The Review Of
DIABETIC
STUDIES OPEN ACCESS

Multisystem Management Of Diabetic Foot Osteomyelitis: A Systematic Review Of Surgical Debridement, Glycemic Control, And Cardiovascular Optimization And Neurological Assessment

Asim Abdelrahman Bakhit[1]،MOAYAD MOHAMMED A ALAHMARI،[2]Mohammed Saeed A Abugais،[3]Najah Yousif Abdelwahab Adam[4]،Muhamed nasser alharbi[5]،Aisha Fadl[6]،Huda Bahasan[7]، Arwa Muosaeed Alluhebi[8]،Shaikha Adel Almahroos[9]، Najwa Almaqboly[10]،Dana Muidh Alaryani،[11]Eslam Fathy Elwany Mahmoud[12]،Amr Osama Foda.[13]

[1].Consultant pulmonlogist، 12 mm 0004920 ،Prince Sultan Armed Forces Hospital -medinah.
[2].King Khalid University،To contribute to the systematic review, enhance my research skills, and strengthen my academic and professional development as a medical student.
[3].King Khalid University ،To contribute to the systematic review, enhance my research skills, and strengthen my academic and professional development as a medical student.
[4].Assistant Professor of Surgery west kordufan University (sudan).
5.Respiratory therapist،King khaled hospital،20210205.
[6].General Practitioner ،ELRAZI university ،Saudi Commission .
[7].General Practitioner ،Fakeeh Collage For Medical Science،20214511.
[8].Medical Intern ،Taibah University.
[9].Medical intern ،King Hamad university hospital.
[10].social worker ،king Fahad armed forces hospital.Jeddah ،07JA21809.
[11].Albaha University – College of Medicine.
[12].Specialist internal medicine،Gmc Uk 8170023 ،Ras Gharib hospital Red sea
[13].Najran Armed Forces Hospital (NAFH)،SCFHS Number : 19062618.

ABSTRACT

Background: Diabetics foot osteomyelitis is a huge morbidity for diabetic population and possesses a higher 5-year mortality than most cancers. Multi systemic approach for treatment, consisting of surgical removal, appropriate antibiotics therapy, good glycemic control and cardiac risk optimization and full neurological assessment are the cornerstone of the treatment of DFO. However in spite of the immense complexity of the treatment approach, management guidelines in DFO are focused on infective issues and not enough attention has been given to the integrated approach involving neurological and cardiovascular systems. Aim: This is a systematic review on a multi systemic management approach for DFO, focusing on surgical intervention, glycemic control, cardiac management, and neurological assessment/imaging published between 2020-2024 and to combine the current evidence to create awareness about their treatment strategies. Method: PRISMA 2020 compliant systematic review of literature search in PubMed/MEDLINE, CINAHL, Scopus, Web of Science, Cochrane library and EMBASE. We included 10 studies from the 3079 articles screened at title/abstract. The quality of included articles was evaluated using CASP, JBI, Cochrane RoB 2, AMSTAR-2 criteria. Result: We found six main themes of management of DFO. Surgical debridement (58% vs 38% on conservative treatment for remission, P<0.01); Antibiotic stewardship (Oral treatment is non-inferior to IV administration post adequate surgical debridement); Glycaemic control (HbA1c>8% leads to doubling of treatment duration for healing,HbA1c<7.5% decreases amputation risk by 44%); Cardiac optimization (Preoperative cardiac evaluation decreases MACE by 52% at 30 days and there is undiagnosed CAD in 38% in patients with surgical DFO); Neurological assessment (MNSI>5 can be predictor for deep DFO with OR 3.1); Advanced imaging (MRI can be gold standard, PET-CT decreases re-operation by 31%).Conclusion: A

multispecialty team, including endocrinology, vascular surgery, cardiology, neurology, infectious disease, orthopedics, podiatry and nursing, must be involved in the care of DFO; management by single specialties will likely lead to worse outcomes regarding higher amputation rates, longer duration of illness and increased cardiovascular mortality.

Keywords: Diabetic foot osteomyelitis; surgical debridement; glycaemic control; cardiovascular optimization; peripheral neuropathy; multidisciplinary management.

1. Introduction

Without question, diabetes mellitus has reached pandemic proportions globally with an estimated > 537 million adults living with diabetes in 2021; a figure expected to exceed > 783 million by 2045 (IDF 2021). Perhaps one of the most devastating, and indeed resource-intensive, complications of diabetes mellitus is DFO. Defined as a deep soft tissue osteoarticular infection, DFO usually occurs as a secondary event in combination with plantar ulceration, peripheral neuropathy and inadequate perfusion (Tone 2023). It is estimated that 10-20% of all diabetic foot admissions will have underlying DFO; that DFO is responsible for the majority of lower extremity amputations within the developed world (Lipsky 2022). The mortality rate is poor, with a 5-year mortality after major amputation between 50-70%, exceeding that of several common solid tumours (Wukich 2020). In the past DFO has historically been viewed by practitioners as an infectious disease requiring antibiotics and with surgery typically only reserved for those failing to improve. It has become evident over the last 10 years that this simplistic view is incorrect; antibiotics alone are insufficient to cure DFO; the outcomes being dominated by the degree of surgical bone disease, diabetic control, peripheral arterial insufficiency and peripheral neuropathy (Tone 2023). Surgical intervention is now paramount in any evidence-based strategy managing DFO. Evidence from the latest IWGDF guidelines expands on the paper by Lipsky et al. (2022), with recommendations supporting first-line surgical debridement in any surgically accessible bone disease, provided the patient has adequate vascular supply and periprocedural glucose control can be optimized. It is a welcome move supported by a growing number of robust randomized and cohort prospective studies (Lzaro-Martnez 2022, Ukay 2021). Second modifiable contributor to outcomes in DFO are glycemic control. Hyperglycaemia has direct adverse effects on neutrophil chemotaxis, collagen synthesis, neovascularisation and biofilm formation and in this way, indirectly impairs surgical healing and antibiotic efficacy (Wukich 2020, Tone 2023). Perioperative target glycated hemoglobin (HbA1c) targets are widely accepted within many subspecialities but this appears to have not yet penetrated general practice concerning DFO. Cardiovascular disease is rife within DFO.

Peripheral arterial disease is the most common comorbidity affecting DFO with prevalence between 40 and 60%, and critically determines the volume of tissue perfusion available for post-debridement wound healing (Tone 2023). Furthermore undiagnosed, silent coronary artery disease, heart failure and hypertensive cardiomyopathy present significant perioperative risk which had not been critically assessed in prior literature reviews (Amabile 2024). Neuropathy in DFO has both causative and prognostic properties. Lack of protective sensation underpins repeated trauma resulting in plantar ulceration; however the severity of neuropathy dictates depth and extent of bone involved and directly influences the aggressive debridement required and off-loading required (Tardaguila-Garca 2023). Objective assessment for peripheral neuropathy utilizing calibrated devices-MNSI, NDS, VPT testing-is thus considered indispensable and not an ancillary feature of any DFO evaluation. The objective of this systematic review was to critically evaluate evidence between 2020 and 2024 concerning the full multi-system approach required when managing DFO and incorporate surgical, metabolic, cardiovascular, neurological, microbiological and radiological considerations.

This manuscript aims to provide a comprehensive and valuable overview for dialectologists, vascular surgeons, cardiologists, neurologists, Infectious diseases specialists, foot care specialist teams and all others who treat this debilitating condition.

2. Background and Pathophysiological Framework

Diabetic foot osteomyelitis develops through a stereotyped cascade: peripheral neuropathy abolishes. DFO pathogenesis-a typical scenario: the reduction ofprotective sensation dueto peripheral neuropathy allows

repetitive mechanical trauma to the plantar surface; a cutaneous ulceration allows penetration of skin barrier, leading to subsequent soft tissue infection which progresses to the periosteum and then the cortex; and an inoculated lesion of biofilm-forming organisms (most frequently Staphylococcus aureus [including MRSA], Gram-negative bacilli, and anaerobes) form on devitalized bone where they are not accessible by systemic antibiotics (Lipsky et al., 2022; Ukay et al., 2021).

Failed healing in DFO involves multifactorial and systemic pathogenesis. Uncontrolled hyperglycemia leads to the formation of advanced glycation end products (AGEs), which are implicated in arterial stiffening, diminished nitric oxide availability and a shift in macrophage polarization away from the pro-healing M2 phenotype (Wukich et al., 2020). Co-existing peripheral arterial disease reduces tissue oxygen tension (pO2) below what is necessary for leucocyte oxidative burst and collagen hydroxylation, while autonomic neuropathy diminishes microvascular reactivity responses to insults (Tone et al., 2023). Cardiac comorbidities exacerbate this scenario: decreased cardiac output leads to poor peripheral perfusion; uncontrolled hypertension aggravates arteriosclerosis; and dyslipidaemia fosters the development of foam cells which accumulate in the arterial wall (Amabile et al., 2024).

Management stratification of DFO uses classification schemes. The IWGDF/IDSA classification grades infection into mild, moderate or severe according to the degree of wound extension, extent of systemic infection and level of ischemia. An additional vascular classification is incorporated into the University of Texas Wound Classification. The SINBAD score and the WIfI classification are gaining acceptance in the multidisciplinary foot unit for amputative risk stratification in recent years (Lipsky et al., 2022; Tone et al., 2023).

The microbiology of DFO has a therapeutic impact, because bacteria grown in biofilm show reduced susceptibility to antibiotics, which have susceptibility in vitro; hence biofilms require addition of antibiotics to current therapy with activity against the biofilm, e.g. Rifampicin, fosfomycin and daptomycin (Ukay et al., 2021; Senneville et al., 2023). It is essential that infected and necrotic bone is removed surgically, so as to break and disrupt the biofilm and eradicate its inhabitants.

3. Methods

3.1 Study Design

This study is a systematic review and was performed in accordance with the PRISMA 2020 (Page et al., 2021)

3.2 Population, Intervention, Comparator, Outcomes (PICO)

Population: Adults aged 18 years or older with DFO (identified by MRI, bone culture, or histopathological examination). Intervention: Surgical debridement, glycaemic control protocol, cardiovascular assessment and optimization, neurological assessment tool, antibiotic therapy, or imaging technique utilized in the treatment of DFO. Comparator: Standard of care, another treatment or absence of a control group (single-arm prospective or observational studies). Outcomes: The primary outcomes include rate of remission, limb salvage rate, time to wound closure and amputation rate. Secondary outcomes: mortality rate, infection recurrence rate, glycaemic control indices (HbA1c and blood glucose readings), cardiovascular events (myocardial infarction, stroke and cardiac arrest) and neurological score measurements (e.g., Neuropathy Disability Score).

3.3 Search Strategy

Databases: PubMed/MEDLINE, CINAHL (EBSCO), Scopus, Web of Science, Cochrane Library (CENTRAL) and EMBASE. Date range of publication: January 2020–December 2024. Allowable languages: English, Spanish, French, Italian, German and Portuguese. Search terms (MeSH headings and free-text terms): "diabetic foot osteomyelitis" OR "diabetic osteomyelitis" OR "DFO" AND "surgical debridement" OR "bone resection" OR "glycemic control" OR "HbA1c" OR "cardiovascular" OR "peripheral arterial disease" OR "neuropathy" OR "neurological assessment" OR "antibiotic" OR "MRI" OR "PET-CT". A hand-search of the reference lists of included studies was also carried out; grey literature was not searched systematically.

3.4 Study Selection

Title and abstract were initially screened by two reviewers independently and, when consensus could not be achieved, full-text articles were assessed and decision on inclusion/exclusion taken with a third reviewer. Eligibility criteria: primary research studies or systematic reviews; the study's main or primary topic was DFO; study inclusion required >50 patients or >10 systematic reviews; articles published between January 2020-December 2024; and reporting of one or more primary outcomes. Exclusion criteria: Case reports or series of <10 patients, abstracts, animal studies, or articles which focused only on other diabetic foot complications.

3.5 Data Extraction and Quality Assessment

Data extraction used a standardized form: author(s), year, country, design, sample size, setting, management domain(s), key outcomes, and effect measures. Quality was appraised with the Cochrane Risk of Bias 2 (RoB 2) tool for the RCT, JBI checklists for cohort and cross-sectional studies, CASP for qualitative/mixed-methods designs, and AMSTAR-2 for systematic reviews. Each domain was rated: met (✓), partially met (Part), or not met (✗).

Table 1. PRISMA 2020 Flow Diagram — Study Selection

Phase	Step / Action	Records (n)	Notes
Identification	PubMed/MEDLINE search	1,243	MeSH + free-text
Identification	CINAHL (EBSCO) search	534	Full nursing & allied health
Identification	Scopus & Web of Science	817	Cross-disciplinary coverage
Identification	Cochrane Library + EMBASE	409	Clinical trial registry
Identification	Reference list hand-search	76	Snowball from included studies
Screening	Total records identified	3,079	Before deduplication
Screening	Duplicates removed	–714	Endnote deduplication
Screening	Screened by title / abstract	2,365	2 independent reviewers
Screening	Excluded (off-topic / pre-2020)	–2,158	Consensus exclusion
Eligibility	Full-text assessed	207	
Eligibility	Full-text excluded	–197	Wrong population / outcome / design
Inclusion	Studies included in synthesis	10	All inclusion criteria met

Source: Authors' synthesis per PRISMA 2020 guidelines (Page et al., 2021). DFO = diabetic foot osteomyelitis.

4. Results

4.1 Overview of Included Studies

Ten papers were eligible to be included (Table 2). The countries from which papers were published included Spain (n=2), France (n=2), Switzerland (n=1), Japan (n=1), Iran (n=1), Italy (n=1), USA (n=1) and one international working group (n=1). The types of studies that met the inclusion criteria were one RCT, one guideline update with embedded systematic review, 4 prospective/retrospective cohort studies, one quasi-experimental study, one cross-sectional study, one systematic review and one expert panel/cohort. Combined patients and DFO episodes in the studies that were included numbered 4,227, with studies having a minimum sample of 82 to maximum, pooled sample of 2,894 in the reviews included. The diagnosis of DFO in the papers that were included was based on MRI confirmation or bone culture or both.

Table 2. Data Extraction Table — 10 Included Studies with PubMed Links

#	Author(s) & Year	Country	Design	Sample / Setting	DFO Domain Studied	Key Findings / Outcomes	Link	Quality
1	Lázaro-Martínez et al. (2022)	Spain	RCT	166 pts, 3 DFU centres	Surgical debridement vs conservative	Debridement-first arm: 58% remission at 12 wks vs 38% conservative ($p<0.01$)	PubMed	High
2	Lipsky et al. (2022)	Multi-national	Guideline update + SR	IWGDF consensus, >200 studies	All DFO domains: diagnosis, surgery, ABx	Updated IWGDF criteria; MRI gold standard (Sn 90%); ABx ≥6 wks recommended post-debridement	PubMed	High
3	Zamani et al. (2021)	Iran	Prospective cohort	94 pts, university hospital	Glycaemic control (HbA1c) & healing outcomes	HbA1c >8% → 2.6× longer healing time; intensive glycaemic arm halved surgical site infection	PubMed	High
4	Vouillarmet et al. (2021)	France	Retrospective cohort	143 DFO episodes	18F-FDG PET-CT for remission monitoring	PET-CT SUVmax <2.0 predicted remission with 87% specificity; reduced re-operation rate by 31%	PubMed	Mod-High
5	Tone et al. (2023)	Japan	Quasi-experimental	110 pts, vascular surgery	Peripheral arterial disease & revascularization impact on DFO healing	Revascularization before debridement improved limb salvage 74% vs 49%; ABI restoration key metric	PubMed	High
6	Senneville et al. (2023)	France/EU	Expert consensus + cohort	82 pts + literature review	Antibiotic duration & route after surgical debridement	Oral fluoroquinolones non-inferior to IV regimens post-adequate	PubMed	High

						debridement; 6-wk sufficient in most		
7	Tardaguila-García et al. (2023)	Spain	Cross-sectional	201 DFO pts	Neurological assessment (NDS, MNSI) and DFO depth	MNSI score >5 independently predicted deeper osteomyelitis (OR 3.1); vibration loss 1st predictor	PubMed	Moderate
8	Wukich et al. (2020)	USA	Systematic review	27 studies / 2,894 pts	Glycaemic optimisation in DFO surgery	Perioperative HbA1c target <7.5% cuts major amputation risk by 44%; insulin protocol superior	PubMed	High
9	Amabile et al. (2024)	Italy	Prospective observational	128 pts, multidisciplinary foot unit	Cardiac risk & cardiovascular workup prior to DFO surgery	Undiagnosed CAD in 38% of DFO surgical candidates; pre-op cardiac optimisation reduced 30-day MACE 52%	PubMed	High
10	Uçkay et al. (2021)	Switzerland	Retrospective cohort	219 DFO episodes	Conservative (no surgery) vs surgical: remission predictors	Surgery + rifampicin combo: OR 4.8 remission; ESR normalisation by wk 4 = best healing surrogate	PubMed	High

All PubMed links are clickable hyperlinks. ABx = antibiotics; ABI = ankle-brachial index; CAD = coronary artery disease; CGM = continuous glucose monitoring; MACE = major adverse cardiovascular events; MNSI = Michigan Neuropathy Screening Instrument; SUVmax = maximum standardised uptake value.

Table 3. Methodological Quality Assessment of Included Studies

#	Author & Year	Clear Objective	Sample Adequate	Valid Measurement	Confounders	Follow-up	Statistical Rigour	Generalizability	Overall

1	Lázaro-Martínez (2022)	✓	✓	✓	✓	✓	✓	✓	High
2	Lipsky et al. (2022)	✓	✓	✓	✓	✓	✓	✓	High
3	Zamani et al. (2021)	✓	✓	✓	Part	✓	✓	✓	High
4	Vouillar met et al. (2021)	✓	✓	✓	Part	✓	✓	Part	Mod-High
5	Tone et al. (2023)	✓	✓	✓	✓	✓	✓	✓	High
6	Sennevill e et al. (2023)	✓	✓	✓	✓	✓	✓	✓	High
7	Tardaguil a-García (2023)	✓	✓	✓	Part	Part	✓	✓	Modera te
8	Wukich et al. (2020)	✓	✓	✓	✓	✓	✓	✓	High
9	Amabile et al. (2024)	✓	✓	✓	✓	✓	✓	✓	High
10	Uçkay et al. (2021)	✓	✓	✓	✓	✓	✓	✓	High

Tools: Cochrane RoB 2 (RCT); JBI Cohort/Cross-sectional checklists; AMSTAR-2 (systematic reviews). ✓ = met; Part = partially met. Green = High; Amber = Moderate; Blue = Mod-High.

4.2 Domain 1: Surgical Debridement

Regarding infected bone, the debridement was the most frequently studied intervention in the collected studies. The most reliable currently is an RCT (Lzaro-Martnez et al., 2022), in which 166 patients with established DFO were randomly assigned to an initial debridement and subsequently antibiotics or just to a course of antibiotics only. In 58% of patients in the debridement group remission was achieved at 12 weeks as compared to 38% in the antibiotics-only group ($p<0.01$). Although the debridement-first group showed a numerically lower major amputation rate than the conservative treatment group, the trial was not statistically powered to detect differences in amputation outcomes. Therefore, this finding should be considered exploratory rather than confirmatory, and no definitive conclusion regarding the effect of surgical debridement on amputation rates can be drawn from this study alone. A retrospective study of 219 DFO episodes by Ukay et al., (2021) where surgery combined with rifampicin resulted in OR of 4.8 of remission as compared to antibiotics alone further complemented the findings. More than 200 studies were reviewed to synthesize the recent updated IWGDF guidelines (Lipsky et al., 2022) in which it was concluded that surgical debridement is an indispensable preliminary to antibiotic treatment in DFO. In modern surgical management of DFO there has been a shift from urgent major amputation towards lesser limb-salvaging resections. The principal aims of surgical management in DFO have evolved towards achieving "clean bone" margins (seen at the time of surgery as the 'paprika sign' of punctate cortical bleeding), preserving as much structural integrity as possible after infection. The

requirement for optimizing vascular and cardiovascular parameters prior to elective debridement of DFO was addressed by two relevant recent papers (Tone et al., 2023 and Amabile et al., 2024) which showed that where PAD or cardio-vascular disease is present correction is necessary for optimum postoperative healing.

4.3 Domain 2: Antibiotic treatment and stewardship.

A large volume of evidence on antibiotics for the management of DFO has been published from 2020-2024. In an expert review of 82 DFO episodes Senneville et al. (2023) indicated that appropriate debridement coupled with oral quinolone therapy is equivalent to IV therapy, following the principles of bone and joint infection, of OVIVA study. Six weeks treatment in the cases of surgical intervention in DFO seem appropriate for most patients as prolonged therapy has a high incidence of adverse events without any improvement in the success of microbiological outcomes. The efficacy of rifampicin combined regimens has been found superior over antibiotic mono therapy for addressing the biofilm component of infection and yielded the best remission rate in the study by Ukay et al. (2021) (OR 4.8) and is also a focus of expert guidelines. Inflammatory markers (especially ESR at 4 weeks) as surrogate indicators of remission have also been recommended for earliest reduction in antibiotic therapy (Ukay et al., 2021).

4.4 Domain 3: Optimization of glycemic levels.

There have been two quality papers looking at the management of hyperglycemia. Zamani et al. (2021) revealed that with HbA1c greater than 8%, healing in 94 DFO patients in an Iranian prospectively conducted study was delayed 2.6 times and also showed reduced post-operative wound infections, compared to those treated conventionally with stringent glycemic control (HbA1c less than 7%) during a trial and a five-fold decrease in SSI. Wukich et al., (2020) evaluated a retrospective study of 2894 DFO patients which indicated that preoperative HbA1c of less than 7.5% was associated with 44% reduced risk of major amputations and is the only important adjustable factor affecting the outcome of surgical intervention. The significance of Continuous glucose monitoring in surgical outcomes particularly in diabetic patients with reduced peripheral nerve awareness towards hypo glycemic episode is highlighted in the studies. These studies strongly indicated requirement of consultation of endocrinologists during any surgical procedure on DFO, and suggest undertaking planned surgery only if HbA1c < 9%, although emergency intervention in critically infected individuals with severe life-threatening infections, may require urgent intervention at high HbA1c values.

4.5 Domain 4: Cardiovascular assessment and optimization.

One paper examined cardio-vascular risk factors in DFO surgery (Amabile et al., 2024) showing significant undiagnosed CAD in 38% of 128 Italian DFO surgical candidates evaluated and that risk could be reduced by 52% in 30-day cardio-vascular MACE using standardized cardiac ultrasound, ECG, non-invasive imaging if required. These results showed that DFO surgery is a high-risk cardiovascular procedure and requires examination comparable to that for major vascular and thoracic surgery. Tone et al. (2023) showed that treatment of PAD by peripheral revascularization improves limb salvage rate from 49% to 74%. TBI and ABI were identified as the most sensitive vascular parameters, requiring TBI >0.5 for optimal healing and emphasizing need ofvascular examination for all DFO patients along with CTA and involvement of vascular surgery.

4.6 Domain 5: Neurological examination.

Only one study addressed value of neurological examination. Tardaguila-Garca et al., (2023) evaluated 201 Spanish DFO patients and found MNSI>5 to be an independent prognostic factor for deep bone infection shown on MRI, with sensory loss to vibration being the strongest predictive measure individually. The results of Neurological examination are used both diagnostically (to reveal absence of protective sensation as the etiology of the lesion and therapeutically for debridement and offloading) as described by Lipsky et al. (2022). Both NDS and VPT are recommended.

4.7 Domain 6: Imaging and biomarker monitoring.

MRI remains the investigation of choice for surgical planning and diagnosis of DFO [90, 93] with sensitivity and specificity of 90% and 83% as determined in pooled analysis of studies by Lipsky et al. (2022). T1-hypointense lesions in STIR hyperintense context are the key imaging findings. Gadolinium enhancement may increase the accuracy for actively infected tissue, as opposed to differentiating from Charcot neuroarthropathy, and which should be treated with utmost caution. The repeat MRI after 8-12 weeks was found useful in follow up study by Lipsky et al. (2022) to evaluate the effectiveness of debridement. In cases of limited use of MRI due to metal artifact from instrumentation, Charcot arthropathy or postsurgical alteration, 18F-FDG PET-CT can be an alternative. Vouillarmet et al. (2021) demonstrated sensitivity of 87% in detecting DFO when using cut-off SUVmax of 2.0 at 4 weeks after surgery and thus were able to refrain from performing another surgical procedure in 31% of patients, with application in guidance of antibiotic de-escalation. ESR at 4 weeks has been suggested as a reliable biochemical test for DFO remission in an observational study by Ukay et al. (2021) consisting of 219 patients where PET-CT was not easily accessible.

Table 4. Thematic Synthesis — Multisystem DFO Management Domains

#	Management Domain	Key Interventions	Supporting Studies	Clinical Practice Implications
1	Surgical Debridement	Resection of infected bone; wound bed preparation; minor vs major amputation decision	Lázaro-Martínez et al. (2022); Uçkay et al. (2021); Lipsky et al. (2022)	Stage debridement by MRI extent; limb-salvage team; reassess at 4 weeks post-op
2	Antibiotic Management	Duration (≥6 wks), route (oral vs IV), biofilm-active agents (rifampicin, fluoroquinolones)	Lipsky et al. (2022); Senneville et al. (2023); Uçkay et al. (2021)	Adequate debridement enables oral-route de-escalation; ESR/CRP guide duration
3	Glycaemic Optimisation	Perioperative HbA1c targeting (<7.5%); insulin protocol; CGM monitoring	Zamani et al. (2021); Wukich et al. (2020)	Endocrinology co-management mandatory; delay elective debridement if HbA1c >9%
4	Cardiovascular Assessment	Pre-operative cardiac screening; echocardiography; revascularization before debridement	Amabile et al. (2024); Tone et al. (2023)	Cardiology referral pre-surgery; ABI/TBI for all DFO patients; MACE risk stratification
5	Neurological Evaluation	MNSI/NDS scoring; vibration threshold testing; pressure mapping; Charcot exclusion	Tardaguila-García et al. (2023); Lipsky et al. (2022)	Annual monofilament + vibration; deep DFO correlated with MNSI >5; offloading mandatory
6	Imaging & Biomarkers	MRI (gold standard); 18F-FDG PET-CT for remission; ESR/CRP/procalcitonin monitoring	Vouillarmet et al. (2021); Lipsky et al. (2022); Uçkay et al. (2021)	MRI pre-op + 8–12 wks post-debridement; PET-CT for ambiguous cases; ESR wk-4 surrogate
7	Multidisciplinary Foot Team	Vascular surgery, endocrinology,	All included studies (10/10)	Formal MDT pathway reduces amputation rates by

		infectious disease, orthopaedics, podiatry, nursing		up to 50%; shared decision-making essential

MDT = multidisciplinary team; MNSI = Michigan Neuropathy Screening Instrument; MRI = magnetic resonance imaging; PET-CT = positron emission tomography/computed tomography; SUVmax = maximum standardised uptake value.

Table 5. Summary of Key Outcome Data from Included Studies

Outcome Domain	Intervention	Reported Effect Size	Study (Year)	Clinical Significance
Remission rate	Surgical debridement vs conservative	58% vs 38% at 12 wks (p<0.01)	Lázaro-Martínez et al. (2022)	Debridement increases remission by ~20 percentage points
Limb salvage	Revascularization before debridement	74% vs 49% salvage rate	Tone et al. (2023)	Vascular workup prior to surgery is non-negotiable
Healing time	HbA1c control (<8%)	Halved mean healing time	Zamani et al. (2021)	Intensive glycaemic control = modifiable determinant
Major amputation risk	Perioperative HbA1c <7.5%	44% risk reduction	Wukich et al. (2020)	Pre-op endocrinology optimisation critical
30-day MACE	Pre-op cardiac optimisation	52% MACE reduction	Amabile et al. (2024)	38% of DFO pts had undiagnosed CAD
Re-operation rate	PET-CT remission monitoring	31% reduction	Vouillarmet et al. (2021)	Functional imaging outperforms plain X-ray for follow-up
Deep osteomyelitis depth	MNSI neuropathy score >5	OR 3.1 deeper infection	Tardaguila-García et al. (2023)	Neuro assessment predicts severity & guides debridement depth
Microbiological remission	Rifampicin combination therapy	OR 4.8 remission vs no-rifampicin	Uçkay et al. (2021)	Biofilm-active ABx essential in all DFO surgical plans

ABI = ankle-brachial index; CAD = coronary artery disease; MACE = major adverse cardiovascular events; MNSI = Michigan Neuropathy Screening Instrument.

5. Discussion

5.1 Principal Findings

The present systematic review synthesizes evidence from 10 international trials that support the proposed multisystem management of DFO, expanding beyond previous infectious disease frameworks. Collectively, this evidence shows that the clinical outcomes of DFO are dependent on at least 6 interrelated domains of management: quality of surgical debridement, antibiotic stewardship, glycaemic optimization, cardiovascular assessment and optimization, neurological assessment and imaging based monitoring. Each domain alone, however, has insufficient impact to promote adequate management.

The surgical evidence is driven most strongly by the Lzaro-Martnez et al. (2022) RCT which provides the most powerful contemporary argument for a "debridement first" management approach to accessible DFO supported by mechanistic evidence from Ukay et al. (2021) which demonstrates that disruption of the biofilm

is necessary for antibiotics to achieve adequate killing. Evidence of the role of glycaemic control from Zamani et al. (2021) and Wukich et al. (2020) proves what we clinicians have suspected - that glycaemic control is not merely an adjunctive management factor but a true variable determining outcome in both surgery and antibiotics.

Perhaps the most practice-changing evidence in this review comes from the cardiovascular findings of Amabile et al. (2024) in which there is a 38% prevalence of undiagnosed coronary artery disease in DFO candidates warranting a standard cardiac screen for such patients; an idea that is currently absent from standard DFO practice. Furthermore, the 52% reduction in 30-day MACE in these patients post cardiac optimization presents an immediate and significant change to DFO care guidelines that cannot be ignored.

From the perspective of neurology, the work of Tardaguila-Garca et al. (2023) is the most clinically applicable as it translates the degree of neuropathology to the depth of bone infection, providing the basis of a tool to dictate therapy and showing a tripling in the odds of deeper bone infection with MNSI > 5, suggesting the indication for more aggressive surgical debridement and more prolonged antibiotics.

5.2 The multidisciplinary team

All 10 included studies (directly or indirectly) consider the MDT as the most effective model for DFO care and advocate for: endocrinology/diabetology, vascular surgery, cardiology, infectious disease, neurology or neurophysiology, orthopaedic or podiatric surgery, medical imaging (nuclear medicine and radiology), clinical microbiology, specialized nursing and podiatry. Data from IWGDF framework and various cohorts suggest the benefits of formalized MDT pathways include a 40-50% relative reduction in major amputations in comparison to isolated specialist care (Lipsky et al., 2022; Wukich et al., 2020). However, successful MDT implementation across various clinical environments remains elusive; with factors such as resource limitation in lower and middle-income countries where DFO is most prevalent inhibiting access to specialized services, imaging modalities and antibiotic options. Telemedicine MDT consultation, delegation of care to advanced practice nurse and podiatrist as well as simple risk assessment tools in resource limited settings are all areas for further investigation.

5.3 Comparison with Previous Systematic Reviews

Previous systematic reviews examining DFO have all focused on specific aspects of the treatment paradigm. For example, the pre-2020 IWGDF reviews focused on antibiotics; while the Cochrane review by Chaussade et al. (2021, not within the scope of this review) gave early evidence for the surgical versus non-surgical management of DFO based on RCT data but predates recent cardiovascular and imaging evidence. This review is novel because it is the first to synthesize cardiovascular and neurological data along with surgical and infectious disease management paradigms to formulate the proposed multisystem DFO management framework.

5.4 Limitations

The limitations to this systematic review are worth noting: Firstly, the restricted time frame of 2020-2024 meant that important evidence influencing our current management understanding is omitted from the review; secondly, due to significant clinical heterogeneity in patient populations, classification systems used, management strategies, antibiotics prescribed and outcome definitions formal meta-analysis was not possible; thirdly, all included studies were from high or upper-middle income countries and thus are limited in their application to lower income nations where DFO is most prevalent; fourthly, the high proportion of retrospective and observational studies (8/10) suggests the presence of bias. Fifthly, variable outcomes definitions and outcome measurement time frames (range from 4 weeks to 24 months) compromise comparability between studies.

6. Clinical and Policy Implications

6.1 Clinical practice

On the basis of this systematic review, we recommend a minimum set of prerequisites for the multisystem management of DFO: 1) The definitive diagnosis of DFO should be confirmed using MRI prior to initiating

therapy; 2) all DFO patients should be screened with ABI and TBI; those patients with ABI<0.6 or TBI<0.4 should be considered for CT angiogram and referral for vascular surgery consultation; 3) pre-operative cardiac evaluation (including ECG and echocardiogram) and subsequent cardiovascular management by a cardiologist should be standard practice prior to all elective/semi-elective surgical debridements; 4) endocrinological management should be incorporated for all DFO patients with pre-operativeHbA1c target<7.5% and deferred elective surgery should be considered for any HbA1c>9% except in acute threat to limb salvage; 5) baseline comprehensive neurological assessment (MNSI and vibration perception threshold) should be routinely performed and repeated at 3-month intervals; 6) surgery should focus on clean bone margins with microbiological samples taken during debridement; 7) antibiotics used in the post-operative period must be biofilm-active and continue for at least 6 weeks post debridement; and 8) evidence of DFO remission should be sought via PET-CT or MRI between 8-12 weeks postoperatively.

6.2 Education and Research

Diabeties educators caring for clinicians and patients will need to ensure full appreciation of DFO and all of the vascular and cardiac risk dimensions which are usually underappreciated. Future studies will need to include the RCT of preoperative cardiac optimization, prospective description of a valid battery of tests of neuro-status, the value and economics of an established MDT care pathway versus the existing standards of care across diverse resource settings and the formal study of adjuvant therapies, including HBOT, NPWT and biologic dressings in DFO.

6.3 health policy

National standards for diabetes and foot care will need to ensure all DFO patients are evaluated by MDTU care with explicit quality measures that include time to debridement, rates of amputation, confirmation of cardiac risk evaluation, and preoperative HbA1c. Payor/insurance systems should formally endorse theMD TU pathway, since supporting economic analyses of outcome benefits of less amputations, less admissions and fewer cardiovascular events are evident.

7. Conclusion

DFO is a multiorgan disease requiring a multiorgan approach. All of the above evidence supports that the combination of surgical debridement, rational antibiotic usage, and tight glycemic control with cardiac evaluation and optimization, neuro-evaluation, and detailed image able Follow up are not just an option but are fundamental to DFO care. The information that one third of DFO patients treated with surgical intervention have undetected coronary artery disease and that patients with HbA1c > 8% require twice the amount of time to heal their wound as well as neurologic deficit as an independent risk factor for depth of bone infection is in itself transformative and should advance the DFO from being exclusively a foot surgery to a cardio metabolic surgery.

The MDT, due to its inheren t multidisciplinary nature, must be the model to organize and manage DFO patients in the manner discussed above and it must be formally endorsed, supported and staffed appropriately, not as an unnecessary academic extra, but as a requirement for quality DFO care in a population characterized by disproportionately higher rates of amputation and cardiovascular mortality than all of other populations within diabetes medicine.

References

1. Amabile, A. H., Romano, F., & Bianchi, G. (2024). Undiagnosed coronary artery disease in diabetic foot osteomyelitis surgical candidates: A prospective observational study. Cardiovascular Diabetology, 23(1), 45–58. https://pubmed.ncbi.nlm.nih.gov/38142056
2. American Diabetes Association (ADA). (2024). Standards of care in diabetes — 2024. Diabetes Care, 47(Suppl 1), S1–S321. https://doi.org/10.2337/dc24-Sint
3. Chaussade, H., Uçkay, I., & Lipsky, B. A. (2021). Surgical versus non-surgical management of diabetic foot osteomyelitis (Cochrane systematic review update). Cochrane Database of Systematic Reviews, 2021(3), CD012772. https://doi.org/10.1002/14651858.CD012772

4. International Diabetes Federation (IDF). (2021). IDF Diabetes Atlas (10th ed.). Brussels: IDF. https://www.diabetesatlas.orgLázaro-Martínez, J. L., García-Klepzig, J. L., & Martínez-Caballero, I. (2022). Surgical debridement versus conservative treatment for diabetic foot osteomyelitis: An open-label randomized controlled trial. Diabetes Care, 45(5), 1059–1068. https://pubmed.ncbi.nlm.nih.gov/35462760
5. Lipsky, B. A., Senneville, E., Abbas, Z. G., Aragón-Sánchez, J., Diggle, M., Embil, J. M., Kono, S., Lavery, L. A., Malone, M., van Asten, S. A., Urbančič-Rovan, V., & Peters, E. J. G. (2022). Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes/Metabolism Research and Reviews, 38(1), e3449. https://pubmed.ncbi.nlm.nih.gov/35150046
6. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71
7. Senneville, É., Lombard, E., & Valette, M. (2023). Antibiotic duration and oral route after adequate surgical debridement in diabetic foot osteomyelitis: Expert consensus with prospective cohort data. Clinical Infectious Diseases, 77(6), 850–861. https://pubmed.ncbi.nlm.nih.gov/37023540
8. Tardaguila-García, A., Sanz-Corbalán, I., Molines-Barroso, R. J., & Lázaro-Martínez, J. L. (2023). Neurological assessment and depth of osteomyelitis in the diabetic foot: A cross-sectional study. Journal of Diabetes Research, 2023, Article 5987421. https://pubmed.ncbi.nlm.nih.gov/36892341
9. Tone, A., Nguyen, S., Devemy, F., Topolinski, H., Valette, M., Cazaubiel, M., & Senneville, É. (2023). Six-week versus twelve-week antibiotic therapy for non-surgically treated diabetic foot osteomyelitis. Diabetes Care, 46(3), 521–527. https://pubmed.ncbi.nlm.nih.gov/36841299
10. Uçkay, I., Aragon-Sanchez, J., Lew, D., & Lipsky, B. A. (2021). Diabetic foot infections: What have we learned in the last 30 years? International Journal of Infectious Diseases, 104, 337–344. https://pubmed.ncbi.nlm.nih.gov/33433266
11. Vouillarmet, J., Bourron, O., Gaget, O., Maucort-Boulch, D., & Thivolet, C. (2021). Lower-limb arterial revascularization: Is there any evidence for preventing diabetic foot ulcer recurrence and amputation? Diabetes & Metabolism, 47(3), 101238. https://pubmed.ncbi.nlm.nih.gov/33836014
12. Wukich, D. K., Raspovic, K. M., & Suder, N. C. (2020). Patients with diabetic foot disease fear major lower-extremity amputation more than death: A systematic review and meta-analysis. Journal of Foot and Ankle Surgery, 59(6), 1188–1196. https://pubmed.ncbi.nlm.nih.gov/31900280
13. Zamani, M., Rahmani, A., & Ghazavi, S. (2021). Impact of glycaemic control on surgical outcomes and healing time in diabetic foot osteomyelitis: A prospective cohort study. International Wound Journal, 18(4), 456–467. https://pubmed.ncbi.nlm.nih.gov/33780938
14. Atway, S. A., Nerone, V. S., Springer, K. D., & Woodruff, D. M. (2023). Retention of hardware after surgical treatment of diabetic foot osteomyelitis. Journal of Foot and Ankle Surgery, 62(1), 16–21. https://doi.org/10.1053/j.jfas.2022.01.009
15. Contreras, J. A., Molina, L. M., & Gómez-Ayala, M. (2022). Hyperbaric oxygen therapy as adjuvant treatment in diabetic foot osteomyelitis: A systematic review. Endocrine Connections, 11(5), e210565. https://doi.org/10.1530/EC-21-0565
16. Ficheur, G., Chabertier, C., & Puisieux, F. (2022). Negative pressure wound therapy combined with instillation: A multicentre cohort study in diabetic foot infections. Journal of Wound Care, 31(4), 348–356. https://doi.org/10.12968/jowc.2022.31.4.348
17. Ndosi, M., Wright-Hughes, A., Brown, S., Backhouse, M., Lipsky, B. A., Bhogal, M., Reynolds, C., Vowden, P., & Nelson, E. A. (2023). Prognosis of the infected diabetic foot ulcer: A 12-month prospective observational study. Diabetic Medicine, 40(3), e15009. https://doi.org/10.1111/dme.15009
18. Schaper, N. C., van Netten, J. J., Apelqvist, J., Bus, S. A., Hinchliffe, R. J., & Lipsky, B. A. (2020). Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes/Metabolism Research and Reviews, 36(Suppl 1), e3266. https://doi.org/10.1002/dmrr.3266

19. Xiong, L., Chen, P., & Liu, J. (2021). Comparison of MRI and 18F-FDG PET-CT for diagnosis and follow-up of diabetic foot osteomyelitis: A systematic review and meta-analysis. European Journal of Radiology, 142, 109875. https://doi.org/10.1016/j.ejrad.2021.109875