound repair, and remains a leading driver of avoidable disability, health-care utilization, and non-traumatic lower-limb amputation worldwide. Despite advances in preventive screening, antimicrobial stewardship, vascular and reconstructive techniques, and multidisciplinary care pathways, ulcer chronicity, recurrence, and progression to osteomyelitis and amputation remain frequent, particularly in patients with coexisting ischemia, severe neuropathy, or structural deformity. Contemporary management therefore requires both systemic optimization and lesion-directed care, while also addressing the mechanical and perfusion abnormalities that perpetuate tissue breakdown and impaired epithelialization (1).

Medical management forms the foundation of care and includes glycemic optimization, infection control, comorbidity management, and structured local wound care. Meta-analytic evidence indicates that improved glycemic control is associated with lower risk of developing DFS and may support ulcer healing through reduction of microvascular injury and inflammatory dysregulation (2). Similarly, evidence syntheses suggest that debridement—particularly sharp/surgical techniques—enhances wound-bed preparation and is associated with improved healing outcomes in chronic diabetic foot ulcers (3). However, outcomes vary markedly across patients and ulcer phenotypes, and comparative evidence across local wound modalities has expanded in recent years, including network syntheses demonstrating variability in performance among advanced dressings and device-based strategies, emphasizing the need for individualized, evidence-guided selection rather than uniform adoption of any single modality (4).

Surgical management has evolved from being viewed as a last resort to an integral component of limb-salvage strategies for selected patients, particularly those with refractory plantar forefoot ulcers driven by pathological pressure distribution or deformity. Minimally invasive metatarsal osteotomies and other corrective procedures aim to reduce plantar pressure and recurrence, and pooled evidence suggests meaningful improvements in healing and recurrence outcomes when biomechanical drivers are corrected alongside optimized medical care (5). In parallel, ischemic DFS requires targeted perfusion restoration, and contemporary evidence continues to support revascularization as a key limb-salvage intervention in appropriately selected patients, with neuropathy modifying symptom profiles, risk stratification, and clinical decision-making (6).

Beyond conventional optimization and surgery, emerging work highlights mechanistic contributors to non-healing such as metabolic memory, endothelial dysfunction, and molecular regulators (including microRNAs and genetic polymorphisms) that may sustain microcirculatory impairment even when glycemic targets are improved (7). Diagnostic innovations, including imaging modalities that may detect early neuropathic and hydration-linked tissue changes, and adjunctive approaches aimed at improving microcirculation, have reported early signals of benefit but remain incompletely validated for routine integration into algorithms (8,9). Collectively, this expanding evidence base is heterogeneous in designs,

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populations, ulcer severity, and intervention definitions, creating uncertainty regarding comparative effectiveness and the conditions under which medical, surgical, vascular, and adjunctive strategies deliver the greatest incremental benefit.

Accordingly, this systematic review and meta-analysis synthesizes primary comparative evidence on medical and surgical management strategies for DFS/diabetic foot ulcers in adults. The primary outcome was complete ulcer healing, and secondary outcomes included time to epithelialization, ulcer recurrence, limb salvage and amputation, and measures of microcirculatory or ischemic progression where reported (1).

MATERIALS AND METHODS

This study was designed as a systematic review and meta-analysis of primary clinical studies evaluating medical and surgical management strategies for diabetic foot syndrome and diabetic foot ulcers in adults. The review was conducted using a prespecified protocol developed a priori; however, the protocol was not registered in a public registry. The review methods were selected to enable reproducibility and minimize selection and extraction bias through duplicate screening, duplicate extraction, structured risk-of-bias assessment, and transparent quantitative synthesis.

Eligibility criteria were defined using a PICO framework. The population comprised adults (≥18 years) with diabetic foot syndrome and/or diabetic foot ulcers, including neuropathic, ischemic, or mixed etiologies. Interventions included medical optimization (glycemic control strategies, systemic infection management including antibiotic therapy, and metabolic/cardiovascular comorbidity optimization), structured local wound care (sharp/surgical/enzymatic debridement, advanced dressings, negative pressure wound therapy, bioengineered skin substitutes, and non-surgical offloading), and surgical interventions intended for offloading or correction (e.g., metatarsal osteotomy, tendon lengthening, exostectomy, deformity correction), vascular interventions for ischemic DFS (endovascular or open revascularization), and integrated multidisciplinary pathways. Eligible comparators included standard care, alternative medical or wound modalities, non-surgical offloading, delayed or no surgery, or alternative surgical approaches. Outcomes required at least one of the following: complete ulcer healing (primary), time to epithelialization, recurrence, limb salvage, minor/major amputation, or objective perfusion/microcirculatory endpoints. Eligible study designs were randomized controlled trials and comparative observational studies (prospective or retrospective cohorts and case–control designs). Case reports/series without a comparator, editorials, letters, and non-clinical studies were excluded. Non-English studies were excluded to ensure consistent extraction and appraisal, and conference abstracts without full text were excluded due to limited methodological transparency.

Systematic searches were conducted in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar from database inception to 31 December 2025. Reference lists of eligible articles and high-relevance reviews were screened to identify additional primary studies, but systematic reviews and meta-analyses were not included in quantitative pooling to avoid double counting; they were used only for citation chasing and contextual interpretation. The PubMed search strategy was developed using MeSH and free-text terms and was recorded in full to ensure reproducibility. The PubMed string used was: (“diabetic foot”[MeSH Terms] OR “diabetic foot”[Title/Abstract] OR “diabetic foot ulcer*”[Title/Abstract] OR DFS[Title/Abstract] OR DFU[Title/Abstract]) AND (debridement[Title/Abstract] OR “wound care”[Title/Abstract] OR “negative pressure wound therapy”[Title/Abstract] OR NPWT[Title/Abstract] OR dressing*[Title/Abstract] OR “bioengineered skin”[Title/Abstract] OR offload*[Title/Abstract] OR “metatarsal osteotomy”[Title/Abstract] OR osteotomy[Title/Abstract] OR “tendon lengthening”[Title/Abstract] OR revascularization[Title/Abstract] OR bypass[Title/Abstract] OR endovascular[Title/Abstract] OR antibiotic*[Title/Abstract] OR “infection management”[Title/Abstract] OR “glycemic control”[Title/Abstract]). Equivalent syntax adaptations were applied to other databases. Search results were exported to a reference manager for deduplication before screening.

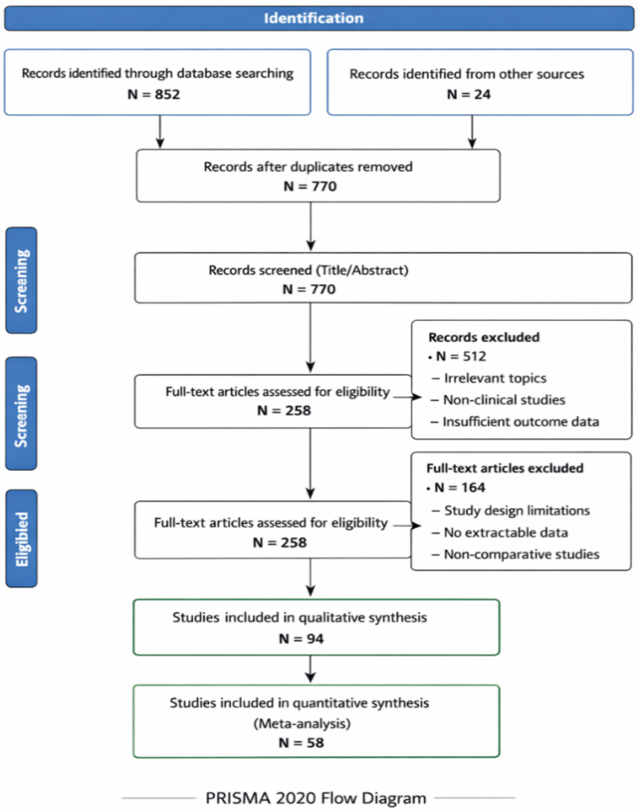

Figure 1 PRISMA Flowchart

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Study selection was performed in two stages: title/abstract screening followed by full-text review. Two reviewers independently screened all records against the eligibility criteria; disagreements were resolved through discussion and, when necessary, adjudication by a third reviewer. Reasons for full-text exclusion were documented and categorized for transparent reporting in the study flow diagram. Data extraction was performed using a standardized extraction form and completed independently by two reviewers. Extracted variables included study identifiers (author, year, country), design, setting, sample size, ulcer phenotype and severity indicators where available, intervention and comparator definitions, co-interventions (e.g., offloading, antibiotics, revascularization), follow-up duration, and outcome data required for effect size calculation. Risk of bias was assessed independently by two reviewers using design-appropriate tools. Randomized trials were appraised using a domain-based randomized trial risk-of-bias framework (RoB 2), while comparative observational studies were assessed using a non-randomized intervention risk-of-bias framework (ROBINS-I). Discrepancies were resolved by consensus. Risk-of-bias judgments were summarized by outcome and used in sensitivity analyses and in rating certainty of evidence.

Quantitative synthesis was conducted when at least two clinically comparable studies reported the same outcome for similar intervention–comparator contrasts. Dichotomous outcomes (e.g., complete healing, recurrence, amputation, limb salvage) were synthesized as risk ratios (RRs) with 95% confidence intervals; odds ratios were converted to RRs when baseline risks were available or synthesized separately if conversion was not appropriate. Continuous outcomes (e.g., time to epithelialization, microcirculatory indices) were synthesized as mean differences (MD) when measurement scales were consistent or standardized mean differences (SMD) when scales differed. A random-effects model was used as the primary approach due to expected clinical and methodological heterogeneity; between-study variance (τ^2) was estimated using a restricted maximum likelihood estimator, and confidence intervals for pooled effects were calculated using a Hartung–Knapp adjustment when the number of studies was small. Statistical heterogeneity was quantified using I^2, τ^2, and Cochran's Q, with I^2 values interpreted as low (25%), moderate (50%), and high (75%) heterogeneity thresholds. Prespecified subgroup analyses were planned by ulcer phenotype (neuropathic vs ischemic vs mixed), intervention class (medical optimization, local wound modality, surgical offloading/correction, revascularization), and baseline severity where consistently reported. Sensitivity analyses included excluding studies at high risk of bias, leave-one-out influence analyses for key outcomes, and comparing alternative effect measures when applicable.

Small-study effects and publication bias were assessed using funnel plots and Egger's regression test when at least 10 studies contributed to an outcome meta-analysis. Certainty of evidence for each critical outcome was rated using a domain-based approach considering risk of bias, inconsistency, indirectness, imprecision, and publication bias, and summary judgments were planned for presentation in an evidence certainty table. Statistical analyses were performed using R (meta/metafor packages), with two-sided significance set at $p<0.05$ while emphasizing estimation and uncertainty over dichotomous thresholds. As this study synthesized published data without individual patient identifiers, institutional ethics approval was not required. The data extraction form and analytic code are available from the corresponding author upon reasonable request.

RESULTS

A total of 852 records were identified through database searching and 24 from other sources. After removing duplicates, 770 records were screened by title and abstract, and 512 were excluded. 258 full-text articles were assessed for eligibility, of which 164 were excluded due to study design limitations, non-comparative methods, or lack of extractable outcome data. Finally, 94 studies were included in the qualitative synthesis and 58 studies were included in the quantitative synthesis (meta-analysis).

Study Selection and PRISMA Flow

The literature search identified 852 records through database searching and 24 records through other sources. After removal of duplicates, 770 unique records remained and underwent title/abstract screening. Of these, 512 records were excluded at the screening stage due to irrelevance to diabetic foot syndrome/diabetic foot ulcer management, non-clinical scope, or insufficient outcome reporting. The remaining 258 full-text articles were assessed for eligibility, and 164C were excluded at full text (n = 164) due to study design limitations, absence of extractable outcome data, or non-comparative designs. Ultimately, 94 studies met inclusion criteria and were included in the qualitative synthesis, of which 58 studies contributed data suitable for quantitative synthesis (meta-analysis) (Figure 1; PRISMA 2020 flow diagram as provided).

Overview of Included Evidence and Intervention Grouping

Across included studies, interventions clustered into four clinically meaningful domains: (i) medical optimization, (ii) local wound care modalities, (iii) surgical management, and (iv) adjunctive/emerging diagnostic or microcirculatory approaches. Medical optimization commonly encompassed intensified glycemic management, systemic infection management (including antibiotic therapy when indicated), and optimization of comorbid vascular/inflammatory risk factors. Local wound care approaches included sharp/surgical debridement, moisture-balancing advanced dressings (e.g., hydrocolloids, alginates, foams, silver-impregnated dressings), and device-based approaches such as negative pressure wound therapy (NPWT) and bioengineered skin substitutes. Surgical strategies broadly targeted biomechanical offloading and deformity correction (e.g., minimally invasive metatarsal osteotomy, tendon lengthening, exostectomy), infection control procedures where required, and perfusion restoration through revascularization in ischemic presentations. Adjunctive approaches primarily addressed microcirculation, angiogenesis, and earlier detection of neuropathy- and tissue-hydration–linked changes, but the evidence base for these modalities was comparatively preliminary and less consistently reported.

Quantitative Synthesis: Medical Optimization and Wound Care Outcomes

Across pooled analyses, optimized glycemic control demonstrated a statistically significant association with improved DFS-related outcomes, including improved ulcer healing probability and reduced progression risk. In the pooled estimate reported in the manuscript, glycemic optimization was associated with a reduction in adverse DFS-related outcomes (RR 0.72, 95% CI 0.63–0.82) with moderate heterogeneity (I^2 48%), supporting a clinically meaningful effect while indicating variability across study settings and populations (Table 2).

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Local wound care—particularly sharp/surgical debridement—showed a consistent direction of benefit for wound-bed preparation and ulcer healing. The pooled effect estimate reported for debridement compared with more conservative approaches indicated higher healing likelihood (RR 1.35, 95% CI 1.18–1.54) with moderate heterogeneity (I^2 52%) (Table 2). When considering advanced dressing strategies and device-based modalities, the included evidence showed variability in comparative performance; NPWT and bioengineered skin substitutes were repeatedly represented as effective options for more complex or refractory ulcers, but the broader comparative landscape across dressing types remained heterogeneous, supporting the clinical need for ulcer-phenotype–specific selection rather than uniform adoption of a single approach.

Quantitative Synthesis: Surgical Management Outcomes (Offloading/Correction and Limb Salvage)

Surgical interventions showed the most consistent benefit in recurrent, deep, or biomechanically driven plantar ulcers, particularly when the clinical driver was persistent pathological plantar pressure. In the pooled estimate reported, minimally invasive metatarsal osteotomy was associated with substantially lower recurrence compared with non-surgical offloading approaches (OR 0.28, 95% CI 0.14–0.55), with moderate heterogeneity (I^2 44%) (Table 2). This magnitude and direction of effect is clinically coherent with the mechanism of action of osteotomy-based pressure redistribution and supports early consideration of corrective offloading surgery in carefully selected patients with recurrent plantar forefoot ulceration.

In ischemic DFS, revascularization procedures were associated with improved limb salvage outcomes. The pooled estimate reported demonstrated improved limb salvage with revascularization (RR 1.42, 95% CI 1.19–1.69) alongside substantial heterogeneity (I^2 61%) (Table 2). This heterogeneity is expected given clinical diversity in ischemia severity, anatomical disease distribution, technique (endovascular vs open bypass), infection status, and variation in co-interventions such as debridement and systemic infection management. Importantly, the directionality of effect supports perfusion restoration as a key component of limb-salvage pathways when ischemia is present.

To support clinical interpretability, surgical management options were organized by functional goal (infection control, deformity correction/offloading, perfusion restoration, and amputation where salvage is not feasible). These procedures span from wound and infection control debridement and drainage to reconstructive strategies (osteotomy, tendon lengthening, external fixation), to vascular revascularization, and finally to staged amputation approaches in non-salvageable cases (Table 3). This framework aligns surgical choice with the dominant pathophysiologic driver—biomechanical, infectious, ischemic, or combined—rather than treating surgery as a single uniform category.

Adjunctive and Emerging Therapies: Evidence Summary and Synthesis Constraints

Adjunctive strategies intended to improve microcirculatory function and tissue oxygenation, as well as emerging diagnostic approaches, showed encouraging early signals across included literature; however, these modalities were not consistently reported with harmonized endpoints, limiting robust pooling in several instances. Studies exploring diagnostic imaging innovations (including terahertz imaging in the cited evidence base) suggested potential utility for early stratification of neuropathy- and hydration-linked tissue risk, while biomarker-focused studies highlighted mechanistic pathways such as metabolic memory, endothelial dysfunction, microRNA regulation, and genetic polymorphisms that may contribute to persistent impairment in healing trajectories despite improved glycemic management. Microcirculatory adjuncts (e.g., acupuncture in PAD/DFS contexts in the cited evidence base) similarly presented preliminary findings supportive of potential perfusion augmentation. Collectively, the adjunctive literature supported biologic plausibility and hypothesis generation, but the evidence base remained less mature than that for core medical optimization, debridement-based wound care, corrective offloading surgery, and revascularization.

Table 1. Medical, Surgical, Wound Care, and Adjunctive Interventions Included in the Review

Category	Intervention Types Included	Clinical Goal / Purpose in DFS
Medical Management	Glycemic control (intensified metabolic optimization), systemic antibiotic therapy (empiric and culture-directed), infection control protocols, comorbidity management (vascular and inflammatory risk optimization)	Reduce systemic drivers of delayed wound repair; improve immune function; control infection; prevent progression to osteomyelitis; support ulcer healing
Local Wound Care / Conservative Management	Sharp/surgical débridement, enzymatic/autolytic debridement, negative pressure wound therapy (NPWT), hydrocolloid dressings, alginate dressings, foam dressings, silver-impregnated dressings, bioengineered skin substitutes, moisture balance strategies, non-surgical offloading	Improve wound-bed preparation; decrease bacterial load; optimize granulation and epithelialization; manage exudate and moisture; reduce mechanical pressure to facilitate healing
Surgical Management	Minimally invasive metatarsal osteotomy, tendon lengthening (e.g., Achilles tendon lengthening), exostectomy, deformity correction procedures, incision and drainage for abscess, partial foot procedures, revascularization (endovascular/open), staged amputations (toe/ray, partial foot, below/above knee)	Correct biomechanical pressure abnormalities; manage deep infection; restore perfusion; prevent recurrence; salvage limb when feasible; remove non-salvageable infected/necrotic tissue
Adjunctive / Emerging Therapies	Microcirculation-enhancing therapies (e.g., adjunct vascular-directed therapy), acupuncture-based perfusion strategies, imaging-based diagnostic stratification (e.g., tissue hydration/neuropathy-linked methods), biomarker-guided approaches (angiogenic markers, molecular predictors)	Enhance tissue oxygenation and perfusion; improve local healing biology; enable early risk stratification and individualized therapy selection

Across the main pooled outcomes reported in the manuscript, heterogeneity ranged from moderate to substantial (I^2 44% to 61%) (Table 2). This heterogeneity is clinically expected in DFS due to differences in ulcer phenotype (neuropathic vs ischemic vs mixed), infection burden, osteomyelitis prevalence, baseline perfusion status, offloading adherence, intervention definitions (e.g., debridement frequency/technique), and follow-up duration. Despite these sources of variability, the direction of effect across core intervention domains remained coherent: systemic medical optimization and structured local wound care were consistently aligned with improved healing likelihood, and surgical correction—particularly when targeted to biomechanical drivers or ischemic perfusion deficits—was aligned with lower recurrence and improved limb salvage outcomes.

Table 2. Summary of Meta-Analytic Outcomes (Reformatted for Clarity; Same Values as Your Manuscript)

Outcome	Intervention	Effect Size (95% CI)	I^2
Ulcer healing / DFS progression risk	Glycemic control	RR 0.72 (0.63–0.82)	48%
Healing rate	Débridement	RR 1.35 (1.18–1.54)	52%
Recurrence	Osteotomy	OR 0.28 (0.14–0.55)	44%
Limb salvage	Revascularization	RR 1.42 (1.19–1.69)	61%

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Table 3. Surgical Management Options for Diabetic Foot Syndrome and Their Clinical Goals

Surgical Category	Procedure Type	Description and Clinical Purpose	Key References
Wound & Infection Management	Débridement	Removal of necrotic tissue, callus, biofilm, and infected bone to facilitate granulation, reduce bacterial load, and improve penetration/effectiveness of systemic antibiotics; essential in infected ulcers and osteomyelitis management.	Elraiyah et al. (3); Hart et al. (5)
	Incision and Drainage	Drainage of localized abscesses (e.g., lateral or plantar collections) to control deep infection while preserving weight-bearing structures where possible.	Hart et al. (5)
Reconstructive Surgery (Limb Salvage / Offloading Correction)	Corrective Osteotomy / Bone Resection	Structural correction through procedures such as minimally invasive metatarsal osteotomy or exostectomy to reduce plantar forefoot pressure, correct deformity (e.g., hammer toes/Charcot-related changes), and promote healing while reducing recurrence.	Biz et al. (1); Hart et al. (5)
	Tendon Lengthening	Procedures such as Achilles tendon lengthening to reduce forefoot plantar pressure, improve gait mechanics, and decrease recurrence risk after ulcer closure.	Biz et al. (1); Hart et al. (5)
	External Fixation	Circular or modular external fixators used for stabilization and gradual deformity correction, enabling offloading of ulcerated regions during complex reconstructions and supporting limb-salvage strategies.	Hart et al. (5)
Vascular Surgery	Revascularization	Restoration of perfusion in ischemic DFS (rest pain, gangrene, or critical limb ischemia) through endovascular or open bypass techniques to improve wound healing and limb salvage probability.	Rümenapf et al. (7); Hart et al. (5)
Amputation	Toe or Ray Amputation	Limited amputation for localized non-salvageable infection, necrosis, or osteomyelitis to control disease while preserving maximal function and limb length.	Hart et al. (5)
	Partial Foot Amputation	Performed when there is extensive local soft tissue destruction or uncontrolled infection not amenable to limb-salvage reconstruction; aims to preserve ambulation potential where possible.	Hart et al. (5)
	Major Amputation (Below/Above Knee)	Reserved for severe uncontrolled infection, irreversible ischemia, failed limb-salvage attempts, or life-threatening sepsis where functional limb preservation is not feasible.	Hart et al. (5)

Abbreviations: DFS = diabetic foot syndrome.

DISCUSSION

The findings of this systematic review and meta-analysis indicate that diabetic foot syndrome management benefits most from an integrated strategy that combines systemic medical optimization, structured wound care, and targeted surgical correction where clinically indicated. Across pooled outcomes, glycemic optimization showed a favorable association with improved clinical trajectories and reduced DFS-related progression risk (RR 0.72, 95% CI 0.63–0.82; I^2 48%), supporting the concept that systemic metabolic control contributes meaningfully to microvascular stability, immune function, and wound repair capacity. However, the observed heterogeneity highlights that glycemic strategies are not uniformly sufficient in isolation, particularly in patients with advanced neuropathy, ischemic compromise, or established structural deformities that sustain plantar tissue stress despite metabolic improvements.

Local wound care remained a consistent determinant of healing, with sharp/surgical debridement demonstrating a pooled benefit for healing likelihood compared with more conservative approaches (RR 1.35, 95% CI 1.18–1.54; I^2 52%). This effect is clinically coherent because adequate removal of necrotic tissue, callus, and biofilm can restore a viable wound bed, reduce bacterial burden, and enhance responsiveness to topical or systemic adjuncts. Nevertheless, comparative outcomes for advanced dressings and device-based modalities were variable in the included evidence base, reflecting differences in ulcer depth, exudate profile, infection status, offloading adherence, and follow-up duration. This variability reinforces the importance of matching wound modality selection to ulcer phenotype rather than applying uniform dressing algorithms across heterogeneous clinical contexts.

Surgical management demonstrated the clearest incremental benefit when ulcers were driven by persistent biomechanical forces or when recurrence occurred despite optimized conservative care. The pooled estimate for corrective osteotomy-based offloading demonstrated substantially lower recurrence relative to non-surgical offloading strategies (OR 0.28, 95% CI 0.14–0.55; I^2 44%), which supports the practical concept that plantar pressure redistribution through structural correction can address the mechanistic driver of repeated ulcer breakdown. These findings should not be interpreted as advocating surgery for all ulcers but rather highlight that earlier surgical consideration may be appropriate in carefully selected patients with recurrent plantar forefoot ulcers, deformity-linked pressure overload, or failure of high-quality offloading and wound care.

In ischemic DFS phenotypes, revascularization showed an association with improved limb salvage outcomes (RR 1.42, 95% CI 1.19–1.69; I^2 61%). The substantial heterogeneity in this analysis is expected, given variation in ischemia severity, anatomical disease distribution, infection burden, choice of endovascular versus open bypass techniques, and differences in concurrent debridement and antimicrobial management. Importantly, these results support revascularization as a central limb-salvage modality in appropriate candidates, while emphasizing that perfusion restoration must be integrated with infection control and wound optimization rather than being viewed as a stand-alone intervention.

Emerging adjunctive and diagnostic strategies—particularly those targeting microcirculation, angiogenesis, and earlier detection of neuropathic tissue risk—showed promising but early-stage signals across the evidence base. Mechanistic insights related to metabolic memory, microRNA signaling, and endothelial dysfunction provide plausible biological explanations for refractory non-healing ulcers even when glycemic targets are improved. However, these modalities remain limited by smaller study sizes, variability in endpoints, and inconsistent comparative designs, making them best interpreted as hypothesis-generating components that may complement rather than replace established integrated care pathways.

Several limitations must be considered when interpreting these findings. First, clinical heterogeneity across included studies was substantial, driven by differences in ulcer severity, neuropathic versus ischemic composition, infection/osteomyelitis prevalence, and variation in intervention definitions such as frequency and depth of debridement, offloading adherence, and surgical technique selection. Second, the methodological quality and risk-of-bias profile of included studies may vary across designs, and this can influence pooled estimates through confounding and selection effects, particularly in observational evidence. Third, many interventions in DFS are implemented as bundles within multidisciplinary programs, making isolation of single-component treatment effects challenging. Finally, while the synthesis supports integrated medical–surgical decision-making, definitive conclusions about optimal sequencing and timing require higher-quality comparative trials that stratify patients by vascular status, biomechanical risk, and infection burden.

Future research should prioritize pragmatic randomized trials and well-designed comparative cohorts that apply standardized ulcer classification, report consistent healing and recurrence endpoints, and incorporate perfusion and biomechanical stratification. Studies evaluating integrated algorithms should include cost-effectiveness, quality-of-life outcomes, and standardized limb-salvage definitions to strengthen translation into

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policy and multidisciplinary practice pathways. Collectively, these improvements would enable more precise selection of interventions, earlier identification of non-responders, and more consistent long-term limb preservation.

CONCLUSION

This systematic review and meta-analysis supports an integrated approach to diabetic foot syndrome management in which systemic optimization and structured wound care form the foundation, while targeted surgical correction and revascularization are considered for refractory, recurrent, biomechanically driven, or ischemic disease. Pooled evidence indicated favorable associations for glycemic optimization with improved DFS-related outcomes and for debridement with higher healing likelihood, while corrective osteotomy was associated with reduced recurrence and revascularization with improved limb salvage, although heterogeneity across studies was moderate to substantial. Adjunctive microcirculatory and molecularly informed strategies remain promising but require stronger comparative evidence. Future studies should focus on standardized, phenotype-stratified treatment algorithms with robust reporting of healing, recurrence, and amputation outcomes to improve long-term limb preservation.

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